Original Article

Comparison of the efficacy of venlafaxine and bupropion in the treatment of depressive episode in patients with bipolar II disorder

Ahmad Fakhri[1], Khatereh Asadi[2], Sirous Pakseresht[2], Shahin Norouzi[2], Hamzeh Rostami[2]

[1]Department of Psychiatry, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, [2]Department of Psychiatry, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Objective: Depressive disorders are common among those with bipolar disorder II (BD II) and may necessitate the use of antidepressants. Because of the lack of quality evidence, there is controversy about the use of antidepressants in BD II. The aim was to compare the efficacy of venlafaxine and bupropion in the treatment of depressive episode in BD II. **Materials and Methods:** This randomized triple-blind clinical trial study was conducted on patient with depressive episode of BD II (based on *diagnostic and statistical manual of disorders* [*DSM-V*] criteria) referred to the specialized clinic of Golestan Hospital. A total of 40 patients were randomly divided into two groups of receiving venlafaxine (75 mg/day) or bupropion (100 mg/day) for 4 weeks. At the end of the intervention, the effectiveness of treatment was assessed using the Hamilton Depression Rating Scale (HDRS). **Results:** The results of this study showed that the HDRS score before treatment (P = 0.43) and after treatment (P = 0.15) was not significantly different between the two groups. HDRS score in both groups significantly decreased after 4 weeks (P < 0.0001). Although the rate of decrease in depression score was more in venlafaxine than in bupropion, these differences were not significant (% 36.7 ± 21.8 vs. % 45.3 ± 17.9, P value = 0.17). **Conclusion:** Our study showed that short-term (4-weeks) treatments of venlafaxine and bupropion were equally effective and could be a safe and effective antidepressant monotherapy for BD II major depression. It is suggested that more studies be conducted with larger sample size and over longer periods of time in a multicenter manner.

Keywords: Bipolar II disorder, Bupropion, depressive episode, venlafaxine

Introduction

Bipolar disorder (BP) is determined by recurrent periods of highs and lows of mood, thinking, activity, of varying severity, duration, and frequency, including combinations of manic or hypomanic and depressive symptoms in the same episode.[1]

Address for correspondence: Dr.Hamzeh Rostami, Department of Psychiatry, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
E-mail: rostami-hamzeh@ajums.ac.ir

Received: 14-04-2022 **Revised:** 24-07-2022
Accepted: 27-08-2022 **Published:** 17-03-2023

Access this article online
Quick Response Code:
Website: www.jfmpc.com
DOI: 10.4103/jfmpc.jfmpc_1258_22

Bipolar I and II represent the most prevalent and severe subtypes of BD.[2] The diagnosis of bipolar I requires the presence of at least one manic episode, with or without a history of major depressive episodes, whereas bipolar II disorder (BD II) requires at least one hypomanic and one major depressive episode.[3]

Even though polarity – the presence or absence of manic/hypomanic episodes – is the defining feature in our classification of primary mood disorders, distinguishing unipolar from BD depression is the dominant pole. Overall, including both bipolar I and II patients, bipolar individuals spend three times as many

How to cite this article: Fakhri A, Asadi K, Pakseresht S, Norouzi S, Rostami H. Comparison of the efficacy of venlafaxine and bupropion in the treatment of depressive episode in patients with bipolar II disorder. J Family Med Prim Care 2023;12:440-5.

weeks depressed as they do manic/hypomanic.[4,5] Depression is related to an increased risk of suicide and disruptive psychosocial function.[6]

The use of antidepressants (ADs) in the treatment of BD is a subject of remarkable controversy. Information on the efficacy and safety of ADs in both acute and long-term treatment of BD is generally changeable.[7-9] The data on effectiveness of ADs in BD II are limited and conflicting.[8,10] Few studies have compared BD I versus BD II patients with respect to clinical correlates of antidepressant use.[11,12] Comprehension of demographic and illness characteristics in BD II patients, could improve our understanding of how and when ADs are used for treatment of BD in clinical practice.

A prior meta-analysis exploring the advantages and risk of long-term ADs treatment for BD patients indicated that long-term adjunctive ADs treatment had little protection for depression relapse while obviously increased risk of affective switch.[13]

To our knowledge, no study has been conducted on the treatment of depressive BD II in Iran; the aim of this study was to compare the efficacy of venlafaxine and bupropion in the treatment of patients with depressive episode of BD II.

