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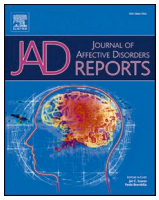

Brief Report

Reduction of symptoms in patients with major depressive disorder after transcranial direct current stimulation treatment: A real-world study

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has been demonstrated in randomized clinical trials (RCTs) to be an effective treatment option for major depressive disorder (MDD). The aim of this study was to characterize the real-life effectiveness and tolerability of tDCS and to identify predictors of treatment outcome in patients with MDD.

Methods: A total of 462 patients with depressive symptoms, who were treated with tDCS as a part of routine clinical practice, were enrolled in the study. Depressive symptoms were evaluated using validated depression scales before and after the tDCS treatment in 410 patients who completed the treatment and for whom all the necessary treatment information was available.

Results: Complete clinical response (CCR) was achieved by 54.9% ($n = 225$), remission by 19.5% ($n = 80$), and minimal clinically important difference (MCID) by 94.6% ($n = 388$) of the study patients after the tDCS treatment completion. At least half of the patients achieved CCR in all severity classes and in patients with and without concomitant use of psychotropics. No serious adverse effects were reported during the treatment.

Limitations: As a non-interventional study based on retrospective data collection from routine clinical practice, the study did not include a control group. Medical history data was available from the tDCS treatment initiation.

Conclusions: This real-world study showed good tolerability and a reduction of depressive symptoms in patients with MDD after tDCS treatment. The results suggest that tDCS is a well-suited treatment alternative for MDD, either as a stand-alone treatment or in combination with antidepressant medication.

1. Introduction

Major depressive disorder (MDD) is the most common, relapsing psychiatric disorder and is a leading cause of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators., 2019). The disorder remains both underdiagnosed and undertreated, and it has been estimated that four in five people with MDD do not receive adequate treatment (Thornicroft et al., 2017) . Antidepressant medication and psychological interventions are the current first-line treatment for MDD. However, achieving a treatment response often takes time and, even after trying several different antidepressants, up to 30% of patients fail to respond (i.e., suffer from treatment-resistant depression) (Sinyor et al., 2010). In addition, antidepressants are often associated with negative side effects, resulting in poor treatment adherence (Melartin et al., 2005).

In recent years, neuromodulatory techniques have been increasingly used to treat MDD (Mutz et al., 2019). Transcranial direct current stimulation (tDCS) is a method of noninvasive neuromodulation, which has been demonstrated in randomized clinical trials (RCTs) to be an effective treatment option for MDD (Brunoni et al., 2017a; Fregni et al., 2021; Sampaio et al., 2018). tDCS relieves depressive symptoms by balancing neuronal excitability at the left dorsolateral prefrontal cortex (DLPFC) with a weak current through the skull (Bennabi and Haffen, 2018; Fitzgerald et al., 2006). Treatment can be administered either as a monotherapy or as an adjunct treatment with antidepressants or psychological interventions (Bennabi and Haffen, 2018). The main advantages of tDCS are ease of use, safety, and good tolerability (Aparício et al., 2016; Bikson et al., 2016).

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Despite the increasing evidence for tDCS as a treatment for MDD, further information is required to optimize treatment outcomes and to identify individual predictors of tDCS response. A majority of relevant RCTs have been conducted in relatively small numbers (<100) of patients, and published experiences on the use of tDCS in a real-world clinical setting are rare (Mutz et al., 2018; Razza et al., 2020). The aim of this study was to characterize the real-life effectiveness and tolerability of tDCS used in routine clinical practice in patients with MDD. In addition, factors associated with clinical response and remission after the tDCS treatment were characterized.

2. Methods

A total of 462 patients with depressive symptoms from seven countries (Bulgaria, Estonia, Finland, Mexico, Pakistan, Romania, and Sweden), who were treated with tDCS as a part of routine clinical practice, were enrolled in the study. The study sample consisted of 410 patients who completed the treatment and for whom all the necessary treatment information was available. After the tDCS treatment completion, feedback from the treatment was collected from the treating physician and from the patient to a structured data collection form. All patients signed informed consent before the data collection. tDCS was delivered at outpatient clinics using the Sooma tDCS™ portable device and a proprietary Sooma head cap. Depending on the routines of each clinic, some of the patients received the treatments at the clinic whereas some of them self-administered the treatment at home after being trained at the clinic. Detailed treatment parameters are described in Supplementary Table 1. A direct current of 2 mA was delivered through electrodes with a diameter of 35 cm^2, an anode positioned over F3, and a cathode over the F4 area (international 10–20 system in electroencephalography) of DLPFC. The treatment was given for 30 min per session with five sessions per week for 2–3 weeks, and after as a maintenance treatment according to each patient's individual needs (the average total number of sessions received by a patient was 16.0 [SD = 4.4]).

