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Transcranial Direct Current Stimulation as an Adjuvant Therapy for Major Depressive Disorder

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *Transcranial direct current stimulation (tDCS) is a non-invasive technique that modulates cortical activity and has shown antidepressant effects, particularly as an adjunctive treatment in patients with major depressive disorder.*
- *International guidelines, such as those from the Canadian Network for Mood and Anxiety Treatments and the European Neurostimulation Consensus, include tDCS as a therapeutic option, especially for treatment-resistant depression.*

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ABSTRACT

Objective: Major depressive disorder (MDD) is a prevalent and debilitating mental health condition, often accompanied by medical and psychiatric comorbidities. Effective treatment strategies are crucial to reducing symptoms and improving the quality of life for affected individuals. This study evaluates the effectiveness of transcranial direct current stimulation as an adjunctive treatment for MDD, analyzing its impact on depressive symptom reduction, safety, tolerability, and effectiveness when combined with conventional pharmacological treatments.

Methods: A historical cohort study was conducted with 60 participants diagnosed with MDD. The Hamilton Depression Scale and 9-Item Patient Health Questionnaire were used to measure depressive symptom severity. Pre- and post-treatment scores were analyzed using ANOVA, with significance set at $P < .05$. Effect sizes were calculated to quantify the magnitude of treatment effects. Demographic data, comorbidities, and concurrent pharmacological treatments were also recorded.

Results: The cohort had an average age of 44.22 ± 19.8 years, with 43 (71.7%) women and 17 (28.3%) men. Anxiety and insomnia were common, reported by 73.3% and 81.7% of participants, respectively, with 65% experiencing both. Medical comorbidities were present in 56.7% of participants. Antidepressant use was noted in 43.3%, with sertraline and escitalopram being the most frequently prescribed. Post-treatment Hamilton Depression Rating Scale scores decreased from 24.23 to 6.78 ($P < .01$), reflecting a 72.02% reduction. 9-Item Patient Health Questionnaire scores dropped from 17.83 to 4.67 ($P < .01$), a 73.81% reduction. No adverse effects were observed, supporting the intervention's tolerability.

Conclusion: Transcranial direct current stimulation, as an adjunct to pharmacological therapy, significantly reduces depressive symptoms in individuals with MDD. These findings support its use as an effective and tolerable treatment option, especially for patients with comorbid medical and psychiatric conditions.

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WHAT DOES THIS STUDY ADDS ON THIS TOPIC?

- *This study provides real-world clinical evidence that tDCS significantly reduces depressive symptoms when used alongside stable antidepressant therapy, even in patients with multiple medical and psychiatric comorbidities. It also demonstrates the safety, tolerability, and feasibility of tDCS in public healthcare settings.*

Keywords: Adjunct therapy, depression pathology, Hamilton Depression Rating Scale, HDRS, PHQ-9, tDCS, transcranial direct current stimulation, 9-Item Patient Health Questionnaire

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental health condition that significantly impacts both personal well-being and societal functioning.[1] It is characterized by a persistent low mood, anhedonia (loss of interest or pleasure in activities that were once enjoyable), negative thoughts, sleep disturbances, and psychomotor retardation.[2] Globally, MDD is a leading cause of disability, and the World Health Organization estimates that by 2030, it will become the leading contributor to the global burden of disease.[3] Despite the availability of various pharmacological and psychotherapeutic treatments, a substantial proportion of patients with MDD fail to achieve full remission. In fact, only about 30% of patients experience full remission, leaving the remaining 70% with partial responses or treatment-resistant depression.[4] This presents a significant clinical challenge, as untreated or inadequately managed depression can lead to increased healthcare costs, frequent medical visits, and a heightened risk of suicide.[5]

