

A Preliminary Randomized Controlled Trial of Different Treatment Regimens for Melancholic Depression

Yun Wang,¹ Xiaohua Liu,^{2,3}
Daihui Peng,² Yan Wu,²
Yun'ai Su,⁴ Jia Xu,⁵
Xiancang Ma,⁶ Yi Li,⁷
Jianfei Shi,⁸ Xiaojing Cheng,⁹
Han Rong,¹⁰ Yiru Fang^{1,3,11}

¹Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; ²Department of Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; ³Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; ⁴Department of Psychiatry, Peking University Sixth Hospital, Peking, People's Republic of China; ⁵Department of Psychiatry, Harbin First Specific Hospital, Harbin, People's Republic of China; ⁶Department of Psychiatry, The First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, People's Republic of China; ⁷Department of Psychiatry, Wuhan Mental Health Center, Wuhan, People's Republic of China; ⁸Department of Psychiatry, Hangzhou Seventh People's Hospital, Hangzhou, People's Republic of China; ⁹Department of Psychiatry, Shandong Mental Health Center, Shandong, People's Republic of China; ¹⁰Department of Psychiatry, Shenzhen Kangning Hospital, Shenzhen, People's Republic of China; ¹¹CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai, People's Republic of China

Correspondence: Daihui Peng; Yiru Fang
Email pdhsh@126.com;
yirufang@aliyun.com

Background: Fluoxetine, bupropion, cognitive behavioral therapy (CBT), and physical therapies (modified electroconvulsive treatment or repetitive transcranial magnetic stimulation) can be used to manage melancholic depression.

Objective: To compare the efficacy and safety of various treatments in patients with melancholic depression.

Methods: This was a preliminary multicenter randomized controlled trial that included patients with depression in their first or recurrent acute episode between September 2016 and June 2019, and randomized to fluoxetine, fluoxetine+CBT, fluoxetine+bupropion, and fluoxetine+bupropion+brain stimulation. The primary endpoint was the decrease in the 17-item Hamilton Depression Rating Scale (17-HDRS). The secondary endpoint included the scores from the Quick Inventory of Depressive Symptomatology (QIDS-SR), QOL-6, and safety. Adverse events (AEs) were monitored. The follow-ups were performed at the end of the 0th, 2nd, 4th, 6th, 8th, and 12th weeks of treatment.

Results: Finally, 113 patients were included in the analyses: fluoxetine (n=37), fluoxetine+CBT (n=27), fluoxetine+bupropion (n=34), and fluoxetine+bupropion+brain stimulation (n=15). The 17-HDRS and QIDS-SR scores decreased in all four groups (all $P<0.05$). There were no differences in the 17-HDRS scores among the four groups at the end of treatment ($P=0.779$), except for fluoxetine alone showing a better response regarding self-consciousness than fluoxetine+bupropion. The QOL-6 scores increased in all four groups. The occurrence of AEs among the four groups showed no significant difference ($P=0.053$).

Conclusion: This preliminary trial suggests that all four interventions (fluoxetine, fluoxetine+CBT, fluoxetine+bupropion, and fluoxetine+bupropion+brain stimulation) achieved similar response and remission rates in patients with melancholic depression, but that fluoxetine had a better effect on self-consciousness than fluoxetine+bupropion. The safety profile was manageable.

Keywords: major depressive disorder, melancholic depression, fluoxetine, bupropion, cognitive behavioral therapy, brain stimulation

Introduction

Major depressive disorder (MDD) is a common and well-known type of depressive disorder. The prevalence of MDD worldwide is approximately 6% per year, with a lifetime prevalence of 20%.¹ Some patients may have specific subtypes of depression, which may be clinically useful for predicting outcomes and choosing treatment: melancholic depression (melancholia), depression with atypical features, MDD with psychotic features, MDD with catatonia, and MDD with anxious

distress.^{1–4} The prognosis for MDD is variable. It is unremitting in about 15% of patients and recurrent in about 35% of patients, with the risk of recurrence increases with each additional episode of major depression.^{1–5}

