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Relapse During Continuation Pharmacotherapy after Acute Response to ECT: A Comparison of Usual Care versus Protocolized Treatment

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Background. *ECT, an effective treatment for major depression, is associated with a high relapse rate. Roughly half of all responders during the acute treatment phase relapse during continuation treatment. Recent literature has pointed out an "efficacy-effectiveness gap" in outcomes of patients enrolled in study protocols when compared to "care as usual." This study compares the effectiveness of usual care versus protocolized pharmacotherapy in preventing relapse following ECT.*
Methods. *One hundred twenty-six depressed patients responded to acute ECT. Seventy-three were randomized to continuation pharmacotherapy consisting of nortriptyline, nortriptyline-plus-lithium, or placebo. The 53 patients that refused to participate in the randomized trial were followed naturalistically for 6 months or until depression relapse in usual care settings.*
Results. *All but one "usual care" patient received pharmacotherapy following ECT; 27 (51%) relapsed within 6 months. Only one usual care patient received continuation ECT as a first-line treatment. The "usual care" relapse rate was intermediate to the relapse rates of the patients receiving protocolized nortriptyline (60%) and nortriptyline-plus-lithium (39%), but superior to placebo (84%).*
Conclusions. *The relapse rate associated with usual care following ECT was comparable to that of protocolized pharmacotherapy. This suggests that high relapse rates following ECT are not due solely to an "efficacy-effectiveness gap."*

Keywords Depression, ECT, Continuation therapy, Relapse, Usual care

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INTRODUCTION

In a recent review of the literature, depression treatment outcomes under usual care are often inferior to outcomes experienced by patients treated in controlled trials (1). Several reasons may explain this "efficacy-effectiveness gap": failure to implement evidence-based treatments, inadequate medication dosing, short treatment duration, limitations in length and extent of doctor-patient interactions, and poor compliance (2–4). To our knowledge, no published study has compared outcomes of pharmacotherapy under protocolized and usual care conditions following ECT.

Nearly 10% of all adult patients admitted to US hospitals with recurrent major depression are treated with ECT (5). ECT provides rapid symptom improvement and a high treatment-response rate, even in patients with a history of treatment-resistant depression (6). However, despite improvements in ECT treatment modality (electrode placement, stimulus intensity, anesthesia management), high acute remission rates in depression, and the known risk of relapse following acute response, ECT relapse rates remain high. Naturalistic studies have documented a relapse rate around 50% following discontinuation of ECT (7–11). In a study by Prudic and others (2004) on the effectiveness of ECT in a community setting, 64% of 154 patients that experienced acute remission of depression with ECT relapsed within 24 weeks (median time to relapse 8.6 weeks). The authors speculate that the high relapse rate following response to ECT may be due to insufficient continuation pharmacotherapy in community treatment. However, this study did not follow a subset of remitters in a continuation pharmacotherapy protocol to compare relapse rates.

Sackeim and colleagues have reported on a randomized controlled trial of continuation pharmacotherapy in depressed patients following response to ECT. Over six months, a lower relapse rate was observed with nortriptyline plus lithium (39%), than with nortriptyline alone (60%), or placebo (84%) (7). We report the outcomes of patients who participated in the acute phase of this trial but elected to receive "care as usual" after responding to ECT, rather than participating in the continuation pharmacotherapy protocol. Given the concern of high relapse rates following ECT, this provides a useful opportunity to explore an "efficacy-effectiveness gap" in the continuation treatment phase of patients following acute response to ECT.

We hypothesized that, due to the known high relapse rates following ECT and the relatively higher percentage of treatment resistant patients, those patients followed naturalistically in usual care settings would not fare as well as patients receiving protocolized administration of nortriptyline plus lithium in a closely monitored research setting.

METHODS

As reported elsewhere, in a multi-center treatment protocol conducted from 1993 to 1998, 159 patients with a major depressive disorder responded to acute ECT. To enter the continuation trial, patients had to achieve at least 60% reduction in the 24-item Hamilton Rating Scale for Depression (HRSD) score relative to pre-ECT baseline, with a maximum score of 10 both 2 days prior to, and 4 to 8 days following, ECT termination. Detailed study methods on ECT administration and subsequent randomization have been described in an earlier report (7). Eighty-four of the ECT responders (53%) participated in a continuation pharmacotherapy trial, randomized to 3 treatment groups: nortriptyline alone (N = 27), nortriptyline and lithium (N = 28), or placebo (N = 29). Continuous rater, blinded assessments were performed weekly with the 24-item Hamilton Rating Scale for Depression (HRSD) for the first 4 weeks, at 2-week intervals for the next 8 weeks, and at 4-week intervals for the remaining 12 weeks. Seventy-three of the 84 subjects (87%) completed the 24-week continuation pharmacotherapy protocol. Time to relapse was the main outcome measure. Relapse was defined as a HRSD absolute score of 16 or greater (maintained for at least one week) and a mean absolute increase of at least 10 points at two consecutive visits relative to continuation trial baseline. The results of this study have been reported (7).