Recent advancements in neurostimulation techniques, such as transcranial direct current stimulation (tDCS), offer promising adjunctive options for treating MDD, particularly in cases where standard treatments have proven insufficient. tDCS is a non-invasive brain stimulation technique that modulates cortical excitability by applying a low-intensity electric current through electrodes placed on the scalp. It has gained increasing attention as a safe and effective intervention for MDD, even in patients with treatment-resistant forms of the disorder.[6,7] Several randomized controlled trials and meta-analyses have demonstrated antidepressant effects of tDCS, with some studies reporting significant reductions in depressive symptom severity.[9] However, other trials have found that tDCS does not consistently outperform placebo, suggesting that its clinical efficacy may vary depending on study design, patient characteristics, and stimulation protocols.[8] These mixed findings highlight the need for further clinical evaluation of tDCS in real-world contexts. Additionally, tDCS has been incorporated into clinical guidelines, such as the Canadian Network for Mood and Anxiety Treatments guidelines and the European guidelines on neurostimulation, further supporting its role as a viable therapeutic option.[10-12]

In this study, the aim was to evaluate the clinical outcomes of patients receiving tDCS as an adjunctive treatment for MDD in combination with pharmacological therapies. Specifically, the reduction in depressive symptoms, the prevalence of medical and psychiatric comorbidities, and the safety and tolerability of tDCS would be analyzed. Given that the institution has implemented this technique with approval from the Federal Commission for the Protection against Sanitary Risks, it is essential to assess its efficacy in the patient population to determine its therapeutic potential and identify areas for improvement in clinical practice.

Moreover, tDCS offers notable advantages over other neuromodulation techniques such as transcranial magnetic stimulation (TMS) or deep brain stimulation. Its ease of application, safety profile, portability, and low cost make it an attractive option for institutions with limited resources or for patients facing logistical barriers. Additionally, its better tolerability may enhance treatment adherence, making it well-suited for public healthcare settings.

Furthermore, this study seeks to contribute to the growing body of evidence supporting the use of tDCS in MDD, particularly in a clinical setting where comorbidities are prevalent. It is well established that patients with MDD often present with medical and psychiatric comorbidities, such as anxiety disorders and insomnia, which complicate treatment outcomes.[13] Understanding how tDCS interacts with these comorbidities will provide valuable insights into optimizing treatment strategies for this population. Additionally, exploring the tolerability and safety profile of tDCS in a real-world clinical setting will help establish guidelines for its broader implementation in psychiatric care.

The findings from this research will provide a foundation for further studies and could potentially guide future clinical decision-making regarding the use of tDCS as an adjunctive treatment for MDD,

especially in patients with refractory depression. It was hypothesized that the combination of tDCS and standard pharmacological treatment would result in significant reductions in depressive symptoms and offer a safe and effective approach to managing MDD.

MATERIAL AND METHODS

This was a retrospective cohort study with an observational approach. Data were collected from medical records of patients diagnosed with MDD who underwent tDCS therapy from January 2022 to May 2023. The study population included all adult patients diagnosed with MDD who received tDCS treatment as part of their therapeutic regimen during the study period. The study covered patients treated with tDCS from January 1, 2021, to December 31, 2023. Following protocol approval on April 19, 2024, data collection occurred between April and May 2024. Statistical analysis and manuscript preparation began in May, with the final submission planned for May 29, 2024.

The inclusion criteria comprised adults (≥18 years) with a confirmed diagnosis of MDD, based on DSM-5 criteria, who had completed both pre- and post-treatment evaluations using the HDRS and PHQ-9 scales. Exclusion criteria included patients receiving tDCS for other psychiatric or neurological conditions and those with incomplete or illegible medical records. The MDD diagnoses were established by board-certified psychiatrists as part of routine clinical care. The HDRS and PHQ-9 assessments were conducted by trained mental health professionals, and all tDCS interventions were administered by certified clinical personnel following standardized protocols. A total of 60 patients met the inclusion criteria and were included in the final analysis.

Adult patients with a confirmed diagnosis of MDD who underwent tDCS therapy and had complete pre- and post-treatment evaluations, including scores on the Hamilton Depression Rating Scale (HDRS) and Patient Health Questionnaire-9 (PHQ-9), were included. Patients who received tDCS for conditions other than MDD, or those with incomplete or illegible medical records relevant to the study variables, were excluded from the final analysis. A non-probabilistic, census-type sampling method was used to include all eligible records that met the inclusion criteria.

The variables collected in this study included demographic data such as sex and age, as well as clinical measures related to depression severity, including HDRS and PHQ-9 scores both before and after tDCS treatment. Additionally, the presence of medical comorbidities and the psychopharmacological treatment prescribed at the start of tDCS were recorded. This study was reviewed and approved by the Ethics and Research Committee of the institution where the study was conducted. After approval, both physical and electronic medical records from the hospital's information system (SIAH) were reviewed. Information from the patients' files, including demographic details, comorbidities, and depression assessment scores, was entered into an Excel database for statistical analysis.

