https://doi.org/10.31925/farmacia.2026.4.10 **ORIGINAL ARTICLE**

LOW-DOSE OLANZAPINE AUGMENTATION OF DULOXETINE IN PATIENTS WITH DEPRESSIVE DISORDERS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Abstract

This retrospective observational study compared the effectiveness of duloxetine augmented with low-dose olanzapine (Group A, n = 34) and duloxetine monotherapy (Group B, n = 26) in 60 patients with depressive disorders. Depressive symptoms and global functioning were assessed using the Hamilton Depression Rating Scale (HAM-D) and the Global Assessment of Functioning Scale (GAFS) at baseline and follow-up. Both groups showed significant improvement, with HAM-D decreasing by 14.0 in Group A and 16.4 points in Group B and GAFS increasing by 34.3 in Group A and 40.6 points in Group B, respectively. The monotherapy group had a higher final GAFS score (76.8 *vs*. 71.6, p = 0.031) and a numerically higher response rate (60.0% vs. 38.2%, p = 0.119). Patients receiving adjunctive olanzapine were older and had a shorter follow-up period, whereas baseline symptom severity was comparable. The observed between-group differences should be interpreted cautiously because treatment allocation reflected routine clinical practice rather than randomization. Prospective controlled studies are needed to further evaluate the role of low-dose olanzapine augmentation in depressive disorders.

Rezumat

Acest studiu observațional retrospectiv a comparat eficacitatea augmentării tratamentului cu duloxetină prin asocierea olanzapinei în doză mică (Grupul A, n = 34) cu monoterapia cu duloxetină (Grupul B, n = 26) la 60 de pacienți cu tulburări depresive. Simptomatologia depresivă și funcționarea globală au fost evaluate la inițierea tratamentului și la momentul urmăririi, utilizând Scala Hamilton pentru Evaluarea Depresiei (HAM-D) și Scala de Evaluare Globală a Funcționării (GAFS). Ambele grupuri au prezentat o ameliorare semnificativă, scorul HAM-D reducându-se cu 14,0 puncte în Grupul A și cu 16,4 puncte în Grupul B, iar scorul GAFS crescând cu 34,3, respectiv 40,6 puncte. Grupul tratat cu monoterapie a înregistrat un scor final GAFS mai mare (76,8 vs. 71,6; p = 0,031) și o rată de răspuns numeric superioară (60,0% *vs*. 38,2%; p = 0,119). Pacienții care au primit tratament adjuvant cu olanzapină au avut vârsta mai înaintată și o perioadă de urmărire mai scurtă, în timp ce severitatea inițială a simptomelor a fost comparabilă între grupuri. Diferențele observate între grupuri trebuie interpretate cu prudență, deoarece tratamentul urmat de pacienți a fost consecința practicii clinice de rutină, nu a unui proces de randomizare. Sunt necesare studii prospective controlate pentru a evalua rolul augmentării tratamentului cu duloxetină prin olanzapină în doză mică la pacienții cu tulburări depresive.

Keywords: duloxetine, olanzapine, depression, real-world evidence

Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and a leading cause of disability worldwide, that impairs life quality, psychosocial functioning, and occupational performance (1, 2). Although several effective antidepressants are currently available, achieving complete symptomatic and functional remission remains a major therapeutic challenge. Approximately one-third of patients fail to respond adequately to first-line pharmacological treatment, and many others experience only partial

remission, with persistent residual symptoms such as anxiety, insomnia, fatigue, impaired concentration, or reduced social functioning (3, 4). These residual manifestations are clinically important because they are associated with poorer long-term outcomes, impaired functional recovery, lower treatment adherence, and an increased risk of relapse. Nowadays, the management of MDD aims not only to alleviate depressive symptoms but also to restore psychosocial functioning and improve patients' overall quality of life (3, 5).

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), is recommended as a first-line treatment for MDD by major international guidelines (6) and has consistently demonstrated efficacy in improving both depressive symptoms and functional outcomes (7). Through the inhibition of serotonin and norepinephrine reuptake, duloxetine exerts antidepressant effects while also alleviating painful physical symptoms frequently associated with depression. Beyond its psychiatric indication, duloxetine is approved for several chronic pain conditions, including diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, reflecting its broader role in disorders involving altered central pain processing (8). Despite adequate dosing and treatment duration, a considerable proportion of patients fail to achieve complete remission, highlighting the need for individualized therapeutic strategies capable of addressing persistent symptoms (9, 10).

