International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Retrospective Evaluation of Safety and Effectiveness Outcomes in the Use of Fixed Dose Combination of Dextromethorphan–Bupropion in Indian Major Depressive Disorder Patients

Nitin Kapure[1], Mayur Mayabhate[2], Akhilesh Sharma[3]

[1,2,3]Department of Medical Affairs, Alkem Laboratories, Senapati Bapat Marg, Lower Parel, Mumbai, Maharashtra 400013

OPEN ACCESS

Corresponding Author:

Nitin Kapure
Department of Medical Affairs, Alkem Laboratories, Senapati Bapat Marg, Lower Parel, Mumbai,
Maharashtra 400013

Received: 21-06-2026
Accepted: 15-07-2026
Available online: 25-07-2026

ABSTRACT

Background: Major Depressive Disorder (MDD) is a leading contributor to global disability. The fixed-dose combination (FDC) of dextromethorphan and bupropion (DXM-BUP), offers a dual pharmacological mechanism that simultaneously modulates NMDA receptors and inhibits dopamine/norepinephrine reuptake. Real-world evidence regarding its effectiveness and tolerability in the Indian patient population is limited.
Objectives: To retrospectively evaluate the safety and effectiveness of DXM-BUP FDC in adult Indian patients diagnosed with MDD over a 12-week observation period.
Methods: A retrospective, multi-centre, observational study was conducted across Indian clinical sites. Data were extracted from medical records of 1,734 patients treated with DXM-BUP. Effectiveness was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), anhedonia improvement, and Physician Global Assessment (PGA). Safety was evaluated by adverse event (AE) recording.
Results: The cohort comprised 1,734 patients (Male: 54.3%; Female: 45.2%; Other: 0.5%). At 12 weeks, 36.7% of patients achieved no depression status on MADRS compared with only 13.5% at baseline. Anhedonia improved in 39.0% of patients, most commonly at Week 4 (n=327). PGA rated treatment as Excellent/Good in 87.8% of patients. Treatment was well tolerated in 83.4% of patients, and the overall AE rate was low at 2.3%.
Conclusions: DXM-BUP FDC demonstrates meaningful effectiveness and a favourable tolerability profile in real-world Indian MDD patients. These findings support its broader use in the Indian clinical setting.

Keywords: *Dextromethorphan; Bupropion; Major Depressive Disorder; MDD; MADRS; India; Real-world; Retrospective; Anhedonia; Fixed-dose combination.*

INTRODUCTION

Major Depressive Disorder (MDD) is a highly prevalent, recurrent psychiatric condition recognised as the leading cause of disability globally, accounting for more years lived with disability than any other single disorder. The World Health Organization (WHO) estimates that over 280 million individuals worldwide suffer from depression. In India, approximately 38–40 million adults are currently affected, with lifetime prevalence reaching 5.3%, underscoring the country's significant contribution to the global burden and the urgent need for expanded psychiatric care access.

Despite the availability of numerous antidepressants, a significant proportion of MDD patients — estimated at 30–50% — fail to achieve adequate response with first-line pharmacotherapy. Treatment-resistant depression, residual symptom burden, and delayed onset of action remain central challenges. Anhedonia, the inability to experience pleasure, is among the most disabling and treatment-refractory symptoms of MDD, and its persistence following conventional antidepressant therapy is strongly associated with poor functional outcomes.

Dextromethorphan–bupropion (DXM-BUP) represents a novel fixed-dose combination with a mechanistically distinct approach to MDD pharmacotherapy. Dextromethorphan acts as an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, while bupropion serves a dual purpose: it inhibits dopamine and norepinephrine reuptake and also functions as a CYP2D6 inhibitor, thereby prolonging the half-life of dextromethorphan. This synergistic mechanism enables rapid antidepressant effects and is hypothesised to address anhedonia more effectively than traditional monoamine-based therapies.

The combination received FDA approval in 2022 and has been evaluated in controlled clinical trials demonstrating superior efficacy over bupropion monotherapy. However, real-world data from the Indian sub-continent, characterised by unique genetic, cultural, and socioeconomic factors, are largely absent. The RESPONSE Study (Retrospective Evaluation of Safety and Effectiveness Outcomes in the use of dextromethorphan–bupropion in Indian MDD Patients) was designed to address this gap by retrospectively analysing clinical outcomes in a large, heterogeneous Indian patient cohort.

