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Transcranial direct current stimulation for unipolar depression and risk of treatment emergent mania: An updated meta-analysis

Introduction

As transcranial direct current stimulation (tDCS) emerges as an investigational noninvasive approach for the treatment of major depressive disorder, there is increasing interest in its safety profile [1]. Several studies and case reports suggest that tDCS may be associated with increased risk of treatment-emergent mania or hypomania (TEM) when used to treat depression [2–4]. In 2017, Brunoni et al. [3] conducted a meta-analysis of TEM in ten randomized controlled trials (RCTs) evaluating antidepressant effects of active tDCS (n = 226) and sham tDCS (n = 190) in unipolar and bipolar depression and failed to demonstrate group differences [3]. Since that time, three large antidepressant RCTs comparing active tDCS (n = 185) with sham (n = 216) in unipolar depression have been published [4–6]; results include four additional cases of TEM occurring in the active tDCS groups and none in the sham groups. The current study aims to provide an updated meta-analysis that evaluates the association between tDCS and TEM in unipolar depression, hypothesizing that active tDCS is associated with increased risk of TEM relative to sham, and represents a safety outcome that merits consideration when designing future treatment protocols and considering risks related to unsupervised tDCS.

Methods

Study and case selection

RCTs of tDCS for unipolar major depressive episodes were identified through Pubmed following the methods described by Brunoni et al. [3], but excluding trials that combined subjects with unipolar and bipolar depression and extending the search through November 5, 2018. This search yielded 11 studies, including eight of RCTs previously identified, analyzed and reported by Brunoni et al. [3], plus three recent large RCTs of tDCS in unipolar depression [4: n = 69, 5: n = 248, 6: n = 84].

Data analysis

A fixed effect model was constructed using the Mantel-Haenszel (MH) method. The 'treatment arm' continuity correction was used for studies with zero events in a single treatment arm, as this has been shown to perform with less bias than a constant factor when studies have unbalanced groups [7]. Studies with zero events in both arms were excluded as recommended by the Cochrane Handbook and others [7,8]. Pooled risk difference was calculated without use of continuity correction. Sensitivity analyses were performed using several alternative meta-analysis methods to assess the robustness of these findings. All analyses were conducted using the 'metabin' command from the 'meta' package from R [9,10].

Results

Five RCTs of tDCS reported 13 cases of TEM. Twelve TEM cases were in the active tDCS groups (12/367 = 3.3%) and one was in a sham group (1/364 = 0.27%). The fixed effect MH method yielded an odds ratio of 5.01 ([1.37–18.26], p = 0.015) with higher risk of TEM in the active tDCS groups (Fig. 1), and a significant pooled risk difference between active and sham treatments (RD = 0.031 [0.011–0.050], p = 0.002). Sensitivity analyses adjusting for method (MH, Inverse, Peto), and use of continuity correction yielded consistently significant odds ratio estimates, ranging from 4.9 to 12.8, with all method permutations suggesting increased risk of TEM in the tDCS group compared to sham (all $p < 0.016$) (Supplemental Table 1). Additional models including studies with zero events in both arms yielded similar results, with lower odds ratios, ranging from 2.7 (Inverse, p = 0.056) to 3.0 (MH, p = 0.029) with treatment arm continuity corrections (Supplemental Table 1).

Discussion

This study demonstrates that individuals receiving active tDCS for unipolar depression are at an increased risk of TEM compared to those receiving sham stimulation. Most treatments for depression carry a modest risk of inducing TEM, either from previously undiagnosed bipolar disorder or as a function of the treatment itself [11]; tDCS appears to be no different in this regard. While it is difficult to assess the severity of the TEM using meta analytic methods, at least one case of psychotic mania [12] required hospitalization, although others appeared to resolve spontaneously [5,12]. As such, future studies should report detailed follow up of TEM cases to provide information on the natural progression and management of tDCS-related TEM.

