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ORIGINAL ARTICLE

Group-based trajectory analysis of depressive symptoms in patients treated with antidepressants in Chinese cohort studies

Jia **Zhou**,[1,2]* Xiao **Wang**,[1,2]* Lei **Feng**,[1,2] Yuan **Feng**,[1,2] Le **Xiao**,[1,2] Xu **Chen**,[1,2] Zizhao **Feng**,[1,2] Gang **Wang**,[1,2] Jingjing **Zhou**[1,2]

[1]*Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders & National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China.* [2]*Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China.* * *These authors contributed equally to this work.*

Objectives: To characterize response trajectories in patients with major depressive disorder (MDD) and identify clinical and demographic predictors of symptom alleviation.
Methods: This study was a secondary analysis of longitudinal data collected from 10 governances of China from November 9, 2016, to December 30, 2020. Depressive symptoms were mainly measured using the 17-item Hamilton Depression Rating Scale (HAMD-17). Group-based trajectory modeling was used to identify symptom trajectories from baseline to week 24.
Results: A total of 1,438 participants were included. Two trajectories were identified: 74.27% of participants belonged to trajectory 1, labeled as the ''rapid symptom reduction trajectory,'' characterized by moderate depression followed by rapid symptom reduction after treatment; and 25.73% of participants belonged to trajectory 2, labeled as the ''delayed symptom reduction trajectory,'' characterized by severe depression and a gradual decline in symptoms over 24 weeks. Compared with those in the rapid symptom reduction trajectory, values (including the HAMD-17 total score at baseline, the proportion of female participants, and the duration of untreated episodes) were significantly higher in the delayed symptom reduction trajectory.
Conclusions: Distinct response trajectories were identified in patients with MDD. Milder baseline severity, shorter untreated episodes, and male sex predicted rapid responses, aiding in treatment guidance.
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Keywords: Major depressive disorder; antidepressants; trajectory

Introduction

Depression is the leading cause of global disease burden, affecting approximately 350 million people worldwide.[1] A cross-sectional epidemiological study in China shows that the lifetime prevalence of major depressive disorder (MDD) in China is 3.4%, and the 12-month prevalence is 2.1%.[2] Depression is also associated with suicide and premature death caused by other diseases, causing a serious burden on society.[3,4] With depression predicted to contribute to an increasing disease burden in the coming decades, efforts to treat this condition have become increasingly important.

At present, the clinical decision-making process and selection of antidepressants for treatment mainly depend on the clinical experience and professional judgment of psychiatrists.[5] Commonly used antidepressants include selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors.[6] It is estimated that approximately 40% of patients with major depression do not respond to antidepressants, characterizing treatment-resistant depression.[7] Moreover, previous studies indicated that more than 60% of patients failed to achieve remission on their first antidepressant medication,[8] and 50% did not respond to the second and subsequent trials of antidepressant medication.[9] To help clinicians clarify which of their patients might be most responsive to such treatment and for which patients other, more appropriate treatments should be sought, identifying moderators of treatment is of great practical significance.[10]

Mostly, metrics used to classify the disease course of MDD have included response, remission, and relapse.

Correspondence: Jingjing Zhou, The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, 5 Ankang Lane, Dewai Avenue, Xicheng District, Beijing 100088, China.
E-mail: jingjingzhou@mail.ccmu.edu.cn
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However, none of these concepts accurately reflect temporal trends.[11] Knowledge about the moderators of individual responses in adult patients with MDD is still lacking. Increasing this knowledge would advance the understanding of treatment response and has important clinical implications. To identify moderators of treatment, more and more longitudinal studies have employed person-centered data-analytic methods to identify subgroups based on similar patterns of change (trajectories) of depressive symptoms.[12,13] Characterizing longitudinal patterns of depressive symptoms provides a richer and more nuanced understanding of symptom relief as compared to more traditional metrics, helps identify distinctive phenotypes, and may be used to inform treatment selection. Trajectory analysis has been used in various studies, which may support classifications of patients.[14] For example, in a psychotherapy-pharmacotherapy study by Stulz et al.,[15] three patient subgroups were identified with typical patterns of change in depression severity during the 12-week acute-phase treatment. The study also found that the choice of treatments and baseline severity of symptoms have predictive effects on trajectory. In a study by Hull et al.,[16] three symptom trajectories from baseline to week 4 of ketamine-assisted treatment, along with outcome predictors, were identified. Su et al.[17] also identified three response trajectories of patients with MDD who underwent electroconvulsive therapy (ECT) and reported that severe symptoms and older age were associated with less response to treatment. Kaster et al.[18] characterized four response trajectories for patients with MDD undergoing repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex, and the only moderator identified in this study was benzodiazepine use.

