Response to Drs Abrams and Kellner: The Cognitive Effects of ECT in Community Settings

To the Editor:

Discussion on the memory effects of electroconvulsive therapy (ECT) evokes extreme views. On the one hand, antipsychiatry activists argue that ECT inevitably produces marked amnesia, reflecting brain damage. On the other hand, some ECT advocates state that all of the cognitive effects of ECT are short-lived, claiming that reports of persistent deficits are false. In an editorial in this Journal, we documented some of these positions and suggested that the field of ECT was moving from such polarization to a more realistic reconciliation.[1] For example, the consent form recommended by the American Psychiatric Association Task Force on ECT states explicitly that long-term amnestic effects can occur, and in some cases, can be profound.[2] Therefore, in this context, it is not surprising that our study documenting that some forms of ECT commonly result in persistent amnesia would meet with opposition from both camps.

Drs. Abrams and Kellner indicate that their critique of our recent article was stimulated in part by the piece by Andre in the Web publication, *Medical News Today*. It is noteworthy that this piece was withdrawn from the Web site and is no longer available. Andre charged that the conclusions of the article repudiated views long held by Dr. Sackeim. To the contrary, the main point of the article, that ECT may produce persistent amnestic effects that are sometimes profound, is consonant with the findings of our research program for the past 25 years, as well as our clinical experience.[3–6] Although embracing the findings of persistent side effects, ironically, Andre also asserted that the article was colored by conflict of interest, given Dr. Sackeim's role as a consultant to the ECT device industry. However, Dr. Sackeim has no financial interests in any ECT device company, and as a standing policy, does not receive financial compensation for consultation with the ECT industry. In essence, Andre wished to embrace the findings of the recent work and exaggerate their implications, while disparaging the leader of the research team.

There are 3 central questions that need to be answered when interpreting the results of our study. First, one can question whether we provided the conditions to allow for a fair and impartial description of the long-term effects of ECT. The second question concerns the attribution of causality. Given that long-term deficits were observed, it is a separate issue whether they should be attributed to ECT. Finally, one must distinguish statistical from clinical significance and ask whether the long-term deficits are sufficiently common or impairing to have practical consequences. Dr. Abrams addressed the first 2 questions by raising concerns about potential bias in the characterization of the long-term effects and the attribution of causality. Dr. Kellner focused on whether these deficits have meaningful impact on patients' lives and willingness to receive ECT in the future.

Dr. Abrams expressed concern about whether the study mined data routinely collected at the 7 hospitals or was a specifically planned investigation, with prespecified hypotheses and analytic plan. The latter was the case because the research involved the repeated assessment of nearly 700 patients at 7 facilities (only the first phase of the study, involving approximately 350 patients, has been reported) using a standardized battery. Specifically, a key prespecified hypothesis was that at the 6-month follow-up, deficits on the Columbia University Autobiographical Memory Interview–Short Form (AMI-SF) indicative of persistent retrograde amnesia would be observed in patients treated with bilateral (BL) ECT. The findings clearly supported this hypothesis.

Dr. Abrams also was concerned that the characterization of the cognitive effects of ECT was biased by clinical evaluators who were not blinded to treatment assignment. The research technicians who administered the neuropsychological tests and clinical interviews also attended treatment sessions and documented the procedures.

The nature of the neuropsychological tests strongly mitigates concern with rater bias. Of the 9 tests in the cognitive battery, 5 were both computer administered and scored. For these tests, the technician's role was limited to reading the scripted test instructions. Thus, the findings of persistent reaction time deficits in patients treated with sine-wave stimulation, based on the computerized tests, is unlikely to reflect rater bias. The key AMI-SF measure, although based on an interview, allows for virtually no technician influence. This test involves administration of 30 invariant questions, recording the answers verbatim, and applying a detailed scoring guide to determine whether answers were fully consistent, partly consistent, or inconsistent with answers given pre-ECT baseline. Scoring of the test requiring the greatest judgment and copying and reproducing a complex figure were conducted by a technician blind to the patient's identity and treatment history, and not the rater who administered the test. Finally, multiple technicians collected the data at any given hospital. Nonetheless, short- and long-term outcomes were found to vary as a function of hospital. These factors all reduce the extent to which rater bias could have influenced the findings.

