# EFFECT OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON SLEEP DISORDERS IN PATIENTS WITH MULTIPLE SCLEROSIS

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## Abstract

**Background**: Sleep disorders are common in multiple sclerosis (MS) patients. These disturbances detrimentally impact both their physical and mental well-being, leading to increased difficulties in executing everyday tasks. To date, there is a lack of comprehensive research regarding the influence of transcranial direct current stimulation (TDCS) on sleep in MS patients.

**Purpose:** This randomized controlled trial was conducted to assess the TDCS effect on sleep subjectively and objectively in MS patients.

**Setting:** Outpatient Clinics of Center for Psychiatry, Neurology, and Neurosurgery, Tanta University.

**Methods:** Thirty-eight female MS patients with remission and relapse course aging from 25 to 40 years were randomly assigned into two equal groups (study and control group). The study group received  active TDCS plus selected physiotherapy program (diaphragmatic breathing exercise and  relaxation technique) and the control group received sham TDCS plus the same selected physiotherapy program. The assessment of daytime sleepiness was conducted through the Epworth Daytime Sleepiness Scale (ESS), while the Pittsburgh Sleep Quality Index (PSQI) was employed to evaluate quality of sleep. Sleep was assessed objectively using Polysomnography (PSD) device. The following parameters were assessed objectively (sleep latency, arousal index, sleep efficiency and total time sleep). Evaluation of all variables took place pretreatment and posttreatment.

**Results:** There were no statistically significant differences between both groups in pretreatment mean values of all measured variables.  There were a statistically significant improvement in all measured variables in both groups after treatment. There were significant differences in all measured variables between both groups,  favoring the study group.

**Conclusion:** Transcranial direct current stimulation could be an excellent supplement to selected physiotherapy program in improving daytime sleepiness and quality of sleep in MS patients.

**Keywords:** Multiple Sclerosis, Transcranial direct current, Sleep disorders, Pittsburgh sleep quality index, Epworth daytime sleepiness scale, Polysomnography.

## Introduction:

Multiple sclerosis (MS) represents a progressive, chronic neurologic condition that induces physiological and dysfunctional structural alterations within the brain and spinal cord's white matter, arising from immune system dysregulation targeting the central nervous system [1]. It affects women 2-3 times more frequent than men with a mean onset of age 30 years [2]. About 70% of MS patients suffer from sleep disturbances [3]. They are associated with several debilitating MS symptoms, such as fatigue, pain, depressive symptoms, and cognitive dysfunction [4]. They are strongly related to worse health-related quality of life in MS patients regardless of other MS symptoms. Therefore, enhancing sleep quality may significantly enhance MS patients' quality of life [5].

Research reveals a connection between stimulating certain areas of the cortex electrically and the quality of sleep [6], including transcranial direct current stimulation (TDCS), which can noninvasively change cortical excitability and significantly modulate brain activity, connectivity, plasticity, and dynamics [7].

According to preliminary research, TDCS may be utilized safely to control sleep disruptions, symptoms of insomnia, and enhance quality of sleep in neurological and neuropsychiatric patients suffering from compromised sleep. This method may be used in conjunction with other therapies and may help to alleviate other symptoms comorbid to sleep disturbances [8].

Given the limited research available on TDCS effectiveness for sleep disorders in MS patients, this study was undertaken to assess its impact.

## Materials and Methods:

This randomized controlled study was performed at Outpatient Clinics of Center for Psychiatry, Neurology, and Neurosurgery, Tanta University in the period from February 2023 to August 2023. Before the initial assessment and recruitment into the study, each patient received a comprehensive explanation regarding the study's aim, procedure and possible benefits. Every participant signed a consent form authorized by the institution. This study was approved by the Ethics Committee at Faculty of Physical Therapy, Cairo University (P.TREC / 012 / 004720).

## 2.1. Study population

Thirty eight female MS patients with remission and relapse course took part in this research. They were diagnosed as having MS based on a careful clinical examination by neurologist and the diagnosis was confirmed by radiological investigations such as MRI. Participants were considered suitable for this study based on the subsequent criteria for eligibility 1) Age ranged from 25 to 40 years old; 2) Demyelinating lesion affecting sleep such as demyelination of suprachiasmatic nucleus; 3) Intact cognition enabling the understanding and execution of instructions; 4) Score on Expanded Disability Status Scale was ≤4; 5) Stable physical and medication-based treatment for a minimum of one month and 6) Free of relapses in the last four months.

