

# Transcranial direct current stimulation in prophylaxis of chronic migraine: systematic review

*Estimulação transcraniana por corrente contínua na profilaxia da migrânea crônica: revisão sistemática*

Helena Renata Silva Cysneiros<sup>1</sup>, Kelly Sukar Cavalcanti de Oliveira<sup>1</sup>, Artur Henrique Galvão Bruno da Cunha<sup>1</sup>, Katia Karina do Monte-Silva<sup>1</sup>, Daniella Araújo de Oliveira<sup>1</sup>, Marcelo Moraes Valença<sup>1</sup>

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** To examine the latest research on transcranial direct current stimulation (tDCS), including protocols and outcomes in patients with chronic migraine who have received prophylactic treatment.

**CONTENTS:** This is a systematic review (PROSPERO - CRD42023454740), covering research in the last 5 years. Studies with simultaneous interventions, reviews, pilots, and special cases were excluded, aiming for a homogeneous sample of patients with chronic migraine. Of the initial 64 articles, 5 met the criteria. tDCS in the primary motor and ventral prefrontal cortex showed positive results, with improvements in quality of life and reduction in frequency and intensity of the episodes, as well as benefits for anxiety and depression. Anodal stimulation in the left primary motor cortex and left ventral lateral prefrontal cortex and cathodal stimulation in the left motor and sensory cortex showed better results.

**CONCLUSION:** tDCS has potential as a prophylactic intervention for chronic migraine, standing out for its tolerability and positive results. More research, with similar protocols are recommended for a more robust analysis of tDCS as an effective therapeutic alternative.

**Keywords:** Headache disorders, Migraine disorders, Transcranial direct current stimulation.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Examinar as pesquisas mais recentes sobre estimulação transcraniana por corrente contínua (ETCC), incluindo protocolos e resultados em pacientes com migrânea crônica que receberam tratamento profilático.

**CONTEÚDO:** Uma revisão sistemática (PROSPERO - CRD42023454740), abrangendo pesquisas realizadas nos últimos 5 anos. Foram excluídos estudos com intervenções simultâneas, revisões, pilotos e casos especiais, visando uma amostra homogênea de pacientes com migrânea crônica. Dos 64 artigos iniciais, 5 preencheram os critérios. A ETCC no córtex motor primário e pré-frontal ventral apresentou resultados positivos, com melhora na qualidade de vida e redução na frequência e intensidade dos episódios, além de benefícios para ansiedade e depressão. A estimulação anódica no córtex motor primário e no córtex pré-frontal lateral ventral esquerdo e a estimulação catódica no córtex motor e sensorial esquerdo apresentaram melhores resultados.

**CONCLUSÃO:** A ETCC tem potencial como intervenção profilática para migrânea crônica, destacando-se por sua tolerabilidade e resultados positivos. Recomenda-se a realização de mais pesquisas, com protocolos semelhantes, para uma análise mais robusta da ETCC como alternativa terapêutica eficaz.

**Descritores:** Estimulação transcraniana por corrente contínua, Transtornos da cefaleia, Transtornos de migrânea.

## INTRODUCTION

Migraine is a neurobiological condition characterized by hypersensitivity to auditory, skin, visual, and olfactory stimuli<sup>1</sup>. Migraine can be chronic (15 or more daily attacks per month over three months) or episodic, with or without aura, the latter being characterized by the occurrence of transient neurological symptoms, such as ocular, auditory, as well as sensory symptoms and

Helena Renata Silva Cysneiros – <https://orcid.org/0000-0001-6467-8177>;  
Kelly Sukar Cavalcanti de Oliveira – <https://orcid.org/0000-0002-6467-7243>;  
Artur Henrique Galvão Bruno da Cunha – <https://orcid.org/0000-0002-8589-8563>;  
Katia Karina do Monte-Silva – <https://orcid.org/0000-0001-7301-2553>;  
Daniella Araújo de Oliveira – <https://orcid.org/0000-0001-8948-8919>;  
Marcelo Moraes Valença – <https://orcid.org/0000-0003-0678-3782>.

1. Federal University of Pernambuco, Department of Postgraduate Studies in Neuropsychiatry and Behavioral Sciences, Recife, PE, Brazil.