Perhaps the most important demonstration that the key findings did not reflect rater bias concerns data currently being prepared for publication. Patients in this study themselves evaluated the global impact of ECT on their memory by rating the extent to which they felt that their memory was improved or impaired after the treatment course. Six months after the ECT course, patients treated with BL ECT reported significantly greater decrements in memory function than patients treated with unilateral ECT. Indeed,

there was a linear relationship between the number of BL ECT treatments and the negativity of this self-evaluation, and no relationship with the number of right unilateral (RUL) treatments. Furthermore, in addition to this association, the degree of retrograde amnesia on the AMI-SF at 6 months covaried with the negativity of this self-evaluation. Thus, the finding that BL ECT produces greater persistent retrograde amnesia than RUL ECT was mirrored in the patients' own ratings of the impact on memory. This substantially undercuts the possibility that the findings were biased by rater preconceptions.

Once we accept the idea that the findings accurately portray the cognitive status of the patients in this study, we must still deal with the question of causality. As we stated in the article, an experimental design that randomly varies a specific dimension of an intervention, such as electrode placement, is the traditional method for establishing a causal influence. Abrams and Kellner correctly noted that because we used a naturalistic design, it is conceivable that the persistent deficits observed at the 6-month follow-up were caused by factors other than those we identified. Hypothetically, the patients with persistent deficits may have differed from patients without such deficits in critical features before receiving ECT, in the medications received during or after the ECT course, in the amount of ECT received after the index course, or in a host of potential relevant unmeasured variables. However, in this study, we can conclude with high confidence that electrode placement was responsible for differences among patients in the degree of persistent retrograde amnesia. Several streams of evidence support this judgment.

First, the findings regarding electrode placement mirrored the effects observed in randomized trials. It is well established that BL ECT results in greater short-term anterograde and retrograde deficits than RUL ECT.[4,6,7] The anterograde deficits are caused more by impairment in the retention of information than in the immediate acquisition.[3] This was precisely the pattern observed at the testing occasion immediately after ECT in our naturalistic study. Second, it is also well established that the anterograde deficits recede rapidly after ECT termination, and that persistent deficits pertain mainly to retrograde amnesia. This is precisely the pattern observed across the sample in our naturalistic study. Third, randomized trials have shown that BL ECT results in greater retrograde amnesia than RUL ECT at longer-term follow-ups. This was reported for 2-month follow-up data and suggested for 6-month follow-ups.[5–8] The randomized studies using small samples have left considerable uncertainty about the extent and generalizability of this differential deficit. The findings of our study were fully consonant with the results of studies in which patients were randomized to RUL or BL ECT. Our naturalistic study provides evidence of long-term differences between the electrode placements suggested by the randomized trials and provides critical information on the extent of the deficit, the risk of marked impairment, and the generalizability of these effects.

Other considerations support these conclusions. Whether patients received RUL or BL ECT was largely determined by the hospital in which they were treated. Some facilities used one or the other placement almost exclusively. Indeed, when treatment technique was statistically controlled, hospital differences in cognitive outcomes disappeared. Therefore, we knew that the major factor determining whether patients received RUL or BL ECT was the specific practice of the hospital in which they were treated. We view the hospital as an instrumental variable with respect to electrode placement because the preferred ECT electrode placement used at a hospital was unlikely to be the reason patients elected to be treated at that facility. In support of this view, we could detect no difference among patients treated primarily with RUL or BL ECT in clinical and demographic characteristics, concomitant medications during or after ECT, amount of ECT received after the acute treatment course, and other characteristics. Thus, from an empirical point of view, there was no evidence that any other factor meaningfully differed in patients treated with RUL or BL ECT. The findings regarding RUL and BL ECT faithfully reproduced and extended the patterns often reported in randomized trials. The major factor that determined the choice of RUL relative to BL ECT was the hospital attended, and hospital attendance was unlikely to have any other meaningful relationship with long-term outcomes. Thus, we place considerable confidence in the conclusion that RUL and BL ECT differed in the magnitude of long-term amnestic effects.

