

Efficacy and Safety of Escitalopram in Alleviating Depression and Anxiety Symptoms in COPD Patients: A Randomized Double-Blind Placebo-Controlled Trial

Zhan Gao^{1,*}, Shasha Tang^{1,*}, Wen Zhang¹, Mingzhou Zhang¹, Zhenghua Wei¹, Zhou Long¹, Bin Wang¹, Heng Qin¹, Hang Qian¹, Yan Yin^{2,*}, Guansong Wang¹, Binfeng He^{1,3}

¹Institute of Respiratory Diseases, Department of Pulmonary and Critical Care Medicine, Xinqiao Hospital, Third Military Medical University (Army Medical University), Chongqing, 400037, People's Republic of China; ²Department of Pulmonary and Critical Care Medicine, the First Hospital of China Medical University, Shenyang, 110001, People's Republic of China; ³Department of General Practice, Xinqiao Hospital, Third Military Medical University (Army Medical University), Chongqing, 400037, People's Republic of China

*These authors contributed equally to this work

Correspondence: Binfeng He; Guansong Wang, Email ldhbf@tmmu.edu.cn; wanggs@tmmu.edu.cn

Purpose: Depression and anxiety negatively impact COPD prognosis, yet evidence for psychopharmacological interventions remains limited. This study evaluated the efficacy and safety of low-dose escitalopram for managing these comorbidities in COPD patients.

Patients and methods: In this double-blind, placebo-controlled trial, 150 COPD patients with moderate-to-severe anxiety and/or depression were randomized (1:1) to receive escitalopram (5–10 mg/day) or placebo for 4 weeks, followed by an 11-month observational follow-up without maintenance study medication. Primary endpoints were changes in HAMA-14 and HAMD-17 scores at Month 1. Secondary outcomes included CAT scores, mMRC ratings, and lung function (FEV₁% predicted) through Month 12.

Results: At Month 1, escitalopram demonstrated significantly greater reductions in HAMA-14 (−9.25 [95% CI −9.67 to −8.82] vs −2.20 [−2.46 to −1.95]) and HAMD-17 (−7.37 [−7.74 to −7.01] vs −1.37 [−1.72 to −1.01]) compared to placebo ($p < 0.01$). These improvements were sustained at Month 12 ($p < 0.01$). CAT scores improved significantly more in the escitalopram group (−6.20 [−6.68 to −5.72]) versus placebo (−2.79 [−3.02 to −2.55]) over the 12-month observational period ($p < 0.01$). No significant differences were observed for mMRC or FEV₁% predicted. Adverse events were mild and comparable between groups.

Conclusion: Short-term treatment with low-dose escitalopram significantly alleviates depression and anxiety in COPD patients. Notably, this brief intervention initiated a sustained positive clinical trajectory over 12 months. Combined with a favorable safety profile, these findings support its potential integration into comprehensive COPD management protocols, pending multicenter validation.

Trial Registration: ChiCTR1800017338 (<https://www.chictr.org.cn/>). Registered 25-July-2018.

Keywords: anxiety, CAT score, COPD, depression, escitalopram

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous pulmonary disease, which is characterized by chronic respiratory symptoms and persistent, often progressive, airflow obstruction.¹ It is considered as one of major threats to global public health due to its high prevalence (up to 10.3%, with nearly 100 million patients in China),^{2,3} high rates of disability and mortality,⁴ and heavy economic and social burdens.⁵ Emerging evidence from clinical practice and research indicates that multimorbidity, defined as the coexistence of two or more chronic conditions, is a key characteristic of COPD.⁶ COPD-associated comorbidities are often underrecognized due to overlapping clinical symptoms and are inadequately managed, exacerbating the disease burden.⁷ This leads to a poor quality of life, increased hospitalizations,

and significantly higher mortality among COPD patients with comorbidities compared to mortality directly attributed to severe airflow obstruction.^{7–9} Therefore, the recognition and management of COPD-associated comorbidities should receive greater attention in the management of the people with COPD.

Anxiety and depression are significant and frequently observed comorbidities in individuals with COPD. Among stable COPD patients, the prevalence of anxiety ranges from 13% to 46%, while depression affects 10% to 42% of this population.¹⁰ Notably, these two conditions often coexist in COPD patients, with a combined prevalence reaching as high as 43%.¹¹ Unfortunately, anxiety and depression are often difficult to identify and are under-diagnosed because their symptoms frequently overlap with those of COPD, resulting in a low proportion of COPD patients receiving appropriate anti-depression and anxiety treatment.^{12–14} Extensive research has demonstrated that anxiety and depression are strongly associated with diminished quality of life, an increased risk of COPD exacerbations, and higher mortality rates.^{15,16} Conversely, poorer quality of life, dyspnea, and the economic burden resulting from frequent hospitalizations further exacerbate the severity of anxiety and depression, thereby creating a vicious cycle.^{17–19} Therefore, anxiety and depression in COPD patients need to be promptly identified and adequately treated.