Transcranial direct current stimulation was applied using electrodes placed at F3 (anode) and F4 (cathode) following the International 10/20 EEG system. The stimulation parameters were set to 2 mA for 30 minutes per session, with a total of 20 sessions administered over 2 weeks (Monday to Friday), with 2 daily sessions and a 30-minute interval between them. The device used was the Sooma tDCS system (Sooma Oy, Helsinki, Finland), a CE-certified medical-grade device designed for non-invasive brain stimulation.[17] Depression severity was measured using the HDRS and PHQ-9 scales before and after the tDCS treatment.

Data were analyzed using STATA 16.0 (16.1, StataCorp LLC, College Station, TX), Statistica 13.5, and Minitab 20.4. Descriptive statistics were used to summarize demographic data and clinical outcomes. Continuous variables were presented as means and SDs, while categorical variables were presented as frequencies and percentages. For pre- and post-treatment comparisons, ANOVA (parametric) and Wilcoxon tests (non-parametric) were performed. Statistical significance was set at $P < .05$. Chi-square tests were used to examine associations between categorical variables, while effect sizes were calculated using Eta-squared.

This study was approved by the Ethics and Research Committee of the institution of the National Medical Center "20 de Noviembre", ISSSTE (Approval no.: 243.2024; Date: April 17, 2024) and conducted in accordance with the Declaration of Helsinki (1975, revised 2013). Although retrospective in nature, all patients had previously signed informed consent forms for tDCS administration, as required by national regulations. All collected data were anonymized and handled according to institutional ethical standards.

RESULTS

The study analyzed 60 cases, and Table 1 provides a characterization of the patients included. The mean age of participants was 44.22 years (range: 18-74 years), with a SD of 19.86 years. The gender distribution showed a higher proportion of women (71.7%, N = 43) compared to men (28.3%, N = 17).

Regarding tolerability, no adverse effects were reported during or after the tDCS sessions in any of the 60 participants. The intervention was well tolerated across the entire sample, including patients with multiple medical comorbidities. No patient discontinued treatment due to discomfort or side effects, supporting the safety profile of tDCS in this clinical setting.

The prevalence of subjective symptoms of anxiety and insomnia was 73.3% (N = 44) and 81.7% (N = 49), respectively. Additionally, 65% (N = 39) of patients experienced both types of symptoms. A comparative analysis of scores on the HDRS showed a clinically and statistically significant reduction of 17.45 points on average (a 72.04% reduction) in symptoms after treatment ($P < .05$). Similarly, PHQ-9 scores showed a notable reduction, with an average decrease of 13.16 points (63.45%) in depressive symptoms (see Figures 1 and 2).

A total of 22 different types of comorbidities were observed. The study revealed that 56.7% (N = 34) of patients had at least 1 medical comorbidity, while 43.3% (N = 26) had no comorbidities. The most common comorbidities were hypertension (19.61%, N = 12), type 2 diabetes mellitus (15.69%, N = 9), hypothyroidism (9.80%, N = 6), fibromyalgia (5.88%, N = 3), and epilepsy (5.88%, N = 3). The distribution of comorbidities per patient was as follows: 35% had 1 comorbidity, 16.7% had 2, 3.3% had 3, and 1.7% had 4 comorbidities.

Regarding psychiatric treatments, the most commonly used medications were sertraline, escitalopram, and fluoxetine. Sertraline was the most frequently prescribed medication, accounting for 17 events

