Randomised Controlled Trial

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The comparison of efficacy of Escitalopram and Bupropion in treatment of depression symptoms in patients with heart failure: randomized clinical trial

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Objective: This study aims to compare the effects of two medicines, Escitalopram and Bupropion, on HF patients who have depression symptoms.

Methods: This double-blind randomized clinical trial study was conducted on HF patients with depression symptoms at the Heart Failure Clinics affiliated with Babol University of Medical Sciences. In this study, 80 participants were examined for depression based on the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS). They were randomly allocated into two groups of 40 participants treated with Bupropion 75 mg and Escitalopram 5 mg. Following the intervention, the individuals were assessed in terms of their depression score at 4, 8, and 12-week intervals. Finally, the data were analyzed using SPSS version 22.0.

Results: In the examination of Beck and Hamilton scores in the two research groups during different follow-ups, a significant decrease was found over time ($P < 0.001$ for both medicines). While the effectiveness of the two medicines was the same at different times ($P > 0.05$ in all cases). Comparing the side effects between the two intervention groups, the orgasm disorder ($P = 0.018$) and sexual dysfunction ($P < 0.001$) were reported significantly more in the Escitalopram group than in the Bupropion group.

Conclusions: The findings of this study showed that Escitalopram has the same efficacy as Bupropion in the treatment of depression symptoms in HF patients.

Keywords: bupropion, depression, escitalopram, heart failure

Introduction

Heart failure (HF) is one of the most common cardiovascular disorders. It is a chronic, progressive, and debilitating syndrome resulting from abnormalities in the structural or functional cardiac disorder[1,2]. The symptoms of this disease generally include chest pain, weakness, fast and irregular heartbeat, etc.[3]. The prevalence of HF is increasing due to population aging, early diagnosis, and recent advances in the treatment of coronary artery diseases[4]. According to the latest statistics, HF affects more than 64 million people worldwide[5]. The incidence of HF in European countries and the United States varies widely from one to nine cases per 1000 people per year[6]. HF can be caused by a variety of factors, which are divided into four categories: (1) underlying factors such as structural abnormalities, (2) basic factors such as imbalance in physiological mechanisms, (3) aggravating factors such as drugs, and genetic causes[7]. An examination and history, as well as blood tests and imaging tests like echocardiography, are used to diagnose HF[8]. HF is treated using a combination of drugs such as Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics, after identifying the treatment method using a classification system [such as the New York Heart Association (NYHA) classification][9]. Shortness of breath, chest pain, and fatigue are common symptoms of HF. Due to similar symptoms to heart disease, such as fatigue, low energy, difficulty sleeping, and difficulty carrying on daily tasks, depression should also be considered[10].

HIGHLIGHTS

- Escitalopram and Bupropion have almost similar effects on the treatment of depression in HF patients with depression.
- There is no statistically significant difference in the recovery rate of Escitalopram and Bupropion in the short term.
- Bupropion has shown a better response than Escitalopram in terms of side effects, and sexual dysfunction and orgasm disorder are less common in Bupropion than Escitalopram.
- These findings can suggest a proper treatment to improve the mood and the quality of life of depressed patients with heart failure.

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Depression is a mental state of low mood and aversion to activity[11]. Depression is one of the most important and potent risk factors for experiencing suicide[12]. This condition is diagnosed by the diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR), of the American Psychiatric Association and has different classifications, including major depressive disorder (MDD)[13]. Depression has various treatments, including medication therapy such as selective serotonin reuptake inhibitors (SSRIs), electroconvulsive therapy (ECT), cognitive behavioral therapy (CBT), and interpersonal psychotherapy (IPT)[14]. According to the report of the Centers for Disease Control and Prevention (CDC) in 2019, 2.8% of adults aged 18 and over experienced severe symptoms of depression in the past 2 weeks. The percentage of adults who experienced any symptoms of depression was highest among those aged 18–29 (21.0%)[15]. Depression has been associated with the development and progression of many cardiovascular disorders, especially HF.

Depression occurs in one-fifth of HF patients, and it is more prevalent in females and whites than in males[16]. Depression symptoms are very common in heart failure patients, with prevalence estimates ranging from around 14% to over 50% across different studies[17–19]. The adverse effects of depression on the outcomes in HF include reduced quality of life, reduced healthcare use, rehospitalization, and increased mortality[20]. Depression appears to increase the risk of HF, and HF also appears to increase the risk of depression. These reciprocal connections suggest a complicated interaction between the two diseases[21]. Despite the difficulty in detecting depression in HF patients, it is essential to identify depression since it remains linked to dramatically augmented morbidity and death in patients with HF[22].

Patients with HF are at risk of depression and anxiety disorders due to the disease's chronicity. These patients need a large number of medicines to treat the underlying disorder (which causes drug interactions for psychiatric symptoms). As a result, we aimed to examine the effect of Escitalopram (a selective serotonin reuptake inhibitor) on depression and anxiety symptoms in HF patients compared to Bupropion. Few studies have been done on this subject.