Methods and Materials

Study design and participants

The present study is a triple-blind randomized controlled clinical trial comparison of bupropion monotherapy versus venlafaxine monotherapy for BD II depression. Forty patients with BD II who were referring to Golestan Hospital affiliated with Ahvaz Jundishapur University of Medical Sciences in 2020 were included in this study. Patients aged more than 18 years old with BD II based on the *DSM-V* diagnosed by a psychiatrist were enrolled in the study if they fulfill the following inclusion criteria: 1) Diagnosis of depressive episode of BD II based on *DSM-V* criteria and confirmation of the patient's hypomania course or courses based on Mood Disorder Questionnaire (MDQ) and 2) the patient has not used any other antidepressant 4 weeks before the start of the study.

Depression caused by a physical illness, substance abuse or medication, existence of any severe and chronic physical diseases, history of gastric ulcer, mental retardation, psychosis, periodic history of mania, consumption of alcohol and drugs during the last 6 months, incidence of intolerable side effects of the drug, psychotic depression, and active suicidal thoughts were the exclusion criteria.

The eligible subjects were randomly assigned to either bupropion ($N = 20$) or venlafaxine ($N = 20$) for 4 weeks using a four-block randomization method. One group was treated with bupropion 100 mg/day and the other group was treated with venlafaxine 75 mg/day. Treatment was started with one pill a day and could be increased up to three times this dose, based on the patient's response and tolerance. In both groups, drugs were similar in terms of shape, color, and size. All patients were followed up by the same psychiatrist at predetermined times: before the treatment initiation, subsequently 4 weeks after treatment initiation.

Measurements and outcomes

In current study, diagnosis of hypomania was assessed based on the MDQ. To assess the severity of depressive disorder, the Hamilton Depression Rating Scale (HDRS) was used. Patients in both groups completed HDRS questionnaire before and after the intervention (at the beginning of the intervention and 4 weeks after starting treatment). Then, the two groups were compared in terms of the severity of depressive disorder. The primary outcomes were change over time in HDRS scores and suicidal thoughts. In current study, all members of the research team, patients, and statistical analyzers were blind of the designed treatment groups.

Ethical considerations

The study was approved by the Medical Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.1398.831), and this trial was registered in the Iranian clinical trial system with the patented number of IRCT20200913048698N1. In this study, the written informed consent was obtained from each patient.

Statistical analysis

Data were analyzed using SPSS software version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation for quantity values and frequency (percentage) for qualitative values. Kolmogorov–Smirnov test was applied to test for the data normality. Differences were compared by using the paired sample *t*-test. Homogeneity of variance was assessed by the Leven test. Pearson's and Chi-square tests were used to investigate the correlation between quantitative and qualitative variables. *P* value less than 0.05 was considered significant.

Results

The current clinical trial study included 20 patients in each group. According to demographic information, the mean age estimate was 34.45 ± 6.95 and 31.05 ± 7.69 in venlafaxine and bupropion groups, respectively. This difference was not statistically significant (*P* value = 0.15). Also, the sex distribution between the two groups was homogenous (*P* value = 1.00).

MDQ was evaluated between two groups and it was found the symptoms of mania/hypomania are not statistically significant (*P* value = 0.326). The mean of section 1 in the MDQ was estimated at 7.35 ± 1.56 and 6.95 ± 0.88 in venlafaxine and bupropion groups, respectively. Besides no difference was seen in Section 2 and 3 of MDQ.

To assess the effectiveness of the intervention, HDRS was compared and it was not found any differences before (*P* value = 0.43) and after the treatment (*P* value = 0.15). In addition, the rate of change in HDRS score was not significantly different between the two treatment groups. HDRS score in both groups significantly decreased after 4 weeks ($P < 0.0001$). Although the rate of decrease in depression score was more in venlafaxine than in bupropion, these differences were not significant (36.7 ± 21.8% vs. 45.3 ± 17.9%, *P* value = 0.17). To evaluate the intervention, the creation of suicidal thoughts was estimated between and within groups. The two groups were homogenous before the intervention (2.00 ± 0.79 vs. 2.10 ± 0.78, *P* value = 0.69), also after the treatment, it was decreased, although the differences were not meaningful between them (1.65 ± 1.33 vs. 1.00 ± 0.97, *P* value = 0.06) [Table 1].

Within comparison has shown significance only in the bupropion group (*P* value < 0.001), whereas the *P* value was estimated 0.26 within the venlafaxine group [Table 2].