Table 1. Characteristics of the Patients Included in the Study

Feature	Value	Statistical Test
Number of cases	60	N/A
Average age (range)	44.22 years (18-74 years)	Mean ± SD
SD	19.86 years	N/A
Gender distribution	Women: 71.7% (43 patients)	Chi-square ($\chi^2 = 2.11$, $P = .13$)
	Men: 28.3% (17 patients)	
Score reduction	Hamilton Depression Scale: 17.45 points on average	F (ANOVA) = X, $P < .05$
	(72.04% reduction, $P < .05$)	
	PHQ-9: 13.16 points on average	F (ANOVA) = X, $P < .05$
	(63.45% reduction, $P < .05$)	
Comorbidities	Patients with comorbidities: 56.7% (34 patients)	Chi-square ($\chi^2 = 3.89$, $P = .049$)
	Patients without comorbidities: 43.3% (26 patients)	
Most common comorbidities	Hypertension: 10 (19.61%)	N/A
	Fibromyalgia: 3 (5.88%)	
	Epilepsy: 3 (5.88%)	
	Hypothyroidism: 5 (9.80%)	
	DM 2: 8 (15.69%)	
Number of comorbidities per patient	One comorbidity: 35% (21 patients)	Chi-square ($\chi^2 = 3.89$, $P = .049$)
	Two comorbidities: 16.7% (10 patients)	
	Three comorbidities: 3.3% (2 patients)	
	Four comorbidities: 1.7% (1 patient)	
Psychiatric treatments	Sertraline: 28.33% (17 events)	N/A
	Escitalopram: 21.67% (13 events)	
	Fluoxetine: 20% (12 events)	
Other psychiatric medications	Quetiapine, alprazolam, bromazepam (frequencies between 8 and 6 events)	N/A
Medication regimen	Monotherapy: 43.3% (26 patients)	Chi-square ($\chi^2 = 2.76$, $P = .098$)
	Dual therapy: 35% (21 patients)	
	Triple therapy: 13.3% (8 patients)	
	Quadruple therapy: 8.3% (5 patients)	

The data is represented as N, % for categorical variables, and mean ± SD for continuous variables. Significance is set at $P < .05$ for all statistical tests. Chi-square tests were used to analyze categorical variables, while ANOVA was used for continuous variables where necessary.
DM, diabetes mellitus; PHQ, Patient Health Questionnaire.

(15.18% of psychiatric treatments) and was administered to 28.33% of patients. Escitalopram was used in 13 events (11.61% of treatments) and was prescribed to 21.67% of patients. Fluoxetine was used in 12 events (10.71% of treatments) and was prescribed to 20% of patients. Other medications, such as quetiapine, alprazolam, and bromazepam, were also relevant, with frequencies ranging from 6 to 8 events.

In terms of medication regimen, 43.3% of patients received monotherapy, 35% received 2 medications, 13.3% received 3 medications, and 8.3% received 4 medications.

Prior to stimulation, HDRS and PHQ-9 were used to assess patients' depression levels. According to HDRS, 34 patients presented with very severe depression (scores above 23), 13 patients had severe depression, and 13 patients had moderate or mild depression.

In a comparative analysis of the median performance of the HDRS before and after treatment. Before treatment, the median HDRS score was 25 points, whereas after treatment, the median score dropped to 6 points. The figure also displays the full range (minimum to maximum) and interquartile range (25%-75%) for pre- and post-treatment scores.

The analysis of HDRS results before and after treatment showed a significant difference between the average scores in both phases. The results indicate that the average HDRS score before treatment was 24.23 ± 7.43, while after treatment, it dropped significantly to 6.78 ± 4.98. This difference is statistically significant, with an F value of $F(1, 118) = 228.43$ and a P-value of less than .0001 (Figure 1), suggesting a considerable improvement in depressive symptoms after treatment, with a reduction of 72.02% ($P < .05$). The effect size for the comparison factor (Treatment Phase: Pre - Post) was 0.659, equivalent to 65.9%.

In a comparative analysis of HDRS scores before and after treatment, the pre-treatment mean was 24.23, which decreased to 6.78 post-treatment, suggesting a notable improvement in symptoms.

