Received: March 25, 2025
Accepted: May 23, 2025

Acad Med J 2025;5(2):73-82
UDC: 616.895.4:616.831-073.97
DOI:
Original article

QUANTITATIVE ANALYSIS OF THE EFFICACY OF TREATMENT WITH NEUROFEEDBACK METHOD IN PATIENTS WITH AFFECTIVE DISORDERS

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Abstract

Introduction: Depression affects approximately 300 million people globally, with about 5% of adults experiencing an episode each year, making it a major public health concern. The limitations of standard therapies and the high prevalence of depression highlight an urgent need for alternative or augmentation of existing types of treatments, such as neurofeedback, which has shown promising results in improving depressive symptoms in patients diagnosed with affective disorders. Despite the wide range of antidepressant drugs with different mechanisms of action, a large number of studies suggest that as much as 1/3 of patients treated with antidepressant drugs (about 30%) remain resistant to treatment.

Aim of the study: The main goal of this study was to measure the effectiveness of the combined treatment of the neurofeedback method and antidepressants in the treatment of patients diagnosed with affective disorder.

Material and methods: A prospective, randomized study was conducted at the University Clinic for Psychiatry in Skopje, over 6 months, involving 100 outpatients diagnosed with affective disorders (ICD-10 codes F32, F33, F34). Participants were randomly assigned into two groups: the study group (SG) received both neurofeedback and antidepressant therapy, while the control group (CG) received antidepressant monotherapy. The Beck (BDI) and CGI scales, alongside with a structured psychiatric interview and sociodemographic questionnaire at baseline, were used to assess depressive symptoms at baseline, and every four weeks in a period of 6 months during the treatment. Data were analyzed with SPSS v23.0, using parametric and non-parametric tests, with significance set at $p<0.05$. The study received ethics approval, and all participants provided informed consent.

Results: The study revealed a significant reduction in depressive symptoms in the SG compared to the CG. At baseline, both groups had similar BDI scores (18.88±5.8 in SG *vs*. 21.0±8.7 in CG; p=0.15). However, by the second follow-up, the SG exhibited a statistically significant improvement (BDI: 16.80±5.7 *vs*. 20.56±8.8; p=0.013), pointing towards a 11.02% score reduction in the SG compared to a 2.09% in the CG. This trend continued throughout the study, with the final assessment showing a mean BDI score of 13.14±5.9 in the SG *versus* 19.58±8.2 in the CG (p=0.00002). As for the CGI scale, a greater reduction in the total CGI scale score was recorded at the second assessment in the SG (12.15%), compared to the CG (2.46%), confirming the faster treatment response with the combined treatment approach. The CGI scores indicated greater

clinical improvement in the SG, with a mean CGI score of 7.34±2.4 compared to 9.54±2.5 in the CG (p=0.000016) at the final assessment.

Conclusion: The combined treatment encompassing neurofeedback training and antidepressant therapy demonstrated superior efficacy in reducing depressive symptoms compared to antidepressant monotherapy.

Keywords: affective disorders; neurofeedback; alternative treatment

Introduction

Depression affects approximately 300 million individuals worldwide, representing a major global health issue that is often neglected despite its significant impact[1]. Each year, around 5% of adults experience an episode of depression, with prevalence rates varying across different regions and demographic groups[1,2]. The highest prevalence is observed in North America (4.4% for women and 2.5% for men) and the lowest in the Western Pacific[3]. Women are disproportionately affected, experiencing depression nearly twice as often as men, with hormonal changes during puberty, menstruation, pregnancy, and perimenopause, as well as different psychosocial stressors, learned behavioral patterns and socio-economic inequities contributing to this disparity[4,5]. While retrospective reports suggest a 10.6% average lifetime prevalence, prospective studies estimate a higher range of 30-40%, underscoring the pervasive nature of this condition and the need for effective treatment strategies[3,6]. Moreover, depression is projected to be the leading cause of disease burden by 2030, particularly affecting women[1,7]. Furthermore, the risk factors associated with the COVID-19 pandemic such as greater exposure to stressors, reduced social interaction, healthcare and economic resources, employment loss, isolation and fear, contributed to a dramatic increase in the global prevalence of depression worldwide reaching 25%, which is seven times higher than the pre-pandemic estimates[4]. This alarming trend highlights the urgency for comprehensive research and interventions to mitigate its widespread consequences. Beyond significant subjective suffering, depression is associated with disability and a high risk of suicide in affected individuals. Additionally, it imposes greater social and economic burden due to high rates of recurrence and relapse[4,7].

