Treatment Failure With a Tricyclic Antidepressant Followed by Lithium Addition and Response to Subsequent Electroconvulsive Therapy

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Objective: To examine the predictive value of resistance to a tricyclic antidepressant (TCA) and lithium with respect to the efficacy of subsequent electroconvulsive therapy (ECT).

Method: This open prospective study was conducted in the inpatient depression unit of a university hospital in The Netherlands. Patients were enrolled in the study from October 1996 to June 2002 and had to meet DSM-IV criteria for major depressive disorder. Eighty-six patients were treated twice weekly with ECT until recovery or no progress during at least 10 bilateral treatments. Patients were maintained drug free during the ECT treatment. Clinical evaluation of depressive symptoms was performed each week; scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) were obtained 1 to 3 days prior to ECT and 1 to 3 days after treatment termination. The primary outcome criterion was defined as the mean difference in HAM-D score before and after ECT for patients who had received adequate treatment with a TCA and lithium compared with patients who had not received adequate treatment with a TCA and lithium. Adequate treatment was defined as 4 weeks taking a predefined plasma level of a TCA; nonresponders had lithium added to the medication, and the minimal duration of the lithium addition was 3 weeks with a plasma level of at least 0.6 mmol/L. Independent samples t test was used to analyze this primary outcome criterion.

Results: According to the primary outcome criterion, patients who had received adequate treatment with a TCA and lithium (N = 56) had a mean difference in HAM-D score pre-ECT and post-ECT of 16.4 compared to a HAM-D score difference of 19.5 in the patient group who had received inadequate treatment with a TCA and lithium (N = 30). This inequality in differences in mean HAM-D scores is not significant (p = .2).

Conclusion: In the present study sample, treatment failure with adequate pharmacotherapy with a TCA and lithium addition appears to be unrelated to outcome following subsequent ECT.

(J Clin Psychiatry 2008;69:1887–1891)

Received Jan. 24, 2008; accepted March 25, 2008. From the Department of Psychiatry, Erasmus Medical Centre, Rotterdam, The Netherlands.

Dr. van den Broek has served on the speakers or advisory boards of Servier and Wyeth, Dr. Birkenhäger has served on the speakers or advisory boards of Servier and Wyeth, and Ms. Heijnen reports no financial or other affiliation relevant to the subject of this article.

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Electroconvulsive therapy (ECT) was recognized as the most effective treatment for major depression before the introduction of antidepressants.[1] Early studies reported that 80% to 90% of depressed patients showed substantial clinical response to ECT.[2] The widespread use of antidepressant pharmacotherapy as a treatment for depression has changed the population that currently receives ECT. In The Netherlands, ECT is mainly used for patients who do not respond to adequate trials of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), TCAs with lithium addition, and monoamine oxidase inhibitors.[3] Thus, failure to respond to antidepressants is the most common indication for ECT. Despite this change in the indication for ECT, there is little consensus about the impact of medication treatment failure on the efficacy of subsequent ECT.

Several uncontrolled studies have suggested that clinical outcome of ECT is independent of previous failure to respond to antidepressant pharmacotherapy.[4–7] These studies were uncontrolled, because response to ECT was only examined among patients who were thought to be medication treatment failures. A comparison patient sample that had not received adequate antidepressant pharmacotherapy prior to ECT was not included. Other methodological concerns included weak or inappropriate criteria for medication resistance and nonuniform outcome criteria.

Two studies used a prospective design to investigate this subject.[8,9] The first study examined a sample of 53 depressed patients.[8] Only patients randomly assigned to bilateral ECT were included. Patients who failed to

respond to adequate antidepressant pharmacotherapy had lower response rates to ECT (50%) than patients who had received inadequate antidepressant pharmacotherapy (86%).[8]

The second study examined a sample of 100 nonpsychotic depressed patients.[9] The patients in this study were treated predominantly with low-dose right unilateral ECT. This form of ECT is considered to be inadequate. Patients who failed to respond to adequate antidepressant therapy again had lower response rates to ECT (63%) compared to patients who had received inadequate antidepressant pharmacotherapy (91%).[9]