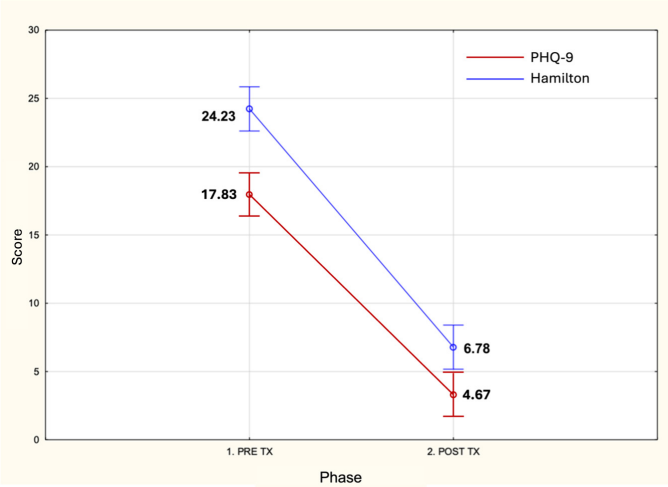

Figure 1. Comparative analysis of the average performance of Patient Health Questionnaire (PHQ) Score and Hamilton Score pre-treatment vs. post-treatment. This figure presents a comparative analysis of the average scores on the PHQ and Hamilton Depression Scales before and after treatment. Data is represented as mean ± SD for both scales. Both scales demonstrated statistically significant improvements after treatment, showcasing the intervention's efficacy.

The SD also decreased from 7.43 to 4.98, indicating less variability in the scores and a more uniform response to the treatment among patients. The maximum value dropped from 38 to 21, while the minimum went from 5 to 0 post-treatment. Overall, these results suggest a positive effect of the treatment in reducing depressive symptoms.

The Eta-squared values of approximately 0.66 for HDRS and 0.59 for PHQ-9 indicate a significant effect size.

In Figure 2, the Gaussian curves in the empirical cumulative distribution analysis demonstrate that the distribution of pre-treatment HDRS shifts to the left, forming the distribution of post-treatment scores. This suggests a significant post-treatment improvement ($P < .01$).

In an empirical cumulative distribution analysis of HDRS before and after treatment, the pre-treatment phase shows a mean of 24.23 with a SD of 7.43, while in the post-treatment phase, the mean decreases to 6.78 and the SD to 4.98 (Figure 2). Both phases include 60 observations each. The solid blue curve shifting to the right in the graph indicates a significant improvement in HDRS after treatment. This suggests that patients experienced a reduction in depressive symptoms. The decrease in the mean and SD in the post-treatment phase reflects a positive response to treatment, with reduced variability in scores and a general trend toward improved patient condition.

In the cumulative frequency of Hamilton Depression Scale scores before and after treatment (Pre vs. Post Treatment) (Figure 3), the distribution of depression severity scores with tDCS demonstrates a significant post-treatment improvement, evidenced by a greater accumulation of lower scores. The score range spans from the minimum to the maximum, including the interquartile range, which represents the central half of the data. Additionally, descriptive statistics such as the mean, standard error of the mean, SD, and quartile values (Q1, Median, Q3) are provided for HDRS before and after treatment.

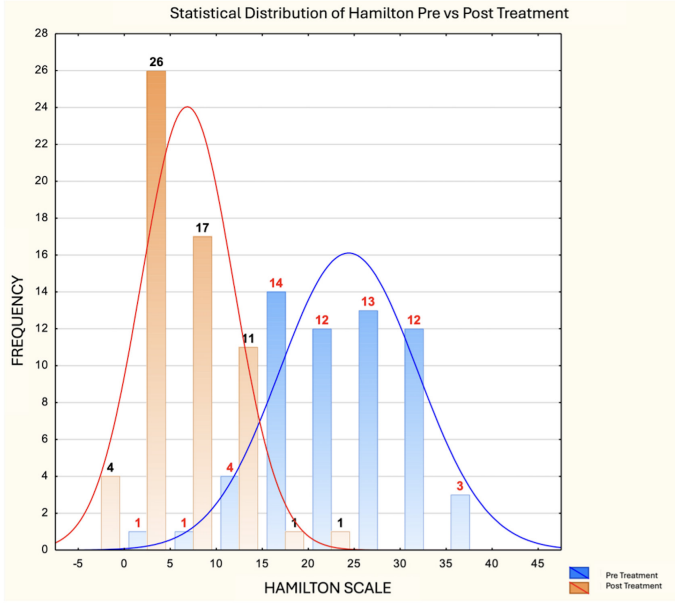

Figure 2. Comparative histograms and Gaussian curves of the Hamilton pre-treatment and post-treatment variables. Statistical distribution of Hamilton Depression Scale scores before and after treatment. Data is represented as frequencies, with Gaussian curves adjusted to each empirical distribution (Pre-treatment: N = 60; Mean = 24.23; SD = 7.43. Post-treatment: N = 60; Mean = 6.78; SD = 4.98). Statistical significance was determined using ANOVA, with $P < .01$ indicating a significant reduction in depressive symptoms post-treatment.