Baseline (pre-treatment) and end-point (post-treatment) depressive symptoms were scored according to one of the following validated depression scales: Hamilton Depression Rating Scale (HDRS)−17/−21/−24, Beck Depression Inventory 21 (BDI-21), Montgomery-Asberg Depression Rating Scale (MADRS), or Major Depression Inventory (MDI) (Supplementary Table 1). Baseline depression score was evaluated before the tDCS treatment initiation and end-point depression score after the treatment completion. Cut-off values used for depression rating are described in Supplementary Table 2. The primary study outcomes were complete clinical response (CCR, defined as >50% reduction from the baseline depression score), and remission (Supplementary Table 2). Data on possible adverse effects were collected from patients during the outpatient visit at the time of treatment completion.

The analyses of the primary outcomes were performed in the total study population and in three subgroups (mild, moderate, and severe) based on baseline depression severity, and in two subgroups (user and non-user) based on concomitant use of any of the following psychotropics: antidepressants, antipsychotics, benzodiazepines, and mood stabilizers. Baseline characteristics and primary outcomes were analyzed using descriptive statistics. Results for categorical variables are presented as the number (n) and proportion (%) of patients per eligible patients. Continuous variables are presented as mean and standard deviation (SD) and/or median, range, and the first (Q1) and the third (Q3) quartile. The association between study outcomes and baseline patient characteristics were estimated using multivariate logistic regression models.

3. Results

3.1. Patient characteristics and treatment parameters

Of the 462 patients enrolled, 410 (88.7%) were included in this study. The main reasons for exclusion from the study population were treatment discontinuation (n = 28, 53.8%) and missing data (n = 16, 30.8%) (Supplementary Table 3).

For those included, the median follow-up time was 21.0 weeks (Q1, 21.0; Q3, 28.0) (Table 1). The study group included more females (n = 237, 57.9%) than males (n = 173, 42.2%). The median age of included patients was 39.0 years (Q1, 30.0; Q3, 49.5). At baseline, approximately half of the patients had moderate depression (n = 213, 52.0%), whereas 38.3% (n = 157) had severe and 9.8% (n = 40) mild depression, based on the clinical evaluation and the results of the evaluation score. A total of 73.9% (n = 303) patients had concomitant use of medication. Antidepressants were the most commonly used drugs, totaling 95.7% (n = 290) of patients using medication. Antipsychotics were used by 25.1% (n = 76), benzodiazepines by 10.9% (n = 33), and mood stabilizers by 2.3% (n = 7) of patients with known medication use.

3.2. Change in depression scores after the tDCS treatment

After the completion of tDCS treatment, 96.6% (n = 396) of all study patients had improvement in depression score (Table 1, Fig. 1). The proportion of patients in remission was 19.5% (n = 80) in the total study population; and 57.5% (n = 23) in the mild, 18.3% (n = 39) in the moderate, and 11.5% (n = 18) in the severe depression subgroups. In the subgroup of patients with concomitant medication use, CCR was achieved by 50.2% (152) and remission by 13.9% (n = 42) of the patients; whereas the corresponding percentages were 68.3% (n = 71) and 35.6% (n = 37) in patients with no medication use. A minimal clinically important difference (MCID) was observed in >92.5% of patients in all study subgroups.

3.3. Predictors of tDCS treatment outcomes

In the multivariate regression model, adjusted for age group, sex, and depression severity at baseline, having concomitant use of psychotropics (antidepressant, antipsychotic, mood stabilizer, or benzodiazepine) was negatively associated with achieving CCR after the tDCS treatment (odds ratio, OR, 0.468; 95% confidence interval, CI, 0.289–0.757; p = 0.002) (Supplementary Fig. 1). In a similar regression model with remission as an outcome, having concomitant use of psychotropics (OR, 0.252; 95% Cl 0.144–0.439, $p < 0.001$), having moderate disease (OR, 0.137; 95% Cl 0.064–0.297, $p < 0.001$), and having severe disease (OR, 0.085; 95% Cl 0.036–0.204, $p < 0.001$) were negatively associated with the outcome (Supplementary Fig. 2).

