Antidepressant treatment strategy with an early onset of action improves the clinical outcome in patients with major depressive disorder and high anxiety: a multicenter and 6-week follow-up study

Xue-Mei Liao[1,2], Yun-Ai Su[1,2], Ying Wang[3], Xin Yu[1,2], Tian-Mei Si[1,2]

[1]Peking University Sixth Hospital & Peking University Institute of Mental Health, Beijing 100191, China;
[2]National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital) & Key Laboratory of Mental Health (Peking University), Beijing 100191, China;
[3]The 984th Hospital of Chinese People's Liberation Army, Beijing 110108, China.

Major depressive disorder (MDD) is a prevalent, often chronic, and highly disabling multidimensional psychiatric illness.[1] Moreover, co-occurring anxiety symptoms are extremely common among patients with MDD; up to 90% of patients present with anxiety symptoms.[2] Notably, high levels of anxiety symptoms may predict worse clinical outcomes because of poor response to pharmacotherapy for MDD.[3] So use of augmentation or combination strategies during early course of treatment could be necessary, but ensuring the accurate and timely change is difficult because of the lack of consensus to assess the early improvement of initial treatment. To date, replicated evidence indicates that the lack of early improvement (eg, <20% reduction in a depression scale score) in 2 weeks can be an accurate predictor to identify eventual non-responders.[4] This study aimed to evaluate the early onset of antidepressant action and clinical outcomes in patients with MDD and high anxiety, and to explore the potential influencing factors of early onset improvement.

This study was a *post-hoc* analysis of a multicenter, randomized, parallel-controlled, open-label study.[5] The study protocol was approved by the independent ethics committee in each research center or the ethics committee of the Peking University Sixth Hospital. All the participants provided written informed consent before the study. A total of 245 patients (aged 18–65 years) were diagnosed with MDD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria. They were required to have a current major depressive episode with a total score ≥17 on the Hamilton Depression Rating Scale 17-item (HAMD-17), and also have a high level of anxiety symptoms with a total score ≥14 on the Hamilton Anxiety Rating Scale (HAMA) at the baseline visit.

All eligible patients were assigned to receive at least 6 weeks of follow-up and antidepressant treatment, including selective serotonin reuptake inhibitors (SSRIs) alone or coupled with a flexible dose of tandospirone.[5] The involved SSRIs were fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram. Notably, not all the patients were naive to any antidepressants at the first visit, but they were not treated with adequate dose of antidepressants for more than 2 weeks in the current episode. Treatment with several sedative-hypnotic drugs for short-term use was permitted as needed for sleep disorders, including zopiclone, lorazepam, alprazolam, clonazepam, midazolam, zaleplon, and zolpidem.

The efficacy measurements were evaluated at different visit points, including week 2, week 4, and week 6. The evaluation tools included HAMD-17 total scores, HAMA total scores, and Clinical Global Impressions Severity Subscale (CGI-S) score. Moreover, short form-12 (SF-12) physical component score (PCS) and mental component score (MCS) were used to assess the quality of life of these patients. Remission assessment was defined as showing an HAMD-17 total score ≤7 points.

At the end of week 2, 240 patients remained and were divided into two groups based on the reduction rate of HAMD-17 total score compared with the baseline: early-improvement group (≥20% decrease in HAMD-17 total score, $n = 134$) and early-unimproved group (<20% decrease in HAMD-17 total score, $n = 106$). Finally,

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Correspondence to: Dr. Tian-Mei Si, Department of Clinical Psychopharmacology in Peking University Sixth Hospital/Institute of Mental Health, No. 51 Huayuan North Road, Haidian District, Beijing 100191, China
E-Mail: si.tian-mei@163.com

