

# Transcranial Direct Current Stimulation for Refractory Auditory Hallucinations in Schizophrenia

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Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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## ABSTRACT

Some patients with schizophrenia may suffer from continuous or severe auditory hallucinations that are refractory to antipsychotic drugs, including clozapine. Such patients may benefit from a short trial of once- to twice-daily transcranial direct current stimulation (tDCS) with the cathode placed over the left temporoparietal cortex and the anode over the left dorsolateral prefrontal cortex; negative, cognitive, and other symptoms, if present, may also improve. At present, the case for tDCS treatment of refractory auditory hallucinations rests on 1 well-conducted randomized, sham tDCS-controlled trial and several carefully documented and instructive case reports. Benefits with up to 3 years of maintenance tDCS have also been described. In patients with refractory auditory hallucinations, tDCS has been delivered at 1- to 3-mA current intensity during 20–30 minutes in once- to twice-daily sessions for up to 3 years with no apparent adverse effects. Transcranial direct current stimulation therefore appears to be a promising noninvasive brain stimulation technique for patients with antipsychotic-refractory auditory hallucinations.

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## Clinical Problem

Mr D is a 32-year-old patient with a 5-year history of schizophrenia. During the past 2 years, he has repeatedly complained about hearing abusive and threatening voices that are present for most of his waking hours; these experiences are markedly distressing and diminish his quality of life. Adequate trials of several different typical and atypical antipsychotic medications failed to attenuate the hallucinatory experiences; clozapine, which he has been receiving for the past 6 months, has also proved unhelpful. Are there other conventional or unconventional approaches that might attenuate the hallucinations?

## Treatment Options for Refractory Auditory Hallucinations

In positive-symptom schizophrenia that is refractory to clozapine, possible treatment strategies include augmentation with a second antipsychotic,<sup>1</sup> augmentation with lamotrigine,<sup>2</sup> or a trial of electroconvulsive therapy (ECT).<sup>3</sup> Experimental strategies include augmentation with valproate,<sup>4</sup> topiramate,<sup>5</sup> or allopurinol,<sup>6</sup> although the efficacy data on these 3 drugs are equivocal, and none has been specifically studied in clozapine-refractory patients. Furthermore, none of the preceding interventions has been studied in patients in whom the target symptom is persistent auditory hallucinations.

Some patients with antipsychotic-refractory auditory hallucinations may respond to a benzodiazepine drug<sup>7</sup>; behavioral interventions, many of which have been described,<sup>8,9</sup> may also result in benefits. The best evidence of efficacy, however, has emerged with the use of low-frequency (eg, 1 Hz) and other types of repetitive transcranial magnetic stimulation (rTMS) applied over the left temporoparietal cortex<sup>10–12</sup>; treatment gains herein may be sustained with maintenance rTMS<sup>13</sup> much as treatment gains with ECT are sustained with maintenance ECT.<sup>14</sup>

Why rTMS? One hypothesis suggests that auditory hallucinations are unrecognized and unsuppressed manifestations of inner speech generated in the speech areas of the brain.<sup>15,16</sup> Therefore, given that low-frequency rTMS inhibits the cortical areas underlying the rTMS coil,<sup>17</sup> low-frequency rTMS should attenuate auditory hallucinations. Evidence for the successful use of rTMS in patients with refractory auditory hallucinations<sup>10–12</sup> encourages the consideration of transcranial direct current stimulation (tDCS) for the same indication.<sup>18</sup>

## What Is tDCS and Why May It Be Useful for Refractory Auditory Hallucinations?

Transcranial direct current stimulation is a noninvasive brain stimulation technique that has been in use for over half a century; it was formerly known as brain polarization therapy.<sup>19</sup> It involves the passage of a continuous direct current of very low amplitude (eg, 1–3 mA) through electrodes at least 1 of which (anode or cathode) is placed on the scalp.<sup>20</sup> The location of the electrodes depends on the indication for which tDCS is being administered. The patient is fully conscious throughout the tDCS treatment session, which is usually about 20 minutes in duration.<sup>20,21</sup>

- In some patients with schizophrenia, auditory hallucinations may be severe and refractory to antipsychotic drug treatment. Such patients may benefit from a short trial of once- to twice-daily transcranial direct current stimulation (tDCS).
- In such patients, cathodal stimulation of the left temporoparietal cortex may suppress the auditory hallucinations, and anodal stimulation of the left dorsolateral prefrontal cortex may attenuate negative symptom severity.
- In patients in whom continuation of tDCS is necessary to maintain treatment gains, administration of once- to twice-daily tDCS across up to 3 years of treatment may be safe and effective.