3.4. Adverse effects and safety

Skin itching under the electrodes during the stimulation was the most common adverse effect reported (n = 181, 44.1%), followed by headache (n = 101, 24.6%), and skin redness (n = 73, 17.8%) (Supplementary Table 4). Hypomania was observed in two patients (0.5%), one with moderate and one with severe depression at baseline. Both of the patients with hypomania had concomitant use of antidepressants during the tDCS treatment, but no other psychotropic medications.

4. Discussion

This study provides the largest real-world dataset hitherto reported on the efficiency and tolerability of tDCS in the treatment of MDD in real-world clinical practice. The results indicated that over half of the 410 patients treated with tDCS achieved a CCR, as assessed after the treatment completion. Remission was achieved by approximately one in five patients, most often those with a mild disease form and no concomitant use of psychotropics. tDCS treatment was well-tolerated by the patients and no serious adverse effects were reported during the treatment.

Although the arsenal of antidepressant drugs has significantly

Table 1
Pre- and post-tDCS treatment characteristics for all patients treated with tDCS ($n = 410$); and in subgroups of patients with mild ($n = 40$), moderate ($n = 213$), and severe ($n = 157$) depression at baseline (before tDCS treatment); and with ($n = 303$) and without psychotropics use ($n = 104$) during the tDCS treatment. Three patients with unknown treatment status were excluded from the treatment subgroup analyses. Classification of the depression severity is based on the scale of the specific depression instrument used.