Subjects with melancholic depression show biological abnormalities than healthy controls. Melancholic depression might be characterized by specific biological changes and it could be associated to more severe abnormalities with respect to non-melancholic depression.⁶ Melancholic MDD requires the following features as part of the standard diagnosis of MDD: lack of interest or pleasure in most or all activities (anhedonia), or lack of reactivity to pleasurable stimuli, and at least three among: distinct quality of depressed mood (experienced differently from the loss of a loved one), symptoms regularly worse in the morning, early morning awakening (at least 2 hours before the usual time of awakening), significant loss of appetite or weight loss, noticeable psychomotor retardation or agitation, and excessive or inappropriate guilt.^{1–4} About 25–30% of the patients with MDD have melancholic features.^{1–4} Melancholia is associated with more severe depression, increased risk of suicide, increased likelihood of treatment response to pharmacotherapy or electroconvulsive therapy over psychotherapy, nonresponse to placebo interventions, decreased likelihood of response to psychotherapy, and high recurrence rate.^{1–4} Melancholia is associated with more severe depression, increased risk of suicide, and a high recurrence rate.^{1–4}

Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, are the first-line treatment.^{1–4} Fluoxetine has a better effect in melancholic depression than in the non-melancholic types, and the patients with melancholic depression show an earlier response and a higher remission rate to a lower dose of fluoxetine.⁵ Cognitive-behavioral therapy helps alleviate depressive symptoms by questioning and challenging the patients' irrational thinking and wrong attitude towards themselves, the surrounding environment, and the future.⁶ Cognitive behavioral therapy (CBT) can be applied in combination with drugs for the acute episode.²⁸ Bupropion is a norepinephrine-dopamine reuptake inhibitor and has a similar treatment effect to SSRI.^{1–4} Bupropion is better in improving some symptoms such as fatigue and drowsiness than certain SSRIs.⁷

The treatment of MDD mainly relies on drugs and psychological intervention.^{1–4} Nevertheless, about 20% of the patients show little improvement in long-term

follow-up studies.^{1–4} Physical therapies, including modified electroconvulsive treatment (MECT) or repetitive transcranial magnetic stimulation (rTMS), can be used to manage the symptoms of depression.^{8–11} The efficacy and acceptability of different ways of physical therapy for depression are different.²⁹ Nevertheless, currently, there is no randomized controlled trial (RCT) research that compares various treatments in patients with melancholic depression.

Therefore, the objective of the present study was to compare the efficacy and safety of various treatments in patients with melancholic depression. The results could provide data for the stratified treatment of MDD.

Methods

Study Design and Participants

This was a multicenter RCT (the participating hospitals are listed in [Supplementary Table S1](#)) that included patients with depression in their first or recurrent acute episode between September 2016 and June 2019. The study was approved by the ethics committees of all the participating centers, and the written informed consent was obtained from the study subjects. This was a preliminary study registered with ClinicalTrials.gov (NCT03219008).

The inclusion criteria were: 1) 18–55 years old; 2) patients with melancholic depression who met the DSM-5 diagnostic criteria of MDD and were in major depression episode (MDE); 3) patients in their first or recurrent acute episode; 4) scored ≥ 17 on the Hamilton depression scale (HAMD-17); 5) did not receive any anti-depression medication, physical or psychological therapies within the past 6 months before being recruited into the study; and 6) did not receive systematic treatment at the participating centers.

The patients were diagnosed with melancholic depression based on a clinical subtype determination by Inventory for Depressive Symptomatology (IDS) scoring of the melancholic and atypical symptoms and HAMD Anxiety somatization factor scoring of the symptom weights.¹²

The exclusion criteria were: 1) patients with severe somatic diseases (history of brain injury or cerebrovascular accident, narrow-angle glaucoma, epilepsy, myocardial infarction, unstable angina pectoris, congestive heart failure, severe liver cirrhosis, acute and chronic renal failure, severe diabetes, aplastic anemia, moderate to severe malnutrition and other severe somatic diseases including

neurological, heart, liver, renal, endocrine and blood disorders or diseases that could interfere with the study; the abnormal indicators had to be at least twice the upper limit of normal (ULN)); 2) patients with HAMD-17 item 3 (suicide) ≥ 3 or patients who attempted suicide within this episode; 3) women in pregnancy or nursing period, or women planning to be pregnant; 4) patients with comorbid psychiatric disorders or psychiatric symptoms, drug abusers (nicotine excluded), patients with history of mania or mild mania present in this episode, or patients with mental retardation, personality disorder or anorexia nervosa/bulimia; or 5) patients with secondary depressive disorder caused by organic lesion or drugs. 6) patients with any contraindications for brain stimulation.