When antidepressant monotherapy provides an insufficient clinical response, several therapeutic approaches may be considered, including dose optimization (9), switching antidepressants (11), combination therapy (12), and adjunctive pharmacological treatment (13). Among these strategies, the addition of second-generation antipsychotics has accumulated the strongest evidence and is recommended by several international guidelines for selected patients with an inadequate response to antidepressants (14). Olanzapine has been primarily investigated in combination with fluoxetine for treatment-resistant depression, being prescribed at substantially lower doses than those used for schizophrenia (15). The therapeutic objective is the improvement of residual anxiety, insomnia, psychomotor agitation, reduced appetite, or incomplete antidepressant response (16). Olanzapine exerts a broad pharmacological activity through antagonism of serotonin 5-HT2A/5-HT2C, dopamine D2, histamine H1, and α1-adrenergic receptors, mechanisms that may contribute to improved sleep, reduced anxiety, appetite restoration, and enhanced overall clinical recovery when used alongside antidepressant therapy (17).

Although duloxetine and olanzapine are frequently co-prescribed in clinical practice, evidence specifically evaluating this therapeutic combination remains limited. Existing studies have mainly focused on pharmacokinetic interactions or treatment-resistant depression, while data regarding its effectiveness in routine outpatient settings are scarce (18-20). Importantly, available pharmacokinetic studies indicate that olanzapine does not produce clinically meaningful changes in duloxetine plasma concentrations, suggesting that concomitant administration does not require dose adjustment based on metabolic interactions (18). Therefore, the decision to prescribe low-dose olanzapine in combination with duloxetine is primarily driven by the patient's clinical presentation and therapeutic needs rather than pharmacokinetic considerations.

The present retrospective observational study aimed to evaluate clinical outcomes associated with duloxetine monotherapy and duloxetine combined with low-dose olanzapine in routine outpatient psychiatric practice. Treatment effectiveness was assessed using changes in depressive symptom severity measured by the Hamilton Depression Rating Scale (HAM-D) and global functioning evaluated by the Global Assessment of Functioning Scale (GAFS). By providing real-world evidence regarding these commonly used therapeutic approaches, this study seeks to contribute to the understanding of the role of low-dose olanzapine as adjunctive therapy in the individualized management of patients with major depressive disorder.

Materials and Methods

Study design, population and outcome measures

This retrospective observational study was based on the review of medical records from a private psychiatric outpatient clinic in Romania. The study included patients who had also required hospitalization at the Department of Psychiatry II, Mureș County Clinical Hospital. The study evaluated treatment outcomes in adult patients diagnosed with major depressive disorder who received duloxetine either as monotherapy or in combination with low-dose olanzapine during routine clinical practice. Treatment decisions were made exclusively by the treating psychiatrist according to individual clinical needs and were independent of study participation. No intervention or modification of therapy was performed for research purposes.

Patients were allocated to two groups according to the pharmacological regimen received: Group A (n = 34) received duloxetine combined with olanzapine, and Group B (n = 26) received duloxetine monotherapy. Treatment decisions were made exclusively by the treating psychiatrist according to individual clinical needs and were independent of study participation. No intervention or modification of therapy was performed for research purposes.

Inclusion criteria were age ≥ 18 years, a documented clinical diagnosis of an affective disorder (depressive affective disorder, coded TAD; or bipolar affective disorder, coded TAB), initiation or continuation of duloxetine with or without concurrent olanzapine, and availability of a baseline and at least one follow-

up assessment of both HAM-D and GAFS. Medical records of eligible patients treated between January 2017, and June 2026 were retrospectively reviewed. One patient in Group B lacked baseline HAM-D and GAFS values and was excluded from all analyses requiring baseline scores; that patient is retained in the description of the cohort, so denominators differ between Table I and Table II where indicated. Only patients with complete baseline and follow-up clinical assessments were included in the final analysis. Therefore, no imputation of missing data was performed.

Demographic and clinical data were extracted from electronic medical records using a standardized data collection form. The following variables were recorded to characterize the study population: age, sex, place of residence (urban/rural), psychiatric diagnosis, disease onset, duloxetine dose at baseline and follow-up, olanzapine dose at baseline and follow-up (when applicable) and body mass index (BMI).

Treatment effectiveness was evaluated using both symptom-based and functional outcome measures. Depressive symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D-17), a clinician-administered instrument widely used to evaluate the severity of depressive symptoms and monitor treatment response (21).

Global functioning was assessed using the Global Assessment of Functioning Scale (GAFS), which provides an overall estimate of psychological, social, and occupational functioning, with higher scores indicating better functional status (22).