Treatment resistant depression (TRD) is a significant concern, affecting approximately 30% of individuals with major depressive disorder (MDD), and accounting for nearly 50% of the total annual economic burden estimated at $43.8 billion in recent US studies[4,8,]. The treatment challenges and high prevalence associated with TRD emphasize the need to explore alternative and adjunctive therapeutic options[9-11].

Neurofeedback training, a non-invasive intervention, has emerged as a promising supplementary treatment for major depressive disorder. It has shown a significant improvement, even in patients who do not achieve sufficient remission with standard pharmacological treatments[12,13]. Systematic reviews and meta-analyses support its potential efficacy as an adjunctive therapy, enhancing the outcomes of conventional treatments, while maintaining a low risk of side effects and beneficial impacts on neuropsychological function[12-16].

The aim of this study was to assess the efficacy of combining neurofeedback training with standard antidepressant therapy in adult patients with affective disorders, and to determine whether this combined approach enhances symptom reduction in comparison to antidepressant monotherapy.

Materials and methods

This prospective, randomized, controlled study was conducted at the University Clinic for Psychiatry, Skopje, North Macedonia, over the course of 6 months. A total of 100 outpatients aged 18 to 65 years, where included in the study. They were diagnosed with affective disorders based on the ICD-10, codes F32 (depressive episode), F33 (recurrent depressive disorder), and F34 (persistent affective disorder). Participants were randomly assigned into two groups of 50: the study group (SG) received a combination of antidepressant therapy and neurofeedback treatment, and the control group (CG) received antidepressant monotherapy. The SG received neurofeedback sessions in addition to antidepressants including selective serotonin update inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and noradrenergic and specific serotonergic antidepressants (NASsA). Neurofeedback was administered using the "Encephalan-EEGR-19/26" device with the “Rehacor” software for alpha/theta training. Each participant underwent 10 neurofeedback sessions, each lasting 25 minutes. The CG was treated with antidepressant monotherapy, including SSRIs (e.g., Sertraline 50 mg), SNRIs (e.g., Venlafaxine 150 mg), or NASsA (e.g., Mirtazapine 45 mg).

Participants in the study were assessed at six time points: baseline, two weeks after treatment initiation, and once monthly for the following four months. Baseline data collection included a psychiatric interview, a sociodemographic questionnaire, and psychodiagnostics assessments using the Beck Depression Inventory (BDI) and the Clinical Global Impression (CGI) scale to evaluate affective symptoms and track changes in clinical symptoms over time.

The Beck depression inventory (BDI) quantifies depressive symptoms by measuring various aspects of daily functioning. It consists of 21 questions, each rated on a scale from 0 to 3, depending on symptom severity. At the end of each psychiatric evaluation, the total score is calculated and subsequent evaluation allow a comparison of results over time[17].

The CGI scale assesses the overall clinical impression reported by the patient during an examination. It evaluates global functioning in nearly all psychiatric disorders, including affective disorders. The CGI scale consists of four parts: severity of illness, overall improvement, therapeutic effect, and adverse effects. Each part is rated on a scale from 0 to 7, and on each assessment point, the total score is calculated[18].

Statistical analysis

To compare the study and control groups regarding demographic and clinical characteristics, as well as total scores on the BDI and CGI scales, non-parametric tests (Pearson Chi-square and Fisher's exact test) and a parametric test (t-test for independent samples) were used. Testing the differences in the total scores on the Beck scale and CGI scale between the three assessment points (baseline, 1 month and six months after treatment initiation) within the groups was performed using the parametric t-test for dependent samples. Statistical significance was defined at a level of $p<0.05$.

