Letters to the Editor

The Role of Bilateral ECT When Right Unilateral ECT Is Inferior

TO THE EDITOR: We read with great interest the important results of the trial by Semkovska et al., published in the April 2016 issue of the *Journal* (1), regarding bitemporal versus high-dose unilateral ECT for depression. While the findings add to the evidence base of the efficacy of right unilateral electrode placement and demonstrate "noninferiority" at the group data level, we should be careful not to dismiss the clinical importance of bilateral electrode placement (2). As noted by the authors, response and remission rates were quite low for both interventions in this study. At the individual patient level, it is likely that a substantial proportion of the 54% of nonremitters in the right unilateral group would have gone on to reach remission had they been crossed over to bilateral placement. In clinical practice, many patients who elect to start ECT with right unilateral placement and who show inadequate response after 1–2 weeks of treatment are switched to bilateral placement with, ultimately, excellent results (3). ECT is a treatment often prescribed for our most severely ill patients, some with life-threatening illness; efficacy should not be compromised for fear of transient cognitive tolerability issues. Right unilateral ECT, both in the form administered in the study by Semkovska et al. and with ultrabrief stimulus waveforms, offers a welcome option for well-tolerated ECT (4). However, for the subset of patients who do not respond to it, right unilateral ECT may actually be inferior.

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Response to Kellner and Farber: Addressing Crossover of High-Dose Right Unilateral ECT to Bitemporal ECT

TO THE EDITOR: We thank Dr. Kellner and Ms. Farber for their comments on our trial report of different forms of brief-pulse ECT for depression. They raise the important clinical issue of what to do if a patient does not respond sufficiently well to unilateral ECT. Intuitively, we would have agreed that switching to bitemporal ECT makes sense. However, there is actually little in the way of high-quality randomized controlled trial evidence to help guide us with regard to high-dose (6× threshold) unilateral ECT.

Including our own pragmatic noninferiority trial, there have now to our knowledge been seven randomized trials that involved comparisons between high-dose (6×–8× threshold) unilateral and low- to moderate-dose (1.0×–2.5× threshold) bitemporal ECT for depression (1). We performed a meta-analysis of these data (number of patients, 792), and our preliminary unpublished data show that both forms of ECT had similar outcomes on Hamilton Depression Rating Scale scores and on remission rates (approximately 52% for high-dose unilateral patients and 53% for bitemporal ECT patients), while high-dose unilateral ECT still had some cognitive advantages. Thus, the proportion of nonremitters is the same with both forms of ECT, at least for persons who are capable of participating in trials.

Only one of these trials (N=319) specifically reported crossover outcomes based on the original ECT assignation (2). This trial compared high-dose (6× threshold) unilateral ECT with bitemporal ECT (1.5× threshold), and it studied the role of concomitant antidepressant use. Sixty patients deemed not to have shown "substantial improvement" after eight or more ECT sessions were crossed over to higher dose (2.5× threshold) bitemporal ECT, which we know increases cognitive side effects (3). Of these, 31 were initially randomized to high-dose unilateral ECT, and 15 (48%) remitted, while 11 (38%) of the 29 initially bitemporal patients remitted. With the caveats that the trial was not designed to test the efficacy of crossover and that this is a secondary analysis, there is not a significant difference between the groups on this outcome.

To our knowledge, no randomized trial data are available on the crossover from high-dose unilateral ECT to bitemporal

ECT at 1.5× threshold, the most commonly used form of bitemporal ECT in recent relevant trials. Nor are there trial data for crossover from bitemporal to high-dose unilateral ECT, which happens occasionally in clinical practice when cognitive side effects are not tolerable.

Dr. Kellner and Ms. Farber remind us that in clinical practice we deal with individual patients. One size of ECT clearly does not fit all. Therefore, some clinical judgment, based on available evidence as well as informed patient preference, is required. For severely ill patients with life-threatening depression, extreme distress, and/or catatonia who typically do not participate in randomized trials, we recommend starting with bitemporal ECT at 1.5× threshold, as this may have a more rapid effect (4). However, non-life-threatening treatment-resistant depression is a much more common indication for ECT. For such patients, based on the evident ratio of harm to benefit, we would recommend beginning with high-dose unilateral ECT. If the patient feels that there is insufficient benefit, then the patient could be switched to bitemporal ECT, initially at 1.5× threshold. In all these scenarios, if there is no benefit from the crossovers, one could consider 2.5× threshold bitemporal ECT, although there is no evidence that this is better than 1.5× threshold bitemporal ECT. However, it may act more rapidly than bitemporal ECT at just 1.0× threshold (5).

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In Support of Neuroimaging Biomarkers of Treatment Response in First-Episode Schizophrenia

TO THE EDITOR: In the March 2016 issue of the *Journal*, Gong et al. (1) selectively review the literature on treatment-related brain abnormalities in patients with first-episode schizophrenia. They emphasize the need for studies focused on patients early in their illness, as well as the potential gains from neuroimaging biomarkers that track and predict treatment outcomes.

In support of the growing literature of prospective studies in first-episode schizophrenia reviewed by Gong et al., we recently reported that longitudinal changes in striatal functional connectivity are associated with efficacious treatment by second-generation antipsychotic drugs (2). This work, conducted within a controlled clinical trial (NCT00320671) with pre- and posttreatment functional imaging, revealed that efficacious treatment was associated with increased striatal functional connectivity with frontal and limbic brain regions mentioned by Gong et al., including the anterior cingulate, middle frontal gyrus, orbitofrontal cortex, and hippocampus. In addition, first-episode patients with less improvement in psychosis demonstrated greater striatal connectivity to parietal regions. Another recent study applied longitudinal neuroimaging to examine treatment-based abnormalities within large-scale functional networks in patients not taking medications, including a subset of treatment-naive first-episode patients (3).

Moreover, in an article published in the January 2016 issue of the *Journal* (4), we reported that baseline functional connectivity of the striatum in first-episode patients with schizophrenia was predictive of the initial response to antipsychotic treatment. We derived an index of striatal connectivity that separated responders from nonresponders in a discovery cohort, and we tested our measure in a more chronic sample of patients undergoing treatment for acute psychosis. The sensitivity and specificity of this measure were 80% and 75%, respectively, in our replication cohort. As highlighted by Gong et al., studies such as ours may be useful for guiding clinicians while taking a step toward precision medicine approaches to the treatment of psychosis.

Our work supports the longitudinal and prognostic framework for studies described by Gong et al., and it stresses the need for biomarker-based treatment trials that trace patient outcomes. Collectively, these results provide momentum toward discoveries that may shed light on the elusive biology underlying the dynamic progression of schizophrenia.

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