The influence of medication resistance on response to ECT has been investigated in The Netherlands in 2 studies[10,11]; neither of these studies found an influence of medication treatment failure on the outcome of subsequent ECT. The first study examined 41 depressed inpatients.[10] No significant difference in response rate was found in patients who had received adequate antidepressant treatment prior to ECT (72%) compared to patients who had received inadequate antidepressant pharmacotherapy (67%).[10]

The second study examined 104 patients who met DSM-IV criteria for major depressive disorder.[11] Again, no significant difference in response rate was found between patients who received adequate antidepressant treatment prior to ECT (62.5%) and patients who received inadequate antidepressant treatment (81.1%).[11]

In the United Kingdom, medication-refractory and medication-nonrefractory patients are also reported to have the same antidepressant response with ECT.[12] Apart from European studies casting doubt on the influence of antidepressant treatment failure on ECT response, a recent study from the United States found that treatment failure with antidepressant medication as assessed by the Antidepressant Treatment History Form (ATHF) was not predictive of remission status after ECT.[13] The ATHF has been the reference in the reported instances of treatment resistance. Thus, the results of the above-mentioned studies regarding the influence of medication treatment failure are somewhat conflicting.

Newer antidepressants have more tolerability and safety benefits than older TCAs. Similar efficacy in unselected depressed samples is suggested by some authors.[14] However, the TCAs demonstrated greater efficacy in severely depressed patients and in depressed inpatients. Other studies have shown TCAs to be more efficacious than SSRIs and other newer antidepressants in depressed inpatients.[15–18]

A substantial number of patients suffering from depressive disorder fail to respond to adequately performed treatment with antidepressants. Several treatment strategies have been proposed to treat such refractory depression, of which the best studied is lithium addition[19]; this latter meta-analysis is quite convincing and confirms the efficacy of this strategy. Two other studies have confirmed the efficacy of the treatment strategy of a TCA followed by lithium addition.[20,21]

It is possible that resistance to a "stronger" antidepressant trial (i.e., adequate treatment with a TCA and lithium) results in a significantly poorer response to ECT. No study has examined the predictive value of treatment failure of a TCA and lithium with respect to the efficacy of ECT; the present study attempts to address this issue.

METHOD

This open prospective study was carried out in the inpatient depression unit of the Department of Psychiatry at the University Hospital-Erasmus Medical Center, Rotterdam, The Netherlands. Patients were enrolled in the study from October 1996 to June 2002. Informed consent was obtained, and written informed consent was also required.

Patients had to meet the DSM-IV criteria for major depressive disorder to be enrolled in the study. Patients with organic brain syndrome, schizophrenia, or bipolar or schizoaffective disorder were excluded. Patients treated with ECT in an earlier episode were excluded from evaluation and analysis. Diagnosis was based on clinical observation during a routinely drug-free period. If patients received more than 1 course of ECT, only the first course was reviewed.

The ECT was administered with a brief-pulse, constant-current apparatus (Thymatron DGx, Somatics, Lake Bluff, Ill.). Seizure threshold was determined during the first session with stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 seconds' duration measured with the cuff method, stimulus charge was increased according to the titration schedule, and the patient was restimulated after 30 seconds.

Seizure threshold was defined as the stimulus dosage that elicited a seizure for at least 25 seconds according to the cuff method. For the second treatment, the stimulus dosage was set at 1.5 times the initial seizure threshold for bilateral treatment. For unilateral treatment, the stimulus dosage was set at 2.5 times the seizure threshold. During the course of ECT, stimulus dosage settings were adjusted upward to maintain a seizure duration of at least 25 seconds as measured with the cuff method.

Patients were initially treated with right unilateral ECT. Patients were crossed over to bilateral ECT if response was inadequate after 6 treatments. Patients in a critical condition started with bilateral ECT.