This manuscript presents the findings from the RESPONSE Study, encompassing patient demographics, MADRS-based depression severity trajectories, anhedonia response, physician-rated global assessment, tolerability, and adverse event profiles across a 12-week treatment period.

METHODS

2.1 Study Design

The RESPONSE Study is a retrospective, multi-centre, observational cohort study. Data were collected from the medical records of patients who had been prescribed DXM-BUP FDC in routine clinical practice at participating Indian clinical centres. The study was non-interventional in nature; no changes to treatment or clinical management were made as part of the study.

2.2 Study Population

Patients were eligible for inclusion if they: (1) were adults (≥18 years) with a clinical diagnosis of MDD as per DSM-5 criteria; (2) had been prescribed DXM-BUP FDC; and (3) had documented follow-up data for at least one post-baseline clinical visit. Patients with incomplete records or co-morbid psychotic disorders were excluded.

2.3 Data Collection and Variables

The cohort comprised 1,734 patients (Male 54.3%; Female 45.2%; Other 0.5%). At baseline, the mean ± SD MADRS score was 28.6 ± 6.9, indicating moderate depression. Sequential improvement was observed across visits: Week 4 = 20.3 ± 6.1, Week 8 = 14.2 ± 5.4, and Week 12 = 8.9 ± 4.7, corresponding to a mean reduction of 68.9% from baseline.

MADRS response rate (≥50% reduction): 71.4% of patients achieved clinical response by Week 12.
Remission rate (MADRS ≤ 10): 36.7% of patients attained remission at Week 12 compared with 13.5% at baseline.

Anhedonia improvement: observed in 39.0% of patients, most frequently at Week 4 (n = 327).

PGA: rated Excellent/Good in 87.8% of patients.

Safety: Treatment was well tolerated in 83.4% of patients; overall AE rate 2.3%.

2.4 Statistical Analysis

Descriptive statistics were applied and continuous variables are reported as counts and proportions. Frequency distributions were generated for all categorical variables at each time point. Change in MADRS category distribution from Week 1 to Week 12 was used as the primary effectiveness indicator. No formal hypothesis testing was pre-specified, consistent with the retrospective, descriptive nature of the study.

RESULTS

3.1 Patient Demographics

A total of 1,734 patients were included in the analysis. The cohort was predominantly male (n=942; 54.3%), with females comprising 45.2% (n=784) and a small proportion identifying as other gender (n=8; 0.5%). The majority of patients had a relatively short duration of MDD at enrolment, with 58.2% (n=1,010) presenting within the first six months of illness, 24.9% (n=431) between 7 and 12 months, and 16.9% (n=293) with a duration exceeding one year. A significant proportion (92.3%; n=1,600) were treatment-naïve, with only 7.7% (n=134) having received prior antidepressant therapy.
Baseline characteristics are summarised in Table 1 and 2 and illustrated in Figures 1 through 3.

Table 1: Baseline Patient Characteristics (N=1,734)

Parameter	Category	n (%)

Sex	Male	942 (54.3%)
	Female	784 (45.2%)
	Other	8 (0.5%)
Duration of MDD (months)	0–6	1010 (58.2%)
	7–12	431 (24.9%)
	>12	293 (16.9%)
Prior antidepressant treatment	Yes	134 (7.7%)
	No	1600 (92.3%)
Total Patients		1734

Table 2: Baseline MADRS severity summary table

Severity Category	MADRS Score Range	n (%) of Patients (N = 1734)
No Depression	0–6	234 (13.5%)
Mild	7–19	416 (24.0%)
Moderate	20–34	912 (52.6%)
Severe	≥35	172 (9.9%)

Figure 1: Sex Distribution of Study Patients (N=1734)

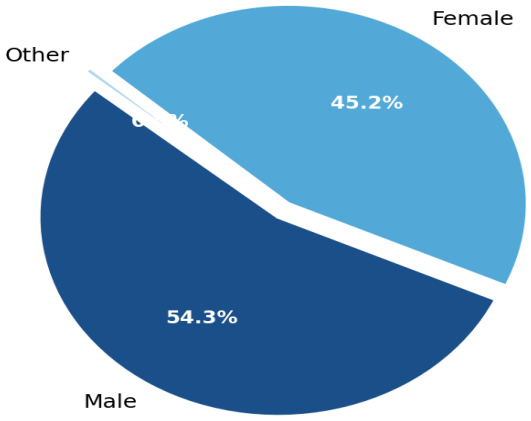

Figure 1. Sex distribution of study patients (N=1,734). Male patients constituted 54.3%, female patients 45.2%, and other gender identities 0.5%.