Methods

Study design

The present study is a randomized double-blind clinical trial conducted on HF patients referred to the Heart Failure Clinics affiliated with Babol University of Medical Sciences and Rouhani Hospital during 2022–2023.

Inclusion and exclusion criteria

The inclusion criteria included patients with heart failure diagnosed by a cardiologist, over 18 years of age, and diagnosed with depression based on the Beck and Hamilton questionnaire approved by a psychiatric specialist. Exclusion criteria included patients with cognitive impairment, mental retardation, history of substance abuse, bipolar disorder, history of depression before HF, and history of seizures.

Research population

The sample size was calculated using G*Power software for repeated-measures ANOVA within-between interactions. Since no similar study was found to compare these two medicines, according to the expert's clinical opinion, the effect size was considered 0.20. Assuming an error of 0.05 and a power of 80% for evaluation four times at the beginning of the study (weeks 4, 8, and 12), the minimum required number of samples was 36 individuals. With a drop rate of 10%, a total of 80 samples participated in the study.

Data collection

In this study, 118 patients referred to Rouhani Hospital and Heart Failure Clinics were examined. Among these patients, 38 were excluded from the study based on the exclusion criteria, and 80 were randomized. The random permutation block method was used for randomization in this study. As a result, the number of blocks is equal to 4, and each block represents an equal number of treatments, with a ratio of 1:1 for each treatment. The random sequence was generated using Statistics and Sample Size Android software. The researcher referred patients to psychiatrists based on the block randomization list. Due to this, the researcher completing the questionnaires did not know what medications the patients received. In addition, the project psychiatrist was not aware of the questionnaire scores of the patients.

The 80 participants were divided into two groups of 40 samples (Fig. 1). The randomization was done using the permuted block technique. The comparative list of patient numbers and desired medicine types (abbreviated as A and B for each treatment group) was determined using a computer and provided to the researcher. Eligible patients were examined according to the inclusion and exclusion criteria. The participants with sufficient literacy completed the BDI. Also, BDI and HDRS were completed by the researcher for illiterate or illiterate patients in form of interview. It should be noted that due to our country's first language being Persian, we had to translate the questionnaire so that patients could fill it out. A full history of symptoms and personal and family history was taken from all the participants and a complete clinical examination was performed. A written informed consent was obtained from the participants after providing full information about the treatment procedures.

Data collection was done using a questionnaire consisting of two parts. Part one included the questions related to the personal and demographic information of the participants. Part two included the questions related to BDI and HDRS. Those who had a score higher than 7 based on HDRS and a score higher than 14 based on BDI were included in the study. Then, based on permuted block randomization, patients were divided into two groups of Bupropion (Wellban 75 mg, Abidi pharmaceutical group) prescribed as 1 daily pill and Escitalopram 5 mg (Abidi pharmaceutical group) prescribed as 1 daily pill. According to the clinical response and side effects, Bupropion can be increased to a maximum of 150 mg, and Escitalopram can be increased to a maximum of 20 mg in this study. The participants were followed up for 12 weeks. The depression severity, response, and remission were assessed before the intervention and in weeks 4, 8, and 12 by BDI and HDRS. The response phase was defined by reducing the HDRS score to a 50% decrease from the initial score, and the remission phase was defined by the response plus HDRS total score less than or equal to 7[23]. Additionally, the adverse effects assessed at the end of the follow-up of each patients.

