RESEARCH PAPER

Early Antidepressant Response to Bupropion-Dextromethorphan Compared with Escitalopram in Major Depressive Disorder: A Prospective Comparative Study

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Abstract
Background: This study compared the efficacy and tolerability of bupropion–dextromethorphan with escitalopram in patients with first-episode Major Depressive Disorder.
Methods: This prospective, randomized, open-label comparative study included 173 adult patients with first-episode major depressive disorder. Patients were randomized to receive either escitalopram (n = 90) or bupropion–dextromethorphan (n = 83) for six weeks. Depressive symptoms were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D) at baseline and Weeks 2, 4, and 6. Sexual function was assessed using the Arizona Sexual Experience Scale (ASEX), and body weight was recorded at baseline and Week 6.
Results: Baseline MADRS and HAM-D scores were comparable between the two groups. The bupropion–dextromethorphan group had significantly lower MADRS scores than the escitalopram group at Week 2 (21.89 ± 2.93 vs. 23.13 ± 3.29; P = 0.009), Week 4 (14.00 ± 3.31 vs. 16.71 ± 3.42; P < 0.001), and Week 6 (9.81 ± 3.31 vs. 13.42 ± 3.60; P < 0.001). HAM-D scores were also significantly lower in the bupropion–dextromethorphan group at Week 4 (10.99 ± 3.03 vs. 12.19 ± 3.12; P = 0.011) and Week 6 (7.61 ± 3.22 vs. 9.20 ± 3.17; P = 0.001). At Week 6, ASEX scores were lower in the bupropion–dextromethorphan group than in the escitalopram group (16.01 ± 1.94 vs. 20.63 ± 2.04; P < 0.001). Mean body weight was also lower in the bupropion–dextromethorphan group at Week 6 (64.49 ± 6.77 kg vs. 66.52 ± 6.02 kg; P = 0.039).
Limitations: This was a single-centre, open-label study with a six-week follow-up period.
Conclusion: Bupropion-dextromethorphan was associated with greater reduction in depressive symptoms than escitalopram and showed a more favourable sexual-function and body-weight profile during six weeks of treatment.
Keywords: Major Depressive Disorder; Bupropion; Dextromethorphan; Escitalopram; Montgomery–Åsberg Depression Rating Scale; Hamilton Depression Rating Scale.
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Introduction

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders worldwide and a leading cause of disability. [1, 2] According to the Global Burden of Disease 2021 study, depressive disorders rank as the second leading cause of years lived with disability among mental disorders and are associated with recurrent illness, impaired functioning, and an increased risk of suicide. [2] Although several antidepressants are available for the treatment of MDD, many patients continue to experience inadequate response or do not receive appropriate treatment, highlighting the need for more effective therapeutic strategies. [9,13] Optimizing pharmacological treatment therefore remains an important objective in the management of MDD. [3]

In recent years, antidepressants targeting glutamatergic neurotransmission have emerged as promising therapeutic options for the treatment of MDD. [4] Dextromethorphan/bupropion is a novel oral antidepressant approved in the United States in 2022 for the treatment of adults with major depressive disorder. [5] Unlike conventional monoaminergic antidepressants, dextromethorphan acts as an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, while bupropion inhibits cytochrome P450 2D6 (CYP2D6), thereby increasing the bioavailability and prolonging the activity of dextromethorphan [5, 6]. Clinical studies have demonstrated significant improvement in

depressive symptoms as early as one week after treatment initiation, with greater clinical response and remission rates than placebo, while maintaining a favourable safety and tolerability profile. [6, 7].

Despite the availability of newer antidepressants, selective serotonin reuptake inhibitors (SSRIs) remain the cornerstone of pharmacological treatment for major depressive disorder. [8] Among them, escitalopram is widely used and remains one of the recommended first-line antidepressants for adults with depression. [9, 10] It exerts its antidepressant effect by selectively inhibiting serotonin reuptake, thereby enhancing serotonergic neurotransmission. [10] Its efficacy and safety have been established in several clinical studies. However, like other SSRIs, escitalopram may be associated with sexual dysfunction, which can affect treatment adherence and quality of life. [8, 10]

Previous studies have demonstrated the efficacy and safety of dextromethorphan–bupropion in patients with major depressive disorder. [3,4] However, direct comparative evidence with established first-line antidepressants such as escitalopram remains limited. [3,4] Therefore, the present study was conducted to compare the efficacy and safety of dextromethorphan–bupropion and escitalopram in patients with first-episode major depressive disorder.