Both HAM-D and GAFS were evaluated to provide a comprehensive assessment of treatment effectiveness.

Statistical analysis

Continuous variables are summarised as mean ± standard deviation (SD). The distributional assumption of normality was assessed with the Shapiro–Wilk test and homogeneity of variance with the Levene test. Between-group comparisons of continuous variables used the independent-samples Student t-test, with the Mann-Whitney U test reported in parallel for variables that deviated significantly from normality. Within-group changes from baseline to follow-up were analysed with the paired t-test and confirmed with the Wilcoxon signed-rank test. Categorical variables were compared with the χ^2 test with Yates continuity correction, and with the Fisher exact test when expected cell counts were small. Treatment response was defined a priori as a reduction of $\geq 50\%$ in HAM-D score from baseline, and remission as a follow-up HAM-D score of ≤ 7.

Effect sizes are reported as Cohen d for between-group contrasts and Cohen dz for within-group change, together with 95% confidence intervals (CI) for the mean difference. To assess whether the measured baseline imbalances accounted for the between-group differences, an analysis of covariance (ANCOVA) was fitted for each follow-up score, with treatment group as the factor and age and the corresponding baseline score as covariates. A sensitivity analysis was performed after excluding the two patients with a bipolar diagnosis. A two-sided p-value < 0.05 was considered statistically significant. No adjustment for multiple comparisons was applied, and the between-group analyses are therefore regarded as exploratory. Analyses were performed in Python 3.11 using the SciPy, stats models and NumPy libraries.

Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (23) and was approved by the Ethics Committee of Mureș County Clinical Hospital, Romania (Approval No. 8836/12.06.2026). Owing to the retrospective nature of the study and the use of anonymized medical records, the requirement for informed consent was waived in accordance with institutional regulations.

Results and Discussion

Baseline characteristics

A total of 60 patients met the inclusion criteria, including 34 patients treated with duloxetine plus olanzapine (Group A) and 26 patients receiving duloxetine monotherapy (Group B). Baseline demographic and clinical characteristics are summarized in Table I. Patients in the combination group were significantly older than the monotherapy group, both at the most recent evaluation (65.4 ± 14.0 *versus* 57.7 ± 13.2 years, p = 0.033) and at treatment initiation (62.5 ± 14.4 *versus* 53.4 ± 12.6 years, p = 0.013). Both groups were predominantly female (73.5% in Group A and 88.5% in Group B, p = 0.268), and residence did not differ significantly (p = 0.394). The observation interval was shorter in the combination group (2.9 ± 2.6 *versus* 4.3 ± 2.8 years, p = 0.048 by Mann-Whitney U test). Baseline symptom severity was comparable between groups: HAM-D was 30.3 ± 5.2 in Group A and 31.6 ± 4.5 in Group B (p = 0.312), and GAFS was 37.4 ± 6.3 and 36.2 ± 5.6, respectively (p = 0.471). The mean baseline duloxetine dose did not differ (51.2 ± 13.9 *versus* 47.3 ± 17.3 mg/day, p = 0.341), and the mean olanzapine dose in Group A was 6.6 ± 2.4 mg/day. Two patients in Group A had a bipolar disorder diagnosis, whereas all remaining participants were diagnosed with depressive disorder (see Tabel I and Figure 1).

Table I

Baseline demographic and clinical characteristics of the study population

Variable	Group A (duloxetine + olanzapine) *n* = 34	Group B (duloxetine) *n* = 26	p-value
Age at most recent evaluation (years, mean ± SD)	65.4 ± 14.0	57.7 ± 13.2	0.033
Age at treatment initiation (years, mean ± SD)	62.5 ± 14.4	53.4 ± 12.6	0.013
Sex, female/male (n)	25/9	23/3	0.268
Residence, rural/urban (n)	18/16	10/16	0.394
Diagnosis, TAD/bipolar spectrum (n)	32/2	26/0	0.501
Observation interval (years, mean ± SD)	2.9 ± 2.6	4.3 ± 2.8	0.048
HAM-D at baseline (points, mean ± SD)	30.3 ± 5.2	31.6 ± 4.5 †	0.312
GAFS at baseline (points, mean ± SD)	37.4 ± 6.3	36.2 ± 5.6 †	0.471
Duloxetine dose (mg/day, mean ± SD)	51.2 ± 13.9	47.3 ± 17.3	0.341
Olanzapine dose (mg/day, mean ± SD)	6.6 ± 2.4	—	—

† n = 25 for baseline continuous scores in Group B (one patient had no baseline assessment)

Continuous variables were compared with the independent-samples Student t-test, except the observation interval (Mann-Whitney U test); categorical variables were compared with the χ^2 test with Yates correction or the Fisher exact test. GAFS = Global Assessment of Functioning Scale; HAM-D = Hamilton Depression Rating Scale; SD = standard deviation; TAD = depressive affective disorder.