In this context, the present study aims to use group-based trajectory modeling (GBTM) to identify patterns of alleviation of depressive symptoms by antidepressants and explore moderators of treatment. We hypothesized that: (a) GBTM would identify at least two depressive symptom trajectories from baseline to 6-month follow-up; (b) baseline clinical characteristics would be associated with different trajectories; and (c) different trajectories would be associated with distinct core symptoms in patients, based on network analysis.

Methods

Study design and participants

This was a multicenter prospective project featuring two cohorts with the same criteria for enrollment and intervention. Assessments were carried out at baseline and weeks 4, 8, 12, 16, and 24. A 6-month period allows sufficient time to assess the initial effects of treatment and to differentiate between patients who experience early improvement versus those who may show a more gradual response. This interval is commonly used in both clinical trials and real-world settings to evaluate the trajectory of symptom remission and recovery, providing a meaningful benchmark for treatment outcomes.[19] In total, 1,438 participants were recruited from hospitals in 10 governances of China, including Beijing, Guangdong, Hebei, Shanxi, Yunnan, Heilongjiang, Jiangsu, Shanghai, Sichuan, and Shaanxi, covering the east, south, north, and west of China. These hospitals are located in densely populated cities. The patients were enrolled from November 9, 2016, to December 30, 2020. A protocol for one of the two cohorts has been published.[20] Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of the research.

The inclusion criteria for participants were as follows: age between 18 and 65 years; diagnosis of MDD according to the DSM-IV criteria; suitability for treatment with escitalopram or duloxetine; a 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR 16) total score of no less than 11 and a 17-item Hamilton Depression Rating Scale (HAMD-17) total score of no less than 14; at least primary-school-level education, literacy, and ability to understand and complete the questionnaires. The exclusion criteria were: presence of other psychiatric disorders; presence of alcohol or other substance abuse problems; a HAMD-17 Item-3 (the item evaluating suicide risk) score no less than 3; presence of serious physical disease; current pregnancy, pregnancy in planning, or lactation (for females); history of intolerance or unresponsiveness to escitalopram or duloxetine.

Antidepressant pharmacotherapy

All patients with MDD were treated with escitalopram or duloxetine. This selection rationale was predicated on their extensive clinical utilization. For the patients treated with escitalopram, the initial dose of oxalate escitalopram was 10 mg per day (d). The dose would be reduced if the patient could not tolerate the drug, and the maximum dose could be 20 mg/d. For the patients treated with duloxetine, the initial dose was 60 mg/d. The dose would be reduced if the patient could not tolerate it, and the maximum dose could be 120 mg/d.

Combination of medication and psychotherapies

For patients in the study, antipsychotics, other antidepressants, mood stabilizers, and physical therapies (e.g., ECT, TMS, phototherapy, electroacupuncture, biofeedback, and vagal nerve stimulation) were prohibited. For patients with severe insomnia, the use of non-benzodiazepines such as zolpidem ($\leqslant$ 10 mg/d), zopiclone ($\leqslant$ 7.5 mg/d), and zaleplon ($\leqslant$ 10 mg/d) was permitted. Benzodiazepines such as lorazepam were permitted in patients with significant symptoms of anxiety except for the 8 hours prior to an assessment. Any systematic psychotherapies (such as psychoanalysis, cognitive comprehension, desensitization therapy, hypnosis therapy, or Morita therapy) were prohibited, but general supportive psychotherapy was allowed.