The study received ethics approval by the Ethics Committee of the Ss. Cyril and Methodius University, Faculty of Medicine in Skopje, and all participants provided informed consent.

Results

Comparative analysis in terms of demographic and clinical characteristics

Patients from both groups, study and control, were homogenous in terms of gender, with no statistically significant difference ($p=0.84$). Female patients were predominant in both groups (52% and 54% in the study and in the control group, respectively) (Table 1).

Forty percent of the SG and 14% of the CG were aged between 18 and 34 years; 30% from the SG and 22% from the CG were aged between 35 and 44 years; 26% from the SG and 60% from the CG were aged between 45 and 64 years; 4% from each group were 65 years of age or older (Table 1).

Table 1. Demographic distribution of patients

Gender	**Groups**			**p-level**
	n	**SG n=50**	**CG n=50**	
Male	47	24(48%)	23(46%)	X^2=0.04
Female	53	26(52%)	27(54%)	p=0.84
Age	**n**	**SG n=50**	**CG n=50**	
18 - 34	27	20(40%)	7(14%)	
35 - 44	26	15(30%)	11(22%)	
45 - 64	43	13(26%)	30(60%)	X^2=13.56
≥65	4	2(4%)	2(4%)	**p=0.0035

X^2 (Pearson Chi-square)

Comparative analysis by Beck Depression Inventory

Scores on the Beck depression scale (BDI) calculated for both groups at baseline and during the rest of follow-up assessments are given in Table 2. The average score on the Beck depression inventory at the second assessment was 16.80±5.7 in the SG and 20.56±8.8 in the CG. The average difference of 3.76 points was statistically significant (p=0.013). Patients treated with both antidepressants and neurofeedback had a significantly lower score on the scale compared to those treated with antidepressants alone (Table 2).

The Beck depression inventory score at the second follow-up assessment was significantly lower in the group treated with both medication and the neurofeedback method compared to the group treated with antidepressants alone (p=0.0032, difference=4.38). In the SG, the average score on this scale was 15.54±5.6, while in the CG, it was 19.92±8.6 (Table 2). At the third follow-up assessment, the average score on the Beck depression inventory was 14.34±5.5 in the SG and 19.80±8.6 in the CG. The average difference of 5.46 points was statistically significant (p=0.00026). Patients treated with both medication and the neurofeedback method had a significantly lower score on the scale (Table 2).

Table 2. Beck depression inventory (BDI) scores on baseline examination, first follow-up assessment and the rest of follow-up assessments

BDI scores		**Groups**		**p-level**
		SG n=50	**CG n=50**	
BDI 0	mean ±SD	18.88±5.8	21.0±8.7	t=1.44
BDI 0	min- max	7-40	3-50	p=0.15
BDI 1	mean ±SD	16.80±5.7	20.56±8.8	t=2.53
BDI 1	min- max	6-36	3-50	*p=0.013
BDI 2	mean ±SD	15.54±5.6	19.92±8.6	t=3.02
BDI 2	min- max	6-34	2-49	***p=0.003
BDI 3	mean ±SD	14.34±5.5	19.80±8.6	t=3.8
BDI 3	min- max	4-31	2-48	***p=0.0002
BDI 4	mean ±SD	13.60±5.5	20.0±8.5	t=4.5
BDI 4	min- max	4-30	2-47	***p=0.00002
BDI 5	mean ±SD	13.14±5.9	19.58±8.2	t=4.48
BDI 5	min- max	3-32	2-47	***p=0.00002

t (Student t-test); X2 (Pearson Chi-square), ***sig p<0.0001

The average score on the Beck depression inventory at the fourth assessment was 13.60±5.5 in the SG and 20.0±8.5 in the CG. The average difference of 6.4 points was statistically significant (p=0.00002). Patients treated with both antidepressants and neurofeedback had a significantly lower score on the scale compared to those treated with antidepressants alone (Table 2). A statistically significant difference in the level of depression between the two groups at the fourth assessment was confirmed, with p=0.005, according to the total BDI score. At the fifth and final assessment, the difference in the average Beck depression inventory score between the study and control groups was 6.44 points (13.14±5.9 *vs*. 19.58±8.2), with a statistically significant difference of p=0.00002. At the final assessment, patients treated with both medication and the neurofeedback method had a significantly lower Beck depression scale score compared to those treated with medication alone (Table 2). The level of depression between patients in the two groups was statistically significantly different (p=0.0009).