Research on tDCS has burgeoned during the last 2 decades, and experimental indications for it include depression,<sup>22–24</sup> tinnitus,<sup>25</sup> motor paresis in patients with chronic stroke,<sup>26</sup> poststroke aphasia,<sup>27</sup> chronic pain,<sup>28</sup> and other conditions. This procedure has also been used as an investigative tool to study brain functioning.<sup>29</sup>

tDCS results in prolonged hyperpolarization in the area of cerebral cortex underlying the cathode and in prolonged depolarization in the area of cortex underlying the anode.<sup>20,21</sup> These effects are roughly analogous to the cortical inhibition and excitation that are associated with low- and high-frequency rTMS, respectively. Because low-frequency rTMS applied over the left temporoparietal cortex attenuates refractory auditory hallucinations<sup>10–12</sup> and high-frequency rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) improves negative symptoms in schizophrenia,<sup>30</sup> it is possible that tDCS may do what rTMS does but with greater convenience and at less expense.

### What Does the Evidence Show?

The evidence for the efficacy of tDCS in patients with medication-refractory auditory hallucinations rests on a few carefully documented and instructive case reports<sup>18,31–35</sup> and 1 well-designed and well-conducted randomized controlled trial (RCT).<sup>36</sup> In all reports and the RCT, treatment with ongoing psychotropic medications continued unchanged during the tDCS course.

In possibly the first report in contemporary literature, Homan et al<sup>31</sup> described a 44-year-old man with schizophrenia who experienced auditory hallucinations that commanded him to attempt suicide. These hallucinations were refractory to antipsychotic medications. The patient received a course of 10 once-daily, 15-minute tDCS sessions with the cathode placed over the left temporoparietal cortex and the anode over the right orbit. The current strength was set at 1 mA. The authors reported substantial reduction in the severity of the auditory hallucinations. This improvement was maintained at a 6-week follow-up.

Shiozawa et al<sup>32</sup> reported a 31-year-old man with long-standing schizophrenia whose complex visual and auditory hallucinations were refractory to antipsychotic medications, including clozapine. He was treated with 20 sessions of tDCS; in 10, the cathode was placed over the occipital area, and in the other 10, over the temporoparietal area. The anode was placed over the left DLPFC during all 20 sessions. A 2-mA current was passed for 20 minutes in each session. There was a small (around 30%) improvement in positive symptom, negative symptom, and general psychopathology ratings. The severity of hallucinations also decreased, and benefits were maintained at a 2-month follow-up. No adverse effects were associated with tDCS, nor were cognitive impairments evident on neuropsychological testing.

Shivakumar et al<sup>33</sup> described a 28-year-old woman with continuous, derogatory auditory hallucinations occurring during a relapse of schizophrenic illness. After 8 days of antipsychotic and benzodiazepine treatment, she was started on tDCS. The cathode was placed over the left temporoparietal junction, and the anode was placed over the left DLPFC. After 5 days of twice-daily, 20-minute tDCS sessions at 2-mA current amplitude, the hallucinations completely remitted; in fact, marked improvement was apparent after the first day of treatment. The authors suggested that the dramatic response of the hallucinations to tDCS, as compared with an only gradual response across several weeks in an earlier episode of illness (when the patient received medications alone), implied that it was tDCS that attenuated the hallucinations and not the ongoing psychotropic medications.

Rakesh et al<sup>34</sup> described a 24-year-old actively psychotic male schizophrenia patient who refused antipsychotic medication but who accepted tDCS for the management of auditory verbal hallucinations. He received ten 20-minute sessions of 2-mA amplitude tDCS administered twice daily for 5 consecutive days. Hallucinations improved dramatically from the very first day, and remission from hallucinations occurred by the end of the 5-day course. These benefits were accompanied by improvement in concentration, interpersonal interactions, and insight, and the patient subsequently agreed to accept antipsychotic medication for his illness. This report suggests that tDCS may effectively attenuate auditory hallucinations even when administered as monotherapy in acutely psychotic patients.