The patients were excluded, if they had 1) Symptoms that disrupt sleep quality like severe spasticity, intense pain, and severe urinary dysfunction; 2) Score on the fatigue severity scale was >36; 3) Presence of other neurological diseases, medical conditions or other treatments capable of influencing sleep quality; 4) Drug addiction and job demands resulting in inadequate sleep; and 5) Metal prostheses in the skull or hearing aids.

## 2.2. Randomization

Patients were randomly allocated into study or control group using sealed envelope with 19 patients in each group. The study group received TDCS alongside the selected physiotherapy program, and control group received sham TDCS alongside the same selected physiotherapy program.

## 2.3. Examination

For all subjects in both groups, the subsequent evaluations were completed both prior to and subsequent to treatment.

**Assessment of daytime sleepiness:** Epworth sleepiness scale (ESS) was utilized to evaluate daytime sleepiness. Its validation has been conducted in various linguistic and clinical environments [9]. It includes eight common situations from daily life, where subjects rate their propensity to doze off or fall asleep [10]. Each situation was evaluated on a scale from 0 to 3. A greater score indicates worse daily sleepiness. Total scores go from 0 to 24 [11].
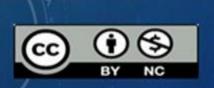
**Assessment of quality of sleep:** Pittsburg Sleep Quality Index (PSQI) was utilized to determine sleep quality. It consists of 19 items and were calculated as the following 7 components: sleep latency, total time, quality, disturbances experienced, efficiency, drug usage, and daytime sleepiness. All components were equally weighted and assessed on a 0 to 3 scale, resulting in an overall score range of 0 to 21. It is considered as the benchmark for assessing sleep quality within a one-month timeframe [9]. Its validity has been proven through research in various patient populations [12].

**Assessment of sleep** objectively using Polysomnography (PSG) Nihon Kohden corporation (1-31-4 Nishiochiai, Shinjuku-Ku, Tokyo 161-8560, Japan, SN: 04142: 2018). Polysomnography is the method with the highest reliability for evaluating time and fragmentation of sleeping [13]. It is mostly performed in sleep labs in which experts perform electrode application on the scalp, face, and extremities for electroencephalography (EEG) and electromyography (EMG) respectively, pulse oximetry, electrooculography (EOG), electrocardiography (EKG) are also applied, chest and belly belts, as well as nasal (or oro-nasal) airflow sensors to track patterns of breathing are used. So, PSG quantifies sleep by quantifying physiological alterations occurring in the cortex and the peripheral areas while sleeping [14].

The PSG contained montages for EEG channels (O1/A2, C3/A2, C4/A1), EOG (LOC-A1/A2 and ROC-A1/A2), surface EMG on the tibial and submental muscles, and modified V2 lead ECG. To capture oral and nasal airflow, we utilized thermistors, and for tracheal sound evaluation, a microphone was employed. Measurement of chest and abdominal efforts was applied using two thoracoabdominal respiratory inductance plethysmography belts. A PSG technician gathered data on total sleep time (TST), sleep latency (SL), sleep efficiency (SE), and arousal index, which were then analyzed by an experienced sleep medicine physician based on the American Academy of Sleep Medicine's criteria.

**During assessment of sleep using PSG, the following instructions given to the patients:**

- Patients were instructed to clean and dry their hair.
- Avoid putting any oils or gels on their hair to prevent interfering with the sensors.
- Avoid having any caffeine (such as: coffee, tea, cola) in the afternoon or evening before PSG session.
- Avoid napping during day.

