ECT and Onset of Action

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Although there is a long-standing clinical belief that electroconvulsive therapy (ECT) is the fastest available treatment for depression, ECT has not been compared directly with drug therapy. For this reason, it is impossible to say whether ECT treatment actually works faster than standard medications. Studies comparing various modalities of ECT have highlighted several factors that should be considered in any assessment of differential onset of antidepressant effect. First, patients are heterogeneous; that is, given any treatment or mode of treatment, some patients will respond, and some will not. Second, the choice of statistical method can significantly affect the interpretation of comparative onset data. Third, improved onset of action sometimes is achieved at the expense of tolerability. Thus, accelerating the onset of therapeutic response should not be an end in itself.

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There is a long-standing clinical belief that electroconvulsive therapy (ECT) is the fastest available treatment for depression. However, there are no comparison studies of ECT with antidepressant medications to support this conclusion. Indeed, methodological problems may preclude such studies. For example, it would be extraordinarily difficult to collect a patient sample that would agree to be randomly assigned to drug or ECT. Although data comparing ECT with drug treatment are not available, there are studies of the onset of action of ECT, specifically one that compares different modalities of ECT, i.e., electrode placement and stimulus dosage to determine whether onset of action of ECT is dependent on mode of administration.

METHODOLOGICAL ISSUES

Before reviewing studies on ECT, it is worthwhile to discuss heterogeneity among patients, a variable that may affect onset of action independent of the treatment given. In most studies of a single treatment, and certainly in studies comparing 2 treatments, patients are considered to be homogeneous. Thus, the only variable that would appear to determine onset of action is the treatment itself. However, patients are heterogeneous in at least 2 respects: type and severity of depressive illness and rate of response to treatment.

Studies by Schweizer et al.[1] and Dornseif et al.[2] illustrate differences in response to treatment. These studies examined whether it was more effective to increase the dose of fluoxetine or simply to extend the duration of the original dose in patients who were nonresponders at 3 weeks. Patients with major depression were initiated on 20 mg/day of fluoxetine and separated into 2 groups at the 3-week point: one that had met criteria for response, a 50% reduction in the baseline Hamilton Rating Scale for Depression (HAM-D) score, and one that did not. The nonresponders were then randomly assigned to either continue 20 mg/day of fluoxetine for 4 additional weeks or have their dose increased to 60 mg/day for the same period of time. In the latter group, raising the dose produced no greater effect on improvement compared with continuing the original dose for 4 more weeks; both groups improved equally. In terms of onset of action, the important finding is that patients responded heterogeneously to the same treatment; some patients responded by 3 weeks and others took longer to do so. In conclusion, variability in onset of action results not only from the treatment, but also from the response of individual patients.

Differences in the severity and type of depression also confound the definition and measurement of onset of action. For example, if onset of action is defined as a 25% reduction in baseline HAM-D score, then severely depressed patients with a significant drop in HAM-D score, e.g., from 36 to 28, will not be classified as having achieved onset of action. In contrast, mildly depressed patients with a significantly smaller drop in HAM-D score, e.g., from 16 to 12, will nonetheless meet the numerical criteria for onset of action. If one administers an antide-

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pressant with a significant hypnotic effect, the HAM-D score of a mildly depressed patient will most likely indicate onset of action. Although it will have the same effect on a severely depressed patient, the magnitude of the drop in the HAM-D score would not be sufficient to meet criteria for onset. Thus, focusing on specific patient populations with similar diagnosis or severity of illness would reduce artifacts in studies of onset of antidepressant action.

A third impediment to the accurate assessment of onset of action is the concomitant use of medication, specifically the use of benzodiazepines or other hypnotics. Depression protocols commonly allow for rescue medications in patients with severe anxiety or insomnia and even allow the use of these medications in patients with antidepressant-induced activation effects. Such medications lower the HAM-D score, often resulting in an improvement that meets criteria for onset of action. To date, studies of onset of action have not consistently controlled for the use of concomitant medications.