Methodology

Study design

This was a prospective, randomized, open-label, comparative study conducted between November 2025 and July 2026 in the Psychiatry Outpatient Department of a tertiary care teaching hospital. Eligible patients were randomly assigned to receive either escitalopram or the combination of bupropion-dextromethorphan and were followed for a period of six weeks. The study protocol was approved by the Institutional Ethics Committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and written informed consent was obtained from all participants before enrolment.

Study participants

Study participants

Patients of either sex aged ≥18 years presenting to the Psychiatry Outpatient Department with a diagnosis of first-episode major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria were screened for eligibility.[11] Eligible patients who fulfilled the study criteria and provided written informed consent were enrolled.

Inclusion criteria

- Adults aged ≥18 years.
- Patients with first-episode major depressive disorder diagnosed according to DSM-5-TR criteria.[11]
- Baseline Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D) scores consistent with moderate-to-severe depression.
- Patients willing to provide written informed consent and comply with study procedures.

Exclusion criteria

- Bipolar disorder, schizophrenia, schizoaffective disorder, or other psychotic disorders.
- Substance use disorder (except nicotine or caffeine dependence).
- Severe suicidal ideation requiring immediate hospitalization.
- Pregnancy or lactation.
- Serious uncontrolled medical or neurological illness.
- History of hypersensitivity or contraindication to either study medication.
- Receipt of antidepressant therapy or electroconvulsive therapy before enrolment for the current depressive episode.
- Patients unwilling or unable to complete the six-week follow-up.

Randomization and treatment allocation

Participants who fulfilled the eligibility criteria were randomly allocated in a 1:1 ratio to receive either escitalopram or the combination of bupropion–dextromethorphan. Randomization was performed using a simple lottery (chit-picking) method, in which each participant independently selected one of two identical sealed chits corresponding to the treatment groups. The study was conducted in an open-label manner; therefore, both the investigators and participants were aware of the allocated treatment throughout the study.

Study interventions

Following randomization, participants received either escitalopram monotherapy or the combination of bupropion–dextromethorphan for a duration of six weeks. Treatment was prescribed by the treating psychiatrist according to routine clinical practice. Participants attended follow-up visits at weeks 2, 4, and 6, during which depressive symptom severity, sexual functioning, body weight, treatment adherence, and adverse events were assessed.

Outcome measures

The primary outcome was the change in depressive symptom severity assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) [13] and the Hamilton Depression Rating Scale (HAM-D) [12] at baseline and at weeks 2, 4, and 6.

Sexual functioning was evaluated using the Arizona Sexual Experience Scale (ASEX) [14] at baseline and week 6. Body weight was recorded at each study visit.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequency and percentage. Baseline demographic and clinical characteristics were compared between the two treatment groups using the independent-samples *t*-test for continuous variables and the Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Treatment groups were compared at each follow-up visit using the independent-samples *t*-test. Mean differences with 95% confidence

intervals (CIs) and between-group effect sizes (Cohen's *d*) were calculated. A two-tailed *P* value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 173 patients with first-episode major depressive disorder were enrolled, of whom 90 received escitalopram and 83 received the combination of bupropion–dextromethorphan. The two treatment groups were comparable with respect to baseline demographic and clinical characteristics (Table 1). The mean age was 39.84 ± 14.25 years in the escitalopram group and 41.04 ± 13.42 years in the bupropion–dextromethorphan group. Males constituted 85.6% and 85.5% of the participants in the two groups, respectively. Baseline MADRS, HAM-D, and body weight were comparable between the groups, whereas baseline ASEX scores were lower in the bupropion–dextromethorphan group.