**2.4. Interventions:** The same physiotherapist was responsible for all training sessions. Patients in both groups received the same selected physiotherapy program (diaphragmatic breathing exercise and Benson relaxation technique). Active TDCS, delivered by the Apex type A device, was applied to individuals in the study group, whereas sham TDCS was given to those in the control group. TDCS was applied on dorsolateral prefrontal area of both sides for 20 minutes for 7 sessions (3 days per week) according to **Bimorgh et al [15].**

**During application of TDCS, the following should be considered:** Electrodes were fixed by a tight comfortable head band. A thorough inspection of the skin was conducted to identify any prior irritations, cuts, scars, or lesions. Enhancing conductivity involved moving hair from the targeted stimulation area and thoroughly cleaning the skin surface of any dirt or lotions, followed by complete drying. Based on the 10–20 international framework for EEG, the placement involved the anode (positive electrode) at the right dorsolateral prefrontal location (F4) and the cathode (negative electrode) at the left dorsolateral prefrontal location (F3). We applied sponge electrodes across a 25 cm$^2$ area on the scalp. These electrodes were moistened with saline without allowing water to drip down onto the patients head to provide a better electrical connection. Study group participants underwent a 20-minute TDCS session, with rising the current slowly to reach 2 mA intensity. In the sham group the current was discontinued after some seconds when the patients felt a burn or tingling in the skin according to **Bimorgh et al [15].**

**The selected physiotherapy program:**

Both study and control group received selected physiotherapy program included diaphragmatic breathing exercise and Benson relaxation technique.

**- Diaphragmatic breathing exercise**

Patients assumed a comfortable crook lying position for diaphragmatic breathing exercise, with one hand placed over the chest and the other hand just beneath the ribcage, they were asked to gently inhale through their nose allowing the abdomen to expand against the lower hand while keeping the upper hand as steady as possible, then exhale through pursed lips letting the stomach muscles fall inward [16]. Patients were asked to repeat this exercise at the rate of 8–10 times/min for 20 min according to protocol of **Liu et al [17].**

- **Benson relaxation technique**

The relaxation technique developed by Benson is recognized as both highly effective and straightforward to use. It incorporates techniques of mindfulness that help in lowering stress, alleviating anxiety, and boosting quality of sleep **[18].** Benson relaxation technique procedures were described for each patient as follow;

❖ Assume a relaxed and comfortable sitting posture.
❖ Allow your eyelids to gently fall shut.
❖ Begin by relaxing your muscles, starting from the bottom of your feet and moving ahead.
❖ Inhale and exhale through your nose, concentrating on your breathing.
❖ Breathe in and out smoothly and confidently, mentally saying "one" on each exhale.
❖ Continue for 15 minutes, maintaining relaxation in your body and muscles while silently repeating the chosen word. Afterwards, gently open your eyes and remain still for a brief moment. Patients were instructed to repeat this technique at home for fifteen minutes twice daily, once in the morning and once at night.

**2.5. Sample Size**

With the objective of avoiding a Type II error, the sample size was determined using PSQI total score data from **Hadoush et al [18],** who examined the impact of

TDCS on sleep in Parkinson's disease patients. G*POWER (version 3.1) software was utilized for sample size calculation, aiming for an 80% power, an alpha level of 0.05, and an effect size of 0.94. Accordingly, this study required a total of 38 patients, with 19 patients allocated to each group.

## 2.6. Data analysis

To compare age differences between the two groups, an unpaired t-test was carried out. Shapiro-Wilk test was used to ascertain the normal distribution of the dataset, and Levene's test was applied to verify variance homogeneity across the groups. To evaluate the within-group and between-group impacts on PSQI, ESS, sleep latency, arousal index, sleep efficiency, and total sleep time, a two-way mixed MANOVA was utilized. For additional multiple comparisons, Bonferroni corrections were applied. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social sciences (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA).

## Results

### - *Patients characteristics*:

Thirty-eight female participants with MS who met inclusion criteria joined and completed the study (dropout=0), all of whom were suffering from sleep disorders. Group A had a mean age of $32.32 \pm 4.14$ years, whereas group B's mean age was $33.84 \pm 4.37$ years. Statistical analysis revealed no significant difference in age means between the groups ($p = 0.27$).

### Effect of treatment on PSQI, ESS, sleep latency, arousal index, sleep efficiency and total sleep time:

Two-way mixed MANOVA identified a significant interaction effect between treatment and time (F= 193.66, $p = 0.001$), along with significant main effects for both time (F= 365.24, $p = 0.001$) and treatment (F= 14.80, $p = 0.001$).

### Within group comparison

In comparison to pretreatment, both groups demonstrated a statistically significant lowering in the mean values of PSQI and ESS scores after the treatment ($p < 0.001$). In group A, the PSQI and ESS scores decreased by

79.53% and 67.17%, respectively, compared to a decrease of 15.50% and 10.37% in group B, respectively. (Table 1).