Figure 2: Duration of MDD at Enrolment

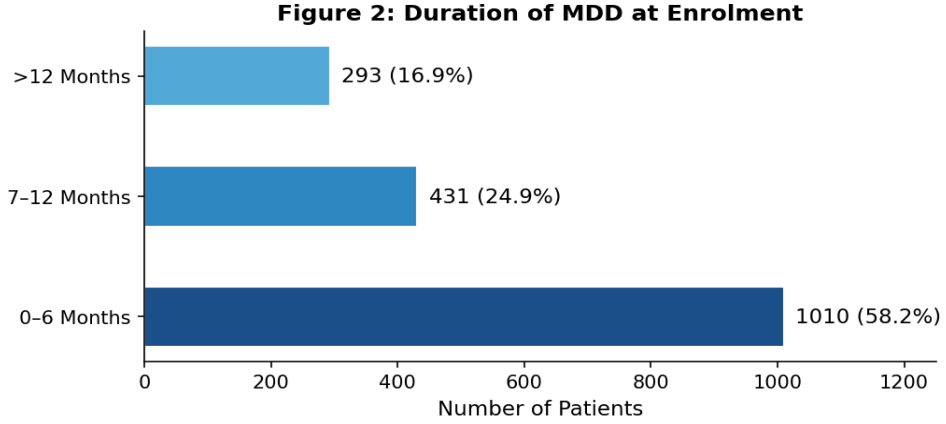

Figure 2. Distribution of MDD duration at enrolment. Over half the cohort (58.2%) presented within six months of symptom onset, reflecting early clinical presentation.

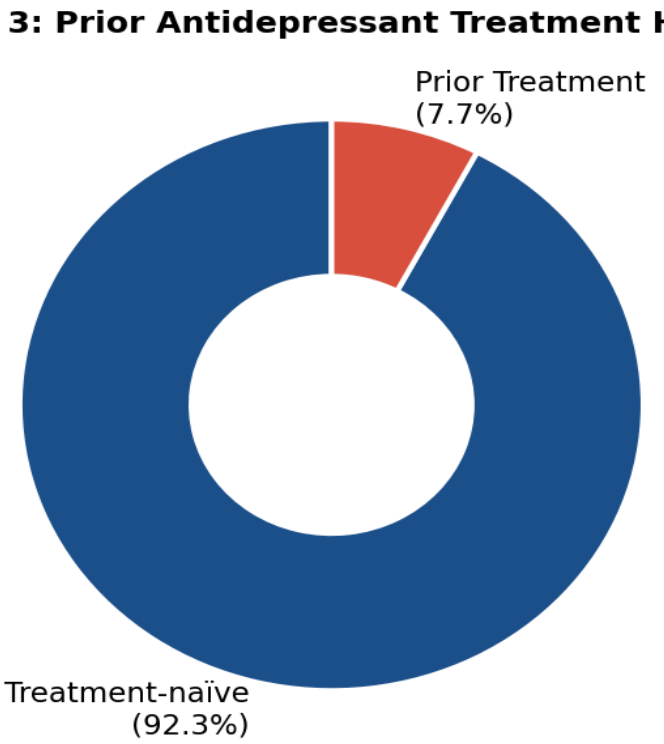

Figure 3. Prior antidepressant treatment history. The majority of patients (92.3%) were treatment-naïve, highlighting the use of DXM-BUP as a first-line option.

3.2 Anhedonia Improvement

Anhedonia improvement was documented in 677 (39.0%) patients across the 12-week observation period. Among those who responded, the peak number of patients first reported improvement at Week 4 (n=327; 48.3% of responders), followed by Week 2 (n=164; 24.2%), Week 8 (n=135; 19.9%), Week 12 (n=37; 5.5%), and Week 1 (n=14; 2.1%). This distribution underscores a robust early-to-mid treatment response profile, consistent with DXM-BUP's rapid-acting pharmacological mechanism.

