Twelve-Month Outcomes for Remitters Following Electroconvulsive Therapy for Depression

To the Editor: We thank Dr Andrade[1] for his interest in our work.[2] What he describes as an observational study was in fact an analysis of 12-month relapse from a randomized trial of unilateral vs bilateral electroconvulsive therapy (ECT) for depression, ie, a planned secondary outcome of an interventional study. The hypothesis underlying the trial was noninferiority of right unilateral versus bitemporal ECT.[3] Randomization and blinding were preserved throughout the follow-up period. In this secondary analysis, we examined long-term outcomes because it could be argued that although acute outcomes were similar in the two groups, remission may be more transient in the unilateral group and the advantage of bitemporal ECT would only become apparent later. As such, electrode placement (ie, treatment group) was the main covariate of interest and cannot be dropped from the regression model simply because it turned out not to be "significant."

Dr Andrade seems to suggest that including a priori known prognostic factors in a regression model is overfitting. On the contrary, this is standard practice. Inclusion of these covariates reduces the amount of residual variance in the model. Choice of covariates is never an easy task, but it is particularly challenging in a situation like this one, in which thousands of clinical and biological datapoints were recorded. Knowing that we would ultimately be faced with a large number of candidate covariates and the danger of observing many (possibly spurious) associations, we limited ourselves to a handful of known prognostic factors found in systematic reviews of the ECT literature and/or large cohort studies of recurrence in treatment-resistant depression in order to avoid overfitting. There is over half a century of prospective research on post-ECT relapse. Several immutable patient and illness characteristics have been shown to predict both acute and long-term ECT outcomes, while ECT technical parameters or the adequacy of post-ECT prophylactic treatment do not moderate long-term outcomes to any clinically meaningful degree, with two known exceptions: lithium[4] and continuation ECT.[5]

Maximizing the chances of a good long-term outcome, therefore, is largely predicated on careful patient selection, ensuring that ECT is delivered only to those who are suitable candidates for it. For these reasons, second-generation antipsychotics were not analyzed since there is, to our knowledge, no evidence demonstrating their usefulness in mitigating post-ECT relapse. Recent large observational studies from Scandinavia have shown that antipsychotics are associated with worse long-term outcomes after ECT in unipolar[6] and bipolar depression.[7] While causality cannot be inferred from these studies, the preliminary evidence is not encouraging. At any rate, the proportion of our remitters maintained on second-generation antipsychotics (mean dose of 8 mg olanzapine equivalents) who relapsed was similar to those treated with other medication classes (Fisher exact $P = .599$), though this is clearly not a randomized comparison.

All of us working in the ECT field agree that very large multicenter studies are needed. In the meantime, clinical decisions must be made daily based on imperfect data. We therefore should not rule out most of the available evidence on post-ECT relapse.

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Research Design and Overfitting: Reply to Jelovac and McLoughlin

To the Editor: I appreciate the interest of Drs Jelovac and McLoughlin[1] in my article[2] on predictors of relapse after electroconvulsive therapy (ECT). In that article,[2] I had stated that their study[3] was observational because the interventions of interest, bitemporal (BT) vs high-dose right unilateral (RUL) ECT, stopped before the period of interest, the 12-month follow-up. During this follow-up, the authors merely observed patients who received individualized rather than standardized continuation pharmacotherapy from treating clinicians; the authors did not intervene. Individualized pharmacotherapy could have improved outcomes in disadvantaged patients, blurring possible differences in long-term efficacy between the ECT groups to which the patients had originally been randomized. Furthermore, because only patients (n = 61 out of 138) who had remitted in their respective ECT groups were eligible for study, it is unlikely that the nature of the original randomization would have been preserved in the follow-up sample. Finally, the maintenance of treatment blind stated by Drs Jelovac and McLoughlin[1] is good research practice but does not have relevance to the conceptualization of research design as observational vs interventional or as randomized vs nonrandomized.[4] In short, what they conducted[3] was a prospective observational cohort study of outcomes in ECT remitter groups to which patients had not been randomized, and not a randomized controlled study of an intervention.

I had suggested that the inclusion of the BT vs RUL ECT variable in the regression may have been unnecessary not because the ECT grouping variable was not significant in the earlier, interventional phase of the study but because it seemed to me that if an intervention is withdrawn after remission has been brought about, it does not matter what brought about the remission when studying what influences relapse. However, I accept that it could equally well be argued that remission brought about by different forms of ECT could differ in duration and therefore merits study.

I agree with Drs Jelovac and McLoughlin that in studies such as theirs, the a priori selection of known or expected prognostic factors is standard practice, and the choice of covariates is not easy. However, overfitting happens when the model includes more covariates than the sample size permits. This risks the creation of a model that reduces residual variance in the regression and explains what fits the sample rather than what fits the population.[5] I had suggested that their analysis may have been limited by overfitting.

Lithium and second-generation antipsychotic drugs have been found effective, some as monotherapy and some as antidepressant augmentation therapy, in patients with major depressive disorder and bipolar depression, and some among these have been found effective in maintenance therapy, as well. So, regardless of how the remission from depression was brought about, it could be reasonable to include the use of lithium and second-generation antipsychotics as regression covariates. Unfortunately, and this is something regarding which I sympathize with the authors,[3] to do this could worsen overfitting. In this connection, I appreciate the clarification that, at least in univariate analysis, maintenance treatment with second-generation antipsychotics was not significantly associated with relapse.[1]

On a parting note, the purpose of my article[2] was not to devalue the studies that I reviewed but to provide teaching on issues related to conducting, reading, and understanding research.

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