Most TEM cases (8/12, 66.6%) occurred in combination with the initiation of, or continued treatment with a selective serotonin reuptake inhibitor (SSRI), often at a low dose, suggesting a possible increased risk of tDCS TEM with co-treatment or co-initiation of SSRI. Previous reviews have suggested that cases of TEM reported in tDCS RCTs may represent TEM caused by antidepressants alone [13], but the current analysis provides evidence against this suggestion, as all studies utilizing SSRI + active tDCS also had SSRI + sham

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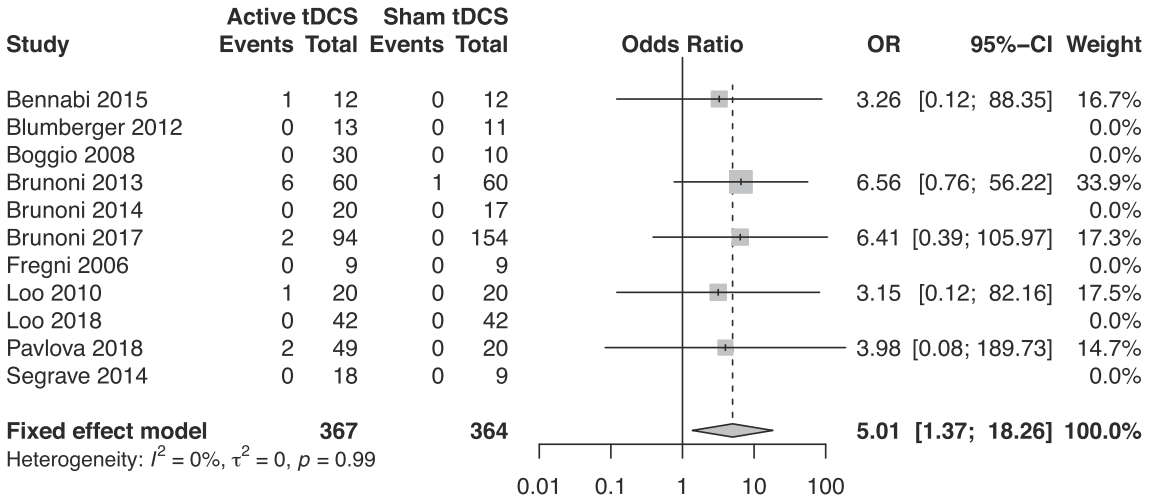

Fig. 1. Summary of the reported cases of treatment emergent mania and hypomania in 11 randomized controlled trials of active vs. sham transcranial direct current stimulation (tDCS) for treatment of unipolar depression.

tDCS groups [2,4,14]. Additionally, four of the cases of TEM [2,5,15] occurred in the absence of antidepressant treatment.

The current study builds on and expands the findings from the earlier meta-analysis of Brunoni et al. [3], in which they observed a rate of TEM of 3.5% in subjects receiving active tDCS for depression, but did not observe statistically significant differences when comparing active and sham tDCS. With the addition of three large RCTs that were not previously available, and an exclusive focus on studies of unipolar depression, we observed a similar rate of TEM of 3.3% that was associated with a significant increased odds ratio and risk difference compared to sham, providing evidence that active tDCS is associated with an increased risk of TEM in unipolar depression. Sensitivity analyses utilizing several alternative meta-analytic approaches yielded similar results, confirming the robustness of these findings [7,16,17]. The observed increased risk of TEM with tDCS is similar to the risks associated with SSRI initiation, suggesting that tDCS requires the same level of caution and risk discussion currently used when treating depression with SSRIs, and indicates another risk to be discussed with individuals utilizing unsupervised tDCS [18].

Conclusion

This study combined the results from recent RCTs assessing the effectiveness of tDCS in unipolar depression, and found that active tDCS was associated with a small but significantly increased risk of TEM compared to sham. Future studies utilizing tDCS for the treatment of psychiatric conditions should monitor for the emergence of symptoms of mania and hypomania. TEM may be particularly important in the context of unsupervised applications of tDCS [18].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.03.025.

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