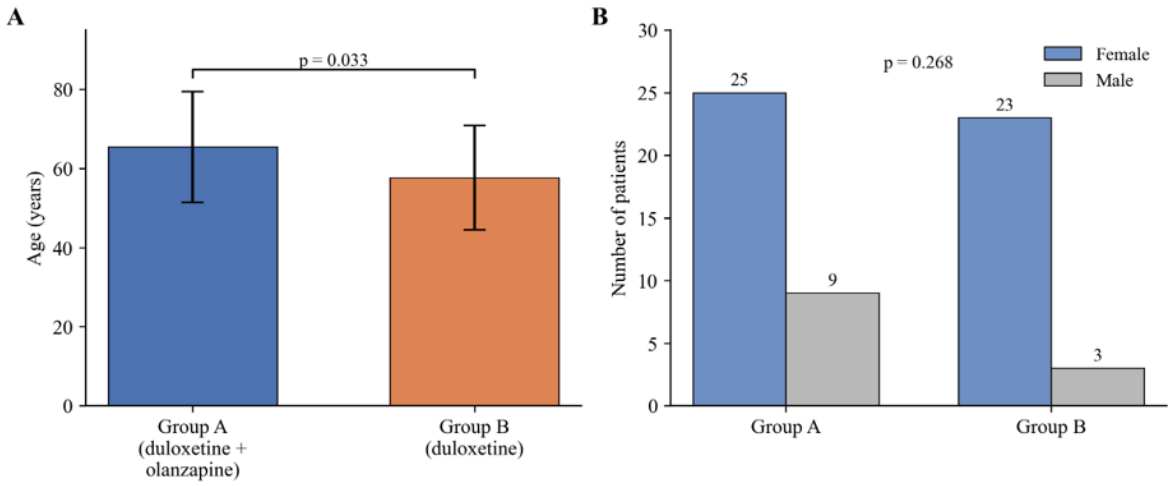

Figure 1.

Baseline demographic characteristics. (A) Mean age at the most recent evaluation, with error bars representing the standard deviation; patients receiving the combination were significantly older. (B) Sex distribution in the two treatment groups

Group A = duloxetine + olanzapine; Group B = duloxetine monotherapy

Efficacy outcomes

Both regimens produced large and highly significant within-group improvements in symptoms and functioning (all paired comparisons $p < 0.001$, confirmed by the Wilcoxon signed-rank test). In Group A, HAM-D fell from 30.3 ± 5.2 to 16.4 ± 4.1 points (mean change - 14.0 ± 6.5; 95% CI - 16.2 to - 11.7; dz = - 2.14), and in Group B from 31.6 ± 4.5 to 15.3 ± 4.3 points (mean change - 16.4 ± 6.2; 95% CI - 18.9 to - 13.8; dz = - 2.64). GAFS increased from 37.4 ± 6.3 to 71.6 ± 10.0 points in Group A (mean change +34.3 ± 13.1; 95% CI 29.7 to 38.8; dz = 2.62) and from 36.2 ± 5.6 to 76.8 ± 7.1 points in Group B (mean change 40.6 ± 8.6; 95% CI 37.1 to 44.1; dz = 4.73). Between-group contrasts were considerably weaker. Neither the change in HAM-D (difference 2.4 points; 95% CI - 1.0 to 5.8; p = 0.161; d = 0.37) nor the final HAM-D score (difference 1.1 points; 95% CI - 1.1 to 3.3; p = 0.334; d = 0.26) differed significantly. Monotherapy was associated with a higher final GAFS score (difference 5.2 points; 95% CI 0.5 to 9.9; p = 0.031; d = - 0.58) and with a greater GAFS improvement (difference 6.3 points; 95% CI 0.3 to 12.4; p = 0.040; d = - 0.56). These two contrasts were, however, only borderline when re-tested non-parametrically (Mann–Whitney U test p = 0.051 and p = 0.072, respectively), which is relevant because the GAFS distributions deviated significantly from normality (Shapiro-Wilk $p < 0.05$). The proportion of patients achieving a reduction of ≥ 50% in HAM-D was 13/34 (38.2%) in Group A and 15/25 (60.0%) in Group B, a difference of 21.8 percentage points that

did not reach statistical significance (95% CI - 47.0 to 3.4; odds ratio 0.41; Fisher exact test p = 0.119). No patient in either group reached the predefined remission threshold of HAM-D ≤ 7 (Table II, Figure 2 and Figure 3).