Measures

17-item Hamilton Depression Rating Scale[21]

The Chinese version of the HAMD-17 has been validated in patients with MDD.[22] As one of the most commonly

used scales to measure symptoms of MDD, it has been used for almost 30 years.[23] HAMD-17 items are scored from 0 to 4 or from 0 to 2. Internal consistency (Cronbach's α) for the HAMD-17 is 0.829.[24] The scale was administered by professionally trained psychiatrists.

16-item Quick Inventory of Depressive Symptomatology-Self-Report

The QIDS-SR16 is a self-reported scale designed to evaluate the overall severity of the nine symptom domains used as criteria to diagnose MDD in the DSM-IV (i.e., sleep, appetite/weight, concentration, energy, sad mood, suicidal ideation, self-concept/guilt, psychomotor activity, and interest).[25] The QIDS-SR16 total score is computed by adding scores for the nine domains. This scale has shown good internal consistency (Cronbach's $\alpha = 0.87$).[26]

Statistical analysis

We used GBTM to identify subgroups that followed distinct longitudinal patterns with respect to depressive symptoms over time among patients with MDD.[13] GBTM provides a unique statistical method for classifying individuals into relatively homogeneous groups based on their trajectories.[27] This method allows one to empirically identify typical symptom trajectories observed in cohort studies based on quantity, shape, and prevalence,[13] thereby providing invaluable descriptions of patterns of change in symptoms. It is helpful in identifying moderators of treatment that differ between trajectories.[28,29]

In the statistical analysis, GBTM was employed using maximum likelihood estimation to simultaneously estimate the trajectories of each group and the corresponding population-level distribution that best fit the observed data.[30] To determine the optimal number of trajectory groups, the Bayesian information criterion (BIC) was used.[13] Models with two to four groups were evaluated and compared based on BIC values, with the level of the polynomial function for each group tested, starting from cubic to linear, until all growth parameter estimates achieved statistical significance. The model with the lowest BIC, indicating the best fit, was selected. BIC values balance model fit with complexity, and a value closer to zero (in negative terms) indicates a better fit.[31] Additional selection criteria included a sufficient group size (at least 10% of participants per group) and a close correspondence between the estimated group membership probabilities and the actual proportion of participants assigned to each group.[13] We conducted a sensitivity analysis on the trajectory grouping of HAMD-17 using QIDS-SR16 and obtained similar results. We used SAS 9.4 with the PROC TRAJ extension (a free downloadable add-on package to SAS, version 9.4; SAS Institute, Cary, NC, USA) to fit GBTM models.

Then, categorical variables were described as numbers (percentages), while continuous variables were described as mean (SD) or median (interquartile range). To determine significant differences between the two trajectories, we used chi-square tests for categorical variables, the independent-sample t-test for continuous variables that were normally distributed, and the Wilcoxon rank-sum test for continuous variables that were skewed. The tests were two-sided at the 0.05 significance level.

To identify the risk factor for each symptom trajectory, we used multinomial logistic regression to generate odds ratios (ORs) and 95%CIs for each trajectory group, using the "rapid symptom reduction" trajectory as the reference group. We included all covariates available at baseline in the multivariable analysis.

Network structure and centrality measures were constructed using the R packages qgraph and bootnet.[32,33] The network is a graphical representation that includes nodes and edges. The nodes within the graphical network represent the 17 symptoms of the HAMD-17; the edges are pairwise correlations among the symptoms. Thicker and more saturated edges indicate stronger correlations, green edges indicate positive partial correlations, and red edges indicate negative partial correlations. The centrality measure, namely the expected influence (EI), was used to identify the prominent node in the network.

Ethics statement

Written informed consent was obtained from all participants prior to any study procedures. The study protocol was registered and approved by a suitably constituted ethics committee of the Institutional Review Board of Beijing Anding Hospital (2016-109 and 2017-24) at all study sites and adhered to the provisions of the Declaration of Helsinki.