In the SG, compared to the CG, a greater reduction in the total score on the Beck depression inventory was observed at the second assessment. The average score significantly decreased by 2.08 points in the IG (p<0.0001) and by 0.44 points in the CG (p=0.022). The percentage reduction in the Beck score was 11.02% in the IG and 2.09% in the CG (Table 3). This is very important as it demonstrates the rapid antidepressant effects of the combined treatment observed at the first follow-up assessment.

Table 3. Total score on Beck scale baseline/first follow-–up assessment

Beck score	SG n=50		CG n=50	
	Baseline	First follow-up	Baseline	First follow-up
mean ±SD	18.88±5.8	16.80±5.7	21.0±8.7	20.56±8.8
difference	2.08		0.44	
p-level	t=10.52 ***p=0.00000		t=2.37 *p=0.022	
% of change	11.02%		2.09%	

*sig p<0.05, ***sig p<0.0001

Figure 1 illustrates the dynamics of the reduction in the Beck depression inventory score in the study and control groups throughout the course of antidepressant treatment.

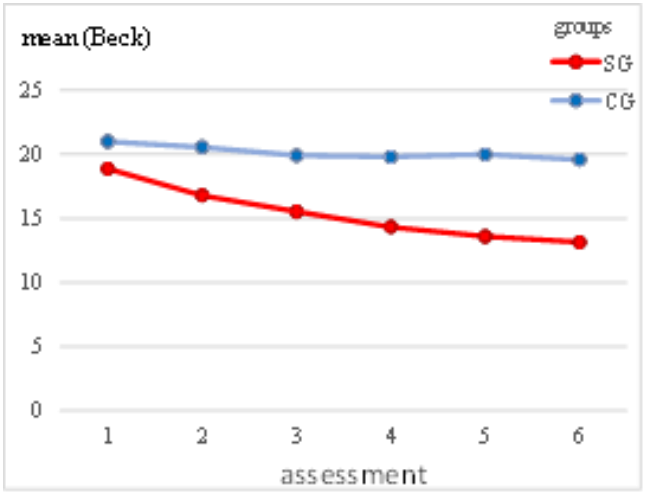

Fig. 1. BDI score dynamics

Comparative analysis based on Clinical Global Impression Scale (CGI)

At the beginning of antidepressant treatment, patients in both groups had a similar CGI scale score (10.04±2.8 and 10.58±2.2 in the study and control groups, respectively), with p=0.296 (Table 4). The average CGI scale score at the second assessment was 8.82±2.5 in the SG and 10.32±2.5 in the CG. The average difference of 1.5 points was statistically significant (p=0.0035). Patients treated with both antidepressants and the neurofeedback method had a significantly lower CGI score compared to those treated with antidepressants alone (Table 4).

The global clinical impression did not differ significantly between the two groups at the third assessment, based on the categorization of the total CGI score (p=0.16). The average CGI score at the fourth assessment was 7.66±2.2 in the SG and 9.66±2.6 in the CG; the difference between the two mean scores was statistically significant (p=0.000076). A significantly lower score on the scale was observed in patients treated with medication and the neurofeedback method. Patients in the SG had a significantly lower CGI score at the third assessment compared to patients in the CG (8.18±2.5 *vs*. 9.82±2.4, difference=1.64, p=0.00112) (Table 4).