Grouping and Blinding

The participants were randomized 1:1:1:1 into four treatment groups using a central system programmed and maintained by an independent third-party biostatistician: 1) fluoxetine; 2) fluoxetine+CBT; 3) fluoxetine+bupropion; and 4) fluoxetine+bupropion+brain stimulation. Only the person who administered the questionnaires was blind to grouping.

The treatment regimens and the dosing of fluoxetine and bupropion were determined by the physicians. The drugs used in the study were fluoxetine (Prozac, Eli Lilly, Indianapolis, IN, USA) and bupropion hydrochloride sustained-release tablets (Funing Pharmaceutical Co. Ltd., Shenyang, China). Brain stimulation included MECT or rTMS. MECT was performed ten times a month as a course of treatment. rTMS was performed ten times every two weeks as a course of treatment. The duration of each treatment varied between 8 and 12 weeks.

Data Collection and Measurement of Indicators

Age, sex, ethnicity, body mass index (BMI), education years, occupation, marital status, the total course of depression, duration of current episode, and severity of depression were collected.

The scales used in the study include the 17-item Hamilton Depression Rating Scale (17-HDRS),¹³ Self-Rating version of Quick Inventory of Depressive Symptomatology (QIDS-SR),¹⁴ and Quality of Life (QOL-6), which are all validated scales for MDD, including their Chinese versions.^{15,16} Adverse events (AEs) were recorded in a log.

The 17-HDRS includes 17 items: 1) depressed emotions; 2) feelings of guilt; 3) suicidal ideations; 4) difficulty in falling asleep; 5) failure in sleeping deeply; 6) early awakening; 7) loss in work and interest; 8) retardant/slow; 9) agitation; 10) spiritually anxious; 11) somatically anxious; 12) gastrointestinal symptoms; 13) general symptoms; 14) sexual symptoms; 15) hypochondriasis; 16) weight loss; and 17) self-consciousness. The items for the melancholic subtypes are #1-2-6-7-8-9-12-16.

Endpoints

The primary endpoint was the decrease in the 17-HDRS scores in the intention-to-treat set. A decrease in the 17-HDRS scores $\geq 50\%$ was considered to be responsive; 17-HDRS total score ≤ 7 was considered to remission. The secondary endpoint included the scores from QIDS-SR and QOL-6.

Follow-Up

The duration of follow-up varied between 8 and 12 weeks. The follow-ups were performed at the end of the 0th, 2nd, 4th, 6th, 8th, and 12th weeks of treatment, including the measurement of the indicators for efficacy and safety, 17-HDRS, QIDS-SR, QOL-6, AE record, evaluation of clinical symptomatology, blood biochemistry, neurological imaging, and electrophysiological examinations. The allowed time window for follow-ups was ± 2 days.

Safety

The AEs included gastrointestinal reactions (such as gastric discomfort, diarrhea, constipation, nausea, vomiting, dry and bitter mouth, and increased appetite), abnormal liver functions, headache and dizziness (dizziness, vertigo, and syncope), fatigue (drowsiness, fatigue, lethargy, and slow response), allergy, tremor (including tremor, shaking hands or feet, feeling tired, myasthenia, night sweat, dyspnea, nervousness, and anxiety), changes in the heart rate (including bradycardia and tachycardia), suicide and self-harm (aggressiveness), and general AEs (bleeding nose, hair loss, pneumonia, and fever).

Statistical Analysis

As this was a preliminary study, no power analysis was performed.