Table II

Efficacy outcomes: within-group changes and between-group comparisons

Outcome	Group A baseline → follow-up	Group B baseline → follow-up	Δ A *versus* Δ B p-value	Final A *versus* B p-value
HAM-D (points)	30.3 ± 5.2 → 16.4 ± 4.1 (Δ −14.0 ± 6.5) ***	31.6 ± 4.5 → 15.3 ± 4.3 (Δ −16.4 ± 6.2) ***	0.161	0.334
GAFS (points)	37.4 ± 6.3 → 71.6 ± 10.0 (Δ +34.3 ± 13.1) ***	36.2 ± 5.6 → 76.8 ± 7.1 (Δ +40.6 ± 8.6) ***	0.040 (0.072) §	0.031 (0.051) §
Response, ≥ 50% HAM-D reduction	13/34 (38.2%)	15/25 (60.0%)	0.119 ‡	—
Remission, HAM-D ≤ 7	0/34 (0%)	0/25 (0%)	—	—

*** Within-group paired t-test p < 0.001 (confirmed by the Wilcoxon signed-rank test). § Values in parentheses are the corresponding Mann-Whitney U test p-values, reported because the GAFS distributions deviated significantly from normality. ‡ Fisher exact test (χ^2 test with Yates correction p = 0.164). Continuous outcomes in Group B are based on n = 25. Δ = change from baseline; GAFS = Global Assessment of Functioning Scale; HAM-D = Hamilton Depression Rating Scale

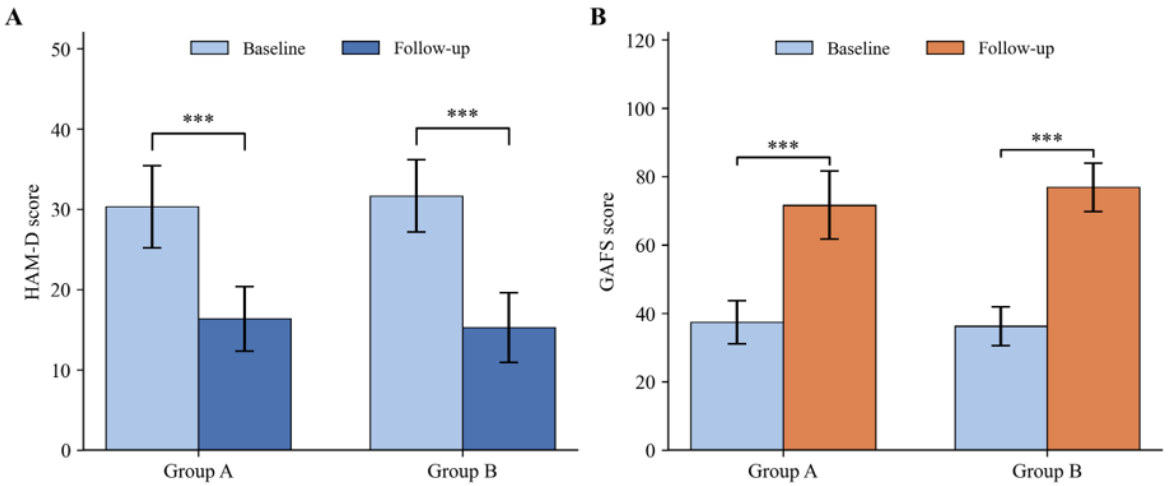

Figure 2.

Mean HAM-D (A) and GAFS (B) scores at baseline and at follow-up in the two treatment groups

Error bars represent the standard deviation. *** p < 0.001 for the within-group change (paired t-test)

GAFS = Global Assessment of Functioning Scale; HAM-D = Hamilton Depression Rating Scale