Therapy of anxiety and depression in patients with COPD remains a formidable challenge. Current management strategies include both non-pharmacological and pharmacological interventions. In addition to long-term telerehabilitation,^{20,21} behavioral interventions, and psychological or lifestyle interventions²² have shown promise in improving mild depression and anxiety. However, these non-pharmacological approaches are often resource-intensive and may be insufficient for patients with moderate-to-severe symptoms. Regarding pharmacotherapy, traditional agents present significant drawbacks. Benzodiazepines are associated with a risk of exacerbations of their COPD, and respiratory tract infections.^{23–25} Similarly, tricyclic antidepressants (TCAs) carry anticholinergic and cardiovascular side effects that may exacerbate comorbidities.²⁶ Given these limitations, selective serotonin reuptake inhibitors (SSRIs) are considered a first-line approach due to their more favorable safety profile.^{27,28} Despite this, evidence for specific SSRIs remains inconsistent.

Escitalopram, a representative SSRI, has demonstrated superior acceptability, effectiveness, and safety in managing psychiatric symptoms across various chronic conditions, including stroke²⁹ and coronary heart disease.^{30–32} However, evidence regarding its use in the COPD population is remarkably scarce. Previous studies on other SSRIs, such as sertraline, have shown only limited benefits with a small reduction in COPD-related depressive symptoms over six weeks.³³ Consequently, the effectiveness and safety of escitalopram in patients with COPD remain unknown.

The aim of this study is to evaluate the efficacy and safety of escitalopram in the treatment of depression and/or anxiety in patients with COPD in a randomized, double-blind, placebo-controlled clinical trial during a 12-month study period, as well as other secondary outcomes.

Methods

Study Design

This was a randomized, double-blind, placebo-controlled trial involving 150 subjects with COPD complicated by moderate or severe anxiety and/or depression. Each subject was followed up for 1 year from the date of enrolment and received escitalopram or placebo.

Sample size calculation was based on the primary endpoint (HAMD-17) using a two-sided significance level (α) of 0.01 and 90% power. Assuming a mean difference of 4.0 points (exceeding the MCID of 2–3^{34,35} and a standard deviation of 5.7,^{36,37} 61 patients were required per group. To allow for 18–20% attrition, the final target was set at 75 patients per group (Total $n = 150$).

Eligibility and Exclusion Criteria

Enrollment occurred from November 2018 to July 2019. Subjects were recruited from stable COPD outpatients or hospitalized COPD patients who had achieved clinical improvement or stabilization and were deemed eligible for discharge from the Xinqiao Hospital. The inclusion criteria are as follows: (1) subjects age between 40 and 80 years; (2) subjects had COPD, defined by a post-bronchodilator FEV1/FVC < 0.70; (3) moderate or severe anxiety and/or

depression (Hamilton Anxiety Rating Scale (HAMA-14) > 21, Hamilton Depression Rating Scale (HAMD-17) > 17). The anxiety and depression of these patients were assessed by psychiatrists and trained physicians in a blinded status; (4) Anxiety and/or depression occurred after COPD diagnosis; (5) subjects were capable of providing signed written informed consent.

Subjects were excluded if they met one or more of the following criteria: (1) Experience of significant family or personal upheaval (eg bereavement, financial crisis) within the previous three months; (2) Any clinically relevant lung disease, including asthma, advanced pulmonary malignancies, or active tuberculosis; (3) Comorbid other serious diseases, such as neurological, endocrine, haematological, hepatic, or renal pathologies, as well as metastatic malignancies; (4) concurrent psychiatric diagnoses such as schizophrenia spectrum disorder or bipolar affective disorder; (5) alcohol or drug abuse; (6) cognitive deficits that interfere with understanding of the study protocol or completion of questionnaires; (7) current enrolment in competing clinical trials; (8) pharmacological regimens with contraindications to escitalopram; (9) they were currently receiving anti-anxiety or antidepressant treatment (including psychotherapy) or had received such treatment within 6 months prior to screening.

Randomization and Masking

Subjects were randomized to escitalopram or placebo in a 1:1 ratio using permuted block randomization with a block size of 4. The vials for escitalopram and placebo tablets were indistinguishable in external appearance, and texture. All study individuals, including physicians, psychiatrists, outcome assessors, independent monitors and investigators, remained blinded to treatment allocation throughout the study. Blinding was maintained until the final data collection and database closure, followed by formal unblinding procedures.

Study Procedures

Considering the elderly demographic and respiratory comorbidities of our cohort, we opted for a conservative 4-week intervention to ensure safety and compliance. Subsequently, participants underwent an 11-month observational follow-up without maintenance study medication. Prescribing information recommends that individuals over 65 years of age initiate treatment at 5 mg/day, with a maximum dosage not exceeding 10 mg/day. Since therapeutic effects are typically achievable within 2 to 4 weeks, a 4-week period was selected. Additionally, consulting psychiatrists and pharmacists advised tapering the dosage to 5 mg/day in the final week to prevent adverse reactions associated with abrupt discontinuation.

Subjects received 5 mg of escitalopram or matching placebo daily for the first week, followed by a dose escalation to 10 mg daily for the next two weeks. In the fourth week, the dosage was tapered to 5 mg/day to minimize withdrawal risks. Cessation was determined by the study protocol rather than individual clinical criteria; thus, all participants followed this fixed-duration regimen.

Scheduled psychiatric evaluations were conducted at baseline, Month 1, Month 6, and Month 12. Subjects were required to attend in-person visits at baseline and at the 12-month endpoint. For the Month 1 and Month 6 follow-ups, data were collected via telephone interviews or outpatient visits.