All data were processed and analyzed using SPSS 22.0 (IBM, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, USA). The continuous variables were tested for normal distribution using the

Kolmogorov–Smirnov test. The continuous variables that followed the normal distribution were presented as means \pm standard deviation and analyzed using ANOVA and post hoc pairwise comparisons with the Bonferroni correction; otherwise, the continuous variables were presented as medians (interquartile range (IQR)) and analyzed using the Kruskal–Wallis test. Changes in the scores within each group were tested using the Wilcoxon signed-rank test. The categorical variables were presented as number (percentage) and analyzed using the chi-square test or Fisher's exact test. All tests were two-sided (except the chi-square test), and P-values <0.05 were considered statistically significant.

Results

Characteristics of the Participants

A total of 186 patients were screened for eligibility and 30 were excluded. Then, 156 were randomized to the fluoxetine (n=38), fluoxetine+CBT (n=37), fluoxetine+bupropion (n=42), and fluoxetine+bupropion+brain stimulation (n=39). During treatment, 43 participants dropped out. Finally, 113 patients were included in the analyses: fluoxetine (n=37), fluoxetine+CBT (n=27), fluoxetine+bupropion (n=34), and fluoxetine+bupropion+brain stimulation (n=15). Their characteristics are presented in Table 1. There were no differences among the four groups regarding any of the characteristics of the participants.

Efficacy Evaluation

The 17-HDRS scores decreased in all four groups (all $P<0.05$). There were no differences in the 17-HDRS scores among the four groups at the end of treatment ($P=0.779$), nor in the response rates (ie, 17-HDRS decreasing by $\geq 50\%$) ($P=0.927$) or the remission rates ($P=0.658$). There was no difference for the total melancholic subscore ($P=0.692$), but a difference was observed regarding item #17 (self-consciousness) ($P=0.019$), especially between the fluoxetine and fluoxetine+bupropion groups ($P=0.010$).

The QIDS-SR scores decreased in all four groups during the follow-ups. The QOL-6 scores increased in all four groups. There were no differences in the QIDS-SR and QOL-6 among the four groups at the end of treatment (Table 2 and Figure 1).

Safety

There were no differences in the occurrence of AEs among the four groups ($P=0.053$). A higher rate of headaches

could be observed in the fluoxetine+bupropion+brain stimulation group ($P=0.035$) (Table 3).

Discussion

Fluoxetine, bupropion, CBT, and physical therapies can be used to manage melancholic depression.^{5–11} The aim of the present preliminary RCT was to compare the efficacy and safety of various treatments in patients with melancholic depression. The results suggest that fluoxetine, fluoxetine+CBT, fluoxetine+bupropion, and fluoxetine+bupropion+physical therapies achieved similar response and remission rates, and the occurrence of AEs showed no difference among the four groups but compared with fluoxetine+bupropion, fluoxetine alone had a better effect on self-consciousness, a component of 17-HDRS, but not of the melancholic subscore.

Fluoxetine is among the first-line drugs for the treatment of MDD, with proved efficacy and safety.^{5,17} Its efficacy is superior to that of nortriptyline¹⁸ and similar to that of sertraline and moclobemide.^{19,20} The combination of fluoxetine with other drugs can lead to higher remission rates in patients with MDD.²¹ Fluoxetine can be combined with bupropion, and this combination has been shown to be effective and safe.^{7,22} CBT incorporates modifying and refocusing dysfunctional beliefs (cognitive restructuring) to impact behavior and functioning.¹ CBT alone has some efficacy in MDD, but its efficacy is considered lower in patients with melancholic MDD,^{3,4} and it is therefore often used in combination with drugs.^{6,23,24} MECT and rTMS can be applied in the management of the symptoms of depression.^{8–11}

The use of a single drug or treatment modality often results in a suboptimal response, and combinations are often required.²⁵ The present study compared fluoxetine vs fluoxetine+CBT vs fluoxetine+bupropion vs fluoxetine+bupropion+physical therapies. All four methods decreased the symptoms of MDD and improved quality of life. Nevertheless, there were no differences among the four groups. CBT did not improve the response when added to fluoxetine, but it is known that patients with melancholic MDD have a lower response to CBT.^{3,4} In addition, melancholic MDD has a high response rate to SSRIs (like fluoxetine) and MECT,^{3,4} which might explain, at least in part, the lack of difference between fluoxetine alone vs fluoxetine+bupropion and fluoxetine+bupropion+physical therapies. Self-consciousness is a type of hypervigilance state that is associated with obsessive-compulsive disorders, as well

