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Original Article

Comparative Efficacy of Bupropion versus Escitalopram for Treating Depression After Coronary Artery Bypass Graft Surgery

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Background: Depression is highly prevalent in patients following coronary artery bypass graft (CABG) surgery and negatively impacts both recovery and clinical prognosis. Selecting an appropriate antidepressant for this cardiac population remains a significant clinical challenge. This study aimed to compare the efficacy and safety of bupropion versus escitalopram in the treatment of major depressive disorder (MDD) among post-CABG patients. Both agents are recognized for their limited cardiovascular side effects and minimal potential for drug–drug interactions.

Materials and Methods: In this double-blind, randomized controlled trial, 100 patients diagnosed with post-CABG depression (according to DSM-5 criteria) were assigned to receive either bupropion (150–300 mg/day) or escitalopram (10–20 mg/day) for 8 weeks. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D) and the Beck Depression Inventory-II (BDI-II) at baseline, and at 2, 4, and 8 weeks post-treatment. The primary outcome was the change in HAM-D scores; the secondary outcome was the change in BDI-II scores.

Results: Both groups demonstrated significant improvements in depression scores over the 8-week period. At week 8, mean HAM-D scores had decreased from 15.8 to 8.1 in the bupropion group and from 16.3 to 7.8 in the escitalopram group ($p > 0.05$). Similar patterns were observed in BDI-II scores. No serious adverse events were reported in either cohort.

Conclusion: Patients post-cardiac surgery remain at an elevated risk of developing depressive and anxiety symptoms. Identifying suitable pharmacotherapies with favourable cardiovascular safety profiles is vital for clinical decision-making. Both treatments were found to be equally effective and well-tolerated in the management of post-CABG depression. These findings support a flexible approach to antidepressant selection, tailored to individual patient profiles.

Keywords: Coronary Artery Bypass Ggraft, Bupropion, Escitalopram, Depression

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Introduction

Depression is one of the most prevalent psychiatric disorders worldwide and a major contributor to the global burden of disease. According to the Global Burden of Disease Study, depression affects more than 264 million people globally and is projected to become the leading cause of disability by 2030 (1). Patients with cardiovascular disease (CVD), particularly those undergoing coronary artery bypass graft (CABG) surgery,

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are at a heightened risk of developing major depressive disorder (MDD). Evidence suggests that up to 40% of post-CABG patients experience depressive symptoms within the first six months following surgery (2).

The pathophysiology of post-CABG depression is multifactorial. Inflammatory cytokines-such as interleukin-6 and tumour necrosis factor-alpha, released during and after cardiopulmonary bypass-have been implicated in neuroimmune activation, which contributes to the development of depressive symptoms (3). Furthermore, stress-related dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, compounded by the psychological impact of major surgical intervention, further exacerbates vulnerability to mood disorders in this population (4). Postoperative depression is associated with poorer cardiac outcomes, including increased rates of rehospitalization, reduced medication adherence, impaired functional recovery, and an elevated mortality risk (5). Despite these implications, depression in cardiac patients remains frequently underdiagnosed and undertreated.

Selective serotonin reuptake inhibitors (SSRIs), particularly escitalopram, are commonly prescribed due to their favorable safety profile in patients with cardiovascular comorbidities (6). While sertraline and citalopram are established treatments, they are associated with potential cardiac adverse effects, including interactions with protein-bound medications and QT interval prolongation. Conversely, bupropion is recognized for its lack of such effects. Escitalopram is noted for its tolerability and minimal potential for drug–drug interactions, rendering it a first-line option in many clinical guidelines. Nevertheless, some patients experience adverse effects-such as sexual dysfunction, sedation, or weight gain-which may compromise treatment adherence (7). Bupropion, a norepinephrine–dopamine reuptake inhibitor (NDRI), presents a distinct pharmacological profile. It is associated with fewer sexual adverse effects, potential weight loss, and an activating effect that may prove beneficial for patients experiencing hypersomnia or psychomotor retardation. Additionally, bupropion may carry a lower risk of QTc prolongation compared to certain SSRIs, suggesting it is a potentially safer alternative for specific cardiac patients (8).