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## HIGHLIGHTS

- Anodal stimulation in the left primary motor cortex and left ventral lateral prefrontal cortex, along with cathodal stimulation in the left motor and sensory cortex, demonstrated significant results.
- The duration and intensity of tDCS protocols exert substantial influence on results.
- TDCS brings positive effects by reducing migraine frequency, intensity, and duration, coupled with a diminished reliance on abortive drugs

Associate editor in charge: Isabela Freire Azevedo Santos

<https://orcid.org/0000-0001-8836-8640>

## Correspondence to:

Helena Renata Silva Cysneiros

E-mail: [helena.cysneiros@ufpe.br](mailto:helena.cysneiros@ufpe.br)



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engines<sup>2</sup>. There is a high impact on activities of daily living in migraineurs, including the individual's ability to work, social functioning, and health-related quality of life (QoL), and this disease affects more than 1 billion people worldwide<sup>3,4</sup>.

Structural and functional changes in the brain of migraineurs were investigated in studies that demonstrated progressive reductions in cortical volume, as the duration and frequency of migraine attacks increased, suggesting that repeated attacks can atrophy brain regions that process pain, such as the bilateral insula, prefrontal cortex, right cingulate cortex, posterior parietal cortex, and orbitofrontal cortex<sup>5</sup>.

Focal changes in cerebral metabolism, hyperexcitability of the cortex in general, and central sensitization were also observed<sup>6</sup>. Despite the efforts of scientists around the world, the pathophysiology of migraine is still poorly understood, and the mechanisms of action responsible for its emergence are not fully elucidated<sup>7</sup>, which greatly complicates the development of more effective therapies.

Some advances have been achieved in specific drug therapies for migraine, which have few side effects, such as monoclonal antibodies that block the effect of Calcitonin Gene-Related Peptide (CGRP, a potent inflammatory trigger) in the body, which prevent or minimize the occurrence of migraine crises. However, these last-line drugs are still inaccessible due to their high cost, with starting prices of around R\$1500.00 (about 300 US dollars)<sup>8</sup>.

Some drugs used to prevent migraines were initially developed to treat other diseases and their prolonged use can be accompanied by several side effects<sup>9</sup>. Examples include propranolol, developed to treat high blood pressure, and amitriptyline, designed to treat depression.

For the treatment of migraine, compared to traditional (drug) treatment, non-invasive brain stimulation (NIBS), which targets transcutaneous peripheral nerves or the brain, is better tolerated and considered a promising alternative<sup>10,11</sup>. Among ECNI methods, transcranial direct current stimulation (tDCS) is a non-invasive technique that has been widely studied in the field of neuroscience. It consists of applying low-intensity electrical current to the scalp, with the aim of modulating brain activity in specific, pre-determined regions. This technology has already been investigated for use in the treatment of some neurological and psychiatric conditions<sup>12,13</sup>.

Studies on the applicability of tDCS in migraine attacks were produced in a systematic review study with meta-analysis<sup>11</sup> and was considered a promising non-pharmaceutical alternative for migraine. Furthermore, another meta-analysis demonstrated that excitatory stimulation of the primary motor cortex (M1) can reduce headache intensity and frequency in patients with migraine<sup>12</sup>.

A meta-analysis, which reviewed studies using tDCS for more than four weeks in the treatment of migraine, revealed that both anodal and cathodal stimulation were significantly effective in reducing pain intensity. Studies with cathodal stimulation targeted the occipital region, while studies with anodal stimulation targeted the M1 or Dorsolateral Prefrontal Cortex (DLPFC)<sup>14</sup>.

In the literature, systematic review and meta-analysis studies were found relating tDCS to migraine for the treatment of migraine aiming to reduce the intensity of pain during the episodes<sup>11,12,14</sup>, however, there is little evidence related to its use in prophylaxis.

This study aims to examine the latest research on tDCS, including the protocols and outcomes in patients with chronic migraine who received prophylactic treatment. The main question this review seeks to address is: what are the results of using tDCS as a prophylactic treatment for chronic migraine patients?