All assessments were conducted by psychiatrists and physicians working in a blind fashion, using standardized guidelines to address potential adverse effects. At baseline, participants underwent spirometry and completed validated questionnaires, including the COPD Assessment Test (CAT) and the modified Medical Research Council Dyspnea Scale (mMRC), and the Smoking Index (SI) was recorded, which was defined as the number of cigarettes smoked per day multiplied by the number of years of smoking. Severity of anxiety and depression was assessed using the HAMD-17 and the HAMA-14, administered jointly by psychiatrists and trained physicians. The minimal clinical important differences (MCID) of CAT score between 2–3 points,³⁸ and MCID of HAMD-17 between 2–3 points.^{34,39} These measurements were repeated at the 1-month, 6-month, and 1-year follow-ups. To minimize subjects' loss to follow-up, internists collaborated with the participants' family physicians to facilitate monthly communication. This approach was designed to enhance participant management and tracking while increasing motivation to remain engaged in the study.

In addition, as some participants experienced recurrent exacerbations of anxiety and depression during the follow-up period, temporary, symptom-based interventions were provided based on psychiatrists' recommendations.

Outcome Measures

The primary outcome was defined as the change in total HAMD-17 and HAMA-14 scores from baseline to Month 1. Secondary outcomes included changes over the 12-month period in the mMRC dyspnea scale score, the CAT score, and the percent predicted forced expiratory volume in 1 second (FEV₁% predicted). Safety and tolerability were assessed by monitoring the incidence rates and severity grading of adverse events, which were systematically documented throughout the follow-up period and reported according to the National Medical Products Administration (NMPA) criteria.

Statistical Analysis

All statistical analyses were performed using SPSS version 27.0 (IBM Corporation, Armonk, NY). Baseline characteristics were summarized based on the intention-to-treat (ITT) principle, including all randomized participants ($n = 150$). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (IQR) according to their distribution, while categorical variables are expressed as frequencies and percentages. Baseline intergroup comparisons used independent samples t-tests for normally distributed continuous variables, Pearson's chi-square tests for binary variables, and the Mann-Whitney U test for ordinal variables.

Primary efficacy analyses were conducted on the full analysis set (FAS), defined as all randomized participants who received at least one dose of the study medication and provided at least one valid post-baseline efficacy assessment ($n = 146$). The Generalized Estimating Equations (GEE) model was employed for primary and secondary endpoints to evaluate treatment-related differences in mean changes from baseline to follow-up, utilizing all available longitudinal data. The GEE models specified a linear link function with a first-order autoregressive (AR1) working correlation structure and were adjusted for clinically relevant covariates: age, body mass index (BMI), smoking index (SI), and baseline FEV₁% predicted.

To assess the robustness of the primary treatment effect on HAMA-14 and HAMD-17 scores at Month 1, an analysis of covariance (ANCOVA) was performed as a sensitivity analysis. The ANCOVA model included the treatment group as a fixed factor, adjusting for the corresponding baseline score, age, BMI, SI, and FEV₁% predicted. Effect sizes for ANCOVA are reported as partial eta-squared (η^2), interpreted as small (0.01), medium (0.06), and large (0.14) effects.⁴⁰

Subgroup analyses stratified by clinical setting (inpatients vs outpatients) were conducted within the GEE framework. These models incorporated a three-way interaction term (subgroup $\times$ treatment group $\times$ time) to test for potential effect modification, adjusting for the same covariates as the primary analysis.

For the correlation analysis between short-term psychological improvement (change in HAMA-14/HAMD-17 from baseline to Month 1) and long-term COPD health status (change in CAT score from baseline to Month 12), multiple imputation was used to handle missing data. Spearman's rank correlations were calculated for each imputed dataset. The resulting correlation coefficients were Fisher's z-transformed, pooled using Rubin's rules, and then back-transformed to present the final Spearman's ρ with 95% confidence intervals. A two-tailed P-value of <0.05 was considered statistically significant.

Results

Between November 2018 and July 2020, 150 out of 323 screened subjects met eligibility criteria, provided informed consent, and were included in the intention-to-treat (ITT) population. Among these, 136 participants (90.67%) completed the study, per the CONSORT flow diagram (Figure 1). Baseline demographic and clinical characteristics are shown in Table 1. The escitalopram and placebo groups demonstrated balanced demographic profiles at enrollment, with no statistically significant differences in age, sex, or baseline BMI (all $p > 0.05$). Furthermore, comparable baseline measures of COPD severity, depressive symptoms, and anxiety severity were observed between treatment arms ($p > 0.05$ for all comparisons). We confirmed that no participants continued specific antidepressant or anxiolytic therapy after the initial 4-week intervention period. No participants reported initiating new psychotropic treatments, nor did they actively seek external psychiatric consultations to obtain such prescriptions from other institutions.