Standard clinical guidelines indicate that an adequate antidepressant response typically requires 4–6 weeks of therapy; therefore, an 8-weeks assessment period was selected to sufficiently evaluate both therapeutic efficacy and the emergence of potential side effects, in accordance with established literature. Despite the theoretical advantages of bupropion, data comparing its efficacy and tolerability with SSRIs in the post-CABG population remain limited. Most existing studies have focused primarily on SSRIs, such as sertraline or citalopram, with minimal investigation into the role of NDRIs in this clinical context (9).

Consequently, this study aims to compare the clinical efficacy, tolerability, and adverse effect profiles of bupropion and escitalopram in the treatment of post-CABG depression. To ensure a systematic evaluation of adverse effects, a standard checklist based on established pharmacological resources was utilized. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D) and the Beck Depression Inventory-II (BDI-II). Both instruments are validated for screening depressive symptoms across all age groups; to ensure consistency, these scales were applied uniformly to all participants, including those aged over 60 years.

Materials and methods

Study Design and Setting

This study was a double-blind, randomized controlled trial conducted at Rouhani Hospital, affiliated with Babol University of Medical Sciences, Babol, Iran. The trial took place between September 2019 and September 2021.

The study protocol received formal approval from the institutional ethics committee (Reference: IR.MUBABOL.REC.1398.011) and was registered with the Iranian Registry of Clinical Trials (Registration Number: IRCT20190525043700N2). All participants provided written informed consent prior to enrolment.

Participants and Sampling

Eligible participants were adults aged 40–75 years who had undergone elective or urgent coronary artery bypass graft (CABG) surgery within the preceding six months and met the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for major depressive disorder (MDD).

The diagnosis was confirmed using the Structured Clinical Interview for DSM-5 (SCID-5-CV), conducted by a trained psychiatrist.

Exclusion criteria were as follows:

Presence of bipolar disorder, psychotic disorders, or substance use disorders.

Severe cognitive impairment (Mini-Mental State Examination [MMSE] score < 23).

Active suicidal ideation.

Contraindications to bupropion or escitalopram (e.g., seizure disorders, recent monoamine oxidase inhibitor [MAOI] use, or prolonged QTc interval).

Use of antidepressants within the preceding four weeks.

Randomization and Blinding

Participants were randomized (1:1) to treatment groups using a computer-generated block randomization sequence (block size = 4). Allocation concealment was ensured through the use of opaque, sequentially numbered, sealed envelopes. Both patients and study personnel, including those conducting follow-up assessments, remained blinded to group allocation. To maintain the integrity of the blinding process, identical capsules were prepared and dispensed by a hospital pharmacist.

Interventions and Outcome Measures

Interventions

Participants were assigned to one of two treatment groups:

Group A (Bupropion SR):

Patients received bupropion sustained-release (SR), initiating at 75 mg twice daily. The dosage was titrated up to 150 mg twice daily, contingent upon clinical response and individual tolerability.

Group B (Escitalopram):

Patients received escitalopram, initiating at 5 mg/day. The dosage was titrated to a maximum of 20 mg/day over a two-week period.

The total duration of the treatment intervention for both groups were eight weeks.

Outcome Measures

The primary outcome measures comprised changes in depression severity, as assessed by the 17-item Hamilton Depression Rating Scale (HAM-D) and the Beck Depression Inventory-II (BDI-II). Assessments were conducted at baseline, and at weeks 2, 4, and 8.

Secondary outcomes included:

Clinical response:

Defined as a reduction of ≥50% in the baseline HAM-D score.

Remission:

Defined as a post-treatment HAM-D score of ≤7.

Adverse events:

The frequency and type of adverse effects were systematically evaluated using a standardized side-effect checklist developed by the research team to ensure comprehensive monitoring.

Sample Size

The sample size was estimated using G*Power software, assuming an alpha (α) of 0.05, a power of 80%, and an effect size of 0.6, which indicated a requirement of 45 participants per treatment arm. To account for a potential attrition rate of approximately 10%, 100 patients were enrolled in total, with 50 allocated to each group.