Patients were treated twice weekly until recovery or no progress during at least 10 bilateral treatments. Clinical evaluation of depressive symptoms was performed each week using the Montgomery-Asberg Depression Rating Scale, and scores on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) were

Table 1. Demographic and Clinical Characteristics for the Total Patient Sample and as a Function of Inadequate and Adequate Treatment With a TCA and Lithium Prior to ECT

Characteristic	Total Sample (N = 86)	Adequate Treatment With a TCA and Lithium (N = 56)	Inadequate Treatment With a TCA and Lithium (N = 30)
Age, mean (SD), y	54.9 (12.7)	54.6 (11.9)	55.5 (14.3)
Female, N (%) (SD)	60 (71) (5)	19 (66) (5)	24 (80) (4)
Psychotic, N (%) (SD)	37 (43) (5)	25 (45) (5)	12 (40) (5)
Length of index episode, mean (SD), mo	18.6 (12.6)	20.8 (11.9)	14.5 (12.9)
Pre-ECT HAM-D score, mean (SD)	28.1 (8.1)	27.7 (7.6)	28.9 (9.0)
Post-ECT HAM-D score, mean (SD)	10.7 (7.8)	11.4 (8.1)	9.3 (7.3)

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, TCA = tricyclic antidepressant.

obtained 1 to 3 days prior to ECT and 1 to 3 days after treatment termination.

Patients were withdrawn from all psychotropic medication before ECT and were maintained medication free during the course of ECT. In case of severe agitation, incidental use of haloperidol was allowed.

Patients were classified as responders when their HAM-D score showed a reduction of at least 50% posttreatment compared to pretreatment. Patients were classified as being in full remission when their posttreatment HAM-D scores were ≤ 7.

Prior to ECT, resistance to treatment with a TCA and lithium during a depressive episode was evaluated. Adequate treatment was defined as 4 weeks taking a predefined plasma level of a TCA; nonresponders had lithium added to the medication, and the minimal duration of the lithium addition was 3 weeks with a plasma level of at least 0.6 mmol/L.

Statistical Analysis

Primary outcome criterion was defined as the mean difference in HAM-D score before and after ECT treatment for patients who received adequate treatment with a TCA and lithium compared with patients who did not receive adequate treatment with a TCA and lithium. Independent samples t test was used to analyze this primary outcome criterion.

Fisher exact test was used to analyze the differences in response rate to ECT and remission rate between patients who received adequate treatment with a TCA and lithium and patients who did not receive adequate treatment with a TCA and lithium. Statistical significance was defined as $p < .05$. All analyses were carried out using SPSS version 13.0 (SPSS Inc., Chicago, Ill.).

RESULTS

The patient sample consisted of 104 inpatients meeting DSM-IV criteria for depressive disorder. Eight patients were excluded because it was not known if they received a TCA and lithium prior to ECT. Three patients were excluded because they had been previously treated with ECT, and 7 patients were excluded because their HAM-D score before ECT was not known. The remaining 86 patients were included for analysis.

Table 1 presents the demographic and clinical characteristics for the total patient sample and as a function of inadequate and adequate treatment with a TCA and lithium prior to ECT. Thirty patients received inadequate treatment with a TCA and lithium, whereas 56 patients received adequate treatment with a TCA and lithium and were classified as medication treatment failures to a TCA and lithium. A comparison of both groups revealed no significant differences with regard to age and psychotic depression. Patients with adequate treatment with a TCA and lithium had a significantly longer duration of current depressive episode ($p = .03$) compared with the inadequately pretreated patients.

Treatment Effects

According to the primary outcome criterion, patients with adequate treatment with a TCA and lithium had a mean difference in HAM-D score pre-ECT and post-ECT of 16.4 compared to a mean difference in HAM-D score of 19.5 in the patient group with inadequate treatment with a TCA and lithium. This inequality in difference in mean HAM-D scores was not significant ($p = .2$).

Again, neither response nor remission was influenced by adequate pretreatment with a TCA and lithium ($p = .3$ and $p = .3$, respectively). Response to ECT after adequate treatment with a TCA and lithium addition was 67% and remission was 39% compared to inadequate treatment with a response to ECT of 77% and remission of 50%. Only 16 patients were treated with right unilateral ECT; the remaining 70 patients were treated with or switched to bilateral ECT.