Only 1 report<sup>18</sup> has described long-term use of tDCS. In this report, a 24-year-old woman with schizophrenia had severe, antipsychotic- and clozapine-refractory, continuous, psychosocially and cognitively disabling auditory hallucinations that left her almost vegetative. She was treated with once-daily 20-minute tDCS sessions at 1-mA intensity. The tDCS cathode was placed midway between T3 and P3, and the anode over F3, in the 10-20 EEG electrode positioning system. There was clear improvement in cognitive and psychosocial functioning within 1 week, followed by progressively increasing attenuation in the experience of hallucinations across 2–4 weeks. Near-total

remission from hallucinations occurred within 2 months, in association with normalization of psychosocial and occupational functioning. Attempts to taper and withdraw tDCS failed. Maintenance tDCS was instituted with treatment protocols involving 1- to 3-mA current intensity delivered in 20- to 30-minute sessions at a frequency of once to twice daily, depending on need. Treatment benefit was confirmed in 2 separate on-off-on situations that occurred inadvertently and under quasi-blinded conditions. At the time of report, nearly 3 years after initiation of treatment, maintenance tDCS continued to demonstrate efficacy without evidence of any clinically apparent adverse effects. The family was trained to administer tDCS from the second week of treatment, and domiciliary treatment was effected almost throughout the treatment period.

In the only RCT on the topic, 30 schizophrenia patients experiencing daily verbal medication-refractory auditory hallucinations for at least the past 3 months were randomized to true or sham tDCS.<sup>36</sup> True tDCS was administered with 2-mA current in 20-minute sessions twice per day (at least 3 hours apart) for 5 consecutive days. The tDCS anode was placed between F1 and FP1 (ie, over the left dorsolateral prefrontal cortex), and the cathode was placed between T3 and P3 (ie, over the left temporoparietal cortex). Patients and raters were blind to the treatment assignment. A small but statistically significant advantage for true over sham tDCS was seen at all time points: reductions in hallucination ratings for true vs sham tDCS were 31% vs 8% at the end of the treatment course, 36% vs 3% after 1 month, and 38% vs 5% after 3 months. Whereas no patient experienced full remission from hallucinations, 6 of the true tDCS patients (40%) had > 50% decrease in hallucination ratings. Additionally, at the end of the tDCS course, negative symptom ratings reduced by 12% with true tDCS but increased by 6% with sham tDCS; this advantage for true tDCS also reached statistical significance. Treatment-emergent adverse events did not differ between true and sham tDCS groups.

Two patients in this RCT<sup>36</sup> were described in a separate report.<sup>35</sup> Both patients showed marked attenuation in the severity of auditory hallucinations as well as modest improvement in negative symptoms. The treatment gains were apparent by the end of the 5-day tDCS course and were maintained for 3 months.<sup>35</sup>

Patients in the case reports<sup>18,31,33-35</sup> showed substantial response to tDCS, whereas those in the RCT<sup>36</sup> showed attenuation of hallucination ratings by only about a third. There are 2 likely explanations for the modest improvement recorded in the RCT. One is that not all patients with refractory auditory hallucinations will improve with tDCS. The other is that patients in the RCT received tDCS for only 5 days; a longer course of treatment might have yielded better outcomes.

As an additional note: a tDCS trial has been performed in pediatric schizophrenia<sup>37</sup>; however, this was a safety study, auditory hallucinations were not an indication for treatment,

and efficacy outcomes were not reported. Other reports of tDCS in schizophrenia and in patients with auditory hallucinations have also been published.<sup>38,39</sup>

### For How Long Should tDCS Be Continued?

In most of the case reports as well as in the RCT reviewed above, tDCS was administered twice daily for a fixed 5-day course. Whereas this schedule appears reasonable and is supported by evidence, in this author's experience, an adequate trial of tDCS for refractory auditory hallucinations requires at least 2 weeks of 20- to 30-minute, once- to twice-daily, treatment sessions, and, in at least some patients, it could take at least a month for peak benefits to accrue.<sup>18</sup> Whereas the literature generally indicates persistence of benefits for a few weeks to a few months after the end of the tDCS course, relapse would indicate the need for reintroduction of tDCS. It is possible that some patients may require maintenance tDCS to sustain treatment gains,<sup>18</sup> much as maintenance ECT is necessary in some patients with depression or schizophrenia.<sup>14</sup> There is anecdotal evidence for the safety and efficacy of tDCS for up to 3 years of maintenance therapy.<sup>18</sup>