Longitudinal analysis using Generalized Estimating Equations (GEE) demonstrated that escitalopram provided significant and sustained improvement in anxiety and depression symptoms compared to placebo (Figure 2A and B and Supplementary Table 1). Significant group-by-time interactions were observed for both HAMA-14 and HAMD-

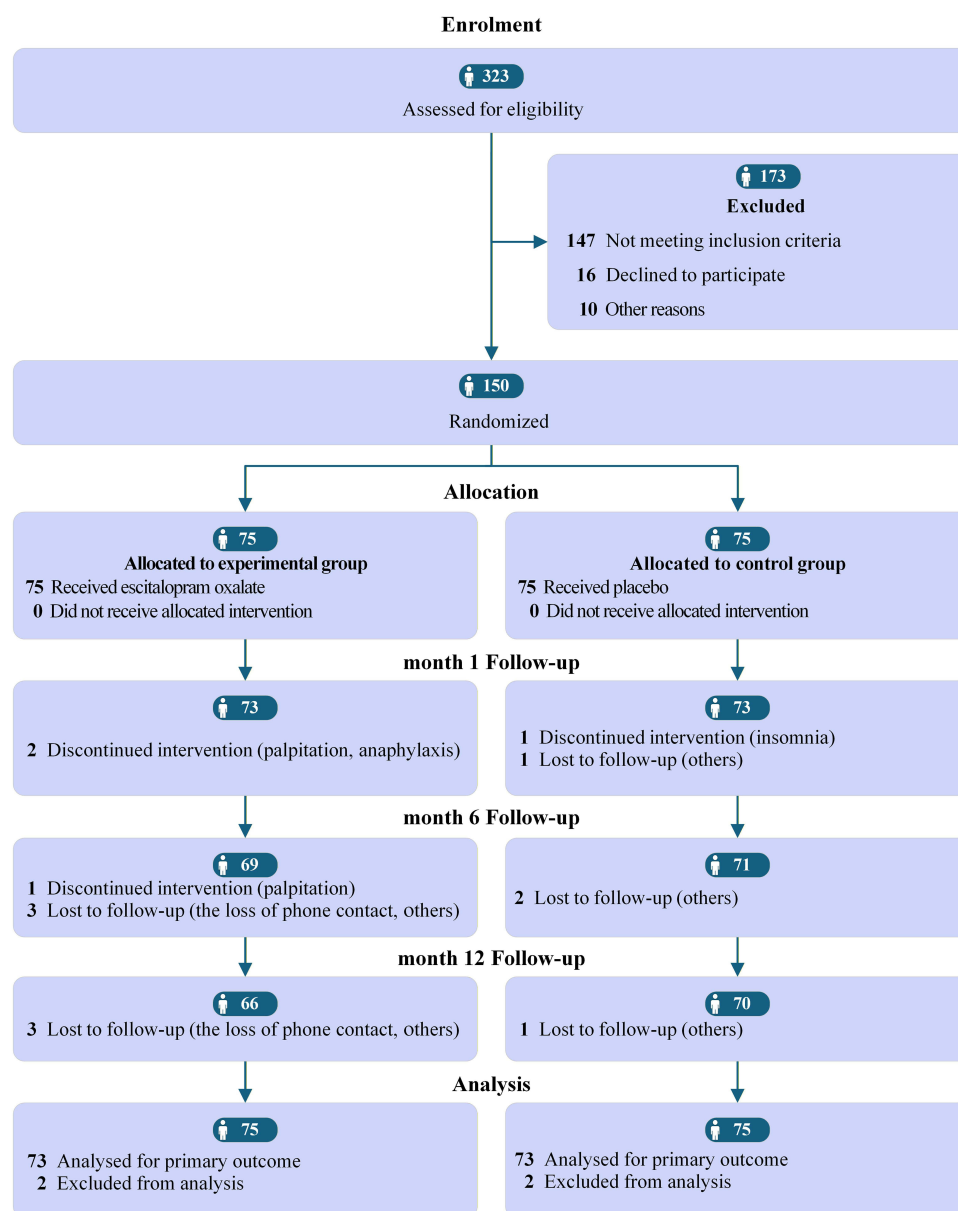


Figure 1 Study flowchart.

17 scores (all $p < 0.001$), indicating distinct symptom trajectories between the two groups over the 12-month period. In the escitalopram group, HAMA-14 and HAMD-17 scores decreased significantly from baseline at Month 1, Month 6, and Month 12. Specifically, after 4 weeks of treatment, the escitalopram group showed marked reductions (HAMA-14: mean change -9.25 , 95% CI -9.67 to -8.82 ; HAMD-17: -7.37 , 95% CI -7.74 to -7.01 ; both $p < 0.01$). These improvements were maintained at the 12-month follow-up (HAMA-14: -4.75 , 95% CI -5.40 to -4.10 ; HAMD-17: -3.43 , 95% CI -3.99 to -2.86 ; both $p < 0.01$). In contrast, while the placebo group exhibited smaller but statistically significant improvements at Month 1 (HAMA-14: -2.20 ; HAMD-17: -1.37 ; both $p < 0.01$), these effects were transient. By Month 12, changes from baseline in the placebo group were no longer statistically significant (HAMA-14: $p = 0.45$; HAMD-17: $p = 0.12$). Additionally, analysis of Covariance (ANCOVA) confirmed the robustness of the primary endpoint at Month 1. Escitalopram demonstrated superiority over placebo with large effect sizes (partial $\eta^2 > 0.14$). The adjusted mean differences were -7.13 (95% CI -7.64 to -6.62) for HAMA-14 and -6.08 (95% CI -6.57 to -5.58) for HAMD-17 ([Supplementary Table 2](#)).

