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Editorial

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Should electroconvulsive therapy (ECT) be banned for schizophrenia?

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In 2019, Read et al published a review of 11 electroconvulsive therapy (ECT) vs sham-ECT randomized controlled studies for depression along with five meta-analyses based on from one to seven of the underlying studies. The authors note that the underlying studies were small, averaging 37 participants each. They describe that at the end of ECT treatment four studies found ECT significantly superior for "severe depression," five found no significant difference between ECT and sham-ECT, and two found mixed results, including one study which found that clinicians identified improvement and patients did not. The authors also characterize these studies as outdated, noting that the last occurred in 1985, some 35 years ago. The authors then go on to note while all of the meta-analyses describe ECT as safe and effective that the meta-analyses ignored multiple methodological flaws in the underlying studies. Moreover, the authors opine that the quality of the data are so poor that the meta-analyses should have drawn no conclusions about the safety or efficacy of ECT. They also note that the benefits of ECT did not endure following completion of ECT treatment. Based on their review, the authors call for a series of well-designed, double-blind, sham-controlled randomized studies to determine the safety and efficacy of ECT for the treatment of depression. Citing high risk of permanent memory loss and a small mortality risk, they also opine that use of ECT should be immediately suspended pending the results of such research.[1]

We agree with the authors' call for rigorous, randomized, double-blind, controlled studies of ECT. It is difficult to argue against well-done studies that examine the benefits and risks of ECT as currently administered. We must strongly disagree; however, with their opinion that use of ECT should be immediately suspended. First, their focus on a handful of small ECT vs sham-ECT studies ignores an immense body of decade upon decade of observational data accumulated since the introduction of chemically-induced therapeutic seizures in 1934 by Meduna and the subsequent introduction of ECT in 1938 by Cerletti and Bini across thousands of patients and hundreds of sites that supports convulsive therapy and later ECT as a life-saving treatment among the severely depressed.[2-4] Second, the authors' review entirely ignores the value and supporting data for ECT in treating a variety of conditions including benzodiazepine non-responsive catatonia, treatment-resistant neuroleptic malignant syndrome, treatment-resistant mania or mixed mood states, Treatment-resistant Parkinson's disease, post-traumatic stress disorder, pregnancy in which pharmacological agents pose unacceptable risks and treatment-resistant schizophrenia and other psychoses.[5-10] Additionally, Read et al cite a "high risk" of permanent memory loss as a reason to suspend use of ECT.[1] In this context, it should be noted that while memory loss during the course of acute ECT treatment is a valid concern, the memory impairment does not typically represent an ongoing memory impairment. That is, memory encoding and recall tends to return to normal following the completion of the course of ECT.[11,12] Finally, with respect to general criticisms of ECT, Read et al point out that the benefits of an acute course of ECT are time-limited.[1] This criticism ignores that most ECT-treated patients receive pharmacological treatment post ECT or maintenance ECT treatment.[13,14]

Now we turn to the central issue of this editorial, that is, should ECT treatment of schizophrenia be suspended or banned? At the outset, it should be noted that antipsychotic medications are the cornerstone of the treatment of schizophrenia and other psychotic illnesses.[15-18] That is, ECT has been used as an adjunctive treatment for those patients who fail to have an adequate response to antipsychotic medications.[19,20] Unfortunately, it is estimated that approximately 33% (circa 0.2% of the general population) of patients suffering from a schizophrenia spectrum disorder become treatment-resistant, that is, have a <7% probability of responding adequately to all antipsychotics except clozapine.[21-23] The response rate to clozapine in this subset of patients suffering with schizophrenia is 40% to 60%, meaning that a substantial portion of treatment-resistant patients have an inadequate response even to clozapine treatment.[24,25] Of course, this conversely means that 40% to 60% of individuals with treatment-resistant schizophrenia fail to respond adequately to clozapine monotherapy. Even worse, responsiveness to clozapine appears to decline beginning after about 2.8 years of treatment-resistant status.[26] This is illustrated in Figure 1 below.