Table 4. CGI scores on baseline examination, first follow-up assessment and the rest of follow-up assessments

CGI scores		Groups		p-level
		SG n=50	CG n=50	
CGI 0	mean ±SD	10.04±2.8	10.58±2.2	t=1.05
CGI 0	min- max	5-17	6-17	p=0.296
CGI 1	mean ±SD	8.82±2.5	10.32±2.5	t=3.0
CGI 1	min- max	4-15	4-17	**p=0.0035
CGI 2	mean ±SD	8.18±2.5	9.82±2.4	t=3.36
CGI 2	min- max	3-13	5-17	**p=0.0011
CGI 3	mean ±SD	7.66±2.2	9.66±2.6	t=4.13
CGI 3	min- max	4-13	5-16	***p=0.000076
CGI 4	mean ±SD	7.50±2.1	9.62±2.5	t=4.53
CGI 4	min- max	4-13	5-17	***p=0.000017
CGI 5	mean ±SD	7.34±2.4	9.54±2.5	t=4.55
CGI 5	min- max	3-13	5-16	***p=0.000016

t (Student t-test) ; X^2 (Pearson Chi-square), ***sig p<0.0001

A statistically significant difference in the global clinical impression between the two groups was confirmed at the fourth assessment (p=0.0225). The difference in the CGI score was also confirmed between the two groups at the fifth assessment and it was statistically significant. The average score on this scale was 7.50±2.1 in the SG and 9.62±2.5 in the CG, with a mean difference of 2.12 points. Patients treated with antidepressants and the neurofeedback method had a significantly lower score on the scale compared to patients treated with antidepressants alone. At the final sixth follow-up, the CGI scale had an average score of 7.34±2.4 in the SG and 9.54±2.5 in the CG, with a mean difference of 2.2 points, which was statistically significant (p=0.0035). Patients treated with medication and the neurofeedback method had a significantly lower global CGI score than patients treated with medication alone.

In the SG, compared to the CG, a greater reduction in the total score on the CGI scale was observed at the second assessment. The average CGI scale score significantly decreased by 1.22 points in the SG (p<0.0001) and by 0.26 points in the CG (p=0.022). The percentage reduction in the CGI score was 12.15% in the SG and 2.46% in the CG (Table 5). This is also very important,

as it demonstrates the rapid antidepressant effects of the combined treatment at the first follow-up assessment.

Table 5. Total score on CGI scale at baseline/ first follow-up assessment - SG and CG

CGI score	SG n=50		CG n=50	
	First examination	Second examination	First examination	Second examination
mean ±SD	10.04 ± 2.8	8.82 ± 2.5	10.58 ± 2.25	10.32 ± 2.5
difference	1.22		0.26	
p-level	t=8.85 ***p=0.000000		t=2.36 *p=0.022	
% of change	12.15%		2.46%	

*sig p<0.05, ***sig p<0.0001

Figure 2 illustrates the dynamics of the reduction in the CGI score in the study and control groups throughout the course of antidepressant treatment.

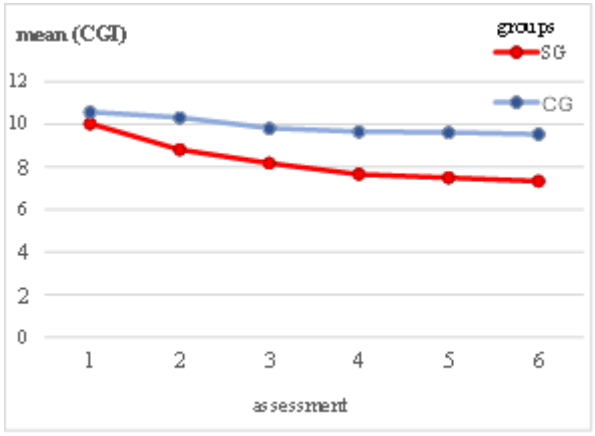

Fig. 2. CGI score dynamics

Discussion

This study is the first in our country to assess the comparative efficacy of antidepressant drug monotherapy *versus* a combined treatment with neurofeedback. It contributes to the growing body of research on alternative and adjunctive treatments for depression, particularly for individuals who do not achieve sufficient remission from standard pharmacological interventions. Several clinical trials have been conducted in our country and the region to evaluate the efficacy of antidepressant drug therapy in treating of affective disorders [19]. Given the high global prevalence of depression, its profound social and economic impact, and the substantial portion of patients experiencing treatment-resistant depression (TRD), exploring effective supplementary treatments such as neurofeedback is essential.