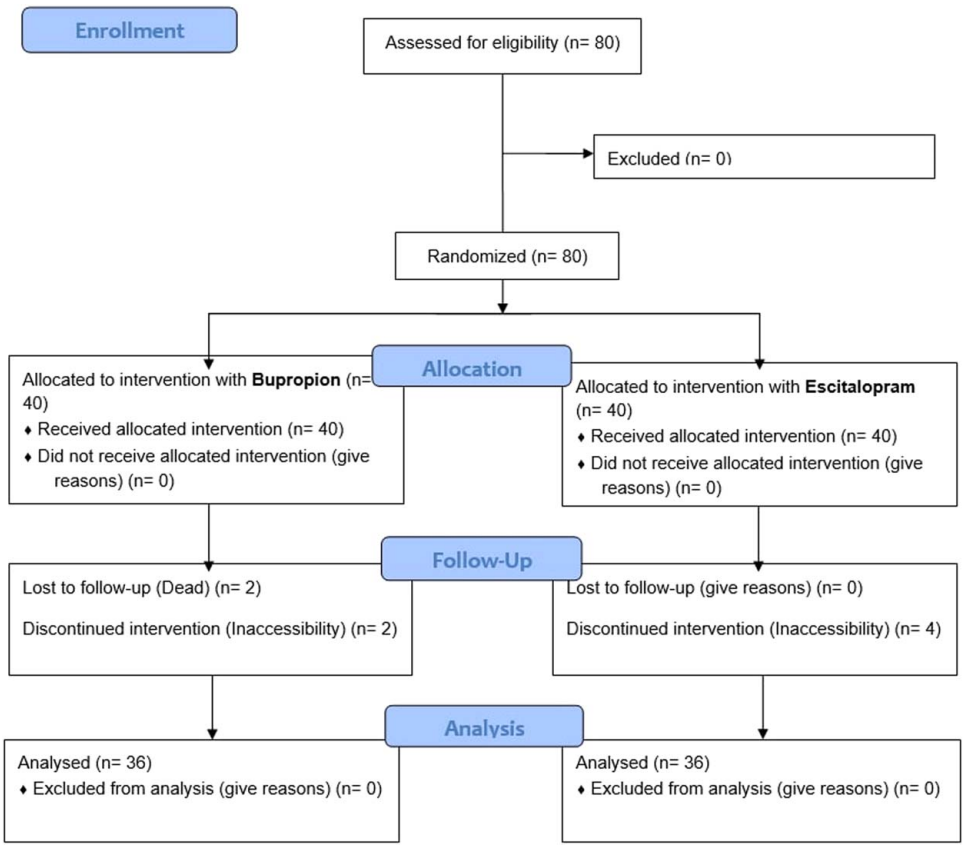

Figure 1. CONSORT flow chart.

Research tools

Hamilton depression rating scale (HDRS)

This tool was written in the late 1950s by Max Hamilton and was originally designed to evaluate the performance of the first group of antidepressants. Scoring is based on the 17-item scale and scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression, and scores over 24 are indicative of severe depression[24].

Beck's depression inventory (BDI)

It is a 21-item self-report inventory used to measure manifestations of depression, each item being scored from 0 to 3. The inventory evaluates key symptoms of depression including mood, pessimism, sense of failure, self-dissatisfaction, guilt, self-dislike, self-accusation, suicidal ideas, irritability, social withdrawal, indecisiveness, insomnia, fatigability, loss of appetite, weight loss, etc. The 21 symptoms and attitudes contained in the BDI create a score that ranges from 0 to 63. By adding the individual's scores in each item, the individual's final score was obtained directly. Scores from 0 through 9 indicate no or minimal depression; scores from 10 through 18 indicate mild to moderate depression; scores from 19 through 29 indicate moderate depression; and scores from 30 through 63 indicate severe depression[25].

Several studies in Iran have proven the validity and reliability of these two questionnaires. According to Daramadi *et al.*[26]'s study, Beck's depression questionnaire has a reliability and validity of 0.85 and 0.76, respectively. Furthermore, Hamilton Depression Rating scale's reliability and validity were reported to be 0.85 and 0.89 in the study conducted by Gharaei *et al.*[27].

Primary outcome

First, the depression score was evaluated using the Beck Depression Inventory and Hamilton Depression Rating Scale (HDRS) at the beginning of the study. Then, the response rate and the remission rate were measured in weeks 4, 8, and 12.

Secondary outcome

The side effects of the medicines were asked from the patients in weeks 4, 8, and 12 using the Side Effects Checklist made by the researcher.

Data analysis

The collected data were analyzed using SPSS 22 software. Descriptive statistics were presented using mean and standard deviation (for quantitative variables) and using frequency and percentage (for qualitative variables). The χ^2 test was used to examine and compare qualitative variables. Also, the independent *t*-test and/or Mann–Whitney U test were used to examine the quantitative and qualitative variables, considering the normality of the data. One-way ANOVA was used to evaluate the effect of a

Table 1

Investigating the basic qualitative characteristics of the two research groups.

Variables	Bupropion frequency (percentage) N = 40, *N* (%)	Escitalopram frequency (percentage) *N* = 40, *N* (%)	*P*
Sex			
Male	16 (40.0)	15 (37.5)	0.818
Female	24 (60.0)	25 (62.5)	
Education			
illiterate	19 (47.5)	16 (40.0)	0.777
High school	18 (45.0)	20 (50.0)	
College education	3 (7.5)	4 (10.0)	
Marital status			
Single	8 (20.0)	12 (30.0)	0.302
Married	32 (80.0)	28 (70.0)	
Job status			
Unemployed	36 (90.0)	38 (95.0)	0.396
Employed	4 (10.0)	2 (5.0)	
MI history			
No	22 (55.0)	22 (55.0)	1.000
Yes	18 (45.0)	18 (45.0)	
NYHA class			
I	13 (32.5)	11 (27.5)	0.718
II	14 (35.0)	19 (47.5)	
III	10 (25.0)	8 (20.0)	
IV	3 (7.5)	2 (5.0)	
Underlying diseases			
No	21 (52.5)	11 (27.5)	0.022
Yes	19 (47.5)	29 (72.5)	

MI, Myocardial infarction; NYHA, New York Heart Association.

quantitative variable in more than two dependent situations. Sidak's post hoc test was applied for pairwise comparison. Repeated measures and linear regression tests were used to examine the required relationships. In this study, there were 8 missing data; so, we used the intention-to-treat (ITT) approach for statistical analysis. It means that even the missed participants were examined to the end of the research and the algorithm EM was used for multiple imputation participants. A significant level was considered ($P < 0.05$) for all analyses.