Regrettably, augmentation of clozapine with pharmacological agents has largely produced clinical benefits of only modest effect sizes.[27,28] The limitations of pharmacological augmentation options have lead to investigation of non-pharmacological neuromodulatory treatment approaches,

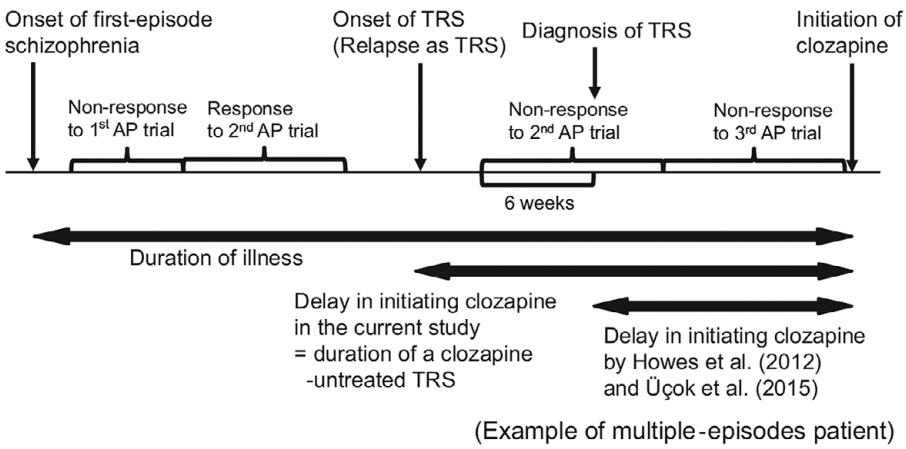

Figure 1. Decay in clozapine treatment responsiveness in treatment-resistant schizophrenia. TRS, treatment-resistant schizophrenia (adaptation from Yoshimura B, Yada Y, So R, et al. The critical treatment window of clozapine in treatment-resistant schizophrenia: secondary analysis of an observational study. *Psychiatry Res* 2017;**250**:65–70).

including ECT.[21] With the exception of ECT, neuromodulatory approaches such as repetitive transcranial magnetic stimulation, direct current stimulation, and phototherapy have had only modest, symptom domain-limited, mixed, or adverse effects.[29-35] Consequently, investigation of ECT as an adjunctive treatment to clozapine in treatment-resistant schizophrenia has been actively pursued.

Wang et al conducted a meta-analysis of 18 randomized controlled trials of ECT augmentation of clozapine treatment in treatment-resistant schizophrenia patients who were resistant to clozapine monotherapy treatment (N = 1769 with 20 active treatment arms) in 2018. Co-primary outcome measures were symptomatic status at ECT completion and at trial termination. ECT plus clozapine was superior to clozapine alone at ECT completion with a standardized mean difference of −0.88 (95% confidence interval = −1.33 to −0.44; I^2 = 86%, P = .0001). At trial end, the standardized mean difference was −1.44 (95% confidence interval = −2.05 to −0.84; I^2 = 95%, P < .00001). The ECT plus clozapine and clozapine groups separated as early as weeks one or two with a standardized mean difference of −0.54 (95% confidence interval = −0.88 to −0.20; I^2 = 77%, P = .002). Combined ECT and clozapine treatment was also superior by study defined outcome criteria at 53.6% vs 25.4% with a risk ratio of 1.94 (95% confidence interval = 1.59 to 2.36; I^2 = 0%, P < .00001). This translated at ECT completion to a number needed to treat of 3 and at trial endpoints to 4. Moreover, at the end of ECT, patients receiving ECT plus clozapine showed a significantly greater remission rate than those treated with clozapine alone, 13.3% vs 3.7%. This remained true at the end-points of the analyzed trials at 23.6% vs 13.3%. ECT did impose adverse effects. Some 24.2% of ECT plus clozapine patients complained of memory impairment vs none of the clozapine patients. Similarly, 14.5% of the ECT plus clozapine-treated patients complained of headache vs 1.6% of the clozapine only patients. No significant differences occurred with respect to treatment discontinuation or other adverse effects. Thus, ECT plus clozapine appeared to be a moderately effective adjunctive treatment in patients resistant to clozapine treatment alone with only an expected and modest adverse effect burden.[36]

In conclusion, Read et al identified methodological flaws in 11 studies of ECT for depression and five related meta-analyses which evaluated 1 to 7 of these studies. Based on their findings, they called for better-designed, more rigorous studies of ECT, as well as immediate suspension of ECT use. While improved research and data are always a worthy goal in medicine and psychiatry, the call for suspension of ECT use ignores decades of data supporting the efficacy of ECT and also ignores a number of different lines of data indicating ECT as effective in a variety of clinical circumstances, including treatment of clozapine-resistant schizophrenia. Unlike a new and untried treatment, suspending or banning ECT in this context would in our opinion constitute an unethical deprivation of treatment for many patients who have few, if any, safe and viable alternatives.

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