Following treatment, both groups displayed statistically significant reductions in the mean scores for sleep latency and arousal index, alongside a significant increase in the mean scores for sleep efficiency and total sleep time when compared to their scores before treatment (p < 0.05). The change percentages for sleep latency, arousal index, sleep efficiency, and total sleep time in group A were 70.54%, 60.26%, 36.22%, and 58.1%, respectively. In contrast, group B experienced changes of 24.17%, 11.96%, 5.17%, and 7.49%, respectively. (Table 2).

**Between group comparison**

There was no statistically significant difference between both groups pretreatment (p > 0.05). while, there was a statistically significant decrease in the mean values of PSQI, ESS, sleep latency, arousal index scores and a statistically significant increase in the mean values of sleep efficiency and total sleep time scores of group A compared with that of group B post treatment (p < 0.001). (Table 2).

**Table 1. Mean PSQI and ESS pre and post treatment of group A and B:**

| | Pre treatment | Post treatment | | | |
| | Mean ±SD | Mean ±SD | MD | % of change | p value |
|---|---|---|---|---|---|
| **PSQI** | | | | | |
| **Group A** | 15.68 ± 2.60 | 3.21 ± 1.47 | 12.47 | 79.53 | 0.001 |
| **Group B** | 15.94 ± 2.01 | 13.47 ± 1.95 | 2.47 | 15.50 | 0.001 |
| **MD** | -0.26 | -10.26 | | | |
| | *p = 0.73* | *p = 0.001* | | | |
| **ESS** | | | | | |
| **Group A** | 11.36 ± 1.89 | 3.73 ± 1.36 | 7.63 | 67.17 | 0.001 |
| **Group B** | 12.15 ± 2.14 | 10.89 ± 2.23 | 1.26 | 10.37 | 0.001 |
| **MD** | -0.79 | -7.16 | | | |
| | *p = 0.23* | *p = 0.001* | | | |

SD, Standard deviation; MD, Mean difference; p value, Probability value.

**table 2. Mean sleep latency, arousal index, sleep efficiency and total sleep time pre and post treatment of group A and B:**

| | Pre treatment | Post treatment | | | |
|---|---|---|---|---|---|
| | Mean ±SD | Mean ±SD | MD | % of change | p value |
| **Sleep latency (min)** | | | | | |
| Group A | 21.35 ± 8.54 | 6.29 ± 2.44 | 15.06 | 70.54 | 0.001 |
| Group B | 22.88 ± 7.72 | 17.35 ± 4.53 | 5.53 | 24.17 | 0.001 |
| MD | -1.53 | -11.06 | | | |
| | *p = 0.56* | *p = 0.001* | | | |
| **Arousal index** | | | | | |
| Group A | 16.96 ± 6.87 | 6.74 ± 3.58 | 10.22 | 60.26 | 0.001 |
| Group B | 18.82 ± 5.31 | 16.57 ± 6.11 | 2.25 | 11.96 | 0.02 |
| MD | -1.86 | -9.83 | | | |
| | *p = 0.35* | *p = 0.001* | | | |
| **Sleep efficiency (%)** | | | | | |
| Group A | 60.55 ± 8.72 | 82.48 ± 10.31 | -21.93 | 36.22 | 0.001 |
| Group B | 59.92 ± 7.64 | 63.02 ± 7.06 | -3.10 | 5.17 | 0.001 |
| MD | 0.63 | 19.46 | | | |
| | *p = 0.82* | *p = 0.001* | | | |
| **Total sleep time (hr)** | | | | | |
| Group A | 3.15 ± 0.54 | 4.98 ± 0.78 | -1.83 | 58.10 | 0.001 |
| Group B | 3.34 ± 0.61 | 3.59 ± 0.68 | -0.25 | 7.49 | 0.01 |
| MD | -0.19 | 1.39 | | | |
| | *p = 0.32* | *p = 0.001* | | | |

SD, Standard deviation; MD, Mean difference; p value, Probability value

## Discussion:

This study was conducted to investigate the TDCS effect on sleep disorders in MS patients. Regarding ESS score, this study's findings indicated a statistically significant reduction in the mean ESS score for the study group that underwent active TDCS post treatment compared with that pretreatment. Regarding ESS score within the study group, the findings of this study come in agreement with those of **Chalah et al [20]** who discovered a significant improvement in daytime sleepiness in group that received active TDCS.