Results

Study cohort and patient characteristics

The study cohort included 1,438 participants with a median age of 31.00 (24.00-43.00) years at baseline. Among the participants, 69.12% were female, and 59.40% were experiencing their first episodes. The proportion of patients with a family history of any mental disorder was 14.12%. Patients were treated with duloxetine (27.07%) or escitalopram (72.93%). Approximately one-half of the patients were married. The median time from episode onset to treatment was 3.00 (1.00-6.50) months. The HAMD-17 total score at baseline was 21.00 (18.00-25.00) (Table 1). The relapse rate was 2.58% for the rapid symptom reduction trajectory group and 28.26% for the delayed symptom reduction trajectory. Regarding remission, the rapid symptom reduction trajectory group had a remission rate of 62.73%, versus only 15.68% in the delayed symptom reduction trajectory group.

Determining depressive symptom trajectories

Two distinct trajectories of depressive symptoms, which provided clinically meaningful insights and exhibited the best statistical fit, were identified (Figure 1). For the HAMD-17, 1,068 (74.3%) patients showed rapid symptom

reduction within the first 4 weeks (trajectory 1; rapid symptom reduction), 370 (25.7%) showed delayed symptom reduction during the 24 weeks (trajectory 2; delayed symptom reduction) (Figure 1A). The distribution of basic characteristics in the two trajectories is shown in Table 1.

Covariates associated with symptom trajectory

In the multivariable-adjusted analysis of the HAMD-17 trajectories, the drug used for treatment, family history, age, first-episode status, educational status, sex, HAMD-17 total score at baseline, and the interval between episode onset and treatment were included. Compared with those in trajectory 2 (delayed symptom reduction), values including the HAMD-17 total score at baseline (OR = 1.791, 95%CI 1.198-2.679), the proportion of females (OR = 1.195, 95%CI 1.148-1.244), and the interval between episode onset and treatment (OR = 1.011, 95%CI 1.000-1.021) were significantly smaller in the rapid symptom reduction trajectory (Table 2).

Sensitivity analysis

For the QIDS-SR16, 937 (65.2%) patients showed rapid symptom reduction within the first 4 weeks (trajectory 1; rapid symptom reduction), 501 (34.8%) showed delayed symptom reduction during the 24 weeks (trajectory 2; delayed symptom reduction) (Figure 1B). The distribution of basic characteristics in the two trajectories is shown in Supplementary Table S1.

As for the two trajectories of the QIDS-SR16, the drug used for treatment, family history, age, first-episode status, educational status, sex, QIDS-SR16 total score at baseline, and the time from episode onset to treatment were included. Compared with those in trajectory 2 (delayed symptom reduction), values including the QIDS-SR16 total score at baseline (OR = 1.564, 95%CI 1.009-2.426), the proportion of escitalopram treatment (OR = 1.311, 95%CI 1.243-1.384), and the time from episode onset to treatment (OR = 1.013, 95%CI 1.001-1.024) were significantly smaller in the rapid symptom reduction trajectory (Supplementary Table S2).

Network analysis

Network models were used to characterize the symptom patterns of patients in the rapid-decline and late-decline trajectories. The network structure of the clusters is shown in Figures 2A and B. Node centrality measures are shown in Figures 2C and D. The centrality measure EI indicated that the "depressed mood" and "retardation" were the most prominent and thus were the core symptoms for patients in the rapid symptom reduction and delayed symptom reduction trajectory, respectively.

Discussion

This is, to our knowledge, the first study to describe the 6-month response trajectories of patients to antidepressant treatment. In a cohort of 1,438 patients, we identified two distinct and clinically relevant trajectories in terms of depressive symptoms over a 6-month follow-up (rapid symptom reduction and delayed symptom reduction). The primary symptom of patients in the delayed symptom reduction trajectory is psychomotor retardation. Our exploratory analysis also identified two consistent clinical characteristics independently associated with the response trajectories: baseline severity and the time elapsed from episode onset to treatment.