## METHODS

This review was duly registered on the PROSPERO platform under registration CRD-42023454740 and the text structure follows the recommendations of PRISMA 2020 expanded checklist<sup>15</sup>. The search was carried out between August 5 and 30, 2023, in the PubMed and Virtual Health Library (VHL or BVS, *Biblioteca Virtual em Saúde*) databases and the descriptors used were (MeSH and Boolean operators): (((((tdcs) OR (transcranial direct current stimulation)) AND (migraine)) NOT (children)) NOT (pilot)) NOT (review). Publications from the last 5 years were included, with full text available, published in English or Portuguese, whose study population was composed of chronic migraine patients aged 18 years or older, of both genders. When available, language and age filters were used.

Studies associating tDCS with other types of intervention, review studies, pilot studies, case series, pre-prints, case studies, gray literature, and studies whose migraine classification complies with any criteria other than those of the International Headache Society were excluded. Studies whose patients presented the following conditions were also excluded: sleep disorders, chronic hypertension, diabetes, malnutrition, psychiatric disorders, and chemical dependency, to avoid confounding bias.

Duplicate articles were removed manually. Next, there was a pre-reading of the title and summary with the help of Rayyan (a research collaboration platform), thus excluding articles that did not meet the eligibility criteria or that presented the aforementioned exclusion criteria.

The next stage involved a full reading of the articles to finalize the selection process according to the presented criteria. Two independent reviewers, HC and KS, carried out the presented steps. Any disagreements that arose during the selection process were resolved by a third reviewer, AC. Furthermore, the reference lists of the selected articles were consulted, and there was no need to contact authors for publication availability.

The outcomes analyzed were parameters used in tDCS, namely: current intensity, stimulus time, number of sessions, and areas of the central nervous system (CNS) in which neuromodulation was performed. The analyzed outcomes related to migraine are frequency, intensity, and duration of attacks, as they are well established in clinical practice as therapeutic indicators.

The degree of recommendation of the selected publications was based on the Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines<sup>16</sup>.