Results

Among the 80 patients included in the study, 49 cases were female (61.2%) and 31 were male (38.8%). The average age of the study participants was 62.19 years (range 17–93 years). The average age of the participants was 62.75 years in the Bupropion group and 61.63 years in the Escitalopram group ($P = 0.769$). In total, the two groups were compatible in terms of the distribution of epidemiological and the etiology of heart failure factors ($P < 0.05$). The only significant difference was in terms of an underlying disease, which was higher in the Escitalopram group than the Bupropion group ($P = 0.022$) (Table 1). Additionally, the average ejection fraction in the Escitalopram group was 27.50 = 9.74 and in the Bupropion group was 24.88 = 10.77, which did not differ statistically between the two groups ($P = 0.256$).

In the examination of the BDI and HDRS, the scores gradually decreased during the follow-up in both groups. In the end, a significant decrease was observed in the score of the BDI and HDRS at the end of the 12th week compared to the baseline score ($P < 0.001$ in both groups). Also, the two groups were compared based on different specified time intervals, in which there was no significant difference between the two groups ($P > 0.05$ at all times). The effectiveness of these two medicines has been the same based on questionnaires at different times (Table 2).

In the study between the treatment group that were or were not in the response phase, 20 patients (54.1%) from the Bupropion group and 24 patients (64.9%) from the Escitalopram group compared to 17 patients (45.9%) from the Bupropion group and 13 patients (35.1%) of the Escitalopram group had entered the response phase ($P = 0.344$). Also, in the study between the treatment group that were or were not in the remission phase, 8 patients (21.6%) from the Bupropion group and 20 patients (54.1%) from the Escitalopram group compared to 29 patients (78.4%) from the Bupropion group, and 17 patients (45.9%) from Escitalopram group had entered the remission phase ($P = 0.004$).

Comparing the side effects of medicines between the two groups, it was found that there was a significant difference in orgasm disorder ($P = 0.018$) and sexual dysfunction ($P < 0.001$), and Bupropion had fewer side effects than Escitalopram in this term. The two research groups had no other significant difference in terms of other side effects ($P < 0.05$) (Table 3).

Table 2

Comparison of the change in average scores to the BDI and HDRS over time.

Variables	Bupropion mean ± SD *N* = 40	Escitalopram mean ± SD *N* = 40	MD (95% CI)	*P*
BDI				
Before intervention	19.40 ± 4.44	19.23 ± 3.67	0.17 (–1.64 to 1.99)	0.848
After 4 weeks	16.05 ± 4.52	16.16 ± 3.76	–0.10 (–1.99 to 1.77)	0.909
After 8 weeks	13.24 ± 4.38	13.54 ± 3.66	–0.29 (–2.17 to 1.57)	0.753
After 12 weeks	10.86 ± 4.54	9.92 ± 4.20	0.94 (–1.09 to 2.99)	0.358
P value*	< 0.001	< 0.001	—	
HDRS				
Before intervention	13.95 ± 5.03	13.65 ± 3.19	0.30 (–1.57 to 2.17)	0.751
After 4 weeks	11.03 ± 4.09	10.76 ± 3.47	0.26 (–1.45 to 1.97)	0.762
After 8 weeks	8.78 ± 3.67	8.46 ± 3.11	0.32 (–1.25 to 1.90)	0.683
After 12 weeks	7.51 ± 3.99	6.86 ± 2.98	0.65 (–0.99 to 2.30)	0.443
P value*	< 0.001	< 0.001	—	

BDI, Beck's Depression Inventory; HDRS, Hamilton Depression Rating scale; MD, mean difference.
*Post hoc tests (Sidak tests) for double comparisons showed a *P* value < 0.05 in all cases and comparisons.