Regarding the PHQ-9, 23 participants were classified as having severe depression, 19 as moderate depression, and 18 as mild or less. A comparative analysis of the average performance of the Pre-Treatment PHQ Score versus the Post-Treatment PHQ Score (Figure 1)

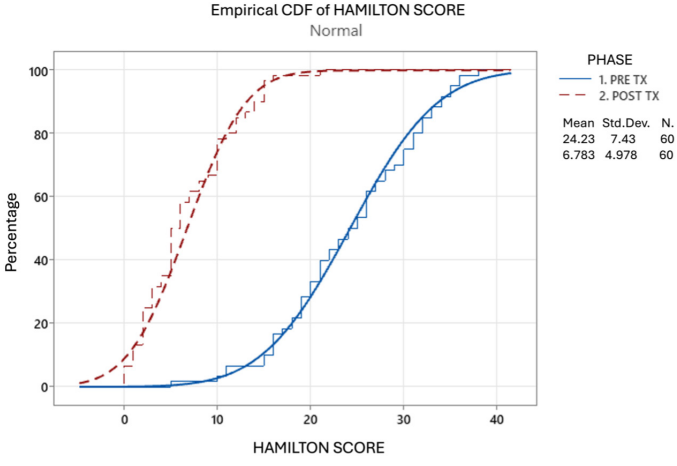

Figure 3. Comparative cumulative frequency of Hamilton variables pre- and post-stimulation. Comparative cumulative frequency distribution of Hamilton Depression Rating Scale scores before and after transcranial direct current stimulation (tDCS). Data is represented as mean ± SD (Pre-treatment: N = 60; Mean = 24.23; SD = 7.43. Post-treatment: N = 60; Mean = 6.78; SD = 4.98). A post-treatment shift in the cumulative curve was observed, indicating a significant reduction in depression severity (ANOVA, $P < .01$).

reveals a significant decrease in scores from 17.83 to 4.67, indicating a notable improvement in the post-treatment phase. Figure 1 shows a clear downward trend, reflecting the reduction in PHQ scores with a statistically significant improvement, as evidenced by a *P*-value of < .001. These results indicate that the treatment had a significant positive effect on participants, substantially reducing their PHQ scores. The statistical significance supports the reliability of these results, suggesting that the improvement is not random but directly attributable to the treatment. This implies that the intervention may be effective in reducing symptoms measured by the PHQ.

The effect size for the comparison factor (Treatment Phase: Pre - Post) was calculated at 0.587240, equivalent to 58.7%.

The results from the table indicate a significant reduction in PHQ scores after treatment, demonstrating the effectiveness of the intervention in alleviating depressive symptoms. The substantial decrease in the PHQ mean score from pre-treatment to post-treatment suggests that the treatment had a considerable impact on the severity of depressive symptoms.

The statistical distribution table for pre- and post-treatment PHQ scores highlights a significant reduction in scores after the treatment (Figure 4). Before treatment, individuals exhibited higher scores, with a mean of 17.83 and a SD of 6.73. Following treatment, the mean score decreased to 4.67, accompanied by a SD of 4.11. These findings indicate a notable improvement in symptoms of depression or anxiety as measured by the PHQ, with a 73.81% reduction, underscoring the effectiveness of the applied treatment.

The description of Figure 4 is similar to that provided for Figure 2. As in the earlier figure, this 1 also contrasts empirical distributions