		By depression severity at baseline			By concomitant medication* use	
	Total ($n = 410$)	**Mild ($n = 40$)**	**Moderate ($n = 213$)**	**Severe ($n = 157$)**	**No ($n = 104$)**	**Yes ($n = 303$)**
Follow-up time (weeks)						
Mean (SD)	23.0 (8.3)	21.6 (7.9)	24.0 (7.0)	22.0 (9.8)	23.5 (7.7)	22.8 (8.5)
Median (Q1, Q3)	21.0 (21.0, 28.0)	21.0 (17.5, 21.0)	21.0 (21.0, 28.0)	21.0 (14.0, 28.0)	21.0 (21.0, 28.0)	21.0 (19.5, 28.0)
Sex						
Missing, n	1	0	1	0	0	1
Femal, n (%)	237 (57.9%)	19 (47.5%)	126 (59.4%)	92 (58.6%)	63 (60.6%)	172 (57.0%)
Age, continuous (years)						
Missing, n	3	0	2	1	0	3
Mean (SD)	40.9 (13.0)	39.3 (11.8)	40.5 (11.5)	41.8 (15.0)	39.0 (12.9)	41.7 (12.9)
Median (Q1, Q3)	39.0 (30.0, 49.5)	37.5 (30.8, 45.5)	39.0 (31.5, 48.0)	41.0 (28.0, 53.0)	36.5 (28.0, 47.0)	41.0 (31.0, 51.0)
Age, categorical (years)						
Missing, n	3	0	2	1	0	3
<20, n (%)	5 (1.2%)	2 (5.0%)	1 (0.5%)	2 (1.3%)	2 (1.9%)	3 (1.0%)
20–39, n (%)	199 (48.9%)	22 (55.0%)	106 (50.2%)	71 (45.5%)	60 (57.7%)	136 (45.3%)
40–60, n (%)	174 (42.8%)	15 (37.5%)	93 (44.1%)	66 (42.3%)	36 (34.6%)	138 (46.0%)
>60, n (%)	29 (7.1%)	1 (2.5%)	11 (5.2%)	17 (10.9%)	6 (5.8%)	23 (7.7%)
Concomitant medication						
Antidepressant						
Missing, n	3	0	2	1	0	0
No, n (%)	117 (28.7%)	10 (25.0%)	64 (30.3%)	43 (27.6%)	104 (100.0%)	13 (4.3%)
Yes, n (%)	290 (71.3%)	30 (75.0%)	147 (69.6%)	113 (72.4%)	0	290 (95.7%)
Antipsychotic						
Missing, n	4	0	3	1	0	1
No, n (%)	330 (81.3%)	36 (90.0%)	180 (85.7%)	114 (73.1%)	104 (100.0%)	226 (74.8%)
Yes, n (%)	76 (18.7%)	4 (10.0%)	30 (14.3%)	42 (26.9%)	0	76 (25.1%)
Benzodiazepine						
Missing, n	4	0	3	1	0	1
No, n (%)	373 (91.9%)	39 (97.5%)	201 (95.7%)	133 (85.3%)	104 (100.0%)	269 (89.1%)
Yes, n (%)	33 (8.1%)	1 (2.5%)	9 (4.3%)	23 (14.7%)	0	33 (10.9%)
Mood stabilizer						
Missing, n	4	0	3	1	0	1
No, n (%)	399 (98.3%)	40 (100.0%)	209 (99.5%)	150 (96.2%)	104 (100.0%)	295 (97.7%)
Yes, n (%)	7 (1.7%)	0 (0.0%)	1 (0.5%)	6 (3.8%)	0 (0.0%)	7 (2.3%)
Baseline severity						
Mild, n (%)	40 (9.8%)	40 (100.0%)	0	0	10 (9.6%)	30 (9.9%)
Moderate, n (%)	213 (52.0%)	0	213 (100.0%)	0	60 (57.7%)	151 (49.8%)
Severe, n (%)	157 (38.3%)	0	0	157 (100.0%)	34 (32.7%)	122 (40.3%)
Depression symptoms after the tDCS treatment						
Post-treatment severity						
Mild, n (%)	248 (60.5%)	17 (42.5%)	153 (71.8%)	78 (49.7%)	48 (46.2%)	198 (65.3%)
Moderate, n (%)	60 (14.6%)	0 (0.0%)	20 (9.4%)	40 (25.5%)	17 (16.3%)	43 (14.2%)
Severe, n (%)	22 (5.4%)	0 (0.0%)	1 (0.5%)	21 (13.4%)	2 (1.9%)	20 (6.6%)
Remission, n (%)	80 (19.5%)	23 (57.5%)	39 (18.3%)	18 (11.5%)	37 (35.6%)	42 (13.9%)
Improvement in depression score after tDCS, n (%)	396 (96.6%)	38 (95.0%)	205 (96.2%)	153 (97.5%)	100 (96.2%)	293 (96.7%)
Improvement (%)						
Mean (SD)	48.2 (21.3)	52.0 (23.4)	48.0 (20.5)	47.5 (22.0)	53.5 (23.7)	46.3 (20.2)
Median (Q1, Q3)	53.0 (38.0, 62.0)	58.5 (38.0, 63.0)	54.0 (39.0, 60.0)	52.0 (32.0, 62.0)	57.5 (39.8, 68.0)	50.0 (36.0, 60.0)
Complete clinical response, CCR (>50%), n (%)	225 (54.9%)	26 (65.0%)	118 (55.4%)	81 (51.6%)	71 (68.3%)	152 (50.2%)
Partial response (>25%), n (%)	360 (87.8%)	37 (92.5%)	190 (89.2%)	133 (84.7%)	93 (89.4%)	264 (87.1%)
Remission, n (%)	80 (19.5%)	23 (57.5%)	39 (18.3%)	18 (11.5%)	37 (35.6%)	42 (13.9%)
Minimal clinically important difference (MCID), n (%)	388 (94.6%)	37 (92.5%)	201 (94.4%)	150 (95.5%)	98 (94.2%)	287 (94.7%)

* Including any of the following psychotropics: antidepressants, antipsychotics, benzodiazepines, mood stabilizers. Q1, first quartile; Q3, third quartile; SD, standard deviation; tDCS, transcranial direct current stimulation.

improved in recent decades, their efficacy has not improved over time (Cuijpers et al., 2020). New treatment alternatives are thus urgently needed to tackle the growing global burden of depression. Increasing evidence indicates that tDCS treatment is superior to sham treatment in patients with acute depressive episode, when regarding endpoint depression scores, clinical response, and remission (Brunoni et al., 2017a). A meta-analysis of 23 sham-controlled RCTs including more than 1000 patients with depressive episodes demonstrated that tDCS is modestly effective in treating depressive disorders, showing small to medium effect sizes (Mutz et al., 2018). A recent systematic review of tDCS clinical trials categorized anodal left DLPFC tDCS as Level A (definitely effective) in improving depression in MDD (Fregni et al., 2021). However, inconsistent results have also been observed and heterogeneity in study settings have complicated the comparison of results between studies (Loo et al., 2018; Mutz et al., 2018).