Gender and age as the baseline covariates were investigated for treatment response. The results of HDRS changes showed venlafaxine had similar efficacy in men and women (*P* = 0.823). Bupropion was more effective in women than men; therefore, HDRS score showed a greater decrease in women than men after 4 weeks (*P* value = 0.007). No relationship was found between treatment response and age of patients (Pearson's correlation = 0.43, *P* value = 0.056).

Discussion

The aim of this study was to evaluate the efficacy of venlafaxine compared with bupropion in the treatment of patients with depressive episode II. In the current study, the two groups were matched in terms of age and sex, and also in terms of the severity of mood disorders before treatment were not significantly different from each other, which indicates that these factors do not affect the results, the samples are completely random.

The results of the present study showed that HDRS decreased significantly after 4 weeks of treatment in each group. On average, after 4 weeks of treatment, the depression score in the venlafaxine and bupropion groups decreased by 36.7% and 45.3%, respectively. But the change in HDRS between the two treatment groups did not show a significant difference. Furthermore, the score of suicidal thoughts before and after treatment was not considerably different between the two groups. These findings indicate similar efficacy of ADs both venlafaxine and bupropion in the treatment of depressive episode of BD II.

Well-designed controlled trials with AD monotherapy for episodes of BD are very limited and have shown conflicting results.[14-16] Several meta-analysis studies have reported the potential efficacy of various ADs in bipolar depression,[17,18] While another study showed the ineffectiveness of ADs in bipolar patients.[19] Despite limited and contradictory studies, there is

Table 1: Baseline and clinical characteristics of patients in two groups

Variables	Venlafaxine (*n*=20)	Bupropion (*n*=20)	*P*
Age	34.45±6.95	31.05±7.69	0.15[†]
Sex (Male: Female)	10: 10 (50%: 50%)	10: 10 (50%: 50%)	1.00[ϫ]
MDQ - section 1	7.35±1.56	6.95±0.88	0.32[†]
MDQ - section 2	20 (100%)	20 (100%)	1.00[ϫ]
MDQ - section 3			
No problem	0 (0%)	0 (0%)	0.57[ϫ]
Slight problem	12 (60%)	12 (60%)	
Medium problem	6 (30%)	4 (20%)	
Serious problem	2 (10%)	4 (20%)	
HDRS score - before intervention	30.95±3.62	29.95±4.27	0.43[†]
HDRS score - after intervention	19.70±7.39	16.50±6.35	0.15[†]
Suicidal thoughts - before intervention	2.00±0.79	2.10±0.78	0.69[†]
Suicidal thoughts - after intervention	1.65±1.33	1.00±0.97	0.06[†]

MDQ=Mood Disorder Questionnaire, HDRS=Hamilton Depression Rating Scale. [†]Independent sample *t*-test. [ϫ]Chi-square test

Table 2: Baseline and clinical characteristics of patients before and after intervention

Variables	Venlafaxine			Bupropion		
	P, χ	After	Before	*P*, χ	After	Before
HDRS Score	30.95±3.62	19.70±7.39	<0.001	29.95±4.27	16.50±6.35	<0.001
Suicidal thoughts	2.00±0.79	1.65±1.33	0.26	2.10±0.78	1.00±0.97	<0.001
Sex Evaluation						
Female	30.80±4.26	19.20±8.37	<0.001	29.40±4.62	12.60±1.64	<0.001
Male	31.10±3.07	20.20±6.69	<0.001	30.50±4.06	20.40±6.97	<0.001
P[§]	0.85	0.77	-	0.57	0.006	-

HDRS=Hamilton Depression Rating Scale. [§]Paired sample *t*-test for sex comparison in each group, before and after separately. χ Paired sample *t*-test for before and after comparison, in each group separately

clear evidence that these drugs are appropriate for some BD patients, and in particular their safety for BD-II depression.[16,20]

Venlafaxine is a class of serotonin-norepinephrine reuptake inhibitors and works by inhibiting the reuptake of serotonin, norepinephrine, and dopamine in the brain. Inhibition of reabsorption of these neurotransmitters increases their access and overall effect.[21]

Amsterdam *et al*.[22] reported that treatment with venlafaxine for 12 weeks significantly reduced HDRS depression score in patients with major depressive episode in BD II and had no serious side effects. In another randomized clinical trial by Amsterdam *et al*.,[23] it was observed that taking venlafaxine monotherapy for 12 weeks significantly improved patients with BD II depressive episode. These results are consistent with the findings of the present study. Venlafaxine monotherapy is a safe and effective option for treating bipolar depression.

