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Research report

Prediction of antidepressant response in both 2.25×threshold RUL and fixed high dose RUL ECT

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Abstract

Some forms of electroconvulsive therapy (ECT) can result in generalized seizures that lack efficacy, therefore physiological markers of treatment adequacy would be helpful. EEG measures of seizure quality, such as EEG regularity and post-ictal suppression, have largely supplanted seizure duration as a marker for seizure adequacy, yet no predictive algorithm has gained wide clinical acceptance. Electrographic seizure durations of less than 25 s still prompt re-stimulation in many settings. We re-examined the utility of EEG seizure duration and other measures of EEG seizure as predictors of antidepressant response to right unilateral (RUL) ECT.
Methods: Seventy-two adult patients with major depression were randomized to either titrated RUL ECT at 2.25 times initial seizure threshold or RUL ECT at a fixed dose of 403 mC. Intent-to-treat responder status (defined by 60% reduction in HRSD scores and final score of 12 or less after the last RUL ECT session) was identified as the dependent variable in a nominal logistic regression model including EEG seizure quality candidate variables, controlled for age and gender.
Results: A model including EEG seizure duration, EEG regularity, post-ictal suppression, age and gender and randomization status was significantly predictive of intent-to-treat responder status at treatment 2 ($R2=.21$ $p<.003$; $N=66$) and treatment 4 ($R2=.27$ $p<.0004$; $N=67$). The model remained significant at these time points even when randomization status (titrated moderately suprathreshold vs. high fixed dosage) was removed (Treatment 2: $R2=.18$ $p<.007$; Treatment 4: $R2=.23$ $p<.0007$).
Conclusion: EEG markers of seizure adequacy, including EEG seizure duration, are modestly predictive of antidepressant response for both titrated moderately suprathreshold and high fixed dosage RUL ECT.

Keywords: ECT; Electroconvulsive therapy; Depression; Major depression; Seizure duration; ROC curves; Antidepressant response; Seizure threshold

1. Introduction

Electroconvulsive therapy (ECT) is the most effective treatment for major depressive episode (MDE) (American Psychiatric Association, 2001). Even so, in a clinical trial setting the remission rate, as defined by a Hamilton Rating Scale for Depression (HRSD) of <7, is usually no better than 80%. Of greater concern, in community settings, the antidepressant remission rate for ECT is well under 50% (Prudic et al., 2004). Given these remission rates, predictors of response that would be available early in the course of ECT would be of value. For example, if a measurement taken at the second or third treatment indicated that the patient was unlikely to respond to the strategy chosen for ECT, then a more aggressive treatment approach could be taken, such as increasing stimulus intensity.

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Seizure duration was the earliest marker of treatment adequacy in ECT. By the 1970s, the field embraced seizure durations > 25 s as an indicator of treatment adequacy. This position was supported by the work of Cronholm and Ottosson in a 1960 paper which examined the effect of lidocaine pre-treatment in ECT. This study showed that "where seizures were shortened by lidocaine the depression-relieving effect of ECT is decreased." The authors also inferred that since "reduction of seizure activity decreases the therapeutic efficiency of ECT…", we "argue in favor of seizure activity as the sole, or at least a dominant factor" in efficacy (Cronholm and Ottosson, 1960).

Fink suggested that motor seizures of less than 15 s in duration rarely exhibited tonic–clonic phases, and these seemed to be clinically less effective than longer seizures. Motor seizures with durations greater than 25 s were usually generalized, and this index was taken as a measure of an adequate treatment. He also stated, "The relationship between seizure duration and clinical outcome in the treatment of depression is poor. We concluded that seizure duration is too imprecise and unreliable to be a criterion of seizure efficacy. These observations are consistent with the findings of Ottosson" (Fink, 1991).

There have been contrary opinions. Maletzky (1978) and Milstein and Small (1984) examined the total duration of seizure activity over the course of treatment in relation to clinical improvement. Malesky found that a minimum total seizure duration of 210 s was needed to achieve a clinical response. Since his patients received an average of 10.8 treatments, this roughly coincides to a minimum seizure duration of 19.5 s per treatment. However, the inferences from this study were confounded by the use of multiple monitored ECT. Milstein and Small, performed a retrospective analysis of 30 patients who had accumulated a monitored seizure time of less then 200 s by their 5th or 6th treatment and compared them with a control group of recently treated patients whose total EEG monitored seizure time by their fifth or sixth ECT was greater than 220 s. They found that those in the control group had significantly greater improvement in the HRSD and BPRS. In 2000, Krystal et al. in trying to answer the question "Are present ECT devices too limited?" found that of those patients whose stimulus intensity was insufficient to consistently induce a seizure lasting at least 25 s in EEG duration, there was only a 32% response rate, compared with 66% of the other subjects (Krystal et al., 2000).

The first serious challenges to the primacy of seizure duration as an indicator of treatment adequacy came from Sackeim. He asserted in 1991 that, "There are no data that support the standard practice of requiring a minimum duration of 20–30 s to consider a treatment adequate. The recommended cutoffs are arbitrary" (Sackeim et al., 1991). A subsequent 1993 paper looking at electrical dose and efficacy of electroconvulsive therapy, comparing high dose and low dose unilateral and bilateral therapy, resulted in 22% of the low dose unilateral group having an initial response to treatment, whereas 70% of the other groups had an initial response to treatment. They concluded that "low dose right unilateral electroconvulsive therapy, resulted in generalized seizures of adequate duration but with little benefit. This contradicts the view that the duration of seizures provides a valid index of maximally effective treatment" (Sackeim et al., 1993).

Other opinions come from Mayur, who stated that "it is clear that occurrence of an adequate seizure duration of 25 s of EEG, although retained in contemporary guidelines of ECT practice, is not sufficient or even necessary to achieve therapeutic response…. It is now well established that seizure duration is no longer a marker for seizure adequacy" (Mayur, 2006), and Rasimas et al., who stated that "…more than about 20–25 s longer seizures do not mean better efficacy. What is not clear is whether very short seizures compromise efficacy" (Rasimas et al., 2007).

Thus, the field of ECT has taken the position that seizure duration cannot serve as a predictor of treatment outcome (Abrams, 2002).

Given the lack of consensus regarding the relative importance of seizure duration in guiding treatment technique and predicting outcome, we examined predictors of response in patients receiving high and low dose RUL ECT. We report a secondary analysis on the relationship between electrographic seizure duration, morphology, and treatment outcome in a sample of patients receiving RUL ECT.

2. Methods

The general methods of this study have been reported in full elsewhere (McCall et al., 2000). A synopsis of the methods is below.

2.1. Patients

The recruitment population consisted of all patients consenting to ECT at Wake Forest University School of Medicine/North Carolina Baptist Hospital, Winston-Salem, North Carolina, between September 1995 and February 1998. All patients met the criteria for major depressive episode (MDE) according to the Structured Clinical Interview for the DSM-III-R (American Psychiatric Association, 1987; Spitzer et al., 1992). All