Changes in depressive symptom severity

Montgomery–Asberg Depression Rating Scale (MADRS)

Both treatment groups demonstrated progressive reductions in MADRS scores over the 6-week study period (Table 2, Figure 1A). Baseline scores were comparable between the groups (P = 0.749). At Week 2, the bupropion–dextromethorphan group showed significantly lower MADRS scores than the escitalopram group (21.89 ± 2.93 vs. 23.13 ± 3.29; P = 0.009). The between-group difference increased at Week 4 (14.00 ± 3.31 vs. 16.71 ± 3.42; P < 0.001) and remained significant at Week 6 (9.81 ± 3.31 vs. 13.42 ± 3.60; P < 0.001), with a large effect size (Cohen's *d* = 1.04).

Hamilton Depression Rating Scale (HAM-D)

HAM-D scores declined progressively in both treatment groups throughout the study period (Table 3, Figure 1B). Baseline scores did not differ significantly between the groups (P = 0.500). Although the difference at Week 2 was not statistically significant (P = 0.058), significantly lower HAM-D scores were observed in the bupropion–dextromethorphan group at Week 4 (10.99 ± 3.03 vs. 12.19 ± 3.12; P = 0.011) and Week 6 (7.61 ± 3.22 vs. 9.20 ± 3.17; P = 0.001).

Sexual functioning

Sexual functioning was assessed using the Arizona Sexual Experience Scale (ASEX) (Table 4). Baseline ASEX scores were significantly lower in the bupropion–dextromethorphan group than in the escitalopram group (13.97 ± 1.41 vs. 15.92 ± 1.40; P < 0.001). At Week 6, ASEX scores increased in both groups, with significantly lower scores observed in the bupropion–dextromethorphan group (16.01 ± 1.94 vs. 20.63 ± 2.04; P < 0.001). The between-group effect size was large (Cohen's *d* = 2.33).

Body weight

Baseline body weight was comparable between the treatment groups (65.61 ± 6.01 kg vs. 65.36 ± 6.76 kg; P = 0.800) (Table 5). At Week 6, participants receiving escitalopram had a significantly higher mean body weight than those receiving bupropion–dextromethorphan (66.52 ± 6.02 kg vs. 64.49 ± 6.77 kg; P = 0.039), although the observed effect size was small (Cohen's *d* = 0.32).

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Escitalopram (n = 90)	Bupropion + Dextromethorphan (n = 83)
Age (years), mean ± SD	39.84 ± 14.25	41.04 ± 13.42
Male, n (%)	77 (85.6)	71 (85.5)
Female, n (%)	13 (14.4)	12 (14.5)
MADRS score at baseline	28.18 ± 2.75	28.05 ± 2.57
HAM-D score at baseline	21.80 ± 2.61	22.06 ± 2.44
ASEX score at baseline	15.92 ± 1.40	13.97 ± 1.41
Body weight (kg) at baseline	65.61 ± 6.01	65.36 ± 6.76

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as number (%). P values were calculated using the independent-samples t-test for continuous variables and the Chi-square test (or Fisher's exact test, where appropriate) for categorical variables.

Table 2. Comparison of MADRS scores between treatment groups over the 6-week follow-up

Time	Escitalopram (n=90	Bupropion + Dextromethorpha	Mean Differenc	t-va	P value	Cohen's d

poi nt	) Mean ± SD	n (n=83) Mean ± SD	e (95 % CI)	lu e		
Bas elin e	28.18 ± 2.75	28.05 ± 2.57	0.13 (−0. 67 to 0.93)	0. 32	0.7 49	0.0 5
We ek 2	23.13 ± 3.29	21.89 ± 2.93	1.24 (0.31 to 2.18)	2. 62	0.0 09	0.4 0
We ek 4	16.71 ± 3.42	14.00 ± 3.31	2.71 (1.70 to 3.72)	5. 30	<0. 00 1	0.8 1
We ek 6	13.42 ± 3.60	9.81 ± 3.31	3.62 (2.58 to 4.65)	6. 87	<0. 00 1	1.0 4

Table 3. Comparison of HAM-D scores between the treatment groups during the 6-week study period

Ti me poi nt	Escita lopra m (n = 90) Mean ± SD	Bupropi on + Dextrom ethorpha n (n = 83) Mean ± SD	Mea n Diffe renc e (95 % CI)	*t* va lu e	*P* va lu e	Co hen 's *d*
Bas elin e	21.80 ± 2.61	22.06 ± 2.44	−0.2 6 (−1.0 2 to 0.50)	−0 .6 8	0. 50 0	0.1 0
We ek 2	17.28 ± 2.97	16.45 ± 2.81	0.83 (−0.0 3 to 1.69)	1. 91	0. 05 8	0.2 9
We ek 4	12.19 ± 3.12	10.99 ± 3.03	1.20 (0.28 to 2.12)	2. 58	0. 01 1	0.3 9
We ek 6	9.20 ± 3.17	7.61 ± 3.22	1.59 (0.63 to 2.55)	3. 27	0. 00 1	0.5 0