In this study, symptoms of patients with severe depression were less likely to decline rapidly. This may

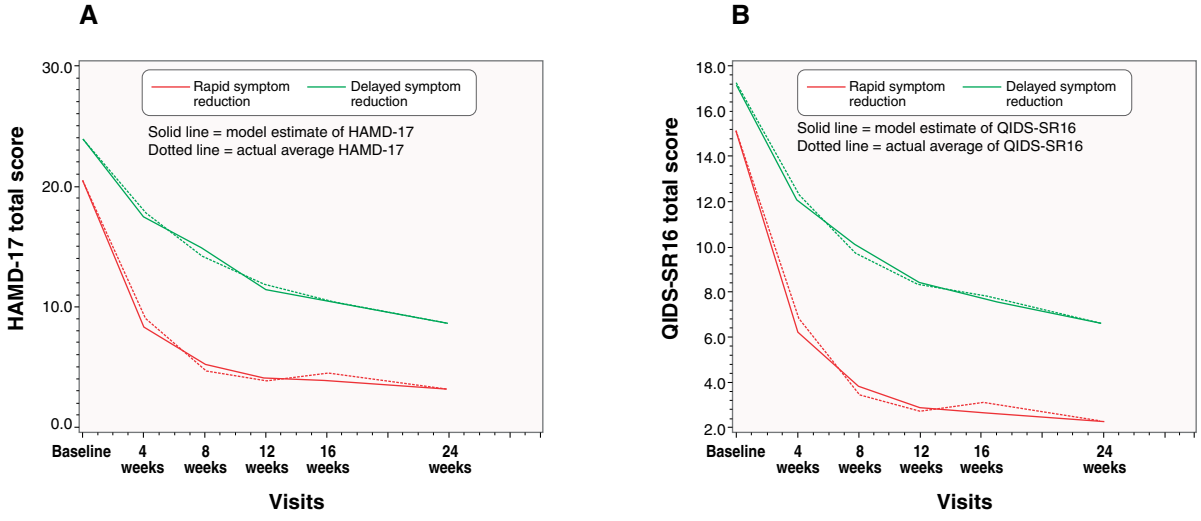


Figure 1 Symptom trajectories based on A) HAMD-17 and B) QIDS-SR16 of 1,438 patients with MDD from baseline to 24 weeks.The participants left in this study at each visit point were 1,047 at week 4, 911 at week 8, 824 at week 12, 744 at week 16, and 710 at week 24. HAMD-17 = 17-item Hamilton Depression Rating Scale; MDD = major depressive disorder; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology.

Table 1 Baseline characteristics of participants from two trajectories of decline in 17-item Hamilton Depression Rating Scale scores

Variable	Total sample (n=1,438)	Rapid symptom reduction (n=1,068)	Delayed symptom reduction (n=370)	Z/χ^2	p-value
Age	31.00 (24.00-43.00)	31.00 (24.00-44.00)	30.00 (24.00-42.00)	-1.38	0.17
Sex				2.56	0.11
Male	444 (30.88)	342 (32.02)	102 (27.57)		
Female	994 (69.12)	726 (67.98)	268 (72.43)		
Family history				0.68	0.41
No	1235 (85.88)	922 (86.33)	313 (84.59)		
Yes	203 (14.12)	146 (13.67)	57 (15.41)		
First episode†				0.75	0.39
No	581 (40.60)	439 (41.26)	142 (38.69)		
Yes	850 (59.40)	625 (58.74)	225 (61.31)		
Educational status†				2.31	0.13
Any higher	882 (61.42)	667 (62.57)	215 (58.11)		
Primary/secondary	554 (38.58)	399 (37.43)	155 (41.89)		
Location†				3.41	0.06
Urban	1159 (80.82)	872 (81.95)	287 (77.57)		
Rural	275 (19.18)	192 (18.05)	83 (22.43)		
Marital status†				0.96	0.33
Married	766 (53.42)	577 (54.18)	189 (51.22)		
Single or divorced	668 (46.58)	488 (45.82)	180 (48.78)		
Work status†				0.45	0.80
Employed	769 (53.66)	576 (54.19)	193 (52.16)		
Student	270 (18.84)	198 (18.63)	72 (19.46)		
Unemployed	394 (27.49)	289 (27.19)	105 (28.38)		
Insurance†				6.26	0.10
Urban basic medical insurance	857 (59.72)	656 (61.60)	201 (54.32)		
Publicly funded medical care	73 (5.09)	53 (4.98)	20 (5.41)		
New rural cooperative medical care	182 (12.68)	127 (11.92)	55 (14.86)		
Out-of-pocket	323 (22.51)	229 (21.50)	94 (25.41)		
Drug for treatment				3.47	0.06
Duloxetine	386 (27.07)	273 (25.78)	113 (30.79)		
Escitalopram	1040 (72.93)	786 (74.22)	254 (69.21)		
HAMD-17 total score at baseline	21.00 (18.00-25.00)	20.00 (17.00-23.00)	25.00 (21.00-29.00)	13.54	< 0.01
Time from episode onset to treatment (months)	3.00 (1.00-6.50)	3.00 (1.00-6.00)	2.00 (1.00-8.00)	-0.04	0.97