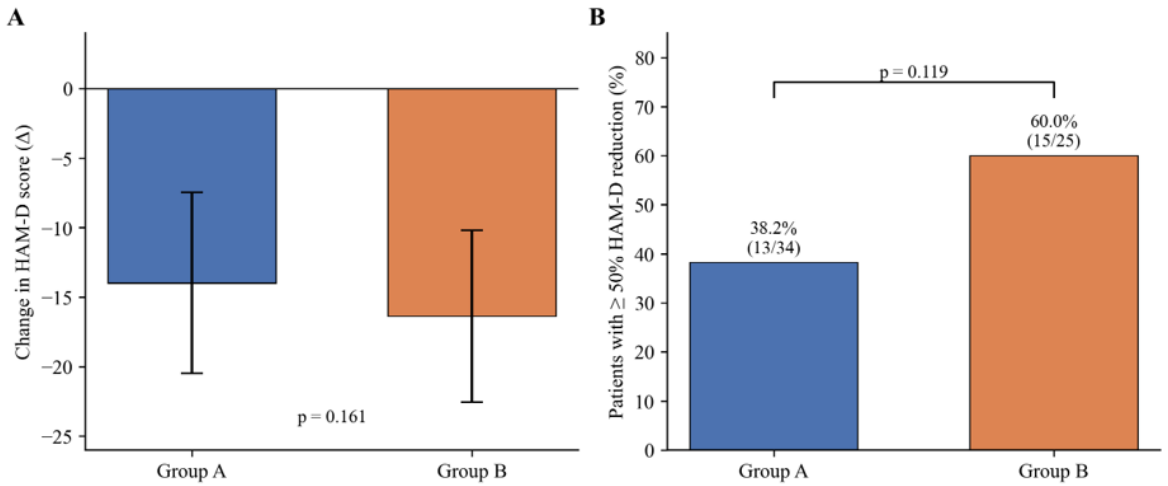

Figure 3.

(A) Mean change (Δ) in HAM-D score from baseline, with error bars representing the standard deviation.

(B) Proportion of patients achieving treatment response, defined as a reduction of ≥ 50% in HAM-D score from baseline

HAM-D = Hamilton Depression Rating Scale

Results interpretation in the light of confounding by indication

Real-world observational studies complement evidence derived from randomized clinical trials by describing treatment effectiveness under routine clinical conditions, where patients often present with greater clinical heterogeneity and multiple comorbidities (24). However, interpretation of observational data requires caution because treatment allocation reflects clinicians' therapeutic decisions rather than randomization (25). Patients receiving adjunctive antipsychotic therapy are frequently characterized by greater symptom severity, persistent insomnia or anxiety, previous inadequate treatment response, or other clinical factors that may independently influence outcomes. Consequently, differences observed between treatment groups should be interpreted within the context of individualized clinical decision-making rather than as direct evidence supporting the superiority of one therapeutic strategy over another (26).

The magnitude of improvement observed in both treatment groups was clinically meaningful, with reductions of approximately 14 - 16 points in HAM-D scores and improvements of 34 - 41 points in GAFS. These findings are consistent with the established efficacy of duloxetine in MDD (27, 28). Nevertheless, no patient achieved full remission (HAM-D $\leq$ 7), indicating a persistent residual symptom burden. This observation is in line with the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which demonstrated that remission becomes progressively less likely after each unsuccessful treatment step and established treatment augmentation as a rational strategy for patients with an inadequate response to antidepressant monotherapy (29).

The findings of the present study should therefore not be interpreted as evidence that duloxetine monotherapy is intrinsically superior to treatment combination with olanzapine. Rather, the observed pattern is consistent with channelling bias (confounding by indication), a well-recognized limitation of observational pharmacoepidemiological studies (26). In routine psychiatric practice, antipsychotic augmentation is typically reserved for patients with persistent symptoms, greater clinical complexity, or an insufficient response to antidepressant therapy (30). Patients receiving combination treatment are unlikely to be directly comparable with those maintained on antidepressant monotherapy.

Several observations support this interpretation. Patients receiving olanzapine augmentation were, on average, older at treatment initiation, suggesting differences in clinical profile between the groups. Moreover, adjustment for age and baseline symptom severity in ANCOVA models did not materially alter the results. While the functional advantage of the monotherapy group remained statistically significant, the difference in HAM-D scores did not, indicating that the measured baseline characteristics alone were insufficient to explain the observed outcomes. More importantly, the clinical factors that most likely influenced the decision to introduce olanzapine (previous inadequate treatment response, symptom persistence, psychotic or agitated features, sleep disturbance, psychiatric and somatic comorbidities, or clinician judgment) were not systematically documented and therefore could not be incorporated into the statistical models. Residual confounding is therefore likely to remain despite statistical adjustment.