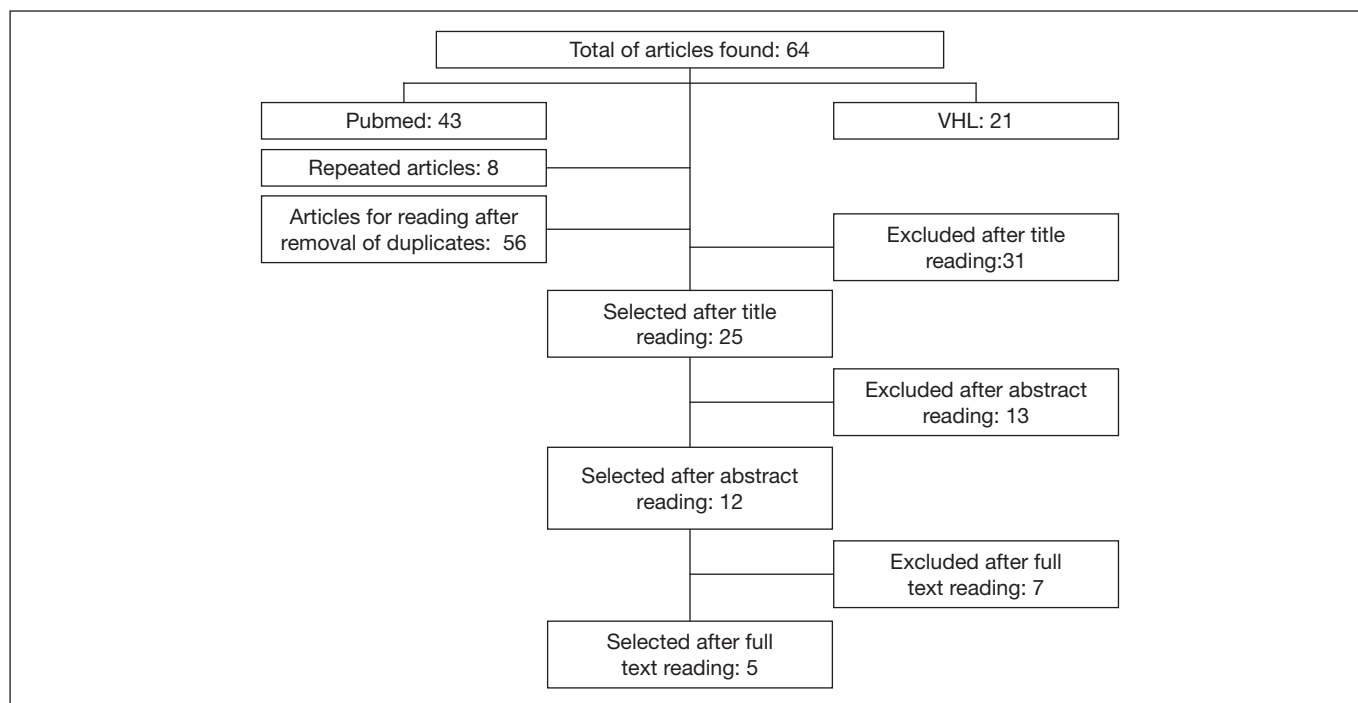
## RESULTS

During the initial search, 64 articles were found. The process of selecting the publications is detailed in figure 1. Finally, 5 publications were selected and they are detailed in table 1.

Except for one study<sup>17</sup>, there was a reduction in the frequency, duration, and intensity of migraine attacks, as well as in the use

of abortifacient drugs, such as triptans and non-steroidal anti-inflammatory drugs (NSAIDs).

The degree of recommendation for four of the five studies included in this review was 1A (strong recommendation, high-quality evidence), except for the study<sup>17</sup>, whose recommendation was 1B (strong recommendation, moderate-quality evidence).



**Figure 1.** Flowchart of the publications found, excluded, and included in the review.

**Table 1.** Summary of the publications selected for the study

Authors	Sample	Protocol	Conclusion	Grade of Recommendation / Description
Grazzi et al. <sup>17</sup>	135 patients of both biological genders	Stimulation was applied daily, for a period of 20 minutes and current intensity of 2mA, for 5 consecutive days during the medication withdrawal program. Patients were randomized to receive anodal, cathodal, or sham tDCS. In all cases, the active electrode was placed over the right-sided primary motor cortex (site C4 of the 10/20 EEG system) with the reference electrode placed over the contralateral supraorbital area.	TDCS did not influence the short- and long-term course of chronic migraine with medication overuse after acute drug withdrawal. Catastrophizing was reduced in both target groups.	1B/strong recommendation, moderate quality evidence
Rahimi et al. <sup>22</sup>	45 patients of both biological genders	The active electrode (cathode) was placed at C4 in the experimental and sham groups. In the sham, the device provided the electrical current only in the first and last 30 seconds of the experiment.	The application of cathodal tDCS in M1 or S1 can be used as a technological intervention for the prophylactic and therapeutic treatment of episodic or chronic migraine.	1A/strong recommendation, high-quality evidence.
Cerrahoğlu Şirin et al. <sup>18</sup>	77 patients of both biological genders	41 patients received sham stimulation and 36 patients underwent three sessions of anodal tDCS stimulation in the left primary motor cortex with a current of 2 mA for 20 minutes.	TDCS is a safe, effective and rapid method for migraine prophylaxis. However, administration of tDCS before allodynia occurs, that is, before the development of central sensitization, will provide greater responsiveness to treatment.	1A/strong recommendation, high-quality evidence.

Continue...

**Table 1.** Summary of the publications selected for the study – continued

Authors	Sample	Protocol	Conclusion	Grade of Recommendation / Description
Hodaj et al. <sup>24</sup>	36 patients of both biological genders	The tDCS protocol consisted of 5 consecutive daily sessions during the first week (week 1) followed by a maintenance phase of 1 weekly session during the following 4 weeks and 2 bimonthly sessions in the following month, for a total of 11 sessions. The anode was placed in C3 to reach the hand area in the left motor cortex and the cathode was placed in FP2, that is, the right supra orbital area. A constant current of 2 mA intensity was applied for 20 min. For the sham, the electrodes were placed in a similar manner, but the current was stopped 30 seconds later.	The monthly number of migraine episodes was reduced after tDCS in the active group compared to the sham group. The response rate was higher 3 months after the tDCS protocol in the active group compared to the sham group.	1A/strong recommendation, high-quality evidence.
Dawood Rahimi et al. <sup>26</sup>	150 patients of both biological genders	Target areas: right ventrolateral prefrontal cortex, left dorsomedial and superior frontal gyrus and the right/left primary motor area, the medial crosstalk of the hemispheres, and the occipital cortex.	There were significant reductions ( $p < 0.05$ ) in chronic migraine symptoms in the intervention groups compared with sham. tDCS can be used as an effective intervention for the prophylactic and therapeutic treatment of chronic migraine.	1A/strong recommendation, high-quality evidence.