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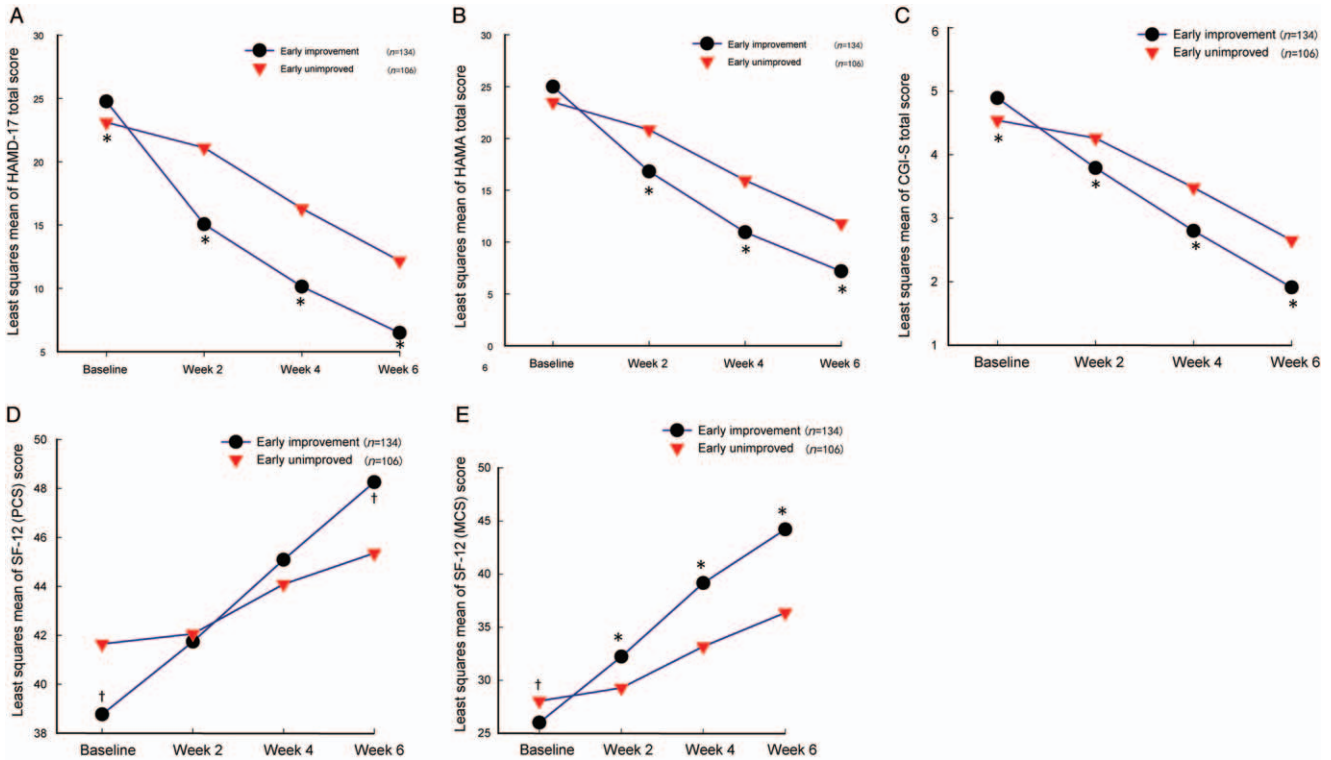

Figure 1: Least squares mean of HAMD-17 total score (A), HAMA total score (B), CGI-S total score (C), SF-12 (PCS) score (D), and SF-12 (MCS) score (E) at each visit in the early-improvement group and the early-unimproved group receiving antidepressant treatment. $^{*}P < 0.01$; $^{\dagger}P < 0.05$. CGI-S: Clinical global impressions severity; HAMA: Hamilton anxiety rating scale; HAMD-17: Hamilton depression rating scale 17-item; SF-12 (MCS): 12-Item short form survey (mental component score); SF-12 (PCS): 12-Item short form survey (physical component score).

230 patients completed the 6-week follow-up, including 128 patients with early-improvement and 102 early-unimproved patients. The comparison of the remission rate between the two groups was conducted in week 6. In addition, the potential influencing factors of early improvement in week 2 were also analyzed.

The data analysis was based on the full analysis set. The data collected at each visit point were analyzed using the mixed-effects repeated-measures model. The influencing factors of early improvement were analyzed by logistic regression. All the statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 24.0 (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

The baseline demographic data were similar between the two groups ($P > 0.05$), except for the number of patients taking sedative-hypnotic drugs. The patients in the early-improvement group showed more combination of sedative-hypnotic drugs compared with the patients in the early-unimproved group (12.7% [17/134] *vs.* 1.9% [2/106], $\chi^2 = 11.979$, $P = 0.002$).

At baseline, the total scores of HAMD-17 (24.76 *vs.* 23.11, $P = 0.007$) and CGI-S (4.89 *vs.* 4.54, $P = 0.002$) in the early-improvement group were significantly higher, and SF-12 (PCS) (38.77 *vs.* 41.65, $P = 0.022$) and SF-12 (MCS) (26.01 *vs.* 28.05, $P = 0.035$) scores were significantly lower than those in the early-unimproved group. The statistical superiority was observed for the early-improvement group in the HAMD-17 total score [Figure 1A], HAMA total score [Figure 1B], and CGI-S total score [Figure 1C] during weeks 2 to 6, SF-12 (PCS) score in week 6 [Figure 1D] and SF-12 (MCS) score between weeks 2 and 6 [Figure 1E].