An additional source of potential bias is the significantly longer follow-up period in the monotherapy group. Because psychosocial functioning generally recovers more gradually than depressive symptoms, the longer observation interval may partly explain the greater improvement in GAFS independently of treatment effect. This interpretation is supported by the attenuation of the functional differences in sensitivity analyses using non-parametric methods and after exclusion of the two patients with bipolar disorder, suggesting that the between-group difference in functioning should be interpreted cautiously. Our results most likely reflect treatment selection in routine clinical practice, where augmentation is preferentially prescribed to patients with a less favourable prognosis. The clinically relevant observation is therefore that patients selected for low-dose olanzapine augmentation still experienced substantial improvements in depressive symptoms and global functioning despite their presumed greater clinical complexity.

The safety implications of this therapeutic strategy also warrant consideration. Olanzapine is associated with a well-established risk of weight gain and metabolic disturbances, whereas duloxetine requires monitoring for hepatic adverse effects, blood pressure changes, and serotonergic interactions (31). In the present study, olanzapine was discontinued in only four patients (11.8%), and the mean maintenance dose remained low (mean 6.6 mg/day), suggesting acceptable long-term tolerability in routine practice. However, the absence of systematic documentation of body weight, metabolic parameters, and laboratory monitoring represents an important limitation of the study and highlights the need for more comprehensive monitoring in future real-world investigations.

Study limitations

Several limitations must be acknowledged. The sample is modest (n = 60), which limits statistical power for multivariable adjustment and robust subgroup analysis. The retrospective design limited the availability of systematically recorded information on treatment duration, adherence, concomitant psychotropic and somatic medication, comorbidities, adverse events, and the clinical reasons for adding or discontinuing olanzapine. The interval between assessments was neither standardised nor equal between groups, which

is itself a source of bias. Metabolic parameters were entirely absent from the records. The diagnostic spectrum was dominated by unipolar depression, with only two patients having documented bipolar features, so the findings do not generalise to bipolar depression. Ratings were performed by treating clinicians who were necessarily aware of the prescribed regimen, allowing for observer bias.

Despite these constraints, the study retains practical value. It documents that duloxetine, whether given alone or combined with modest doses of olanzapine, was associated with clinically relevant symptomatic and functional improvement in a real-world Romanian population. It also provides a worked illustration of why apparent differences in observational data must be interpreted with caution whenever treatment assignment is driven by clinical judgement. Prospective studies with larger samples, standardised follow-up intervals, explicit recording of the indication for augmentation, and systematic metabolic monitoring would substantially strengthen the evidence base for these commonly used combinations.

Conclusions

The present retrospective study demonstrates that both duloxetine monotherapy and duloxetine combined with low-dose olanzapine were associated with clinically meaningful improvements in depressive symptoms and global functioning in patients with affective disorders treated in routine outpatient practice. While modest differences in functional outcomes were observed between treatment groups, these should be interpreted within the context of individualized treatment allocation and the inherent limitations of an observational study design rather than as evidence of superior efficacy of either therapeutic approach.

The findings are consistent with the use of low-dose olanzapine as an adjunctive therapeutic option for carefully selected patients requiring broader symptom control beyond antidepressant monotherapy. At the same time, the potential clinical benefits should be balanced against the well-established metabolic risks associated with second-generation antipsychotics, highlighting the importance of appropriate patient selection and regular metabolic monitoring.

Larger prospective studies with standardized follow-up and comprehensive assessment of both clinical and metabolic outcomes are needed to further define the role of adjunctive low-dose olanzapine in the management of depressive disorders.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Mureș County Clinical Hospital, Romania (Approval No. 8836/12.06.2026), and was conducted in accordance with the principles of the Declaration of Helsinki.

AI use disclosure

AI was used to assist with language editing, improving readability, and refining the academic style of the manuscript. The authors were responsible for the study design, data collection, statistical analyses, interpretation of the results, and all scientific content. All AI-generated suggestions were critically reviewed, verified, and edited by the authors, who take full responsibility for the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther. 2024;9(1):30.
2. Sălcudean A, Cîmpian DM, Popovici RA, Vasiesiu AM, Muntean DL. Pharmacological insights with impact on depressive symptoms. Farmacia. 2025;73(2):296-307.
3. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. 2022;27(1):58-72.
4. Yu M, Ji W, Zhang Y, Si Z, Yu X, Jiang Z, et al. Meta-analysis of effectiveness of combined Shugan Jieyu capsules and selective serotonin reuptake inhibitors versus monotherapy with selective serotonin reuptake inhibitors in patients with depression. Farmacia. 2025;73(4):842-855.
5. Israel JA. The impact of residual symptoms in major depression. Pharmaceuticals (Basel). 2010;3(8):2426-2440.
6. Kirwin JL, Gören JL. Duloxetine: a dual serotonin-norepinephrine reuptake inhibitor for treatment of major depressive disorder. Pharmacotherapy. 2005;25(3):396-410.
7. Dueñas H, Brnabic AJ, Lee A, Montejo AL, Prakash S, Casimiro-Querubin ML, et al. Treatment-emergent