## DISCUSSION

The present study demonstrates that tDCS can be used to treat chronic migraine prophylactically, depending on the area of stimulation and application parameters.

One publication<sup>18</sup>, which aimed to verify whether allodynia could be an important factor in the effectiveness of tDCS in migraine prophylaxis, carried out research with 77 people diagnosed with migraine. In 41, simulated stimulation was performed and in 36, 3 sessions of anodal tDCS were performed over the left primary motor cortex (according to the 10-20 EEG system, at location C3), and the reference electrode (cathode) in the contralateral supraorbital region, for 20 minutes and current of 2mA.

No stimulation was performed during the migraine attack. Regardless of allodynia, a significant improvement was observed in the group treated with tDCS compared to the sham group. Allodynia serves as an indicator of central trigeminal neuron sensitization and the intensity and duration of allodynic symptoms correlate with the duration and frequency of migraine attacks, as well as an individual's migraine history<sup>19</sup> and these findings demonstrate that tDCS provides an improvement in this symptom and also in the analgesic response to the disease.

The depression and anxiety scores of patients with allodynia before tDCS were higher than those of non-allodynic individuals. After tDCS, an improvement in depression and anxiety scores was detected in both groups studied (active and sham), as well as the number of headache days in the active tDCS group significantly decreased compared to the sham group. The average duration of post-tDCS headache in the active group was significantly shorter compared to the sham group, with a decrease in pain intensity and the use of attack abortive drugs.

Migraineurs frequently face mental illness issues, being two to four times more likely to experience depression and anxiety com-

pared to adults in the general population<sup>20</sup>. Depression and anxiety have multiple repercussions, increasing the risk of suicide and treatment resistance, adding to their financial and migraine illness burden as well<sup>20,21</sup>.

Considering the study<sup>18</sup> findings, tDCS can be beneficial in the mental health aspect of migraine as well, with potential to improve overall QoL. The degree of recommendation for this study was 1A (strong recommendation, high-quality evidence).

The research developed by study<sup>22</sup> highlights the effectiveness of cathodal tDCS in the motor and sensory cortices in 45 individuals who had chronic migraine and found positive results with the application of tDCS in the prophylactic treatment of migraine, considering that the results point to significant effect of tDCS protocols applied to M1 (primary motor cortex) and S1 (sensory cortex) in reducing the frequency, duration and intensity of migraine pain.

Migraine operates as a cyclical excitatory disorder, with neural substrates implicated in the somatosensory system, originating from the brainstem and extending to the S1 region before migraine onset<sup>23</sup>. The positive results of applying tDCS to S1 could be justified by the relation between the cyclical migraine extending to the S1 region.

Chronic migraine is established when the individual has 15 or more headache days per month over a period of 3 months, with the following characteristics on at least eight days per month: commonly unilateral attacks, with pulsatile pain, of moderate to severe intensity, lasting from 4 to 72 hours, with concomitant symptoms of nausea and/or vomiting, photophobia and/or phonophobia<sup>2</sup>.

According to the findings, tDCS in the right primary motor cortex did not demonstrate significant benefits when neuromodulation was applied for 5 consecutive days and 20 minutes in each session [17]. At least 10 tDCS application sessions are required,

with a stimulation time that may be longer, for the positive effects to be perceived and maintained<sup>11</sup>.

It can be concluded that there was no significant improvement in patients with chronic migraine when the number of treatment sessions was reduced or when the area stimulated during the application of anodic current did not show significant results. The study was given a strong recommendation with high-quality evidence (degree of recommendation 1A).