Statistical Analysis

Data were analyzed using SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). The assumption of normality for continuous variables was assessed using the Shapiro–Wilk test and Q-Q plot. A repeated-measures analysis of variance (ANOVA) was utilized to compare depression severity scores (HAM-D and BDI-II) across the four assessment time points, both within and between the study groups. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. Quantitative variables were compared using t-test or Mann-Wheitney U test. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Participant Flow and Baseline Characteristics

A total of 128 patients were screened for eligibility. Of these, 100 participants met the inclusion criteria and were randomized in a 1:1 ratio to either the bupropion group (n=50) or the escitalopram group (n=50). Six participants (3 in each group) discontinued the intervention owing to non-adherence or loss to follow-up. Consequently, the final per-protocol analysis included 94 patients (n=47 per group). The baseline demographic and clinical characteristics of the participants are summarized in Table1. No statistically significant differences were observed between the study groups regarding age, sex distribution, comorbid conditions, or baseline depression severity scores.

Depression Score Trends Over Eight Weeks

Both treatment groups demonstrated significant

improvements in HAM-D and BDI-II scores from baseline through to week 8. Within-group analyses revealed statistically significant reductions in depression severity across all measured time points ($p < 0.001$ for both cohorts). Between-group comparisons, utilizing repeated-measures ANOVA, indicated no statistically significant difference in either HAM-D or BDI-II scores at any assessment interval ($p > 0.05$). Whilst escitalopram demonstrated a marginal trend toward a more rapid reduction in scores at week 2 compared with bupropion, this observation did not reach statistical significance (Table 2).

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Bupropion)N=47)	Escitalopram)N=47)	Total (n=94)	P-Value
(SD) Age,mean	60.6 (6.9)	59.4(6.8)	60.0 (6.8)	0. 318
Male,n(%)	(76)38	39(78)	77 (77)	0.811
(%)n,Diabetes mellitus	22 (44)	20 (40)	42	0.684
(%)n ,Hypertension	(70)35	36(72)	71(71)	0.820
Ejection Fraction	48.2 (6.1)	49.0 (5.9)	48.6 (6.0)	0.412

Table 2. Depression Scores at Each Time Point

Timepoint	HAM-D(Bupropion)	HAM-D(Escitalopram)	BDI-II(Bupropion)	BDI-II(Escitalopram)
Baseline	15.8	16.3	18.9	18.7
Week2	13.2	12.9	15.6	15.2
Week4	10.7	10.1	13.2	12.8
Week8	8.1	7.8	10.7	10.1

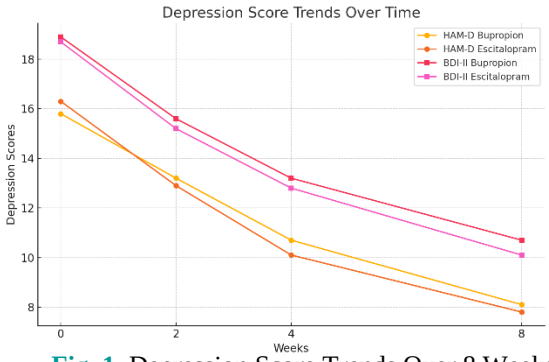

Fig. 1. Depression Score Trends Over 8 Weeks

Clinical Response and Remission

At week 8:

Clinical response (≥50% reduction in HAM-D):

Bupropion: 36/47 (76.6%)

Escitalopram: 38/47 (80.9%) (p = 0.612)

Remission (HAM-D ≤ 7):

Bupropion: 24/47 (51.1%)

Escitalopram: 26/47 (55.3%) (p = 0.684)

There were no statistically significant differences in response or remission rates between groups.

Adverse Effects

The most common adverse effects were mild and self-limiting.

In the escitalopram group, the most frequent side effects were:

Sexual dysfunction (29.7%)

Fatigue (21.3%)

Mild gastrointestinal discomfort (14.9%)

In the bupropion group:

Insomnia (25.5%)

Mild agitation (17.0%)
Weight loss (12.8%)
No serious adverse cardiac events were reported in either group during the 8-week trial.

Discussion

This randomised clinical trial demonstrated that both bupropion and escitalopram significantly reduced depressive symptoms in patients following coronary artery bypass graft (CABG) surgery. Both agents were well tolerated, with no statistically significant differences in efficacy or remission rates observed between the two groups at week 8. These findings align with existing evidence suggesting that the pharmacological treatment of post-CABG depression can lead to clinically meaningful improvements in psychiatric and, potentially, cardiac outcomes (10). Both agents are recognised in psychiatric literature for their limited cardiovascular side effects and favourable profiles regarding drug-drug interactions with standard cardiovascular therapies. Whilst other, newer antidepressants have been developed, their cardiovascular safety profiles remain less established, and they were not included in this study due to ethical considerations regarding the requirement for robust cardiac safety data.