Table 1 Baseline Characteristics of Study Participants

	All (n=150)	Escitalopram (n=75)	Placebo (n=75)	Statistic value	p value
Male (%)	137 (91.3%)	70 (93.3%)	67 (89.3%)	0.758	0.384
Age, years	63.41 (8.21)	63.03 (7.97)	63.80 (8.48)	0.575	0.566
BMI (kg/m ²)	23.13 (3.40)	23.60 (3.51)	22.65 (3.23)	-1.715	0.089
Smoking history					
Yes	130 (86.7%)	63 (84.0%)	67 (89.3%)	0.923	0.337
No	20 (13.3%)	12 (16.0%)	8 (10.7%)		
Smoking Index	600 (700)	600 (700)	700 (600)	0.998	0.320
Clinical setting					
Inpatient	27 (18.0%)	15 (20.0%)	12 (16.0%)	0.407	0.524
Outpatient	123 (82.0%)	60 (80.0%)	63 (84.0%)		
FEV ₁ % predicted	54.03 (15.77)	54.07 (16.17)	54.00 (15.48)	-0.027	0.978
Comorbidities					
Hypertension	22 (14.7%)	12 (16.0%)	10 (13.3%)	0.213	0.644
Diabetes Mellitus	7 (4.7%)	4 (5.3%)	3 (4.0%)	0.000	1.000
CVD	43 (28.7%)	26 (34.7%)	17 (22.7%)	2.641	0.104
GOLD grade					
1	8 (5.3%)	5 (6.7%)	3 (4.0%)	2804.00	0.972
2	70 (46.7%)	33 (44.0%)	37 (49.3%)		
3	61 (40.7%)	32 (42.7%)	29 (38.7%)		
4	11 (7.3%)	5 (6.7%)	6 (8.0%)		
mMRC					
0	1 (0.7%)	0 (0.00%)	1 (1.30%)	2739.50	0.757
1	36 (24.0%)	18 (24.0%)	18 (24.0%)		
2	87 (58.0%)	46 (61.3%)	41 (54.7%)		
3	26 (17.3%)	11 (14.7%)	15 (20.0%)		
4	0 (0.0%)	0 (0.0%)	0 (0.0%)		
CAT score,0-40	19.27 (4.62)	19.51 (4.45)	19.03 (4.79)	-0.635	0.526
HAMA-14 score,0-56	23.59 (2.05)	23.28 (2.17)	23.89 (1.89)	1.847	0.067
HAMD-17 score,0-52	19.53 (1.64)	19.45 (1.82)	19.60 (1.44)	0.547	0.585

Notes: Data are presented as mean(SD), median (IQR) or n(%). Intergroup comparisons used the independent samples t-test (reported as t), Pearson's chi-square test (reported as χ^2), or the Mann-Whitney U-test (reported as U), as appropriate for the variable type and distribution.

Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease, CVD: Cardiovascular Disease (includes coronary artery disease, heart failure, peripheral artery disease), GOLD grade: based on post-bronchodilator, FEV₁% predicted:the percent predicted forced expiratory volume in 1 second.

We evaluated the impact of treatment on COPD-specific health status and lung function using the adjusted GEE model ([Supplementary Table 3](#)). For the CAT score, a significant group-by-time interaction was observed ($p < 0.001$). Although between-group differences were not significant at Month 1 or Month 6 (both $p > 0.05$), the escitalopram group achieved a significantly lower adjusted mean score than the placebo group at Month 12 (13.30 vs 16.22; adjusted mean difference -2.93, 95% CI -4.13 to -1.73; $p < 0.001$). Furthermore, the within-group reduction from baseline to Month 12 was substantially greater with escitalopram ($\Delta = -6.20$, $p < 0.01$) than with placebo ($\Delta = -2.79$, $p < 0.01$). Conversely, no significant group-by-time interactions or between-group differences were found for mMRC scores or FEV₁% predicted at any time point (all $p > 0.05$). Both groups showed small, significant within-group improvements in mMRC scores from baseline to Month 12 ($p < 0.01$). For FEV₁% predicted, a significant within-group improvement was observed only in the escitalopram group ($\Delta = 3.70$, $p < 0.05$), whereas the change in the placebo group was not significant.

Subgroup analyses stratified by clinical setting (inpatients vs outpatients) were performed to assess the consistency of treatment effects ([Figure 3](#) and [Supplementary Tables 4–5](#)). For the primary endpoints (HAMA-14 and HAMD-17), the three-way interaction terms (Time $\times$ Group $\times$ Clinical setting) were not statistically significant (HAMA-14: $p = 0.172$; HAMD-17: $p = 0.236$). This indicates that the longitudinal trajectory of the treatment effect relative to placebo was