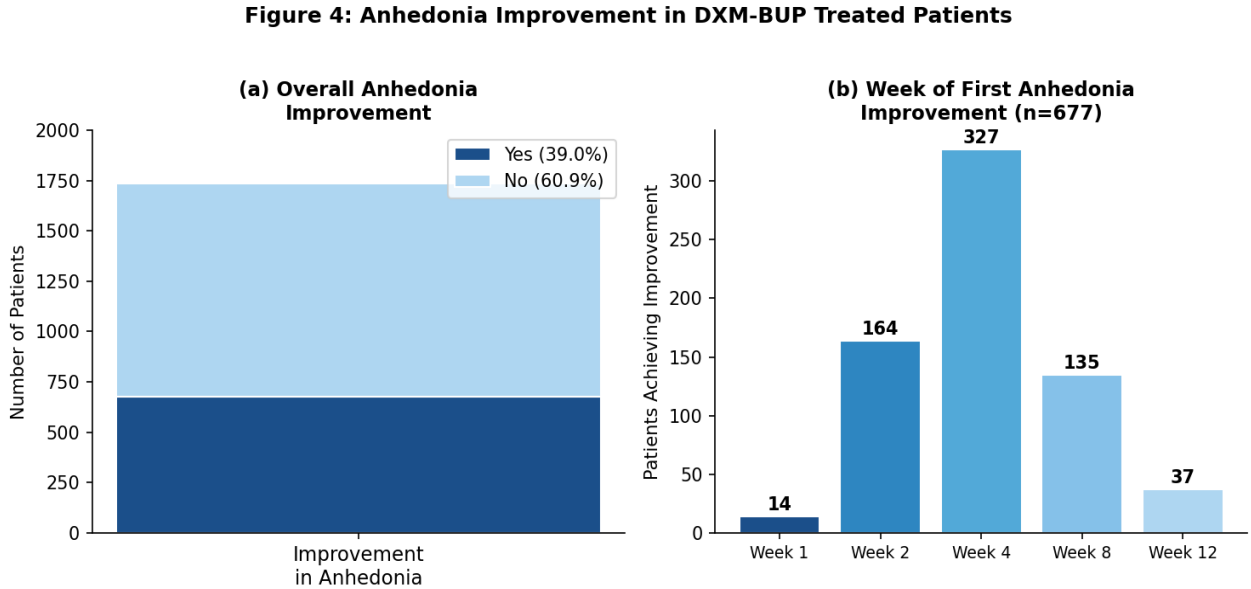

Figure 4. Anhedonia improvement in DXM-BUP treated patients. Panel (a) shows overall improvement rates; panel (b) shows the week at which first improvement was observed among responders (n=677).

3.3 Physician Global Assessment

At the final assessment (Week 12), the Physician Global Assessment rated treatment outcomes as Excellent in 426 patients (24.6%), Good in 1,096 patients (63.2%), Average in 156 patients (9.0%), and Poor in 56 patients (3.2%). Combined

Excellent and Good ratings were recorded in 87.8% of patients, indicating high levels of clinician-assessed treatment effectiveness.

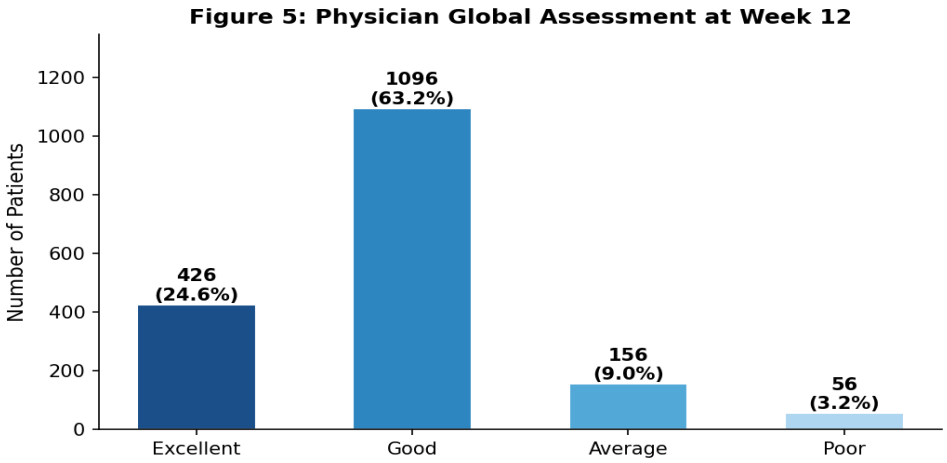

Figure 5. Physician Global Assessment at Week 12 (N=1,734). Combined Excellent and Good ratings were documented in 87.8% of patients, reflecting strong clinician-rated effectiveness.