Comparison with Prior Literature

Our results are consistent with large-scale trials such as SADHART and ENRICHD, which established that selective serotonin reuptake inhibitors (SSRIs), such as sertraline, are effective and safe in cardiac populations (11,12). Similarly, a meta-analysis by Baradaran *et al.* (2023) indicated that escitalopram may possess the most favorable cardiovascular safety profile among the SSRI class (13). Conversely, fewer studies have specifically investigated bupropion in patients with cardiac disease. Roose *et al.* (1991) reported that bupropion was not associated with adverse cardiac events and was well tolerated in patients with ischaemic heart disease (14). The present study expands upon these findings by directly comparing bupropion with an SSRI, demonstrating comparable efficacy and safety within a post-CABG cohort.

Mechanistic Insights

The pharmacological differences between these two agents offer distinct implications for clinical practice. Bupropion, a norepinephrine–dopamine reuptake inhibitor (NDRI), may be particularly beneficial for patients presenting with fatigue, anergia, or hypersomnia. Furthermore, its profile is advantageous for patients concerned about sexual side effects, which are more prevalent with SSRI therapy (15).

Additionally, emerging evidence suggests that bupropion may exert anti-inflammatory effects by modulating pro-inflammatory cytokines and oxidative stress, which may be particularly relevant in the post-surgical recovery phase (16). Conversely, escitalopram enhances serotonergic transmission and may modulate brain-derived neurotrophic factor (BDNF), thereby supporting neuroplasticity and emotional regulation (17).

Clinical Implications

Given that both agents demonstrated comparable efficacy, clinicians should tailor antidepressant selection to individual patient profiles. Bupropion may be preferable for patients experiencing lethargy or those concerned with sexual dysfunction or weight gain associated with SSRIs. Escitalopram may be more appropriate for patients with comorbid anxiety, given its well-documented anxiolytic properties (18). From a cardiovascular perspective, both agents appeared safe over the 8-week study period; notably, no serious arrhythmias or changes in ejection fraction were observed.

Strengths and Limitations

The strengths of this study include its double-blind design, the use of structured psychiatric assessments (SCID-5), and the comprehensive monitoring of adverse effects. However, there are limitations. The sample size, whilst adequate for initial efficacy comparisons, may be underpowered to detect rare cardiac adverse events. Furthermore, the follow-up duration was restricted to 8 weeks, meaning longer-term outcomes-such as depression relapse rates or cardiac-related rehospitalizations-were not assessed. Further large-scale, longitudinal studies are required before these findings can be definitively integrated into routine clinical practice.

Conclusion

In this randomized controlled trial of patients with major depressive disorder following coronary artery bypass graft (CABG) surgery, both bupropion and escitalopram significantly reduced depressive symptoms over an 8-week treatment period. No statistically

significant differences were observed between the two agents regarding clinical response rates, remission, or adverse effect profiles. These findings suggest that both medications are effective and well-tolerated therapeutic options, and that treatment selection should be guided by individual patient profiles, side-effect tolerability, and specific clinical contexts.

Given the high prevalence of depression in cardiac patients and its established association with adverse clinical outcomes, routine screening and timely pharmacological intervention should be integrated into standard postoperative cardiac care. Whilst this study provides robust initial data, the existing literature remains limited. Future research, utilizing larger, heterogeneous samples and extended follow-up periods, is required to definitively compare the relative efficacy of these agents and to evaluate the long-term impact of antidepressant therapy following CABG. Furthermore, assessing the impact of these treatments on long-term health-related quality of life and functional recovery will be essential to optimizing holistic care for this patient population.

Declaration

Availability of data and materials

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

Conflict of Interest

The authors declare that there are no conflicts of interest, financial or otherwise, relevant to the contents of this manuscript.

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Authors' contribution

All authors were participated in the concept and design, analysis and interpretation, data collection, writing the article, critical revision, final approval, statistical analysis, overall responsibility.

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Ethics approval and consent to participate

The study protocol was reviewed and received formal approval from the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1398.011) and was registered with the Iranian Registry of Clinical Trials (IRCT20190525043700N2). Written informed consent was obtained from all participants prior to enrolment. All procedures were conducted in strict accordance with the ethical standards set forth in the Declaration of Helsinki.

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