Data presented as n (%) or median (quartile).
† Missing values.

Table 2 Logistic regression of predictors for trajectories of HAMD-17

Parameter	Estimate	SE	Wald χ^2	p-value	OR, 95%CI
Intercept	-5.2100	0.6389	66.5014	$<.0001$	
Drug for treatment (escitalopram vs. duloxetine)	0.1379	0.2289	0.3632	0.5467	1.148, 0.733-1.798
Family history (yes vs. no)	-0.2815	0.2613	1.1605	0.2814	0.755, 0.452-1.259
Age	-0.0134	0.0096	1.9757	0.1598	0.987, 0.968-1.005
First episode (yes vs. no)	0.2707	0.1977	1.8736	0.1711	1.311, 0.890-1.931
Educational status (primary/secondary vs. any higher)	0.0494	0.2175	0.0517	0.8202	1.051, 0.686-1.609
Sex (female vs. male)*	0.5829	0.2054	8.0542	0.0045	1.791, 1.198-2.679
HAMD-17 total score at baseline*	0.1779	0.0204	75.7360	< 0.0001	1.195, 1.148-1.244
Time from episode onset to treatment*	0.0106	0.00525	4.0988	0.0429	1.011, 1.000-1.021

HAMD-17 = 17-item Hamilton Depression Rating Scale; OR = odds ratio; SE = standard error.
* Indicates $p < 0.05$, considered statistically significant.