Table 3

Comparison of the side effects of bupropion vs. escitalopram

Variables	Bupropion frequency (percentage) $N=40$, N (%)	Escitalopram frequency (percentage) $N=38$, N (%)	P
Sleep disorders			
No	34 (85.0)	30 (78.95)	0.486
Yes	6 (15.0)	8 (21.05)	
Other sexual disorders			
No	37 (92.5)	21 (55.26)	<0.001
Yes	3 (7.5)	17 (44.74)	
Ejaculation disorder			
No	36 (90.0)	26 (68.42)	0.018
Yes	4 (10.0)	12 (31.58)	
Weight gain			
No	37 (92.5)	34 (89.47)	0.640
Yes	3 (7.5)	4 (10.53)	
Weight loss			
No	39 (97.5)	34 (89.47)	0.195
Yes	1 (2.5)	4 (10.53)	
Nausea			
No	30 (75.0)	32 (84.21)	0.314
Yes	10 (25.0)	6 (15.79)	
Diarrhea			
No	37 (92.5)	31 (81.58)	0.149
Yes	3 (7.5)	7 (18.42)	
Constipation			
No	36 (90.0)	37 (97.37)	0.184
Yes	4 (10.0)	1 (2.63)	
Headache			
No	37 (92.5)	37 (97.37)	0.330
Yes	3 (7.5)	1 (2.63)	
Shaking			
No	38 (95.0)	36 (94.74)	0.958
Yes	2 (5.0)	2 (5.26)	
Sweating			
No	38 (95.0)	34 (89.47)	0.360
Yes	2 (5.0)	4 (10.53)	
Dry mouth			
No	33 (82.5)	32 (84.21)	0.839
Yes	7 (17.5)	6 (15.79)	
Insomnia			
No	34 (85.0)	31 (81.58)	0.685
Yes	6 (15)	7 (18.42)	
Heart beat			
No	38 (95.0)	36 (94.74)	0.958
Yes	2 (5.0)	2 (5.26)	

Comparing the effectiveness of Escitalopram and Bupropion in the treatment of depression in HF patients using NYHA Class I–IV based on HDRS results, the effectiveness of each of these two medicines increased significantly over time from class I to IV ($P<0.001$ in all cases). However, the effectiveness of the two medicines compared to each other was almost similar (respectively, for class I: $P=0.130$, class II: $P=0.352$, class III: $P=0.659$ and class IV: $P=0.886$) (Fig. 2).

Comparing the effectiveness of Escitalopram and Bupropion in the treatment of depression in HF patients using NYHA Class I-IV based on BDI results, the effectiveness of each of these two medicines increased significantly over time from class I to IV ($P<0.001$ in all cases). However, there was no statistical difference between them (respectively, for class I: $P=0.105$, class II: $P=0.163$, class III: $P=0.767$, and class IV: $P=0.790$) (Fig. 3).

Discussion

This study aimed to compare the effectiveness of Escitalopram and Bupropion in the treatment of depression in HF patients. In this study, 80 eligible patients were enrolled, of which 40 were in the Escitalopram group and 40 were in the Bupropion group. During the study, two patients died in the Bupropion group, and a total of 8 patients could not continue to participate in the study.

In this study, the efficacy of Escitalopram and Bupropion was examined along with other variables such as sex, underlying disease, NYHA classification, etc. The results of the present study showed that sex, education level, marital status, occupational status, ischemic etiology, and NYHA class were not different in the two treatment groups with Escitalopram and Bupropion, and the only significant difference was in terms of an underlying disease, which was higher in Escitalopram group than Bupropion group. Therefore, the assimilation of the groups was done as much as possible. Based on the results of the statistical analysis, during the 12-week follow-up based on BDI and HDRS, the depression symptoms of both treatment groups decreased, and both groups experienced improvement, but this relationship was not significant. In other words, both medicines have had the same effectiveness on patients. The other variables examined between these two groups were the rate of response and remission, which unlike the response phase, we have seen a significant difference between the frequency of the two treatment groups and the Escitalopram had better results in the remission phase.

Escitalopram and bupropion are used to treat depression with different mechanisms of action[28,29]. Escitalopram's mechanism of action is selective serotonin re-uptake inhibitor, while bupropion acts as a norepinephrine/dopamine reuptake inhibitor[30,31]. Nonetheless, there have been few studies investigating this therapeutic effect in patients with heart disease, especially in patients with heart failure. Angermann *et al.*[32] found that treatment with Escitalopram for 18 months did not significantly reduce mortality or hospitalization in patients with chronic heart failure with reduced ejection fraction and depression compared to placebo, and there was no significant improvement in depression symptoms observed. These findings do not confirm the use of Escitalopram in patients with chronic systolic heart failure and depression. These contrary results could be due to the difference in the amount of treatment with Escitalopram and the use of the negative control group. In addition, Angermann *et al.*[32] found that treatment with Escitalopram improved depression remission after 6–12 months compared to no treatment. Escitalopram-treated patients in our study had a shorter follow-up period but were mostly in remission. As a result of a systematic review by Hedric and colleagues, selective serotonin reuptake inhibitors such as Escitalopram seem to be a safe option for treating depression and HF patients. They noted, however, the necessity of conducting more RCT studies on these patients due to unique study designs and mixed results for various antidepressants[33].