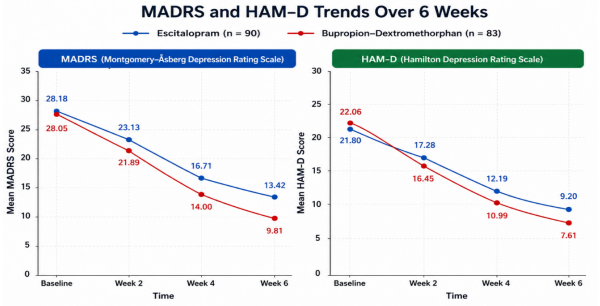


Figure 1. Changes in MADRS and HAM-D scores over the 6-week treatment period. (A) Mean MADRS scores and (B) mean HAM-D scores in patients receiving Escitalopram and Bupropion–Dextromethorphan. Both treatment groups showed progressive improvement over 6 weeks, with greater reductions observed in the Bupropion–Dextromethorphan group.

Table 4. Comparison of ASEX scores between the treatment groups

Ti me poi nt	Escita lopra m (n = 90) Mean ± SD	Bupropi on + Dextrom ethorpha n (n = 83) Mean ± SD	Mea n Diffe renc e (95 % CI)	*t* va lu e	*P* val ue	Co hen 's *d*
Bas elin e	15.92 ± 1.40	13.97 ± 1.41	1.95 (1.53 to 2.37)	9. 09	<0. 00 1	1.3 9

Week 6	20.63 ± 2.04	16.01 ± 1.94	4.62 (4.03 to 5.21)	15.18	<0.001	2.33

Table 5. Comparison of body weight between the treatment groups

Time point	Escitalopram (n = 90) Mean ± SD	Bupropion + Dextromethorphan (n = 83) Mean ± SD	Mean Difference (95 % CI)	*t* value	*p* value	Cohen's *d*
Baseline	65.61 ± 6.01	65.36 ± 6.76	0.25 (−1.67 to 2.17)	0.26	0.800	0.04
Week 6	66.52 ± 6.02	64.49 ± 6.77	2.03 (0.11 to 3.95)	2.09	0.039	0.32

Discussion

The present prospective randomized comparative study evaluated the efficacy and safety of dextromethorphan–bupropion compared with escitalopram in patients with first-episode major depressive disorder. Both treatment groups demonstrated significant improvement in depressive symptoms over the 6-week study period; however, the dextromethorphan-bupropion group achieved significantly greater reductions in MADR-S and HAM-D scores, along with better sexual functioning and a more favourable weight profile. These findings are consistent with the Phase III GEMINI trial, which demonstrated rapid and sustained antidepressant efficacy of dextromethorphan–bupropion with higher response and remission rates than placebo [6]. McCarthy et al. further concluded that dextromethorphan–bupropion is an effective and well-tolerated novel antidepressant, while the updated CANMAT guidelines recognize it as an evidence-based treatment option for major depressive disorder [15]. The present study extends this evidence by providing a prospective head-to-head comparison with escitalopram in an Indian population [3].

The present study demonstrated greater improvement in depressive symptoms with dextromethorphan–bupropion than with escitalopram, as reflected by significantly larger reductions in MADRS and HAM-D scores. These findings are consistent with the GEMINI trial, which reported significantly greater reductions in MADRS scores, earlier symptom improvement, and higher response and remission rates with dextromethorphan–bupropion than placebo. Similar findings were confirmed by a recent systematic review and network meta-analysis, which demonstrated superior remission rates with AXS-05 while maintaining an acceptable safety profile. [6,16] In contrast, Shen et al. found that bupropion XL was non-inferior, but not superior, to escitalopram, suggesting that the enhanced efficacy observed in the present study may be attributable to the addition of dextromethorphan. [10] Furthermore, previous studies have shown that early clinical improvement is strongly associated with subsequent remission, supporting the clinical significance of the greater symptom reduction observed in our study. [17, 18] Although escitalopram remains an effective first-line antidepressant, its onset of action is comparable to that of other contemporary antidepressants. [19] Overall, our findings align with current evidence supporting the superior antidepressant efficacy of dextromethorphan–bupropion.