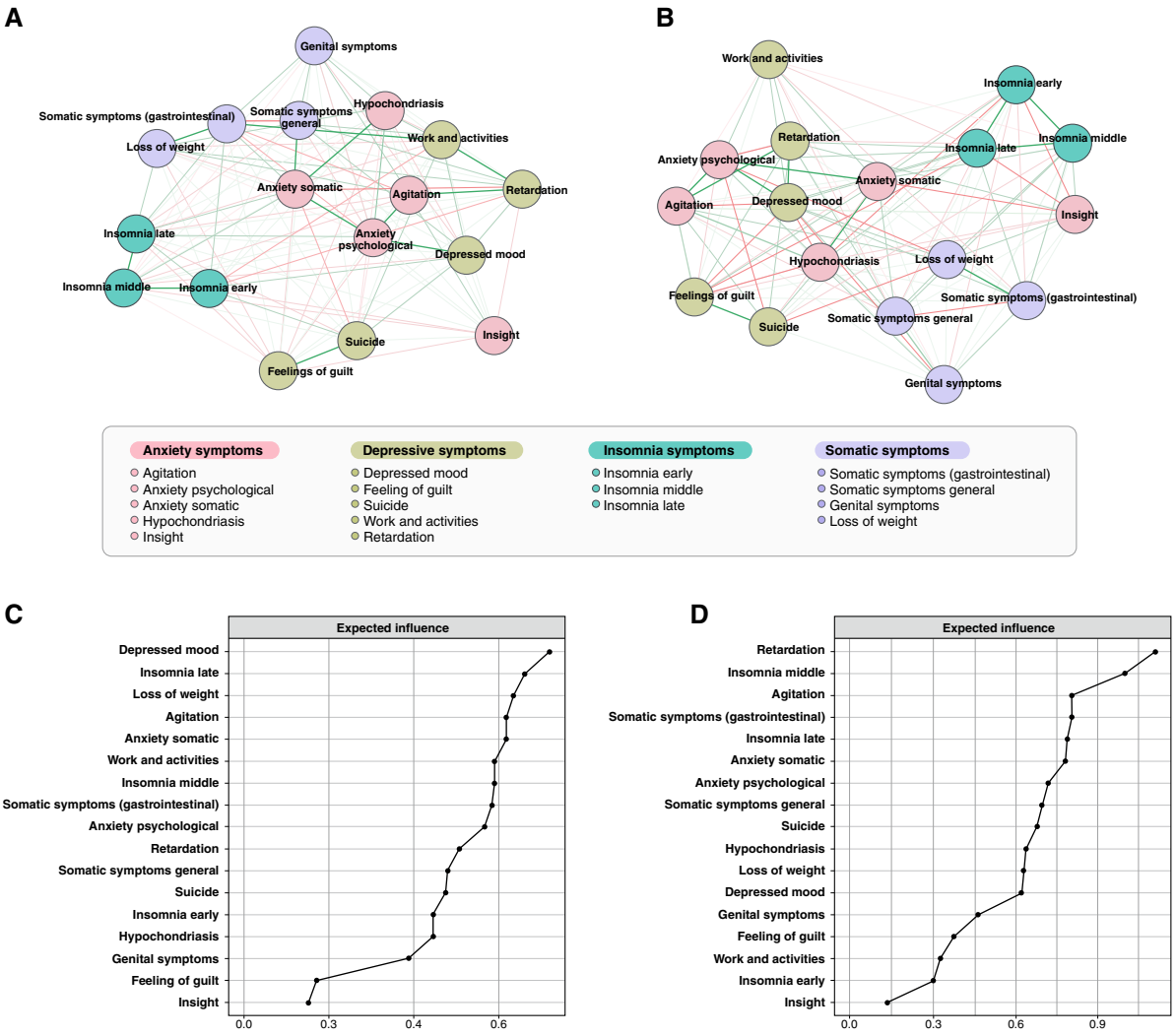


Figure 2 A) Network structure of rapid symptom reduction trajectory. B) Network structure of delayed symptom reduction trajectory. C) Centrality of rapid symptom reduction trajectory. D) Centrality of delayed symptom reduction trajectory.

be due to the fact that patients with severe depression typically have more complaints of physical discomfort, a higher risk of suicide and recurrence, severer impairment of social function, and a worse prognosis.[34] Consistent with this hypothesis, the study by Howland et al.[35] indicated that patients with severe symptoms respond less well to pharmacotherapy or require a longer time to respond. Many studies have also replicated the findings that, overall, outcomes of patients with severe depression are often worse than those of patients with mild depression, and the greater the severity of depressive symptoms, the lower the efficacy of treatment with antidepressants.[36-40] In addition, most guidelines give different treatment recommendations for mild versus moderate-to-severe major depression.[41,42] This presupposes that the response to treatment is moderated by the baseline severity of depression. However, although this assumption might seem commonsensible, empirical studies have drawn opposing conclusions over the years. For example, a meta-analysis[43] of antidepressant trials submitted to the U.S. Food and Drug Administration since 1979 (228 trials, 73,178 participants) found that patients who were more severely depressed at baseline demonstrated more significant treatment effects than those who were less severely depressed. This inconsistency in findings may be attributed to variations in study sample characteristics, as well as differences in the tools and methods used across studies. In particular, we also found that male sex was associated with a rapid decline in depressive symptoms. A potential explanation may be that women often encounter additional challenges, such as caregiving responsibilities, socioeconomic disadvantages, and gender-based stressors like workplace discrimination and inequities in domestic labor, which may contribute to more prolonged depressive episodes, potentially leading to a slower response to treatment compared to men.