Table 1 Baseline Characteristics of the Participants with Melancholic Depression According to the Treatment Groups

Indicators	Fluoxetine (n=37)	Fluoxetine + CBT (n=27)	Fluoxetine + Bupropion (n=34)	Fluoxetine + Bupropion + Brain Stimulation (n=15)	P
Age (years)	28 (23.35)	28 (24.36)	27 (23.37)	24 (22.28)	0.328
Sex, n (%)					
Male	14 (37.8%)	12 (44.4%)	10 (29.4%)	7 (46.7%)	0.569
Female	23 (62.2%)	15 (55.6%)	24 (70.6%)	8 (53.3%)	
Ethnicity, n (%)					
Han	36 (97.3%)	27 (100%)	34 (100%)	15 (100%)	>0.99
Others	1 (2.7%)	0	0	0	
Body mass index (kg/m ²)	21.72 (18.83,24.82)	20.32 (19.03,24.62)	21.185 (18.73,23.88)	21.14 (19.14,25.95)	0.912
Marital status, n (%)					
Single	22 (59.5%)	14 (51.9%)	21 (61.8%)	10 (66.7%)	0.712
Married/common law partner	13 (35.1%)	13 (48.1%)	11 (32.4%)	4 (26.7%)	
Divorced/separated	2 (5.4%)	0	2 (5.9%)	1 (6.7%)	
Occupations, n (%)					
Employed	22 (59.5%)	18 (66.7%)	19 (55.9%)	8 (53.3%)	0.510
Retired	1 (2.7%)	0	1 (2.9%)	0	
Student	10 (27.0%)	8 (29.6%)	6 (17.6%)	4 (26.7%)	
Unemployed	4 (10.8%)	1 (3.7%)	8 (23.5%)	3 (20%)	
Education (years)	15 (12.16)	16 (13.16)	16 (13.16)	14 (12.16)	0.255
Total course of depression (months)	16 (4.69)	15 (4.36)	5 (2.24)	20.5 (6.48)	0.148
Duration of current episode (months)	9 (4.32)	8 (4.20)	8 (4.12)	12 (3.28)	0.827
Severity of depression, n (%)					
Not evaluated	0	0	0	1 (6.7%)	0.197
Normal	1 (2.7%)	0	0	0	
Marginal	0	0	0	0	
Mild	2 (5.4%)	1 (3.7%)	0	1 (6.7%)	
Moderate	13 (35.1%)	14 (51.9%)	13 (38.2%)	7 (46.7%)	
Significant	17 (45.9%)	7 (25.9%)	14 (41.2%)	5 (33.3%)	
Severe	4 (10.8%)	5 (18.5%)	7 (20.6%)	0	
Most severe	0	0	0	1 (6.7%)	

Abbreviation: CBT, cognitive behavioral therapy.