Notably, the patients in the early-improvement group showed greater improvements in several important rating scales compared with the patients in the early-unimproved group at the endpoint visit. The least-squares (LS) mean in the HAMD-17 total score was statistically lower for the early-improvement group than the early-unimproved group (6.48 *vs.* 12.17, $P < 0.001$). The LS means in both HAMA total score (7.19 *vs.* 11.8, $P < 0.001$) and CGI-S total score (1.91 *vs.* 2.65, $P < 0.001$) were also significantly lower in the early-improvement group than in the early-unimproved patients. The greater improvements were observed in both SF-12 (PCS) score (48.26 *vs.* 45.36, $P = 0.014$) and SF-12 (MCS) score (44.21 *vs.* 36.36, $P < 0.001$) for the early-improvement group than for the early-unimproved group. In addition, the early-improvement group showed a significant difference in the remission rate in week 6 compared with the early-unimproved group (62.8% [80/128] *vs.* 29.4% [30/102], $\chi^2 = 25.424$, $P < 0.001$).

The logistic regression model was used to analyze the influencing factors for early improvement. The dependent variable was a dichotomous variable, which was an early improvement *vs.* early un-improvement. The independent

variables included in the model were treatment (SSRIs + tandospirone *vs*. SSRIs), combination with sedative-hypnotic drugs, age, body weight, sex, age of onset of psychiatric symptoms, course of recent episode, and baseline total scores of HAMD-17, HAMA, CGI-S, SF-12 (MCS), and SF-12 (PCS) scales. Of these variables, the combination with sedative-hypnotic drugs was statistically significant (odds ratio: 7.556, 95% confidence interval: 1.607–35.530, $P = 0.010$), indicating that the combination with sedative-hypnotic therapy was more helpful for early improvement.

The present study successfully replicated the findings of previous major studies, which demonstrated a significant relationship between early improvement within the first weeks of antidepressant treatment and later remission rate in patients with MDD.[6] Specifically, a similar association was found in patients with MDD and high level of anxiety symptoms. The results showed that patients who achieved the early improvement of the depressive symptoms in week 2 after antidepressant treatment also obtained the sustained relief of symptoms and improved quality of life during weeks 2 to 6. Further, these patients with early improvement displayed more significant clinical remission of depressive symptoms in week 6.

According to the logistic regression analysis, the results revealed that the combination with sedative-hypnotic drugs was a significant predictor of early improvement in week 2. Benzodiazepines are primarily used as a sedative-hypnotics in patients with MDD to alleviate anxiety symptom and insomnia, and they might contribute to the response to antidepressants in the first two weeks because they produce a faster onset of effect on anxiety symptoms than antidepressants alone. Thus, it may be justifiable to combine benzodiazepines as a short-term treatment in patients with MDD and high-level anxiety.

In summary, the early improvement within the first 2 weeks of receiving antidepressant treatment is a powerful predictor of outcome in patients with MDD and a high level of anxiety. Notably, the short-term combination with sedative-hypnotic drugs within the first few weeks may augment the early-onset improvement of antidepressant therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

References

1. Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, *et al*. Recognition and treatment of cognitive dysfunction in major depressive disorder. Front Psychiatry 2018;9:655. doi: 10.3389/fpsyt.2018.00655.
2. Wu Z, Chen J, Yuan C, Hong W, Peng D, Zhang C, *et al*. Difference in remission in a Chinese population with anxious versus nonanxious treatment-resistant depression: a report of OPERATION study. J Affect Disord 2013;150:834–839. doi: 10.1016/j.jad.2013.03.012.
3. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, *et al*. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 2008;165:342–351. doi: 10.1176/appi.ajp.2007.06111868.
4. Kudlow PA, Mclntyre RS, Lam RW. Early switching strategies in antidepressant non-responders: current evidence and future research directions. CNS Drugs 2014;28:601–609. doi: 10.1007/s40263-014-0171-5.
5. Lin J, Su Y, Wang C, Yang F, Xu Y, Yuan Y, *et al*. Effects of tandospirone augmentation in major depressive disorder patients with high anxiety: a multicenter, randomized, parallel-controlled, open-label study. J Psychiatr Res 2018;99:104–110. doi: 10.1016/j.jpsychires.2018.01.020.
6. Wagner S, Engel A, Engelmann J, Herzog D, Dreimüller N, Müller MB, *et al*. Early improvement as a resilience signal predicting later remission to antidepressant treatment in patients with major depressive disorder: systematic review and meta-analysis. J Psychiatr Res 2017;94:96–106. doi: 10.1016/j.jpsychires.2017.07.003.

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