The study of Fraguas *et al.*[34] in Brazil examined 72 patients with major depression who also had EF less than 50% and their results were inconsistent with the present study. In their study, 37 patients were randomly selected and 19 patients were treated with Escitalopram and 18 patients were treated with a placebo. They started an 8-week double-blind treatment phase. Escitalopram treatment in elderly patients with HF was well tolerated and it is associated with a low rate of side effects, but it was not significantly more effective than placebo

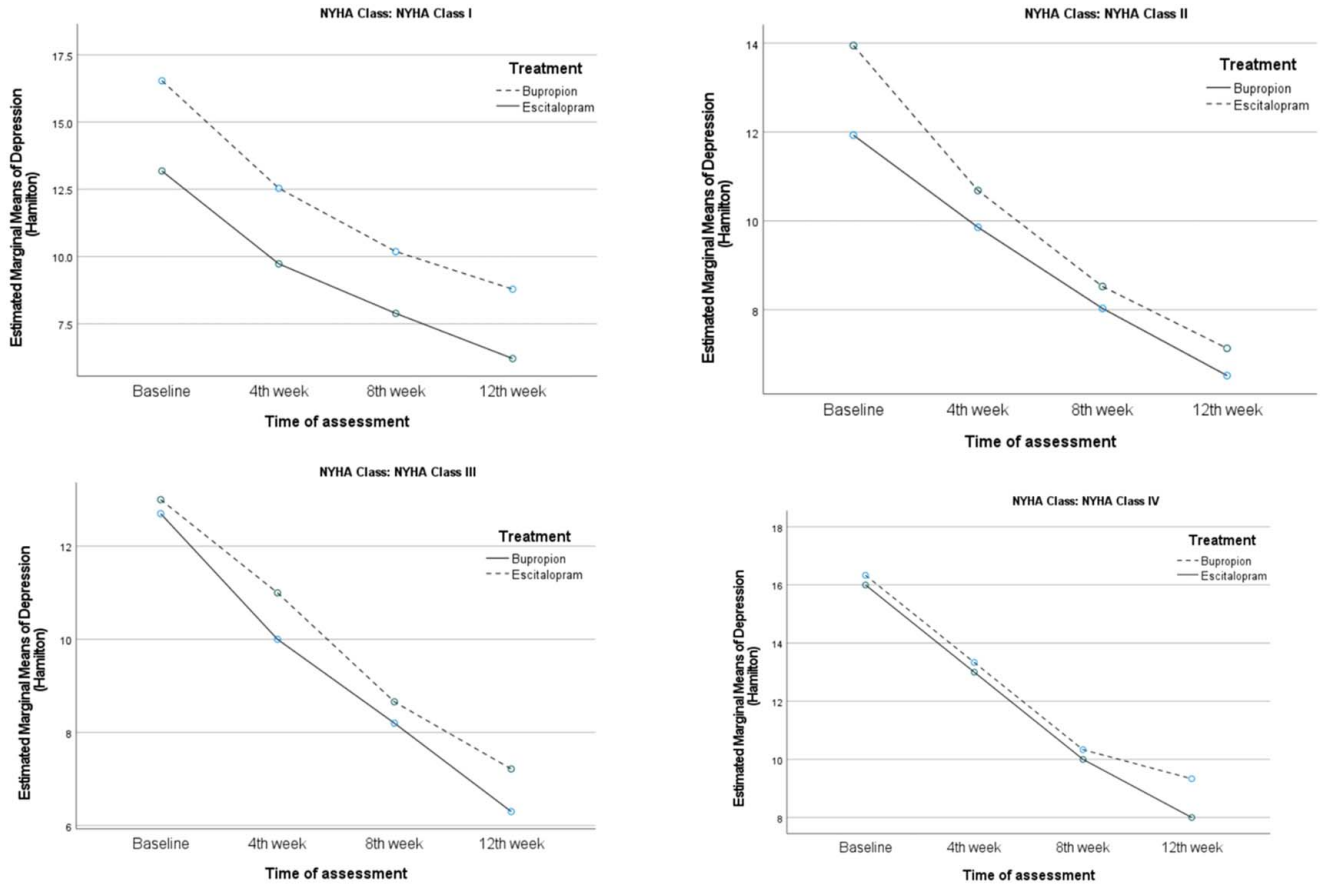

Figure 2. Comparing the effectiveness of Escitalopram and Bupropion in the treatment of depression in HF patients using NYHA Class I–IV based on HDRS results. HDRS, Hamilton Depression Rating Scale; NYHA, New York Heart Association.