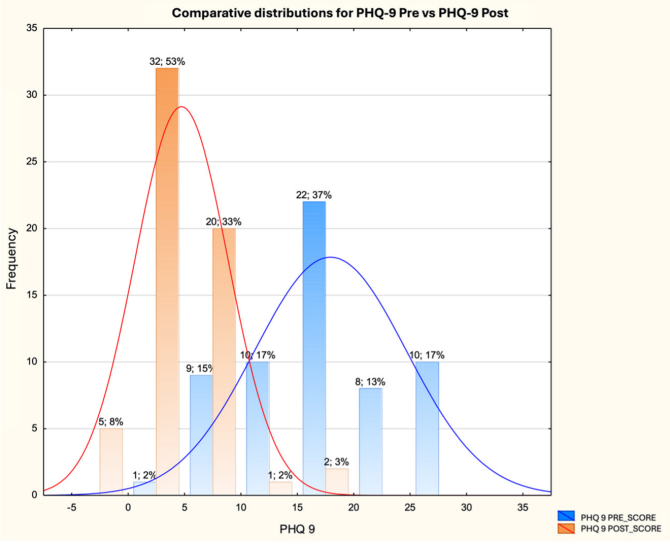

Figure 4. Comparative histograms of Patient Health Questionnaire and post-treatment Patient Health Questionnaire variables. Comparative histograms for Patient Health Questionnaire-9 pre-treatment and post-treatment variables. Data is represented as frequency distribution (Pre-treatment: N = 60; Post-treatment: N = 60). The distribution shows a significant shift toward lower scores post-treatment, indicating a marked reduction in depressive symptoms following the intervention. The Gaussian curves represent the probability distributions for both pre- and post-treatment Patient Health Questionnaire-9 scores.

supported by theoretical Gaussian distributions. The evidence provided by the empirical distributions (histograms) is statistically validated through Gaussian distributions.

DISCUSSION

Major depressive disorder is a serious mental illness with a high prevalence in the general population, leading to significant personal and societal costs.[1] Transcranial direct current stimulation (tDCS) has emerged as a promising intervention for the treatment of MDD. It is a safe and non-invasive technique that can enhance the efficacy of pharmacological therapy in patients with depression.[7,8,10,14] In this study, the clinical outcomes of patients who received tDCS as an adjunctive treatment for MDD were evaluated.

The results indicate a significant improvement in depressive symptoms after receiving tDCS combined with antidepressant therapy. This was evidenced by a significant reduction in scores on both the HDRS and the PHQ-9 following treatment. The *P*-values of < .05 and < .001 confirm the statistical significance of these improvements. The Eta-squared values of approximately 0.66 and 0.59 for the scales used indicate a large effect size, suggesting that the treatment is effective in reducing depressive symptoms. This is consistent with clinical significance, further reinforcing the efficacy of the treatment in a real-world context.

The use of tDCS allows for the stabilization of pharmacological therapy while adding a safe, non-invasive intervention to increase treatment efficacy. Ongoing research suggests that combining tDCS with pharmacological treatment may offer an effective alternative for patients with major depressive disorder, including treatment-resistant depression.[15] However, more evidence is needed to confirm these findings and establish clear usage guidelines.

Both the HDRS and the PHQ-9 showed consistent results in terms of significant symptom reduction after treatment. This suggests that both assessment methods are useful for measuring patient improvement and treatment efficacy. The decision to use both scales is based on their differing applications, as the PHQ-9 is self-administered. Studies have shown that the PHQ-9 is satisfactory in terms of reliability, validity, and its ability to differentiate depression severity. It is a simple, quick, effective, and reliable tool that can be used as an alternative to the Hamilton scale for assessing depression severity.[14]

Over half of the participants presented with 2 or more comorbidities, which can complicate depression treatment. However, the study showed that even with the presence of comorbidities, patients experienced significant improvements in depressive symptoms. This suggests that the treatment is effective even in patients with additional medical conditions. This aligns with previous research showing that depression is one of the most common comorbidities of chronic diseases, including cancer, cardiovascular, metabolic, inflammatory, and neurological disorders.[16] The prevalence of depression in these patient groups is significantly higher than in the general population, making it crucial to adapt management strategies to address these complexities.

Globally, it is estimated that 3.8% of the population experiences depression, with women being more likely than men to have depression.[3] In this study, the gender distribution showed a higher proportion of women (71.7%, N = 43) compared to men (28.3%, N = 17).

It would be interesting to analyze whether this gender difference affects treatment response and whether there are particularities in how different populations react to therapy.

Monotherapy was the most common strategy (43.3%, N = 26), followed by the use of 2 medications (35%, N = 21). Although multiple medications may be necessary for some patients, the treatment efficacy was significant across all groups, suggesting that both monotherapy and combination therapy can be effective.