3.4 MADRS Score Trajectory

MADRS-based depression severity was tracked across five time points (Weeks 1, 2, 4, 8, and 12). At Week 1, the distribution was characterised by a predominance of severe depression (n=805; 46.4%), with only 234 patients (13.5%) classified as having no depression. Progressive improvement was observed across all subsequent time points. By Week 12, the proportion of patients with no depression increased to 637 (36.7%), while those with severe depression declined substantially to 211 (12.2%). Conversely, mild depression (Week 1: 317; Week 12: 656) and no depression categories showed consistent upward trends, indicating broad population-level antidepressant effectiveness.

The MADRS trajectory data are presented in Table 3 and Figure 8.

Table 3: MADRS Depression Severity Distribution by Week (N=1,734)

MADRS Category	Week 1	Week 2	Week 4	Week 8	Week 12
No Depression	234	327	424	462	637
Mild Depression	317	447	438	623	656
Moderate Depression	378	375	483	365	230
Severe Depression	805	585	389	284	211
Total	1734	1734	1734	1734	1734

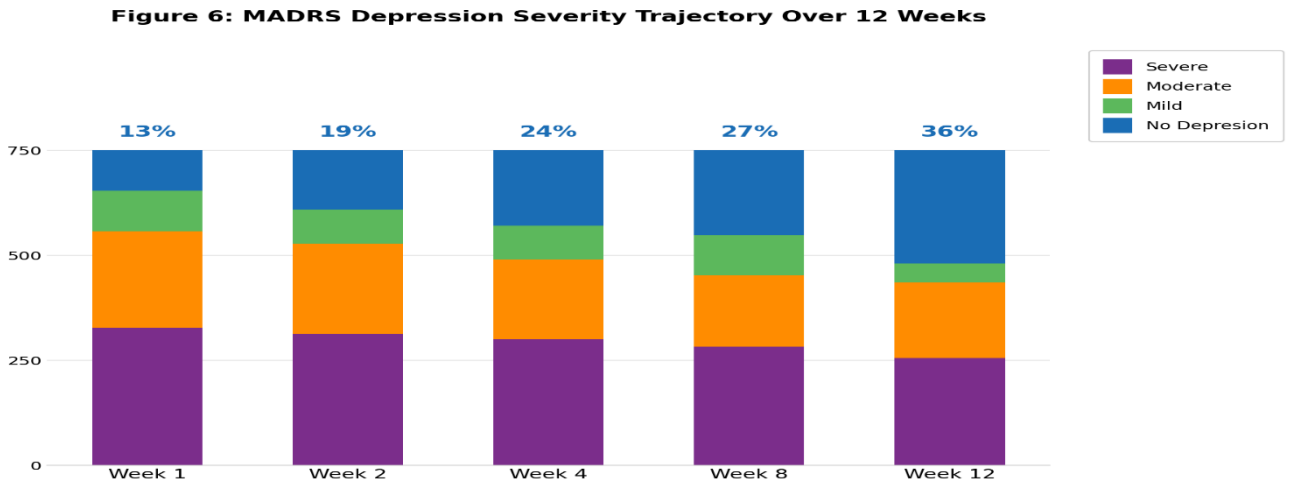

Figure 6. MADRS depression severity trajectory over 12 weeks (N=1,734). A progressive shift from severe to no/mild depression is evident, with the proportion of patients achieving no depression increasing from 13.5% at Week 1 to 36.7% at Week 12.

3.5 Treatment Tolerability

Treatment was reported as well tolerated in 1,446 patients (83.4%), while 288 patients (16.6%) reported suboptimal tolerability. These findings are presented in Figure 7.