This prospective randomized controlled study evaluated the efficacy of combined neurofeedback and pharmacological treatment *versus* antidepressant monotherapy in patients with affective disorders. Our sample was demographically balanced, with a slight female predominance in both the study group (SG) and control group (CG), 52% and 54% respectively. This aligns with epidemiological findings indicating a higher prevalence of affective disorders in women due to biological and psychosocial factors.

At the start of treatment, both groups displayed comparable levels of depressive symptoms on the BDI and CGI scales, with average total scores of 18.88±5.8 in the SG and 21.0±8.7 in the

CG for BDI scale, and 10.04±2.8 in the SG, and 10.58±2.2 in the CG for CGI, indicating homogeneity before intervention. At the first follow-up assessment, conducted one month after the start of the treatment, the SG compared to the CG, showed a greater reduction in the total score on the Beck depression inventory. The average score significantly decreased by 2.08 points in the SG ($p<0.0001$) and by 0.44 points in the CG ($p=0.022$). The percentage reduction in the BDI score was 11.02% in the SG and 2.09% in the CG. Regarding the CGI scale, in the SG, compared to the CG, showed a greater reduction in the total score on the CGI scale at the second assessment. The average CGI scale score significantly decreased by 1.22 points in the SG ($p<0.0001$) and by 0.26 points in the CG ($p=0.022$). The percentage reduction in the CGI score was 12.15% in the SG and 2.46% in the CG. This early improvement in the SG may highlight the potential of neurofeedback to accelerate therapeutic responses when used as an adjuvant for the antidepressant medication. At the third and fourth examination, the average score on the BDI scale was 14.34±5.5 in the SG and 19.80±8.6 in the CG. The difference of an average of 5.46 points was statistically significant ($p=0.00026$). Regarding the results from the CGI scale, the mean score at the fourth assessment was 7.66±2.2 in the SG and 9.66±2.6 in the CG; the difference between the two mean scores was statistically significant ($p=0.000076$).

At the final assessment, patients treated with both medication and the neurofeedback method had a significantly lower scores on BDI scale compared to those treated with medication alone. The level of depression between patients in the two groups was statistically significantly different ($p=0.0009$). The efficacy of the combined treatment in the reduction of depressive symptoms was further confirmed by the results from the CGI scale with an average score of 7.34±2.4 in the SG and 9.54±2.5 in the CG, with a mean difference of 2.2 points, which was statistically significant ($p=0.0035$). This sustained effect supports the hypothesis that neurofeedback may enhance long-term outcomes in the treatment of depression by reinforcing neural regulation, as evidenced in a substantial body of literature incorporated in the recent meta-analysis by Xia *et al.* (2024) and the systematic review by Patil *et al.* (2023) that report neurophysiological improvements alongside the reduction in affective symptomatology[12,13]. This is in line with previous studies that demonstrate neurofeedback value in lowering symptom intensity in depressive patients who are not fully responsive to medication alone[20].

Due to its non-invasive nature, minimal side effects, and relatively low cost, neurofeedback has emerged as a valuable adjunct to pharmacological treatments of affective disorders. Our findings are consistent with those presented by Cheon EJ *et al*., who demonstrated that neurofeedback treatment could improve depressive symptoms significantly [14]. Similarly, our results are consistent with the conclusions of Wang SY *et al*., who found that patients who responded to neurofeedback treatment experienced a decrease in anxiety and depression scores compared to those who did not respond[15]. Many studies in their review emphasized the role of neurofeedback in reducing depressive symptoms, reinforcing its potential as a promising non-pharmacological option. Collectively, these conclusions support the efficacy of neurofeedback observed in our study, highlighting its therapeutic value as an adjunctive treatment for individuals with treatment-resistant or major depressive disorder[21,22].

Conclusion

The combined treatment, consisting of neurofeedback training and antidepressant therapy, demonstrated superior efficacy in reducing depressive symptoms compared to antidepressant monotherapy. Patients in the SG consistently exhibited greater and faster improvement as measured by the BDI and CGI scales, suggesting that neurofeedback is a promising adjunctive

treatment for affective disorders. Further research is warranted to confirm its long-term benefits and optimal integration into clinical practice.

Conflict of interest statement. None declared

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