The findings from previous studies regarding the duration of untreated episodes and its impact on response to antidepressant treatment align closely with our results,

reinforcing the importance of early intervention in managing depressive symptoms. In our study, we found that a shorter interval between episode onset and treatment initiation was associated with a more rapid alleviation of depressive symptoms. This finding is consistent with previous work by Ghio et al.,[44] which demonstrated that early treatment initiation led to a faster reduction in depressive symptoms. Furthermore, the work of de Diego-Adeliño et al.[45] supports our results by suggesting that a shorter duration of the untreated episode leads to a more favorable response to antidepressant treatment. Several factors contribute to the observed association between early treatment and quicker symptom alleviation. First, in the early stages of depression, the brain is more adaptable and responsive to treatment, particularly through the restoration of disrupted neural circuits. Neuroplasticity is stronger in the early phase of depression, which means interventions such as pharmacotherapy (e.g., antidepressants) can more effectively reverse the brain changes that contribute to depressive symptoms. If treatment is delayed, these neurobiological changes may become more entrenched, making it more challenging for the brain to recover. In addition, untreated depression often leads to a worsening of cognitive and emotional patterns.[46] Chronic symptoms can reinforce negative thought patterns and increase emotional dysregulation, making it more difficult to break the cycle of depression. Early intervention helps prevent reinforcement of these maladaptive patterns, facilitating quicker recovery. Both a 4-week trial of antidepressant treatment[47] and a 2-year follow-up study[48] support the notion that timely intervention is crucial in preventing the progression of depressive episodes, which could otherwise lead to more severe or chronic symptoms. A meta-analysis[49] including data from 10 studies reported that a longer duration of untreated episodes was a significant predictor of a poorer response to antidepressant treatment, a lower rate of remission, and a higher risk of chronicity. A retrospective study[50] assessed the impact of untreated episode duration on antidepressant efficacy and found that patients who received antidepressants early after episode onset had significantly higher remission rates compared to those with depression lasting 6 months or longer. Similar findings have been observed in other psychiatric disorders, such as bipolar disorder[51] and schizophrenia,[52] where longer untreated episodes were associated with poorer outcomes. These findings further support the generalizability of the concept that early treatment of mental health conditions is critical to improving long-term prognosis.

This study was strengthened by a large, multi-site sample of individuals with MDD and the use of group-based trajectory analysis to characterize prognostic patterns. Additionally, the predictive effect of the characteristics at baseline was explored. However, some limitations need to be acknowledged. First, participants in this study were mainly adults aged 18 to 65, so the sample may not represent children, adolescents, or older adults. Second, due to time constraints, this study only observed a trend of 24 weeks of antidepressant treatment; a longer follow-up may be able to provide more information for the exploration of more dynamic trajectories. Finally, depressive symptoms were measured approximately every 4 to 8 weeks, which means we could not rule out the possibility that some individuals may have experienced short-lived changes in their depressive state during the interval between two measurements.

Our study identified two symptom trajectories that could characterize prognostic patterns of MDD. Male sex, milder depressive symptoms, and prompt treatment are modifiable factors for rapid relief of depressive symptoms in patients in China. These results highlight the importance of considering gender differences and symptom characteristics in treatment selection. It also suggests that each depressive episode should be treated promptly, as this may influence clinical consequences for patients.

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Disclosure

The authors report no conflicts of interest.

Data availability statement

All data can be obtained from the corresponding author upon reasonable request.

Author contributions

JZ: Methodology, Validation, Formal analysis, Writing – original draft.
XW: Data curation, Resources, Investigation, Writing – original draft.
LF: Data curation, Resources, Investigation.
YF: Data curation, Resources, Investigation.
LX: Data curation, Resources, Investigation.
XC: Data curation, Resources, Investigation.
ZF: Writing – review and editing.
GW: Supervision, Funding acquisition.

JZ: Project administration, Conceptualization, Writing – review and editing.
All authors have read and approved of the final version to be published.

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