One study verified the long-term prophylactic efficacy of tDCS in 36 chronic migraine<sup>24</sup> subjects. Anodal tDCS was performed on the left primary motor cortex, in the hand region, in 5 consecutive daily sessions followed by a maintenance phase, and it was observed that the frequency of seizures was reduced, and the response rate was higher 3 months after the end of the protocol, with a significant reduction in the use of triptans in the treated group compared to SHAM.

The activation of the left primary motor may indirectly induce an inhibition of the cortical regions involved in pain processing, improving pain control<sup>25</sup>. Significant prophylactic effect of tDCS treatment was observed, with early and lasting benefits. Study's grade of recommendation: 1A (strong recommendation, high-quality evidence).

A previous study<sup>17</sup> used the same tDCS protocol as the study conducted by other study<sup>24</sup> but without a maintenance phase. However, no significant results were found in the former publication. This suggests that the maintenance phase carried out in the latter study, which involved a weekly tDCS session for 4 weeks, followed by 2 bimonthly sessions the following month, may have been important in achieving significant results for the prophylactic treatment of chronic migraine. The maintenance phase was implemented after the initial 5 consecutive sessions.

Considering that a standard protocol was used for the withdrawal of acute treatment drugs (intravenous administration of dexamethasone 4 mg and ademetionine 200 mg in saline solution and oral bromazepam 1.5 mg three times a day, for five consecutive days) and that both protocols (withdrawal of acute treatment drugs and tDCS) were performed concomitantly and daily for five consecutive days, the degree of recommendation of this publication was 1B (strong recommendation, moderate quality evidence).

Another study carried out on 150 patients applied tDCS in different areas of the CNS and demonstrated that tDCS can be an effective intervention for the prophylactic and therapeutic treatment of chronic migraine<sup>26</sup>. Moreover, the effects on frequency, duration and intensity of migraine attacks reflected significant intragroup differences for the group submitted to protocol 1: anode in the right ventrolateral prefrontal cortices, cathode in the left medial back and superior frontal gyrus (first montage), anode in the right primary motor area, cathode in the medial crosstalk of the hemispheres (second montage). This study presents a grade of recommendation 1A (strong recommendation, high-quality evidence).

There is a limitation in identifying the best parameters and areas of application of tDCS for migraine prophylaxis due to the absence of more studies following similar protocols. The-

refore, there is a need for more investigations and publications on this technology, its techniques, and applications. Publishing new randomized clinical studies for the prophylactic treatment of chronic migraine, along with new systematic reviews and meta-analyses, may allow for more effective analyses of tDCS as a treatment alternative.

## CONCLUSION

There are specific tDCS application protocols that are effective for the prophylactic treatment of chronic migraine. The areas of the cortex that have shown significant results for the prophylactic treatment of chronic migraine are as follows: anodal stimulation in the left primary motor cortex and left ventral lateral prefrontal cortex, and cathodal stimulation in the left motor and sensory cortex.

The stimulation is performed for 20 minutes with a current intensity of 2mA. The sessions can range from 5 to 10 consecutive sessions and positive results have also been observed when tDCS was applied as maintenance, with weekly stimulation for 1 month followed by bimonthly stimulation in the following month after the initial consecutive stimulation.

Considering the findings of all selected studies, it is possible to conclude that tDCS has positive effects in reducing the frequency, intensity, and duration of migraine episodes, as well as decreasing the use of abortive drugs for migraine episodes.

## AUTHORS' CONTRIBUTIONS

### Helena Renata Silva Cysneiros

Statistical analysis, Data Collection, Conceptualization, Methodology, Writing - Preparation of the original, Writing - Review and Editing

### Kelly Sukar Cavalcanti de Oliveira

Statistical analysis, Data Collection, Research, Methodology, Writing - Preparation of the original

### Artur Henrique Galvão Bruno da Cunha

Data Collection, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing

### Katia Karina do-Monte-Silva

Project Management, Supervision, Visualization

### Daniella Araújo de Oliveira

Project Management, Supervision, Visualization

### Marcelo Moraes Valença

Project Management, Supervision, Visualization

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