Bupropion with unique pharmacocytics as an aminoketone and a reabsorning norepinephine-dopamine has been approved by the FDA since 1989.[24] In addition, bupropion is widely used to treat BD II, especially people with depression episodes.

Furthermore, because of its ability to improve the symptoms of depression at a lower risk of shifting than other antidepressant, some guide-based bipolar treatment, monotherapy, or in combination with other medications is recommended.[25]

The results of a meta -analysis by Li *et al*.[26] aimed at evaluating the effectiveness of bupropion in the treatment of BD showed that the bupropion significantly improves the severity of the disease in BD, and there is no significant difference in the effectiveness of bopropion therapy compared to other ADs. These results match the findings of the present study. Other studies have reported that the effectiveness of the bopropion in reducing the severity of the symptoms of depression in BD is similar to other ADs.[27]

Post *et al*.[28] Reported that the three ADs bupropion, venlafaxine, and sertraline had similar efficacy in response to treatment and remission in patients with BD for 10 weeks.

Also in a meta-analysis study with 11 randomized controlled trials consisting of 692 patients on the effectiveness of various depressants (including popropion and venlafaxine) for BD, the results showed that ADs reduced new episodes of depression, without increase the risk of manic and hypomanic episodes, both monotherapy and in combination with mood stabilizers were superior to placebo and mood stabilizers.[29]

The results of Leverich *et al*.[24] study showed that the treatment with different ADs (venlafaxine, sertraline, and bupropion) for patients with depressive episode of BD II in a short time (10 weeks) causes a response to treatment and significant improvement in patients. The total rate of switching to hypomania was 19.3% that the highest and lowest rates were reported for venlafaxine and bupropion, respectively. In another meta-analysis, a review of 1,117 patients from three random trials showed that bupropion was as effective as venlafaxine in treating patients with major depressive disorder and reducing the HDRS depression score,[21] which is similar to the results of our study.

According to our findings, venlafaxine had similar efficacy in male and female but bupropion had better efficacy in female than male, so that HDRS score after 4 weeks of treatment was significantly lower in female.

Briefly, the results of the current study showed that treatment with two ADs, bupropion and venlafaxine, is effective, has no dangerous and serious side effects, and can be used as an affordable and safe drug in the treatment of depressive episodes in patients with BD II.

Because both venlafaxine and bupropion act by boosting certain neurotransmitters in brain, including norepinephrine and dopamine, their similar efficacy in reducing depressive symptoms is not unexpected. Mechanisms of noradrenergic/dopaminergic action play an important role in BD, and the balance of these neurotransmitters can help improve mood, better sleep, improve appetite, and focus. Although the use of ADs to treat depressive episodes in patients with BD raises concerns about the shift from depression to mania and rapid cycling, these are commonly prescribed for bipolar depression.[30] Therefore, because of the lack of sufficient evidence in this field, randomized controlled clinical trials are necessary to determine the role of different ADs in the treatment of bipolar depression.

This study had several limitations. First, only short-term effects of drugs were studied and the effects of using these drugs for a longer period and their effect on disease recurrence were not evaluated. Second, the placebo group was not considered, which did not determine the true efficacy of the drugs in BD II depression. Third, the effect of the number of previous episodes and the history of previous psychiatric hospitalization on the effectiveness of drugs was not investigated. Finally, we can point to the small number of samples.

Conclusion

The results of the present study showed that the two ADs venlafaxine and bupropion are equally effective in treating the depressive episode of BD II and no significant difference was observed in reducing depressive symptoms based on the HDRS between the two groups. Therefore, because of their safety and effectiveness, these two ADs can be used clinically to treat patients with BD II, in addition to reducing patients' symptoms, to alleviate the high cost of treatment and possible complications because of depression in these patients. It is suggested that further studies be performed to compare the efficacy of venlafaxine and bupropion as adjuvant therapy, with larger sample size, over longer periods of time and the effect on disease recurrence.

Acknowledgements

The authors acknowledge financial support from the Ahvaz Jundishapur University of Medical Sciences (Grant Number: U-98247).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest..