Table 2 Evaluation of Treatment Efficacy

Indicators	Fluoxetine (n=37)	Fluoxetine + CBT (n=27)	Fluoxetine + Bupropion (n=34)	Fluoxetine + Bupropion + Brain Stimulation (n=15)	P
Primary endpoint					
17-HDRS	9 (4.14)	8 (4.16)	9.5 (4.15)	8 (0.16)	0.779
Response (17-HDRS score decrease $\geq 50\%$), n (%)	22 (59.5%)	18 (66.7%)	22 (64.7%)	10 (66.7%)	0.927
Remission (17-HDRS total score ≤ 7), n (%)	16 (43.2%)	14 (51.9%)	13 (38.2%)	8 (53.3%)	0.658
Melancholic subscale [#]					
HAMD-01	5 (1.7)	4 (1.7)	4.5 (2.8)	1 (0.8)	0.692
HAMD-02	1 (0.2)	1 (0.2)	1 (0.1)	0 (0.1)	0.510
HAMD-03	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0.937
HAMD-04	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.2)	0.906
HAMD-05	1 (0.1)	1 (0.1)	0 (0.1)	0 (0.2)	0.901
HAMD-06	1 (0.1)	0 (0.1)	0.5 (0.1)	0 (0.1)	0.874
HAMD-07	0 (0.1)	0 (0.1)	1 (0.2)	0 (0.1)	0.110
HAMD-08	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.3)	0.896
HAMD-09	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0.843
HAMD-10	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0.189
HAMD-11	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0.949
HAMD-12	0 (0.1)	1 (0.1)	0.5 (0.1)	0 (0.1)	0.790
HAMD-13	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.1)	0.947
HAMD-14	1 (0.1)	1 (0.1)	0 (0.1)	0 (0.2)	0.660
HAMD-15	0 (0.1)	0 (0.1)	0 (0.1)	0 (0.0)	0.575
HAMD-16	0 (0.0)	0 (0.0)	0 (0.1)	0 (0.0)	0.940
HAMD-17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.891
					0.019
QIDS-SR	8 (3.12)	11 (4.15)	10 (5.17)	5 (0.19)	0.433
QOL-6	20.7 \pm 2.96	20.21 \pm 2.17	19.56 \pm 3.72	20.71 \pm 3.99	0.541

Note: [#]The items for the melancholic subtypes are #1-2-6-7-8-9-12-16.

Abbreviations: CBT, cognitive behavioral therapy; 17-HDRS, 17-item Hamilton Depression Rating Scale; QIDS-SR, Self-Rating version of Quick Inventory of Depressive Symptomatology; QOL-6, Quality of Life 6.