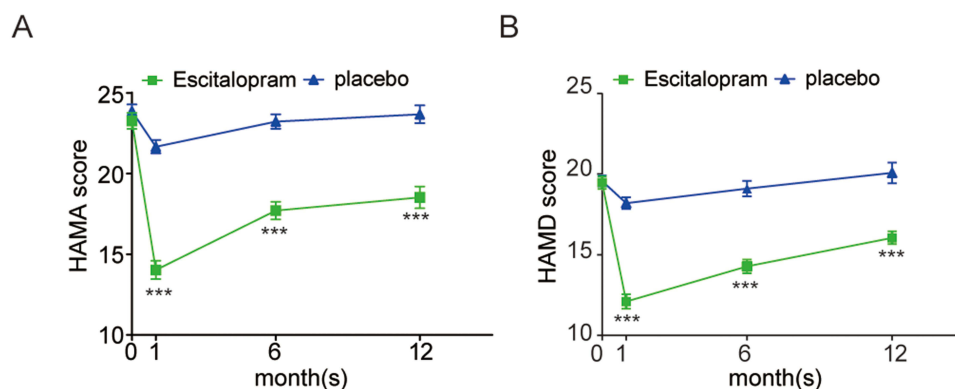


Figure 2 Longitudinal changes in anxiety and depression scores over 12 months in patients with COPD. **(A)** HAMA-14 scores. **(B)** HAMD-17 scores. Data points represent the mean scores, and error bars indicate the standard error (SE). ***, $p < 0.001$ for the comparison between the escitalopram and placebo groups at the specified time points.

consistent across inpatient and outpatient settings. However, a significant two-way interaction (Group $\times$ Clinical setting) was noted for the HAMA-14 score ($p = 0.044$), suggesting a potential difference in the magnitude of the overall treatment effect between settings, whereas no such interaction was found for HAMD-17 ($p = 0.835$). Regarding secondary endpoints, the CAT score showed a pattern similar to HAMA-14: no significant three-way interaction ($p = 0.500$) but a significant two-way interaction ($p = 0.006$). No significant three-way or two-way interactions were observed for mMRC scores or FEV₁% predicted (all $p > 0.05$).

We also examined whether early psychological improvement predicted long-term COPD outcomes by analyzing the correlation between changes in psychiatric scores at Month 1 and changes in CAT scores at Month 12 (Table 2). Using pooled estimates from multiply imputed datasets, a strong positive correlation was identified. The reduction in anxiety (HAMA-14) from baseline to Month 1 was significantly correlated with the improvement in CAT scores at Month 12 (Pooled Spearman's $\rho = 0.638$, 95% CI 0.534 to 0.726, $p < 0.001$). Similarly, early improvement in depression (HAMD-17) strongly correlated with long-term CAT reduction (Pooled $\rho = 0.639$, 95% CI 0.531 to 0.728, $p < 0.001$).

The proportion of patients experiencing at least one mild or moderate adverse event was similar between escitalopram (9.33%) and placebo (2.67%) ($p > 0.05$). The most common AEs were insomnia (3 [4.00%] in the escitalopram group vs 2 [2.67%] in the placebo group), palpitations (3 [4.00%] vs 0 [0.00%]) and allergic reaction (1 [1.33%] vs 0 [0.00%]). No serious adverse events were observed in any patients (Table 3).

Discussion

To the best of our knowledge, this is the first randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of escitalopram for comorbid depression and anxiety in patients with COPD. Our results demonstrate that a short-term (4-week) course of escitalopram significantly alleviated depression and anxiety symptoms, with benefits emerging rapidly and, notably, persisting throughout the 11-month observational follow-up after treatment cessation. Furthermore, escitalopram treatment was associated with clinically relevant improvements in overall COPD-specific health status (CAT scores) by Month 12, despite no significant impact on physiological FEV₁% predicted or mMRC. Adverse event rates were comparable to placebo, supporting the safety profile of this intervention in a comorbid COPD population.

Escitalopram is a widely recommended first-line treatment for depression and anxiety,^{41–45} and there is strong evidence for its use in patients with somatic comorbidities.^{29,31,32,46–48} Consistent with the above literatures, our findings confirm that escitalopram effectively reduces HAMD and HAMA scores. The rapid improvement we saw at Month 1 matches the known effects of SSRIs.^{29,49} Crucially, while anxiety and depression levels in the placebo group tended to revert to baseline post-cessation, the escitalopram group maintained their clinical gains up to Month 12. This trajectory suggests that early pharmacological intervention may have successfully interrupted the recursive “anxiety/depression-dyspnea” feedback loop.¹⁹ However, the improvement in our patients was modest compared to those with primary