In this study, approximately three in four patients had concomitant use of psychotropics during the tDCS treatment. Improvement in depression score was observed in both psychotropic users and non-users,

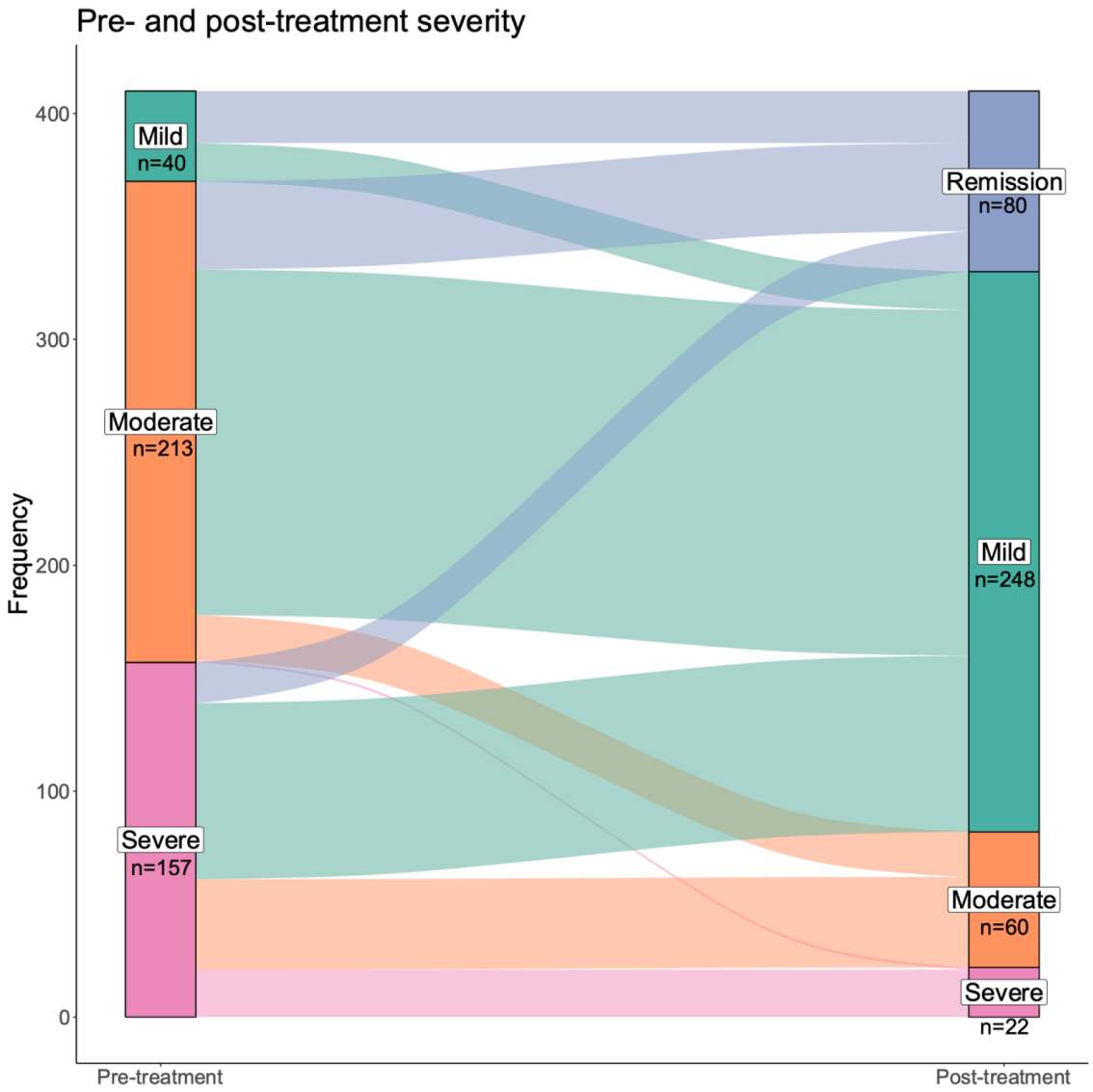

Fig. 1. Change in relative size of depression severity groups pre- and post-tDCS treatment. Post-tDCS treatment severity was analyzed in patients who continued the treatment as planned and had the necessary information available (n = 410). Classification of the depression severity is based on the scale of a specific depression instrument used.