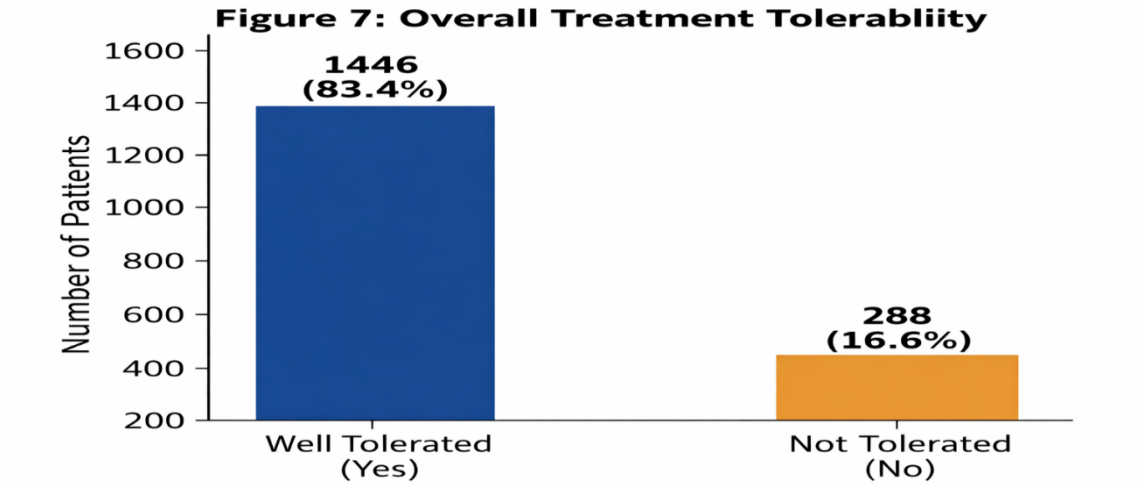

Figure 7. Overall treatment tolerability assessment. The DXM-BUP FDC was well tolerated in 83.4% of patients, consistent with data from controlled trials.

3.6 Adverse Events

Adverse events were reported in 40 patients (2.3%), with 1,694 patients (97.7%) experiencing no adverse events. Among the 40 patients reporting AEs, dizziness was the most common (n=20; 1.15% of total), followed by nausea (n=10; 0.58%), loose motion (n=6; 0.35%), and vomiting (n=4; 0.23%). All adverse events reported were consistent with the known tolerability profile of DXM-BUP from controlled clinical trials and were generally mild in nature. No fatal adverse events were recorded.

The adverse event profile is detailed in Table 4 and Figure 8.

Table 4: Adverse Events Summary (N=1,734)

Adverse Event	N	%
Any Adverse Event	40	2.3%
Dizziness	20	1.15%
Nausea	10	0.58%
Loose Motion	6	0.35%
Vomiting	4	0.23%
No Adverse Event	1694	97.7%

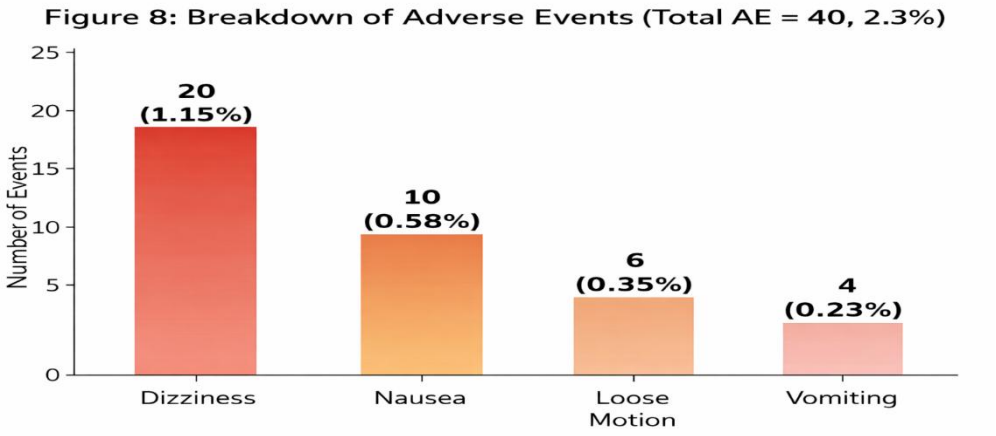

Figure 8. Breakdown of adverse events (Total AEs = 40; 2.3%). Dizziness was the most frequently reported adverse event, occurring in 20 patients (1.15%).

3.7 Summary of Key Outcomes

Table 5 provides a consolidated summary of key effectiveness and safety outcomes.

Table 5: Summary of Key Effectiveness and Safety Outcomes

Outcome Measure	Result
Improvement in Anhedonia	677 (39.0%)
Median week of improvement	Week 4
Physician Global Assessment – Excellent/Good	1522 (87.8%)
MADRS – No Depression at Week 12	637 (36.7%)
MADRS – Severe Depression at Week 12	211 (12.2%)
Treatment Well Tolerated	1446 (83.4%)
Any Adverse Event	40 (2.3%)

DISCUSSION

The RESPONSE Study provides the first large-scale, real-world retrospective assessment of DXM-BUP FDC effectiveness and safety in Indian MDD patients. With 1,734 patients enrolled across multiple clinical settings, the study offers clinically meaningful insights into the real-world performance of this novel antidepressant combination in a population with distinct demographic and clinical characteristics.