DISCUSSION

In the present study sample, resistance to adequate pharmacotherapy with a TCA and lithium addition appears to be unrelated to both the primary outcome criterion (mean difference in HAM-D score pre-ECT and post-ECT treatment) and the secondary outcome criterion

(response and remission to subsequent ECT). This is in accordance with several previous studies[11–13] but in contrast with others.[8,9,22]

Different staging methods can be used to assess levels of treatment resistance in depression.[23] We used a rigorous definition of medication resistance. All of our patients were inpatients. Diagnosis was ascertained during a routinely psychopharmacologic drug-free observation period of at least 1 week. Those patients belonging to the medication-resistant group all had at least 4 weeks of adequate plasma levels with a TCA. Doses of TCAs were routinely adjusted to obtain adequate plasma levels, which were monitored weekly. With lithium addition, the dose was adjusted in order to achieve a lithium level of 0.6 to 1.0 mmol/L for at least 3 weeks.

Baseline psychotropic medication use is mostly quantified with the ATHF.[9,24] This is a clinician-rated instrument to assess treatment resistance. The cut-off point for treatment resistance is a score ≥ 3. This score is already achieved when treated with an adequate dosage of a single SSRI for 4 weeks, which would probably not be considered as a "strong" antidepressant trial by many clinicians. No criterion for treatment adherence or accuracy of the diagnosis is required. Moreover, the strategy of a TCA with lithium addition is considered to be very efficacious.[19–21]

The accuracy of diagnosis in our sample was greatly enhanced by our routine drug-free observation period before ECT. This procedure benefits the selection of patients suitable for ECT. This is in contrast with previous reports in which details about patient selection were not disclosed.[8,9]

Psychotically depressed patients have a significantly higher difference in HAM-D score (22) pre-ECT and post-ECT compared to nonpsychotic depressed patients (13, $p < .001$); this is in accordance with the consideration that psychotically depressed patients have a superior response rate with ECT relative to nonpsychotic patients.[25,26]

It seems reasonable that patients with more difficult-to-treat illness will respond less well to all subsequent treatments, ECT included; however, the greater efficacy of ECT in psychotic depression (generally viewed as the more severe form of depression) argues against this.

In the present study, comparison of the group with adequate treatment with a TCA and lithium and the group with inadequate treatment revealed no significant differences regarding age, sex, psychotic depression, and pre-ECT HAM-D score. Patients adequately treated with a TCA and lithium had a significantly longer duration of index episode ($p = .03$) compared to patients who were treated inadequately with a TCA and lithium; this difference has also been reported in previous trials.[9,10,12] A reason for this difference could be the fact that some time is needed to adjust a TCA and lithium to an adequate dosage for each individual.

A previous study used predominantly unilateral ECT,[8] whereas in the present study, only 16 patients were solely treated with unilateral ECT, and the remaining 70 patients were started directly with bilateral ECT or started with unilateral ECT but were switched to bilateral ECT. Bilateral ECT is considered to be the most effective electrode placement of ECT; the unilateral placement and dosing used in the present trial are considered to be less effective.[22,27] Our patients were not randomly assigned to electrode placement for this trial, and conclusions about electrode placement and efficacy are therefore not permitted. Nevertheless, the large percentage of patients treated with bilateral ECT in this trial can also contribute to the efficacy of ECT since bilateral ECT is considered to be the most efficacious electrode placement.

Limitations

While the criteria used in the ATHF to rate medication resistance are based on data from efficacy trials and expert judgment, these criteria are arbitrary. It is not known to what extent imposing more stringent cut-offs (such as requiring a minimum treatment duration of 6–8 weeks to define an adequate trial) would have altered the findings of this study. Furthermore, the 2 groups had an unequal sample size, and both had a relatively small sample size, which also could have influenced the results.

CONCLUSION

In the present study, sample resistance to adequate pharmacotherapy with a TCA and lithium appears to be unrelated to the primary outcome criterion (mean difference in HAM-D score pre-ECT and post-ECT treatment for patients who received adequate treatment with a TCA and lithium compared to patients who did not receive adequate treatment with a TCA and lithium) and response or remission to subsequent ECT. Moreover, the concept of "medication resistance" as defined by arbitrary (ATHF) criteria is irrelevant in the decision for a trial of ECT in patients with severe depressive illness, whether psychotic or nonpsychotic.

It is encouraging that even in severely depressed inpatients who have failed to respond to a TCA and lithium, ECT can be an effective treatment. Patients with a depressive disorder not responding to a strong antidepressant trial (adequate treatment with a TCA and lithium) can still largely benefit from subsequent ECT.

Drug names: haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others).

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