Regarding ESS score, this study's findings indicated a statistically significant reduction in the mean ESS score for the control group that received sham TDCS after treatment in comparison to before treatment. For the control group, this study's result contradicts those of **Chalah et al [20]** who reported statistically insignificant effect of sham TDCS on daytime sleepiness.

The difference between two studies might be attributed to different methodology and physiotherapy intervention. In this study, control group received sham TDCS alongside a selected physiotherapy program as diaphragmatic breathing and Benson relaxation technique, but in study of **Chalah et al [20],** control group received only sham TDCS.

The significant improvement in the control group in this study could be associated with the physiological outcomes of the breathing exercise and Benson relaxation technique. This explanation was confirmed with **Abd El Khalik et al [16]** who found that breathing exercise practice influences bodily functions, brain activity, and autonomic nervous system balance, thus it represents a prime method for inducing relaxation and improving sleep quality.

Regarding PSQI score, findings of this study demonstrated a significant improvement in sleep quality in the study group post treatment compared with pretreatment. These results align with **Mohebbian et al [21]** who observed that TDCS significantly enhance sleep quality in 10 male participants suffering from poor sleep quality by delivering a 10-minute anodal TDCS to the left dorsolateral prefrontal area through 10 successive sessions.

The significant improvement in quality of sleep exhibited by the study group participants might be explained by several mechanisms, the first was that stimulation of dorsolateral prefrontal area by anodal TDCS which activates apart of the gammaaminobutyric acid -mediated systems, which is responsible for sleep beginning and maintenance through suppressing the ascending reticular activating system involved in awakening, and that results in simultaneous hyperpolarization of neurons in the cortex and thalamus. The second was that it activates a part of the serotonergic system, significantly contributing to the initiation of sleep **[21].**

Regarding scores of objective sleep measure (PSG), the study's findings demonstrated a statistically significant improvement in sleep after treatment compared to before treatment within the study group (statistically significant decrease in the mean values of SL and arousal index scores and statistically significant increase in the mean values of SE and TST scores).

The results of this study regarding scores of objective sleep measure are in accordance with **Pilloni et al [22]** who found an improvement on sleep quality after 10 anodal TDCS sessions targeting primary motor area (M1) in MS patients, which results in an increase in SE and TST, and a reduction of wake after sleep onset measured by an actigraphy device.

On the contrary, **Chalah et al [20]** concluded that TDCS had statistically insignificant impact on objective sleep measures (Actigraphy). The contradiction between two studies might be attributed to different methodology, duration of treatment and different sample size. In study of **Chalah et al [20]** patients received five daily sessions of TDCS but in this study patients received seven sessions of TDCS three days per week. A small sample size in study of **Chalah et al [20]** (only 7 MS patients who completed the study).

Significant improvement in sleep might be attributed to several mechanisms as explained by **Zhou et al [23]** (1): Regulation of the activity and concentration of GABA and glutamate neurotransmitters by TDCS which are contributed to the synaptic plasticity within the cortex of the brain and the modifications to long-term depression and potentiation's physiological processes, (2): targeting dorsolateral prefrontal cortex (DLPFC) by TDCS which is considered one of the cortical areas associated with sleep function which identified by EEG studies, also, source modeling EEG and functional magnetic resonance imaging have found an association between slow-wave sleep and activity in both the left and right DLPFC.

Additionally, TDCS may enhance sleep by modulating cortical activity and regulating the pace of oscillatory brain activity, which are fundamental for creating the oscillatory cycles that coordinate brain function during sleeping **[11].**

The present study has some limitations: Firstly, the way by which study sample was selected (convenient sampling) rather than random sample which may affect generalization of the results. Secondly, this study included only female patients, therefore conducting similar research with both male and female participants is essential to confirm TDCS effect. Finally, lack of follow up to explore the prolonged effects of TDCS on sleep among individuals with MS.

## Conclusion:

The addition of TCDS to selected physiotherapy program provide more improvement of sleep in patients with MS.

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