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Letter to the Editor

Electroconvulsive therapy in ultra-resistant schizophrenia: A case series

Dear Editor,

Clozapine, considered to be the most effective medication for treatment resistant schizophrenia, does not induce a significant improvement in 40–70% of cases (Porcelli et al., 2012). The resulting "ultra-resistant schizophrenia" (URS) is associated with a lower quality of life, a decreased autonomy and a high financial burden (Cloutier et al., 2016). Among augmentation strategies, electroconvulsive therapy (ECT) seems to be particularly promising with response rates ranging from 37.5 to 100% (Grover et al., 2015). ECT would be more efficient if administered in well-defined patients (those who are currently experiencing psychotic exacerbations, have catatonic symptoms or who had responded favourably to ECT in the past) (Kumar et al., 2018; Mitra and Thirthalli, 2018). The role of gender has not yet been clarified in the response to treatment (Chanpattana and Sackeim, 2010). Furthermore, there is a lack of randomized controlled trials and long-term follow-up data to support these findings (Petrides et al., 2015). In addition, many aspects are insufficiently investigated such as the seizure most reliable efficacy criteria; the most suitable anesthesia protocol; the optimal number and frequency of sessions and the necessity of maintenance ECT.

This clinical series reports characteristics and outcomes in nine patients with URS who had ECT as a potentiation strategy, with an analysis of the procedure used in these cases. It was a retrospective study, including patients treated at the Rouvray hospital of Rouen in France, from January 2009 to August 2018. Included patients had treatment resistant schizophrenia and did not respond to clozapine during at least three months with plasma levels of clozapine above 350 ng/ml. These patients had been prospectively assessed with the Brief Psychiatric Rating Scale (BPRS) before and after ECT. The stimulation device was "spectrum 5000Q, MECTA". The considered seizure efficacy criteria were an electroencephalogram (EEG) seizure lasting either more than 20 s or 15 to 20 s with presence of a postictal suppression. To determine the seizure threshold, the individual titration method was used. The initial stimulation during the first session was administered at twice threshold. In case of inefficacy, another stimulation with a one-step increase of 50% was delivered. The general anesthetic used was propofol (2,6 di-isopropylphenol) at doses of 1 to 2 mg/kg until induction onset, with suxamethonium chloride at doses of 0.3 to 0.8 mg/kg for short-term paralysis. ECT was bilateral and administered twice a week.

Of the nine patients of the study, seven were male. All of them were single and unemployed. The mean age was 36 years (SD = 7, range 25–48) when ECT was started. Schizophrenia was with prominent paranoid features for all the patients. The mean age of schizophrenia onset was 23 years (SD = 5, range 16–30) and the mean duration of the illness before ECT was 13 years (SD = 9, range 4–28). The mean dosage of clozapine was 589 mg/day (SD = 215, range 300–1000) and the mean plasma clozapine concentration was 598 ng/mL (SD = 174, range 380–888). The mean BPRS score before ECT was 78 (SD = 7, range = 68–90). The mean number of ECT sessions for all patients was 24 (SD = 18, range 7–60). Two patients, with a particularly severe initial symptomatology and aggressive behavior, had maintenance ECT with a total of 50 and 60 sessions, over periods of 12 and 36 months, respectively. For all patients, there was an average decrease of 29.8% in BPRS score (SD = 11.5, range 11–44). Eight patients, including those who received maintenance ECT, had a decrease of more than 20% in BPRS score and were therefore considered as responders to ECT. An outpatient care was possible for six patients; among them one patient had not been readmitted to hospital during the study period, and the mean duration before readmission for the other patients was 18 months (SD = 31, range 2–80). The only significant side effect was a spontaneous seizure which happened after 19 sessions of ECT and led to discontinuation of ECT for the patient.

In the scientific literature, the seizure efficacy criteria are rarely defined for ECT in patients with URS. In addition, some authors used motor seizure criteria (Grover et al., 2017), while others considered EEG criteria (Kho et al., 2004; Pawełczyk et al., 2014). The duration threshold was also different from one study to another. In this study we used the criterion of an EEG seizure lasting more than 20 s – supposed to be sufficiently prolonged – or a shorter EEG seizure lasting 15–20 s with presence of a post-ictal suppression because it would be correlated with restoration of the GABAergic activity in the frontal area of the brain and effectiveness of ECT in general (Suppes et al., 1996). Concerning anesthetic management during ECT in general, mainly thiopental, methohexital, etomidate and propofol have been used in most studies with a different impact on seizure duration, as well as on ictal and postictal electrophysiological indices (Eser et al., 2010). For all patients of this case series, the modern anesthetic propofol (1–2 mg/kg) was used and seemed not to alter the efficacy of ECT in this indication. Some studies used unilateral electrode placement (Kho et al., 2004) but in most studies, as well as in this case series, ECT was bilateral, which would be more effective. In this study, a frequency of two sessions per week was the rule for all patients since higher frequencies have not proved more effective (Charlson et al., 2012).

The number of needed ECT sessions for significant clinical improvement in patients with URS was found to be between 16 and 20 (Hustig and Onilov, 2009; Pawełczyk et al., 2014), which is consistent with findings of this case series. Very few data about utility of maintenance ECT in patients with URS are available. Some authors have suggested that ECT acted synergistically with clozapine but that this effect disappeared rapidly without maintenance ECT (Kales et al., 1999). In this study, maintenance ECT was beneficial for patients with severe initial symptomatology and aggressive behavior which has been already suggested by some authors (Hustig and Onilov, 2009).

In conclusion, bilateral ECT appears to be effective and well tolerated when combined to clozapine for patients with URS. It should consist of 16–20 sessions, twice a week, with maintenance sessions

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when patients have aggressive behavior before ECT. One suitable anesthetic agent could be propofol and the post-ictal suppression should be taken into account in evaluating the seizure efficacy criteria. These modalities need to be tested in randomized controlled conditions, which is currently being done as part of a clinical trial involving 13 different French psychiatry centers (NCT03542903).

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