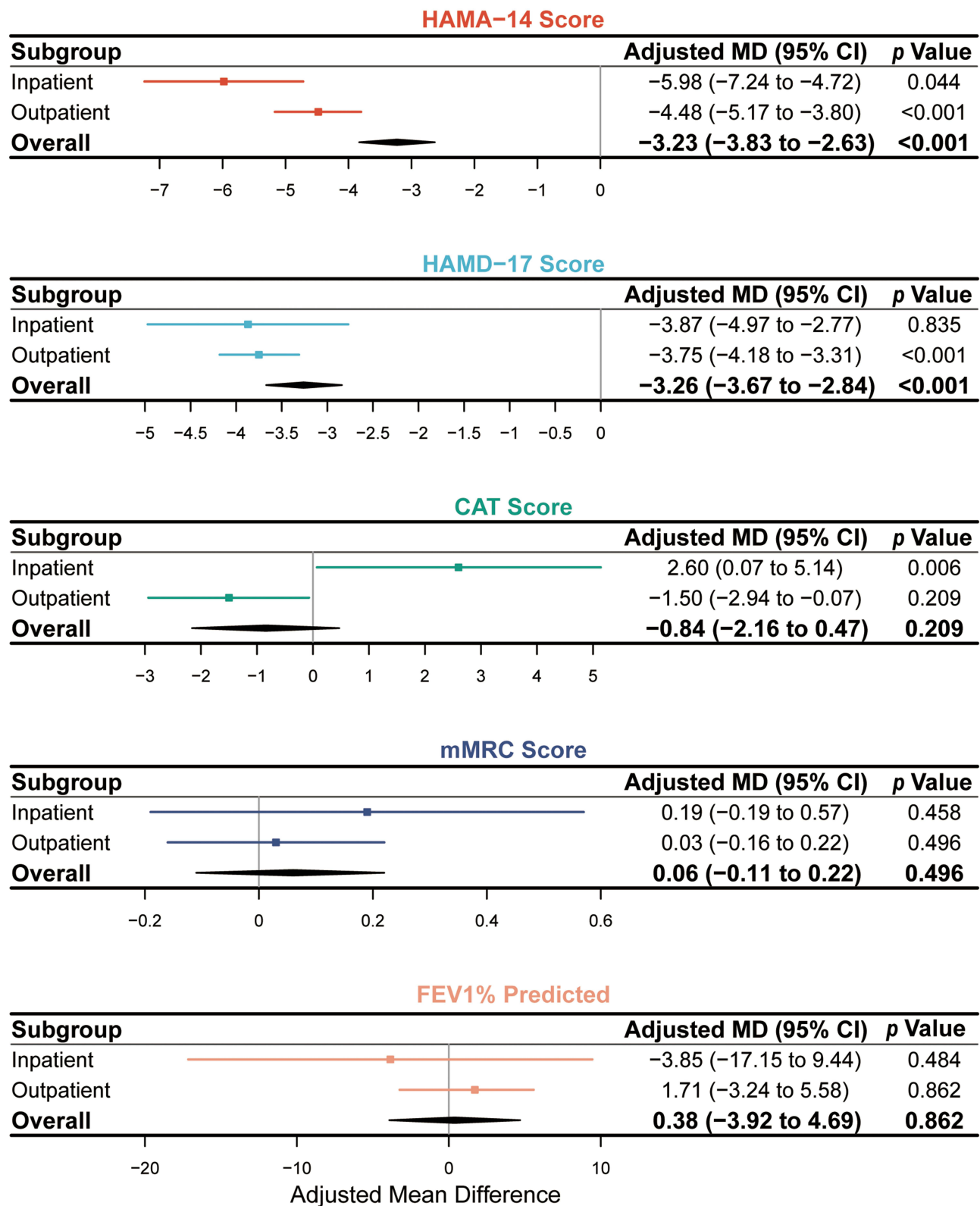


Figure 3 Forest plot of subgroup analyses by clinical setting. Estimates represent adjusted mean differences (MD) and 95% CIs derived from GEE models. The results reflect the average treatment difference across the full study period. For each specific subgroup (Inpatient/Outpatient), the point estimate denotes the adjusted MD within that setting; the corresponding p values test the treatment group $\times$ clinical setting interaction effect, which assesses whether the treatment effect differs statistically between the inpatient setting and the reference (outpatient) group. The Overall estimate (black diamond) reflects the adjusted MD for the total population, with its p value testing the main effect of treatment across all setting.

Table 2 Pooled Spearman Correlations Between Short-Term Symptom Improvement and Long-Term Health Status Change

Measure 1 (Short-Term Change)	Measure 2 (Long-Term Change)	n	Pooled ρ (95% CI)	p value
Δ HAMA-14 (Baseline to Month 1)	Δ CAT (Baseline to Month 12)	136	0.638 (0.534 to 0.726)	<0.001
Δ HAMD-17 (Baseline to Month 1)	Δ CAT (Baseline to Month 12)	136	0.639 (0.531 to 0.728)	<0.001

Notes: Δ , change from baseline. n denotes the number of subjects with paired data available for both measures in the analysis. Pooled Spearman correlation coefficient (ρ) and 95% CI were derived by applying Rubin's rules to estimates from 5 multiply imputed datasets. P values are from two-tailed tests of the null hypothesis that the population correlation coefficient is zero.

Table 3 Adverse Reactions During Treatment

Adverse Reaction	Total (n=150)	Escitalopram (n=75)	Placebo (n=75)	P value
Insomnia	5(3.33%)	3(4.00%)	2(2.67%)	0.166
Palpitations	3(2.00%)	3(4.00%)	0(0.00%)	
Allergic reaction	1(0.67%)	1(1.33%)	0(0.00%)	

psychiatric disorders.^{50–52} This is likely due to two factors: the persistent physical burden of COPD,^{17,18} and our conservative dosing strategy to ensure safety in this elderly population.⁵³

Previous studies showed that the treatment of comorbid anxiety and depression demonstrates therapeutic potential for enhancing quality of life and functional capacity in COPD patients.^{22,54} We observed a distinct dissociation between subjective health status and physiological parameters over time. While CAT scores improved significantly by Month 12, lung function (FEV₁% predicted) and mMRC remained largely unchanged. This discrepancy suggests that escitalopram may improve treatment adherence and exercise tolerance, while reducing the “symptom amplification” inherent to comorbid COPD and anxiety/depression,⁵⁵ rather than by changing respiratory mechanics. The delay in CAT score improvement likely reflects the time needed for behavioral adaptation. Although a 4-week course was too short to change physiological markers, it appears to have set patients on a positive path, possibly by boosting self-efficacy or adherence once their distress was relieved.