in the treatment of depression. This could be due to the small number of samples and the shorter follow-up period in the Fraguas and colleagues study. In a study similar to our study, Fortner in the United States investigated the effect of Bupropion-SR for 8 weeks on 18 elderly people with major depression (based on DSM-IV criteria) and one or more important comorbidities (e.g. heart failure, type 1 diabetes, irritable bowel syndrome) with 12 weeks follow-up. The results showed that Bupropion-SR is well tolerated and may improve depression, insomnia, physical symptoms, work performance, and some measures related to quality of life in depressed elderly with medical disorders[35]. In the study of Shen *et al.*[36], they examined the effectiveness of Bupropion XL versus Escitalopram oxalate in Chinese patients with major depressive disorder. The results of their study showed that the effectiveness of Bupropion XL in Chinese patients with Major depressive disorder (MDD) was not lower than Escitalopram oxalate. They also found that Escitalopram oxalate had more remission than Bupropion XL, and the response was not significantly different between the two groups. Furthermore, they examined the effect of long-term remission between the two groups, which did not differ much from each other. However, remission was higher in Escitalopram oxalate group than Bupropion XL. The results of Shen *et al.*'s study was similar to the present study. A study conducted by Clayton *et al.*[37] in the United States found no statistically significant difference between treatment with bupropion and citalopram during 8-week follow-up. Similarly to this study, our findings indicate that even though bupropion and citalopram affect patients with different mechanisms, their effectiveness is not significantly different for treating depression symptoms in HF patients. There have also been studies in which the Escitalopram and Bupropion were prescribed simultaneously in patients with MDD. Their results showed that the combination of Escitalopram and Bupropion-SR is effective and well tolerated, and they have a reducing effect on depression symptoms[38], which is consistent with the results of the present study.

In terms of side effects, our results showed that there was a statistically significant difference between Escitalopram and Bupropion, especially in sexual dysfunction and orgasm disorders. Interestingly, the prevalence of these side effects was significantly higher in the Escitalopram group compared to the Bupropion group. This difference in the incidence of sexual dysfunction and orgasm disorders between the two medicine groups emphasizes the significant difference in their effect on sexual health. A study by Clayton *et al.*[37] examining side effects related to Escitalopram has provided compelling evidence regarding the sexual tolerance profile of Bupropion and Escitalopram in subjects with MDD. They showed that

