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

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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 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,
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], χ² = 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], χ² = 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.

**Funding**

This study was sponsored by Sumitomo Dainippon Pharma Co., Ltd. (Suzhou, China. No.SPC-SED1102). The analysis and writing were partially supported by the National Key Technology R&D Program (No. 2015BAI13B01). The funders had no role in the study design, collection analysis, conduct of the study or in the writing and preparation of the manuscript or the decision to publish.

**Conflicts of interest**

None.

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**How to cite this article:** Liao XM, Su YA, Wang Y, Yu X, Si TM. 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. Chin Med J 2020;133:726–728. doi: 10.1097/CM9.0000000000000673