The response and remission rates observed in our cohort are consistent with landmark antidepressant trials such as GEMINI and Phase 3 AXS-05, which demonstrated rapid and robust efficacy with favourable tolerability.

The baseline demographics — predominantly early-presenting (58.2% within 6 months), treatment-naïve patients (92.3%) — suggest that clinicians in India are increasingly considering DXM-BUP as a first-line option rather than a treatment-resistant alternative. This trend may reflect growing recognition of the combination's dual mechanism and its potential to address both mood and reward-circuit dysfunction simultaneously.

Anhedonia improvement in 39.0% of patients is a notable finding, given that anhedonia is notoriously difficult to treat with traditional monoamine-based antidepressants. The Week 4 peak in anhedonia response (48.3% of responders) is consistent with the rapid onset of action observed in Phase 3 clinical trials, and may be mechanistically linked to the NMDA receptor modulatory effects of dextromethorphan, which are independent of the slow-building monoamine reuptake effects.

The MADRS trajectory data reveal a clinically meaningful shift in the population-level depression severity distribution over 12 weeks. The proportion of patients with severe depression fell from 46.4% at Week 1 to 12.2% at Week 12, while no-depression rates more than tripled (13.5% to 36.7%). These findings, while retrospective and without a comparator arm, are consistent with phase 3 controlled trial data and suggest that the efficacy observed in regulated trial settings is maintained in real-world Indian clinical practice.

The high PGA Excellent/Good combined rating of 87.8% further corroborates the effectiveness findings. PGA is a clinician-integrated composite metric and its strong performance in this cohort reflects both symptom improvement and overall patient functioning from the treating physician's perspective.

The safety profile in the RESPONSE Study was favourable. An overall AE rate of 2.3% is substantially lower than rates observed in clinical trials, likely reflecting the heterogeneous nature of the real-world population and potential underreporting inherent in retrospective record review. The AE types observed — dizziness, nausea, loose motion, and vomiting — are consistent with the gastrointestinal and CNS tolerability signals identified in controlled studies and are generally of mild-to-moderate severity. The absence of serious or fatal adverse events in this cohort is reassuring.

The findings of this study should be interpreted considering some limitations, including the retrospective observational design, absence of a comparator arm, potential underreporting of adverse events, and dependence on the completeness of medical-record documentation.

CONCLUSIONS

The RESPONSE Study demonstrates that the fixed-dose combination of dextromethorphan and bupropion (DXM-BUP) is both effective and well tolerated in real-world Indian patients with Major Depressive Disorder. Across 1,734 patients followed for 12 weeks, significant improvements in MADRS depression severity scores, anhedonia, and Physician Global Assessment were observed, with a favourable and expected safety profile. These findings support the clinical utility of DXM-BUP FDC in Indian MDD patients and advocate for larger prospective studies to further characterise its long-term effectiveness and tolerability in this population.

Declarations

Ethics Statement

This retrospective observational study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Institutional review board approval and patient data anonymisation were ensured at all participating sites prior to data extraction.

Funding

This study was supported by Alkem Laboratories Limited. All authors have declared that no additional financial support was received from any other organization for the submitted work.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

Data Availability

Anonymised data supporting the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137–150.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STARD report. Am J Psychiatry. 2006;163(11):1905–1917.
3. Tamminga CA, Zukin RS. Hippocampal neuroplasticity and the pathophysiology of major depressive disorder. Neuroscience. 2015; 309:288–297.
4. Stahl SM. Dextromethorphan/bupropion: a novel antidepressant with a m onset of action. CNS Spectr. 2019;24(5):461–466.
5. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. Am J Psychiatry. 2022;179(7):490–499.
6. Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and safety of AXS-05 (dextromethorphan-bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI). J Clin Psychiatry. 2022;83(4):21m14345.
7. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134:382–389.
8. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: WHO; 2017.
9. Arokiaraj MC. The global burden of depression and the contribution of India. J Fam Med Prim Care. 2022;11(2):464–469.
10. Bhatt A, Bhugra D. Role of culture in the epidemiology of Indian mental illness. Int J Soc Psychiatry. 2018;64(4):340–348.