The superior antidepressant efficacy of the dextromethorphan–bupropion combination may be attributed to its novel glutamatergic mechanism of action. Dextromethorphan acts as an NMDA receptor antagonist and sigma-1 receptor agonist, promoting synaptic plasticity and neuroplasticity beyond conventional monoaminergic pathways.[5,15,20] Bupropion further enhances this effect by inhibiting CYP2D6, thereby increasing dextromethorphan exposure and prolonging its therapeutic activity.[15,21] Rapid-acting NMDA modulators have been shown to produce earlier symptom improvement through restoration of glutamatergic neurotransmission,[22] which is consistent with the significant clinical improvement observed as early as Week 1 in the GEMINI trial.[6]

In the present study, the dextromethorphan–bupropion group demonstrated significantly lower ASEX scores than the escitalopram group, indicating better preservation of sexual function. This finding is consistent with Clayton et al., who reported significantly lower rates of treatment-emergent sexual dysfunction with bupropion than escitalopram while maintaining comparable antidepressant efficacy.[23] Similarly, Razali et al. found that bupropion significantly improved sexual desire in women with sexual dysfunction.[24] Ashwin et al. further confirmed the favorable tolerability of the dextromethorphan–bupropion combination without increased treatment discontinuation.[16] Preserving sexual function is clinically important as it enhances treatment adherence, patient satisfaction, and quality of life.

In the present study, patients treated with the dextromethorphan–bupropion combination experienced significantly less weight gain than those receiving

escitalopram. This finding is in line with previous evidence showing that, unlike many antidepressants, particularly SSRIs, bupropion is generally associated with weight neutrality or modest weight loss rather than weight gain [25]. Maintaining a favourable weight profile is clinically important because weight gain is a common reason for poor adherence and treatment discontinuation. The overall safety and tolerability of the dextromethorphan–bupropion combination reported in previous studies further supports its use as a long-term treatment option for patients with major depressive disorder [16].

Both treatment groups were well tolerated, with no unexpected safety concerns observed during the 6-week study. However, patients receiving the bupropion–dextromethorphan combination demonstrated earlier and greater improvement in depressive symptoms, with significantly lower MADRS scores from Week 2 onward (21.89 ± 2.93 vs. 23.13 ± 3.29; $P = 0.009$), lower ASEX scores at Week 6 (16.01 ± 1.94 vs. 20.63 ± 2.04; $P < 0.001$), and lower body weight (64.49 ± 6.77 kg vs. 66.52 ± 6.02 kg; $P = 0.039$) than the escitalopram group. These findings are consistent with previous evidence showing that dextromethorphan–bupropion is generally well tolerated, with predominantly mild-to-moderate adverse events [15], while bupropion has been associated with improved sexual functioning [24] and a favourable weight profile that may enhance long-term treatment adherence [25]. Collectively, these findings suggest that the bupropion–dextromethorphan combination may be a valuable treatment option for patients with major depressive disorder, particularly when early symptom improvement, preservation of sexual function, and minimization of weight gain are important treatment goals.

This study is strengthened by its prospective randomized design, direct comparison of bupropion–dextromethorphan with escitalopram, and the use of validated scales to assess both efficacy and tolerability. However, its single-centre, open-label design, modest sample size, and 6-week follow-up limit the generalizability and assessment of long-term outcomes. Larger multicentre, double-blind studies with longer follow-up are needed to confirm these findings and evaluate long-term effectiveness, safety, and quality of life.

Conclusion: In conclusion, the bupropion–dextromethorphan combination was associated with greater improvement in depressive symptoms, earlier clinical response, better preservation of sexual function, and a more favourable weight profile than escitalopram over 6 weeks. Both treatments were well tolerated. These findings support bupropion–dextromethorphan as a promising treatment option for major depressive disorder, although larger multicentre studies with longer follow-up are needed to confirm its long-term efficacy and safety.

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