This study has several limitations that should be acknowledged. First, its retrospective design may introduce selection and information biases that could affect the internal validity of the results. Second, the sample size of 60 patients, while informative, may not be representative of the broader population of individuals with major depressive disorder, thus limiting the generalizability of the findings. Additionally, the study did not control for the duration of depressive episodes, the number of prior treatment failures, or the specific combinations of pharmacological therapies, which may have influenced treatment response. The absence of a control group, sham stimulation, randomization, and blinding further restricts the ability to establish causality. However, it is important to consider that the intervention was implemented in a public hospital setting, where tDCS is used as a therapeutic measure for patients with clinical needs. Therefore, a retrospective design was deemed the most feasible and ethically sound approach to evaluate the real-world clinical impact of tDCS in this population.

Although various studies and meta-analyses support the effectiveness of tDCS, its superiority over placebo has not been consistently demonstrated across all contexts. For example, Loo et al[8] found that while tDCS may provide antidepressant benefits, its effects did not consistently exceed those of sham stimulation. These mixed findings underscore the need for further research to clarify the specific conditions under which tDCS is most effective, as well as to identify the patient profiles most likely to benefit from it.

Nevertheless, tDCS offers notable advantages over other neuromodulation techniques such as TMS or deep brain stimulation. Its ease of application, safety profile, portability, and low cost make it an attractive option for institutions with limited resources or for patients facing logistical barriers. Moreover, its better tolerability may enhance treatment adherence.

All patients included in this study were already receiving pharmacological treatment prior to the initiation of tDCS, and no adjustments to medication type or dosage were made during the stimulation period. This therapeutic stability supports the assumption that the observed reductions in HDRS and PHQ-9 scores are primarily associated with the neuromodulatory intervention rather than pharmacological changes. While the concurrent use of antidepressants prevents complete attribution of outcomes to tDCS alone, the absence of medication adjustments during treatment strengthens the interpretation that the clinical improvements were influenced—at least in part—by the stimulation protocol.

This study provides evidence supporting the use of tDCS in a real-world clinical population with a high burden of comorbidities—a context that is rarely represented in randomized controlled trials. By presenting outcomes under routine clinical conditions, this work helps bridge the gap between experimental research and practical application. This perspective may contribute to more pragmatic and context-sensitive treatment decisions, particularly in public or mixed healthcare systems.

It is also important to acknowledge that the observed improvements cannot be exclusively attributed to tDCS, as all patients were simultaneously receiving pharmacological treatment. This concurrent administration reflects real-world clinical practice, where tDCS is commonly used as an adjunctive strategy rather than a stand-alone intervention. While this therapeutic combination may yield enhanced clinical outcomes, the precise contribution of each component remains difficult to isolate in a non-randomized design. Future research with factorial designs or stratified analyses could help elucidate potential synergistic effects between pharmacotherapy and neuromodulation, thereby optimizing personalized treatment strategies for patients with major depressive disorder.

The present findings suggest that the combination of tDCS and antidepressant therapy may be an effective strategy for managing major depressive disorder. This therapeutic approach may be especially valuable for patients with treatment-resistant depression or significant medical comorbidities, expanding the options available for complex clinical cases.

In conclusion, this study emphasizes the potential of tDCS as an adjunctive treatment for depression when combined with antidepressant therapy. The combination of pharmacological treatment and tDCS significantly improves depressive symptoms, with a notable reduction in scores on the Hamilton and PHQ-9 scales. These results indicate that tDCS is an effective tool for reducing symptoms of MDD, particularly in patients with medical and psychiatric comorbidities.

The integration of tDCS with conventional pharmacological treatments, such as sertraline and escitalopram, further enhances treatment outcomes. While the findings are promising, they serve as a foundation for further investigation. Larger, prospective studies are required to validate these results and examine the long-term benefits of tDCS in clinical practice.

The study underscores the importance of exploring innovative treatment approaches like tDCS to address the complexities of depression, especially in patients with additional medical conditions. Continued research in this area will be critical to advancing therapeutic options and improving outcomes for those affected by this prevalent mental health condition.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the National Medical Center "20 de Noviembre", ISSSTE (Approval no: 243.2024, Date: April 17, 2024).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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