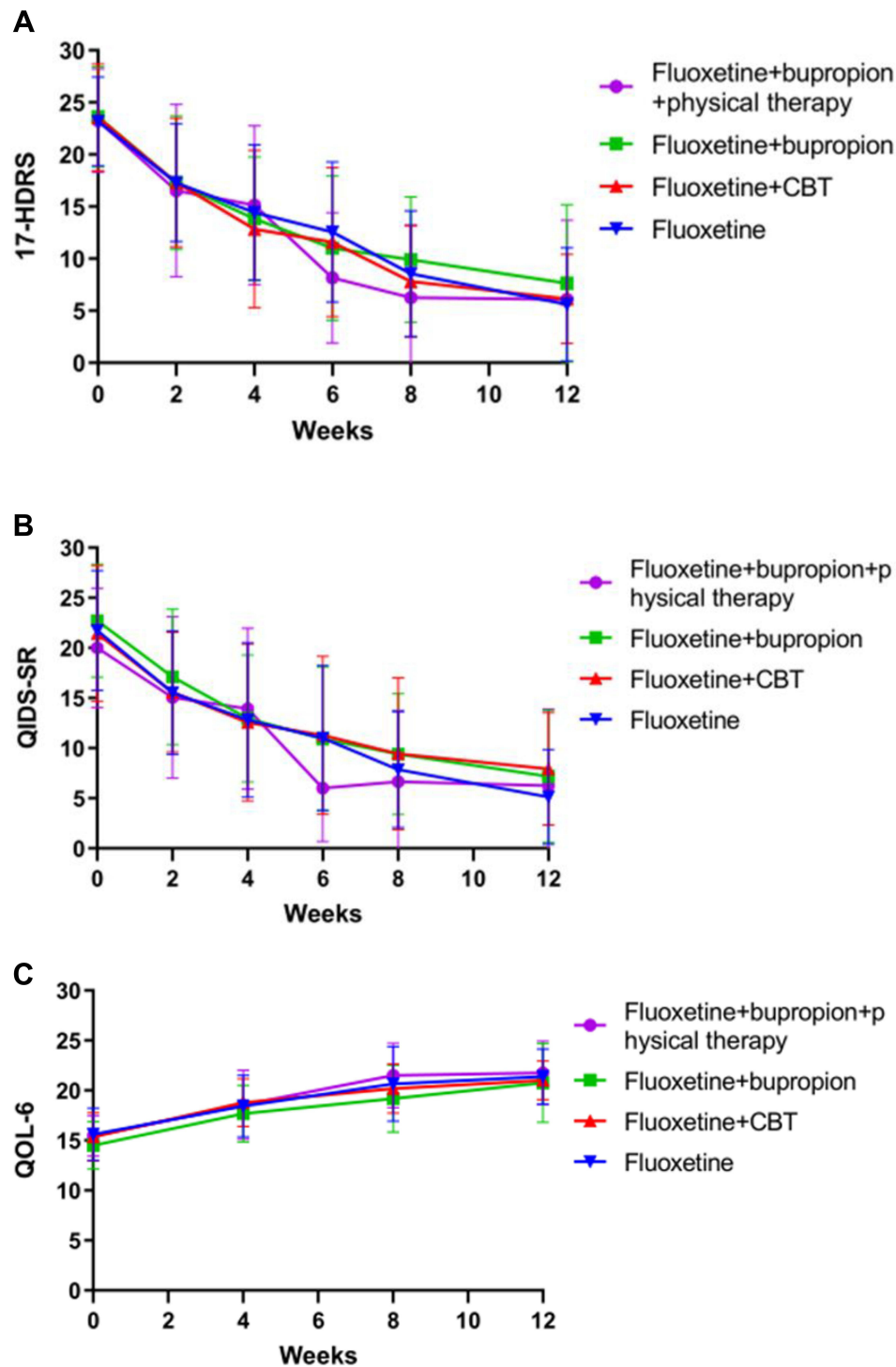


Figure 1 Treatment effect in each group. The treatment effect in each group was plotted using time as the x-axis (0, 2, 4, 6, 8, and 12 weeks) and the indicators. **(A)** 17-item Hamilton Depression Rating Scale (17-HDRS). **(B)** The self-rating version of the Quick Inventory of Depressive Symptomatology (QIDS-SR). **(C)** Quality of Life 6 (QOL-6).

as with cognitive impairment due to intrusive thoughts.^{26,27} Therefore, decreasing self-consciousness could lead to a better quality of life, but additional studies are necessary to determine whether this difference might be clinically relevant.

Fluoxetine, bupropion, MECT, and rTMS are considered safe and well-tolerated.^{3,4} Nevertheless, as could be expected, more AEs were reported for the fluoxetine +bupropion+physical therapies since this group was exposed to the cumulative risk of AEs from all three

Table 3 Adverse Events in the Four Groups

Indicators	Fluoxetine (n=37)	Fluoxetine + CBT (n=27)	Fluoxetine + Bupropion (n=34)	Fluoxetine + Bupropion + Brain Stimulation (n=15)	P
Adverse events, n (%)	0	3 (11.1%)	5 (14.7%)	2 (13.3%)	0.053
Gastrointestinal dysfunction	0	2 (7.4%)	2 (5.9%)	1 (6.7%)	0.303
Abnormal liver functions	0	0	0	0	/
Headache	0	0	3 (8.8%)	2 (13.3%)	0.035
Fatigue	0	0	1 (2.9%)	0	0.673
Allergy	0	0	0	0	/
Tremor	0	0	1 (2.9%)	1 (6.7%)	0.217
Tachycardia/ bradycardia	0	0	0	0	/
Selfharm	0	1 (3.7%)	0	1 (6.7%)	0.136
Common	0	0	0	0	/

Abbreviation: CBT, cognitive behavioral therapy.

treatments. This could also explain the small number of patients who completed the treatment in this group.

This study has limitations. This was a preliminary trial with a small sample size, which was not confirmed by a power analysis. In addition, the drop-out rate was high, especially in the group receiving combined physical therapies.

In conclusion, the results suggest that fluoxetine, fluoxetine+CBT, fluoxetine+bupropion, and fluoxetine+bupropion+brain stimulation achieved similar response and remission rates in patients with melancholic depression, except that fluoxetine alone had a better effect on self-consciousness than fluoxetine+bupropion. The safety profile was manageable. Further studies should be performed to confirm those results. A non-inferiority trial might be necessary.

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Disclosure

All authors declare that they have no conflicts of interest for this work.

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