Drs. Abrams and Kellner raised 3 other issues that might bear on the attribution of causality. A minority of patients was treated with sine-wave stimulation, and this subgroup almost exclusively received BL ECT. Could the findings regarding electrode placement be colored by the inclusion of these patients? Sine-wave stimulation, per se, did not impact on amnesia measures but had a marked and persistent effect on reaction time measures. When we removed the sine wave–treated subgroup, the major findings of the study were unaltered, and the differences between RUL and BL ECT in persistent retrograde amnesia remained. Similarly, some patients received a mixture of treatments involving RUL, BL, or bifrontal ECT, and the concern was raised that the mixture of treatment techniques might have somehow biased the findings. An advantage of the large sample is that we could reanalyze the data restricting the sample to patients treated solely with RUL or BL brief-pulse ECT. The findings were unchanged in these 2 more homogeneous subgroups. Finally, Dr. Kellner noted that clinical outcome in this community sample was less favorable than that reported in research samples, and questioned whether cognitive outcomes might be have been poorer as a result. We presented evidence that ECT was frequently terminated prematurely in this community sample, leaving a substantial number of patients considerably improved, but with notable residual symptoms. It was this premature termination that resulted in the inferior rates of remission. We controlled for degree of concurrent symptoms (Hamilton Rating Scale for Depression scores) when conducting the analysis of the cognitive outcomes, and RUL and BL ECT did not differ in clinical outcomes. Given the relationship between number of BL ECT treatments and retrograde amnesiaat the long-term follow-up, we suspect that provision of additional BL

treatments to achieve full remission would have intensified the amnestic effects.

Dr. Abrams raised the issue of what should constitute the proper control group in a study of this type. Control groups serve different functions. If one is concerned that the natural progress of depressive illness or the provision of pharmacotherapy can bias the results, it might be appropriate to use a non-ECT patient sample treated with pharmacotherapy as a control. In an observational study, this would likely produce an imbalance in patient characteristics because ECT samples matched with other inpatients for overall depression severity have been shown to have poorer neuropsychological performance at baseline and greater impairment in functional activity.[9,10] Unless patients are randomized to medication or ECT, an impractical design in this era, it is not possible to guarantee equivalence in baseline factors impinging on cognitive outcomes.

For psychometric purposes, we recruited and tested a normal control sample. Some neuropsychological tests show practice effects, that is, improvement on readministration, whereas others do not. We adjusted the AMI-SF score for the change in performance seen in healthy volunteers over time. This indicated that the deficits observed acutely and in the long-term, especially with BL ECT, were substantially beyond the type of memory loss that occurs in healthy individuals.

The final issue raised by Dr. Kellner concerns the clinical significance of the findings. To what extent does the long-term retrograde amnesia have functional consequences? Do these deficits have a meaningful impact on work or other activities? Do they result in personal distress? Does their severity or persistence impact on the likelihood of receiving ECT in the future? At present, we have little systematic information about any of these important questions. Undoubtedly, many patients state that the clinical benefits of ECT outweigh the experienced memory loss. Many patients are also cognizant of memory loss and are distressed by it to a varying extent.

Our study involved a large and prospectively followed sample treated at diverse facilities. Given the importance of the findings for the clinical administration of ECT, replication will be important. We believe that this study adds substantially to the body of evidence indicating that ECT treatment technique has long-term impact on cognitive function. Innovation in ECT technique may substantially reduce the risk of these adverse cognitive outcomes.

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