Our stratified analysis by treatment setting revealed notable differences in outcomes. For anxiety, inpatients showed a greater reduction in HAMA-14 scores compared to outpatients. This stronger response likely reflects higher baseline anxiety in hospitalized patients, which allows for a larger margin of improvement, or perhaps the added benefit of intensive monitoring in the inpatient setting. However, the pattern for CAT scores was different. Significant improvement in health status was seen only in the outpatient cohort, with no benefit observed in inpatients. This data suggests that in stable outpatients, treating anxiety effectively breaks the “anxiety/depression-dyspnea” feedback loop, thereby improving subjective respiratory symptoms. In contrast, for inpatients in the convalescent phase of an exacerbation, symptom relief is driven primarily by physiological recovery and intensive medical management rather than emotional (anxiety and/or depression) modulation. This robust physical improvement likely overshadowed the impact of anxiety or depression reduction on somatic COPD symptoms. These findings suggest that while escitalopram is effective for treating anxiety and depression in both settings, its additive benefit for somatic COPD symptoms may be less discernible during the dynamic recovery phase of an exacerbation compared to stable outpatient conditions.

The correlation analysis offers further insight into this recovery trajectory. The strong positive correlation between short-term psychological relief (Month 1) and long-term health status improvement (Month 12) identifies the first month of treatment as a critical “therapeutic window.” This “early response–long-term benefit” pattern implies that managing anxiety and depression is not merely an adjunct to COPD care but a driver of long-term symptomatic improvement. Mechanistically, rapid alleviation of depression and anxiety may break the vicious cycle of anxiety/depression-dyspnea

early on, enabling patients to better engage with pulmonary rehabilitation, improve treatment adherence, and adopt lifestyle modifications that cumulatively improve CAT scores.

Given that the efficacy of different antidepressants in older adults may differ from that in younger adults due to age-related pharmacokinetic changes, polypharmacy risks, and high rates of medical comorbidity alter medication efficacy compared to younger populations.⁵³ Therefore, safety is an important consideration when choosing an antidepressant/anxiety medication for COPD patients, most of whom are elderly and may have multiple comorbidities. Escitalopram demonstrates favorable tolerability in older adults with depression and anxiety disorders.^{56–58} Previous research confirms its safety in preventing depressive episodes among patients with acute coronary syndrome or stroke,^{48,59,60} while also effectively reducing anxiety and depressive symptoms in chronic conditions such as coronary heart disease (CHD).^{31,61} Consistent with the above literature, our results showed that a 4-week low-dose escitalopram treatment is safe for depression and/or anxiety in COPD patients, with only mild adverse effects (insomnia, palpitations, allergic reactions) observed. We did not use a higher dose ($\geq 20\text{mg}$) because previous studies have shown that higher doses may increase the risk of adverse events.^{58,62,63} Although several adverse events, such as falls, anorexia and respiratory harm,^{60,64,65} were not observed in this study, we still need to pay attention to these patients with COPD taking escitalopram, as these adverse events may be caused by COPD and its complications.

Our study has several limitations. First, as a single-center trial, the findings require validation in larger, multi-center studies to ensure their generalizability to broader populations. Second, potential biases from uncontrolled clinical variables must be considered. Specifically, patients who had recently used intravenous corticosteroids were not excluded. Since the treatment setting and steroid use can influence mood and symptom scores (eg, CAT and mMRC), these factors might affect the results, although randomization likely balanced these differences between groups. Third, FEV₁% predicted data were not collected at Month 1 or Month 6. We limited testing to baseline and Month 12 to avoid burdening our elderly patients. Furthermore, as the intervention targets symptom perception rather than airflow, we did not anticipate immediate physiological changes in lung function; the stability observed at Month 12 supports this perspective. Finally, the 11-month follow-up was observational. Although participants stopped the study drug after Month 1, they were allowed to use other symptom-based treatments if needed. Thus, the long-term results reflect the clinical course following the initial intervention rather than demonstrating sustained pharmacological efficacy over the 11-month period.

Conclusion

In conclusion, short-term escitalopram treatment demonstrates both efficacy and safety in the management of comorbid depression and anxiety in stable COPD patients. The intervention significantly reduced symptoms within the 4-week active treatment phase, and notably, initiated a sustained positive clinical trajectory that was maintained for up to 11 months post-treatment. This study proposes a viable short-term intervention strategy to break the anxiety/depression-dyspnea cycle and alleviate long-term symptom burden in clinical practice.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; SSRIs, selective serotonin reuptake inhibitors; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; CAT, COPD Assessment Test; FEV₁% predicted, forced expiratory volume in one second percent predicted; ITT, intention-to-treat.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Our study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Medical Ethics Committee of Xinqiao Hospital of Third Military Medical University [2017-028-01]. Chinese Clinical

Trial Registry number, ChiCTR1800017338). All participants were informed about the study procedures, and the trial conforms to the Consolidated Standards of Reporting Trials (CONSORT) statement.

Consent for Publication

All authors have read and approved the final version of the manuscript and give their consent for its publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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