References

1. Benazzi, F., Bipolar disorder—focus on bipolar II disorder and mixed depression. Lancet 2007;369:935-45.
2. Datto C, Pottorf WJ, Feeley L, LaPorte S, Liss C. Bipolar II compared with bipolar I disorder: Baseline characteristics and treatment response to quetiapine in a pooled analysis of five placebo-controlled clinical trials of acute bipolar depression. Ann Gen Psychiatry 2016;15:9.
3. Widiger TA, Costa PT.Personality Disorders and the Five-Factor Model Of Personality.American Psychological Association; 2013.
4. Baldessarini RJ, Salvatore P, Khalsa HM, Gebre-Medhin P, Imaz H, González-Pinto A, *et al.* Morbidity in 303 first-episode bipolar I disorder patients. Bipolar Disord 2010;12:264-70.
5. Gitlin MJ. Antidepressants in bipolar depression: An enduring controversy. Focus (Am Psychiatr Publ) 2019;17:278-83.
6. López P, Mosquera F, de León J, Gutiérrez M, Ezcurra J, Ramírez F, *et al.* Suicide attempts in bipolar patients. JClin Psychiatry 2001;62:963-6.
7. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, *et al.* The international society for bipolar disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013;170:1249-62.
8. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: Asystematic review and meta-analysis. JClin Psychiatry 2010;71:953.
9. Antosik-Wójcińska A, Stefanowski B, ŚwięcickiŁ. Efficacy and safety of antidepressant's use in the treatment of depressive episodes in bipolar disorder–review of research. Psychiatr Pol 2015;49:1223-9.
10. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. J Affect Disord 2015;185:31-7.
11. El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, *et al.* Antidepressants worsen rapid-cycling course in bipolar depression: ASTEP-BD randomized clinical trial. J Affect Disord 2015;184:318-21.
12. Lorenzo LS, Vázquez GH, Zaratiegui RM, Tondo L, Baldessarini RJ. Characteristics of bipolar disorder patients given antidepressants. Hum Psychopharmacol 2012;27:486-91.
13. Ghaemi S, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: Meta-analyses of benefits and risks. Acta Psychiatr Scand 2008;118:347-56.
14. Tondo L, Baldessarini RJ, Vázquez G, Lepri B, Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. Acta Psychiatr Scand 2013;127:355-64.
15. Vazquez G, Tondo L, Baldessarini R. Comparison of antidepressant responses in patients with bipolar vs. unipolar depression: A meta-analytic review. Pharmacopsychiatry 2011;44:21-6.
16. Gitlin MJ. Antidepressants in bipolar depression: An enduring controversy. IntJBipolar Disord 2018;6:25.
17. Zhang Y, Yang H, Yang S, Liang W, Dai P, Wang C, *et al.* Antidepressants for bipolar disorder: A meta-analysis of randomized, double-blind, controlled trials. Neural Regen Res 2013;8:2962-74.
18. Vázquez GH, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. Int J Neuropsychopharmacol 2013;16:1673-85.
19. Sidor MM, MacQueen GM. An update on antidepressant use in bipolar depression. CurrPsychiatry Rep 2012;14:696-704.
20. Altshuler LL, Sugar CA, McElroy SL, Calimlim B, Gitlin M, Keck PE Jr, *et al.* Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: A randomized double-blind comparison. Am J Psychiatry 2017;174:266-76.
21. Maneeton N, Maneeton B, Eurviriyanukul K, Srisurapanont M. Efficacy, tolerability, and acceptability of bupropion for major depressive disorder: A meta-analysis of randomized–controlled trials comparison with venlafaxine. Drug DesDevelTher 2013;7:1053-62.
22. Amsterdam J, Wang G, Shults J. Venlafaxine monotherapy in bipolar type II depressed patients unresponsive to prior lithium monotherapy. Acta Psychiatr Scand 2010;121:201-8.
23. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: A randomized open-label study. J Clin Psychopharmacol 2008;28:171-81.
24. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, *et al.* Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232-9.
25. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, *et al.* Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2013. Bipolar Disorders 2013;15:1-44.
26. Li DJ, Tseng PT, Chen YW, Wu CK, Lin PY. Significant treatment effect of bupropion in patients with bipolar disorder but similar phase-shifting rate as other antidepressants: A meta-analysis following the PRISMA guidelines. Medicine (Baltimore) 2016;95:e3165.
27. Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: Asystematic review and meta-analysis. JClin Psychiatry 2008;69:1589-601.
28. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, *et al.* Mood switch in bipolar depression: Comparison of adjunctive venlafaxine, bupropion and

sertraline. Br J Psychiatry 2006;189:124-31.

29. Liu B, Zhang Y, Fang H, Liu J, Liu T, Li L. Efficacy and safety of long-term antidepressant treatment for bipolar disorders–A meta-analysis of randomized controlled trials. JAffect Disord, 2017;223:41-8.
30. Fountoulakis KN. An update of evidence-based treatment of bipolar depression: Where do we stand? Curr Opin Psychiatry 2010;23:19-24.