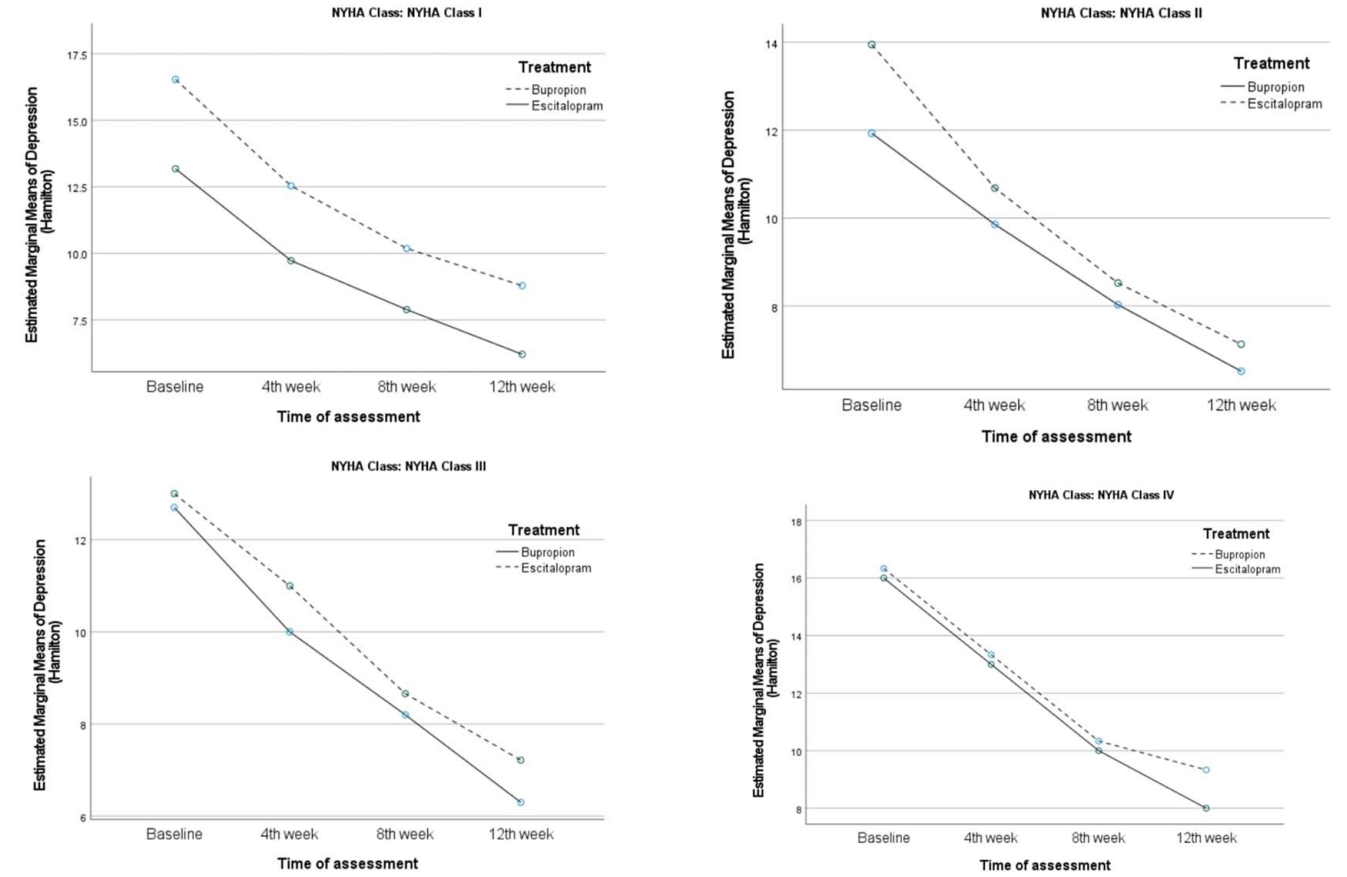

Figure 3. Comparing the effectiveness of Escitalopram and Bupropion in the treatment of depression in HF patients using NYHA Class I–IV based on BDI results. BDI, Beck Depression Inventory; NYHA, New York Heart Association.

Bupropion has a significantly superior sexual tolerance profile compared to Escitalopram in this particular group of patients. Sidra and colleagues in 2023 studied 744 patients with depression and found that the most prominent side effect of citalopram was delayed ejaculation[29]. Similarly, the citalopram group was significantly more likely to suffer from ejaculation disorders than the bupropion group based on our study.

According to a meta-analysis by Reichenpfader *et al.*[39], most second-generation antidepressants are associated with a similar risk of sexual dysfunction. Bupropion had the lowest rate of sexual dysfunction compared to other second-generation antidepressants, while escitalopram and paroxetine had the highest rate of sexual dysfunction as compared to other second-generation antidepressants[40]. According to a review including multiple trials, bupropion does not cause sexual side effects. SSRI-induced sexual side effects can be reversed by bupropion, according to the same review, mostly based on open-label studies[41]. A limited amount of information is available regarding the effects of antidepressants on males and females. Furthermore, there is a lack of data regarding the effects of antidepressants at different phases of the sexual cycle[42].

The results of a systematic review by Pereira *et al.*[43] suggest that Bupropion could potentially serve as an alternative treatment for people struggling with depression, and can offer a unique advantage by bypassing the annoying sexual side effects commonly associated with most antidepressants. Macdonald *et al.*[44] in a recent review of all available evidence on the effectiveness of Bupropion on depressive disorders showed that there is direct and indirect evidence suggesting that the risk of sexual dysfunction may be lower with Bupropion than with other antidepressants (citalopram, paroxetine, sertraline, and fluoxetine). According to the studies reviewed, the higher incidence of these side effects in the Escitalopram group may prompt further research into the mechanisms by which Escitalopram affects sexual performance and whether there are potential mitigating measures to reduce these adverse effects. These findings have outcomes for both clinical practice and patient education because understanding the different side effect profiles of these medicines can be helpful in the treatment decisions and inform patients about potential challenges they may face during treatment.

Strengths and limitation

This study also had some limitations such as the small sample size and single-center study, which may limit the generalization of the findings. A larger and more diverse research population as well as a multi-center study could provide stronger results in terms of the relative effectiveness of Bupropion and Escitalopram in the treatment of depression in HF patients. As discussed in the method section, different doses of Escitalopram and Bupropion

were prescribed based on the severity of the disease and the response of the patients to treatment, but due to the small sample size, it was not possible to conduct a proper analysis to determine the relationship between these drugs at different doses. Therefore, we recommend future studies investigate the effects of these drugs in heart failure patients who are depressed at different doses. Also, a twelve-week follow-up period may not show the long-term effects and durability of the treatment results. Long-term follow-up is valuable to assess sustained efficacy and potential relapse rates for both medicines. In the absence of a placebo control group, it is difficult to determine whether the observed improvements in depression symptoms are due solely to the effects of the medication or could be influenced by placebo effects.

Conclusions

Based on the findings of the present study, Escitalopram and Bupropion have almost similar effects on the treatment of depression in HF patients with depression. Also, there is no statistically significant difference in the recovery rate of Escitalopram and Bupropion in the short term. Bupropion has shown a better response than Escitalopram in terms of side effects, and sexual dysfunction and orgasm disorder are less common in Bupropion than Escitalopram. These findings can suggest a proper treatment to improve the mood and the quality of life of depressed patients with heart failure.

Ethics approval

This study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. This research plan has been approved by the ethics committee of Babol University of Medical Sciences with the code (MUBABOL.REC.1401.085). It was also registered in the Iranian Registry of Clinical Trials with code IRCT20190525043700N5.

Consent

Written informed consent was obtained from all patients.

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Author contribution

All authors of this paper have directly participated in the planning, execution, or analysis of this study. R.M., A.H., and A.R.: concepting the work and study design; N.Z., R.M.: data acquisition and literature searching; S.A., H.S.: drafting the manuscript; H.H. and N.T.: reviewing and editing for intellectual content; All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

For register of research needs to pay charge. we are in international sanction so unable pay or transfer register fee.

Guarantor

Naghmeh Ziaie.

Data availability statement

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

Provenance and peer review

Not commissioned, externally peer-reviewed.

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