although a higher percentage of non-users achieved a clinical response (68.2%) and remission (35.6%) compared to psychotropic users (50.2% and 13.9%, respectively). In part, this could be explained by the fact that the psychotropic users -group is expected to include more of the severe cases as well as treatment resistant MDD patients, who are known to be difficult to treat. Also, there are potential interactions between some psychotropics and tDCS. Especially, the use of benzodiazepines or anticonvulsants will enhance the inhibitory- and suppress the excitatory tone of the brain and that way can interfere with the neuroplasticity mechanisms of tDCS (Brunoni et al., 2012). Recent meta-analysis suggested that tDCS as a monotherapy was more effective than tDCS as an augmentative or add-on therapy (Mutz et al., 2018). However, it has also been suggested that combining tDCS with an antidepressant, sertraline, may be superior to either of them as monotherapy (Brunoni et al., 2013). It should be noted that the number of study patients did not enable us to study different drug groups and pooling all medication users in one group may mask the effects of individual drugs.

This study demonstrated that, irrespective of the disease severity before the tDCS treatment initiation, a vast majority (>90%) of patients showed improvement in depression score and >50% achieved a CCR after tDCS treatment. We found that concomitant use of psychotropics was negatively associated with achieving both a clinical response and remission, whereas having a more severe disease at baseline was negatively associated with remission only. These results suggest that patients with milder depression severity and no concomitant use of psychotropics have the greatest decrease in depression score when using tDCS. We had no information available on patient medication or disease history, and thus could not exclude the possibility that other confounding factors explain the observed differences between various subgroups. Importantly, achieving a clinical response may, in general, be more difficult in patients with severe than in mild disease. However, our results show that the improvement by tDCS was clinically relevant in each severity class, as majority of the patients reached at least down to the level of mild depression, if not to remission (Fig. 1). Importantly, our findings call for further studies on optimizing the treatment dose and schedule to treat the more severe MDD cases more effectively.

The main benefit of tDCS over psychotropics is fewer adverse effects. As the method has no systemic effects, it can also be used in patients for whom drugs are not suitable or recommended. In comparison with other neuromodulatory methods, the major advantages of tDCS are ease of use and low costs: treatment can be introduced at home or in an outpatient setting without intensive monitoring (Baeken et al., 2019; Mutz et al.,

2019). In this study, no serious adverse effects were observed during the median follow-up period of 21 weeks, and the most common adverse effects were similar to what has been reported previously (Bikson et al., 2016; Razza et al., 2020). Although some of the initial studies suggested that tDCS could induce a treatment-emergent mania, more recent meta-analyses have shown that the risk is not superior to sham treatment (Brunoni et al., 2017b). The results of this study support the findings of meta-analyses: of 410 patients included, hypomania was reported only in two patients.

4.1. Limitations

As a real-world study based on data collection from routine clinical practice, this study has certain limitations. The study did not include a sham or active control group, thus possible placebo effects associated with tDCS treatment could not be evaluated. However, it should be noted that significant placebo effects, producing neurobiological changes in the brain, have also been shown to be associated with antidepressants (Kirsch, 2019).

Together, the results of this real-world study strengthen the evidence for the effectiveness and tolerability of tDCS in patients with MDD. As a method with few adverse effects, tDCS is a well-suited treatment alternative for MDD, either as a stand-alone treatment or in combination with antidepressant medication. New data from both controlled, large-scale trials as well as routine clinical practice are crucial for optimizing tDCS treatment targeting and outcomes in the future.

4.2. Ethical considerations

All patients signed informed consent before the data collection. Patient data were de-identified prior to data entry. The Clinical Outcomes Registry was maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The data was collected as a part of the post-market surveillance efforts. Collection and analysis of clinical care data in this way does not require local Institutional Review Board approval.

Declaration of Competing Interest

Mika Nikander is employed by Sooma Oy.

Tuomas Neuvonen is a shareholder at Sooma Oy.

Margus Lookene, Nikola Markov, and Dancho Dilkov do not have conflicts of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2022.100347.

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