### How Safe Is tDCS?

With very few exceptions related to curious electrode positioning,<sup>40</sup> there have been no safety concerns with tDCS despite more than half a century of use.<sup>20</sup> Adverse effects that have been described are mostly mild, and of the nature of itching or burning at the electrode site; if present, these are usually limited to the initial minutes of the session when stimulation is initiated, or when current is ramped up. Adverse effects are uncommon after the treatment session; if present, these are again related to local itch or discomfort. Redness may occur at the electrode site if the current density is high or if there is inadvertent direct contact between the electrode and skin. Dropout due to adverse effects does not appear to occur with tDCS. No persistent or longer term adverse effects have been reported with tDCS as currently practiced.<sup>20,41</sup> No adverse effects or safety concerns have been reported, even after up to 3 years of once- to twice-daily use.<sup>18</sup>

### Can tDCS Be Combined With Psychotropic Drugs?

In all case reports<sup>18,31-33,35</sup> bar 1<sup>34</sup> and in the RCT<sup>36</sup> as well, ongoing treatment with antipsychotic and other medications continued unchanged during the tDCS trial. It therefore appears that tDCS can be safely and effectively combined with antipsychotic medication.

Many patients in the RCT were described to be receiving high-dose antipsychotic medication.<sup>36</sup> At least 1 report, each, has described tDCS in combination with clonazepam<sup>33</sup> and clozapine.<sup>18</sup> However, given that tDCS influences cortical excitability, more information is necessary on how drugs that influence cortical excitability (benzodiazepines and other anticonvulsants; clozapine and other proconvulsants) modulate the efficacy of tDCS.

## How Does tDCS Compare With rTMS?

There are no head-to-head trials comparing tDCS and rTMS for auditory hallucinations in schizophrenia. With specific regard to refractory auditory hallucinations, far more efficacy data exist for rTMS<sup>10–12</sup> than for tDCS. Additionally, rTMS may be superior in efficacy potential if only because it is capable of deeper cortical penetration (but this may not be a necessary criterion for efficacy).<sup>42</sup> Nevertheless, tDCS does offer several advantages. The tDCS device is far simpler than the rTMS instrument, and so treatment with tDCS is less expensive than that with rTMS. Despite more than half a century of use, tDCS has not been associated with serious adverse effects, whereas rTMS has rarely been reported to trigger seizures.<sup>43</sup> Importantly, tDCS can simultaneously inhibit the temporoparietal cortex (cathodal stimulation) and stimulate the DLPFC (anodal stimulation); the latter can improve mood, cognition, and negative symptoms.<sup>18,36</sup> Unlike rTMS, tDCS is portable. Last, but not least, domiciliary treatment is feasible with tDCS when maintenance therapy proves necessary<sup>18</sup>; this is not possible with rTMS.

## Conclusions

tDCS appears to be a safe, effective, inexpensive, and promising treatment for antipsychotic-refractory auditory hallucinations in schizophrenia. A modest body of evidence demonstrates that cathodal stimulation over the speech cortex can attenuate auditory hallucinations, and 1 report suggests that cathodal stimulation over the visual cortex may attenuate visual hallucinations, as well. Anodal stimulation over the left DLPFC may attenuate mood, cognitive, and negative symptoms associated with the illness.

Auditory hallucination improvement related to tDCS may be dramatic, functioning as early as after just 1 day of treatment; however, in some patients, it can take 1–2 weeks or longer for benefits to become apparent and 1–2 months for benefits to peak. Hallucinatory experience attenuation related to tDCS may be associated with gains in psychosocial and occupational functioning. Correct electrode placement is important. For example, changes in electrode positioning from that described here may result in a loss of treatment gains from which recovery (after correction of electrode positioning) may be slow.<sup>18</sup>

The literature reviewed suggests that tDCS may be effective against auditory hallucinations either as monotherapy or in augmentation of antipsychotic drugs and in acutely psychotic patients as well as those with chronic illness. In patients with relapsing symptoms, once- or twice-daily sessions of maintenance tDCS may maintain treatment gains across years of treatment without occasioning noticeable adverse effects. Relatives of patients can be trained to safely and effectively administer tDCS at home, but periodic checks should be scheduled to confirm that stimulation protocols are being properly followed.

Interested readers may refer to several excellent reviews for technical and other information.<sup>20,21</sup>

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