sexual dysfunction with SSRIs and duloxetine: effectiveness and functional outcomes over a 6-month observational period. Int J Psychiatry Clin Pract. 2011;15(4):242-254.
8. Dhaliwal JS, Spurling BC, Molla M. Duloxetine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [updated 2023 May 29; cited 2026 Mar 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549806/.
9. Baykan O, Altunoz S, Yilmaz Uyanik D, Baykan H. Dose-concentration relationship and clinical outcomes of duloxetine in generalized anxiety disorder. J Clin Med. 2026;15(3):1211.
10. Cuijpers P, Christensen H. Are personalised treatments of adult depression finally within reach? Epidemiol Psychiatr Sci. 2017;26(1):40-42.
11. Keks N, Hope J, Keogh S. Switching and stopping antidepressants. Aust Prescr. 2016;39(3):76-83.
12. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: a systematic review and meta-analysis. JAMA Psychiatry. 2022;79(4):300-312.
13. Jha MK, Mathew SJ. Pharmacotherapies for treatment-resistant depression: how antipsychotics fit in the rapidly evolving therapeutic landscape. Am J Psychiatry. 2023;180(3):190-199.
14. Wang J, Li W, Li M, Wu H, Qiu Z. Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults: a systematic review and network meta-analysis. Medicine (Baltimore). 2023;102(38):e34670.
15. Bobo WV, Shelton RC. Olanzapine and fluoxetine combination therapy for treatment-resistant depression: review of efficacy, safety, and study design issues. Neuropsychiatr Dis Treat. 2009;5:369-383.
16. Pardo JV, Sheikh SA, Schwindt G, Lee JT, Adson DE, Rittberg B, et al. A preliminary study of resting brain metabolism in treatment-resistant depression before and after treatment with olanzapine-fluoxetine combination. PLoS One. 2020;15(1):e0226486.
17. Shi X, Chen X, Ma X, Li R, Yang J, Chen C, et al. Molecular mechanisms of olanzapine against agitation in schizophrenia and bipolar disorder based on network pharmacology and molecular docking. Sci Rep. 2025;15(1):40279.
18. Römer N, Gaebler AJ, Neuner I, Haen E, Hiemke C, Schoretsanitis G, et al. Effects of the augmentation with quetiapine or olanzapine on the metabolism of duloxetine: a retrospective analysis. Expert Rev Clin Pharmacol. 2025;18(5):297-303.
19. Bi B, Shan L, Zhou D. Combined use of duloxetine and olanzapine in the treatment of urologic chronic pelvic pain syndromes refractory to conventional treatment: a case report. Clin Psychopharmacol Neurosci. 2018;16(1):122-125.
20. Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry. 2007;68(2):224-236.
21. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56-62.
22. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976;33(6):766-771.
23. World Medical Association. WMA Declaration of Helsinki – ethical principles for medical research involving human subjects [online]. Ferney-Voltaire: World Medical Association; 2024 [cited 2026 Mar 21]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki/.
24. Thadhani R. Formal trials versus observational studies. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry disease: perspectives from 5 years of FOS [online]. Oxford: Oxford PharmaGenesis; 2006. Chapter 14. [cited 2026 Mar 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11597/.
25. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35(11):1763-1774.
26. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol. 1999;149(11):981-983.
27. Rodrigues-Amorim D, Olivares JM, Spuch C, Rivera-Baltanás T. A systematic review of efficacy, safety, and tolerability of duloxetine. Front Psychiatry. 2020;11:554899.
28. Allgulander C, Hartford J, Russell J, Ball S, Erickson J, Raskin J, et al. Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. Curr Med Res Opin. 2007;23(6):1245-1252.
29. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-1917.
30. Zhou X, Keitner GI, Qin B, Ravindran AV, Bauer M, Del Giovane C, et al. Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. Int J Neuropsychopharmacol. 2015;18(11):pyv060.
31. Oruch R, Rajab HA, Elderbi MA, Pryme IF, Fasmer OB, Lund A. Drawbacks of olanzapine therapy: an emphasis on its metabolic effects and discontinuation. J Clin Med. 2025;14(22):8125.