STUDIES OF ECT

The onset of symptom reduction may or may not lead to full response. For example, Segman et al.[3] reported a correlation of 0.57 between the number of ECT treatments needed to manifest significant symptom reduction (≥ 30% decrease in HAM-D score) and that needed to manifest clinical response (≥ 60% reduction in HAM-D score), indicating only 32% shared variance. Perhaps the most important clinical issue implicit in evaluation of speed of response is the question of whether one can accurately predict endpoint nonresponse at earlier timepoints during a treatment trial. Knowledge of these conditional probabilities would inform physicians when it is appropriate to stop treatment in a nonresponding patient whose likelihood of response is minimal. Only one study conducted such an analysis in major depression. Segman et al.[3] found that symptomatic improvement, defined as ≥ 30% reduction in HAM-D score after the sixth bilateral ECT treatment, correctly identified 31 of 34 endpoint responders and 11 of 13 nonresponders. Statistically significant prediction of endpoint outcome status was possible after only 2 treatments.

The most informative study to date on the issue of onset of action in ECT was authored by Nobler et al.[4] and resulted from the long-term systematic study of the effect on response and side effects of varying electrode placement and stimulus dosage in ECT treatment. In this study, hospitalized patients with major depression were randomly assigned to receive 1 of 4 ECT treatment modalities: (1) right unilateral, low dose (stimulus intensity just above threshold); (2) right unilateral, high dose (stimulus intensity 150% above seizure threshold); (3) bilateral, low dose; or (4) bilateral, high dose. Since the patient population was hospitalized, it was possible to rate patients more frequently and thereby avoid the problem of left censored data. ECT was given 3 times per week, and blinded clinical raters administered the HAM-D twice weekly on nontreatment days. Unlike medication trials in which there is an a priori fixed duration, the number of ECT treatments received was determined by a clinical evaluation team, and there was not a prescribed number of treatments for patients who were responding. However, if a patient failed to show at least a 20% reduction in HAM-D score after 8 treatments, he or she was considered a nonresponder and received an open course of bilateral, high-dose ECT treatment.

Ninety-six patients were randomly assigned, and of the 4 treatment conditions, the response rate in the right-unilateral low-dose group was only 22% compared with 70% in the other 3 conditions. Therefore, to prevent confusion between the issues of efficacy and onset of action, only the patients in the right-unilateral high-dose or bilateral treatment groups were included in subsequent analyses. The data were analyzed using 4 different statistical techniques. In 2 methods, time was considered as an independent variable. The analysis of variance (ANOVA) on slopes evaluated the patient's rate of change in HAM-D score per each ECT treatment. The random regression analysis modeled the HAM-D score as a linear function of time, which in this case is equivalent to the number of ECT treatments received. Two alternative statistical strategies considered time as a dependent variable. Predetermined points were defined that would indicate milestones of clinical improvement, e.g., a 30% decrease in baseline HAM-D score. To avoid discrepancies between sustained improvement or improvement with significant variability in the course of response, patients were considered to reach a milestone only if they maintained that level of improvement on all subsequent assessments. ANOVA was conducted on the time necessary for each patient to achieve a predetermined point indicating significant clinical improvement. In the last statistical approach, Kaplan-Meier survival analysis curves were plotted using the reduction from baseline HAM-D score (30%, 40%, 50%, 60%, and 70%) as the critical event.

The authors found that conclusions on onset of action derived from the 3 treatment modalities varied, depending on which statistical method was applied to the data.[4] Analyses that considered time an independent variable were the least sensitive in detecting differences, whereas survival analysis showed that the bilateral high-dose modality treatment had a consistently faster onset of action than either bilateral low-dose or right-unilateral high-dose treatment.

While onset of action is a desirable feature of antidepressant treatment, resulting side effects must also be assessed. For example, right-unilateral ECT is associated with less cognitive disturbance than bilateral ECT, so one cannot conclude, on the basis of onset of action alone, that bilateral high-dose treatment is the modality of choice.

Furthermore, the point of reviewing this study is not to conclude that survival analysis is the "best" statistical approach to analyze onset of action, but rather to illustrate that in this area the choice of statistical approach can have a defining impact.

SUMMARY

For various methodological reasons, ECT has not been compared directly with drug therapy; thus, it is impossible to say whether such treatment truly works faster than standard medications. However, studies comparing various modalities of ECT (e.g., unilateral vs. bilateral) have detected some significant differences in onset of antidepressant effect. In addition, these studies have highlighted several problems inherent to all assessments of onset of action. First, patients are heterogeneous; that is, given any treatment or mode of treatment, some patients will respond, and some will not. Second, the choice of statistical method can significantly affect the interpretation of comparative onset data. Finally, improved onset of action sometimes is achieved at the expense of tolerability; thus, accelerating the onset of therapeutic response should not be an end in itself.

Drug name: fluoxetine (Prozac).

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