Therapeutic Neurostimulation and Schizophrenia

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The authors review the evidence for the use of ECT and other novel neurostimulation techniques in the treatment of schizophrenia.

Neurostimulation has shown promising benefits in the treatment of schizophrenia over the years. Here we review the evidence for the use of ECT and other novel neurostimulation techniques in the treatment of schizophrenia.

**Electroconvulsive therapy**

Schizophrenia and schizoaffective disorder are indications for use of ECT, according to the FDA executive summary for the Neurological Devices Panel Meeting. In the US, ECT is predominantly used in the treatment of mood disorders, whereas in Asian countries, it is commonly used in the treatment of schizophrenia despite the relatively modest evidence for efficacy. Randomized controlled trials (RCTs) that compare ECT with sham treatment for schizophrenia have yielded mixed results. Trials conducted before the 1980s consistently reported nonsignificant differences in efficacy between groups; however, later reports indicate that there may be significant benefits. This discrepancy may be due to the fact that the patient population in the older studies had a chronic, unremitting course and there was no concomitant use of antipsychotics.

The combined use of antipsychotics with ECT has proved to be beneficial in antipsychotic nonresponders. One study showed that a combination of high-dosage bilateral ECT and flupenthixol in patients with schizophrenia speeds the clinical response and lessens the number of treatments and days to remission. Another RCT indicates that the adjuvant use of ECT with olanzapine was more effective than its use with sulpride or risperidone.

A prospective open trial of adjuvant ECT with risperidone or olanzapine in patients with treatment-resistant schizophrenia (TRS) reported significant improvement in global assessment of functioning and clinical global impression. Conversely, ECT with concomitant haloperidol in patients with first-episode psychosis showed no difference in efficacy compared with sham treatment, but this may have been due to methodological limitations.

An 8-week single-blind study of 39 patients with TRS showed a 50% response in the clozapine plus ECT group, versus 0% in the clozapine group. There are safety concerns in combining ECT with clozapine because the latter is a proconvulsant, but the researchers reported no safety issues—the only adverse effect was mild confusion that required postponement of the ECT. Patients with schizophrenia and prominent depression, positive symptoms, and recent-onset catatonia may be the best candidates for ECT. Suzuki and colleagues reported remarkable improvement in symptoms in patients with catatonia. However, relapse rates after completion of acute ECT were high, and combined use of continuation or maintenance ECT with neuroleptics was important to prevent relapse.

ECT is safe and effective as an adjuvant for treatment of schizophrenia, and it should be considered in patients who do not respond to adequate trials of antipsychotics. It can improve positive, negative, affective, and vegetative symptoms as well as quality of life in patients with schizophrenia. There is adequate evidence for use of ECT in schizophrenia, although the mechanisms of antipsychotic effect of ECT are still unclear.

**Transcranial magnetic stimulation**

Repetitive transcranial magnetic stimulation (rTMS) is a nonconvulsive brain stimulation technique that has gained popularity in the past 2 decades. There is ongoing exploration of the use of rTMS in schizophrenia and other neuropsychiatric disorders as well as in stroke and movement disorders. rTMS has the potential to alter the excitability of the underlying cortex with persisting after effects. The reports of beneficial effects of rTMS in the treatment of schizophrenia symptoms, such as auditory hallucinations and catatonia, have led to additional studies. Low-frequency stimulation (less than 5 Hz) was found to diminish excitability of the underlying cortex, and the changes resembled long-term depression; high-frequency stimulation (10 Hz) excited the underlying cortex...
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and caused long-term potentiation. The rTMS stimulus parameters and electrode montage used depend on the target symptoms.

Low-frequency stimulation has shown benefits in the treatment of auditory hallucinations of schizophrenia, and it significantly reduced the number of positive symptoms. In addition, rTMS could be used to prevent relapse of antipsychotic-refractory auditory hallucinations. Auditory hallucinations may be associated with cortical activation in the perisylvian language areas. This activation in language areas is reversed by the stimulation of temporoparietal rTMS. The dominant and nondominant temporoparietal areas are sites for intervention for auditory hallucinations. Hallucinations can vary between the left and right side of the brain; thus, it is important to locate the area of abnormality before stimulation. High-frequency stimulation of the prefrontal cortex was found to significantly improve the negative and cognitive symptoms of schizophrenia.

Although there are studies of rTMS with negative results, the evidence in support of its use is promising. More research is needed to explore its potential in acute and maintenance phases as monotherapy and as an adjunctive treatment. Future research should also explore neuronavigation guidance to further individualize treatment in patients with schizophrenia.

Transcranial direct current stimulation (tDCS) is another novel, nonconvulsive brain stimulation technique that has gained popularity in the treatment of schizophrenia in the past 3 years; however, it is not FDA-approved. tDCS involves stimulation of the brain with low-amplitude direct current via 2 scalp electrodes (anode and cathode). It can be used to either stimulate or inhibit the underlying cortex, similar to rTMS. The anodal stimulation of the motor cortex enhances cortical excitability, whereas the cathodal stimulation reduces excitability.

The first case report for schizophrenia was the use of cathodal tDCS over the left temporoparietal cortex in a patient with medication-refractory auditory hallucinations. Symptom improvement was seen at 6-week follow-up. A randomized sham-controlled trial reaffirmed the benefits of tDCS in patients with medication-refractory auditory hallucinations. The study indicated that benefits lasted for 3 months. Symptom improvement may be attributable to the neuroplasticity effects of tDCS. In 2 cases, tDCS was used successfully as an adjunct to antipsychotics in TRS. In one of the cases, it was safely used for more than 3 years and resulted in improvement from vegetative state to near-normal functioning. In the other case, improvement in positive and negative symptoms was also seen. Anodal tDCS over the left dorsolateral prefrontal cortex improved negative symptoms of schizophrenia. Symptom improvement was also seen in a patient with catatonic schizophrenia refractory to treatment with a combination of clozapine and ECT. Moreover, tDCS may have the potential to be used as monotherapy. The results from studies of tDCS use for the treatment of schizophrenia are promising and research is ongoing. The tDCS device is less expensive than other brain stimulation devices and it has the potential to be an economical treatment.

Disclosures:
Dr Surya is Chief Resident, Dr Miller is Associate Professor, Dr Rosenquist is Professor and Vice Chair, and Dr McCall is Case Distinguished University Chairman in the department of psychiatry and health behavior at the Medical College of Georgia of Georgia Regents University in Augusta. Drs Surya, Miller, and McCall report no conflicts concerning the subject matter of this article; Dr Rosenquist reports that he has received research support from the NIMH, Neuronetics, Cyberonics, and NeoSync.

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