The remaining 75 ECT remitters (47% of the 159 entering continuation treatment) were not eligible for the continuation pharmacotherapy protocol due to medical conditions precluding the use of nortriptyline or lithium (N = 17; 23%), could not participate due to travel limitations (N = 20; 27%), or declined to participate (N = 38; 51%) because they preferred to be followed by their referring psychiatrists, preferred another continuation treatment, or were concerned about the placebo condition in the pharmacotherapy trial. These patients received usual care and were invited to participate in a naturalistic follow-up study. They were assessed by phone with the 24-item HRSD at 2, 4, and 6 months following ECT. In the naturalistic study, relapse was defined as an HRSD score of 16 or greater, or an increase in score > 10 points. Written informed consent was obtained for all subjects following local Institutional Review Board procedures.

RESULTS

Determination of relapse could not be made reliably in 22 eligible patients in the naturalistic study since they were unreachable for some or all of the follow-up assessments. Thus, follow-up data for up to 6 months or until relapse were obtained in 53 of the 75 patients (71%). Demographic and clinical characteristics of these 53 "usual care" patients and the 73 pharmacotherapy protocol completers are presented in Table 1. Usual care patients did not differ significantly from patients receiving protocolized pharmacotherapy with respect to age, gender, age of depressive episode onset, medication resistance, presence of psychotic features, physical illness burden, or mean HRSD score either pre- or post-ECT.

Table 1 Characteristics of Subjects Receiving Protocolized Pharmacotherapy or Usual Care

	Protocol Treatment	Usual Care	t or X2 (df)	P
N	73	53		
Mean (SD) age	56.1 (17.4)	58.7 (18.5)	0.82 (124)	0.41
N (%) female	50 (68.5%)	39 (75.0%)	0.63 (1)	0.43
Mean (SD) age of onset	38.2 (17.3)	42.4 (19.7)	1.29 (124)	0.20
Mean (SD) number of previous hospitalizations	2.5 (2.7) median = 2	1.6 (1.6) median = 1	Wilcoxon Exact p = 0.12	
N (%) medication resistant	38 (52.1%)	28 (52.8%)	0.01 (1)	0.93
N (%) with psychotic depression	27 (37.0%)	13 (24.5%)	2.20 (1)	0.14
Mean (SD) CIRS score[a]	5.8 (4.0)	6.0 (4.6)	– 0.27 (124)	0.79
Mean (SD) pre-ECT HRSD score	35.5 (8.1)	33.4 (7.3)	– 1.47 (124)	0.14
Mean (SD) post-ECT HRSD score[a]	5.8 (3.3)	5.7 (3.4)	0.03 (124)	0.97

CIRS: Cumulative Illness Rating Scale (Miller, 1992); HRSD: Hamilton Rating Scale for Depression
[a]SQRT transformation used in the analyses. Means and standard deviations reported in original units.

All but one "usual care" patients received some form of pharmacotherapy post-ECT; one received continuation ECT alone. Forty-seven of these 53 "usual care" patients (89%) received a selective serotonin reuptake inhibitor, tricyclic antidepressant, or venlafaxine. Thirteen (25%) were treated with lithium to augment an antidepressant. Two patients received valproic acid (one was later switched to lithium). Only one patient was prescribed an antipsychotic. Fourteen patients (26%) received ECT at some point during the six-month follow-up period. In all but two, ECT was reinitiated following a relapse while on pharmacotherapy.

Overall, 27 of the 53 "usual care" patients (51%) experienced a relapse within 6 months (see Figure 1). This relapse rate did not differ statistically from the one associated with protocolized administration of nortriptyline alone (60%, n = 15/25; Fisher Exact p = 0.48) or nortriptyline plus lithium (39%, n = 9/23; Fisher Exact p = 0.45). Of the 27 relapsers, two thirds (N = 16; 59%) did so within two months post-ECT, and all but one within 4 months (N = 26; 96%).

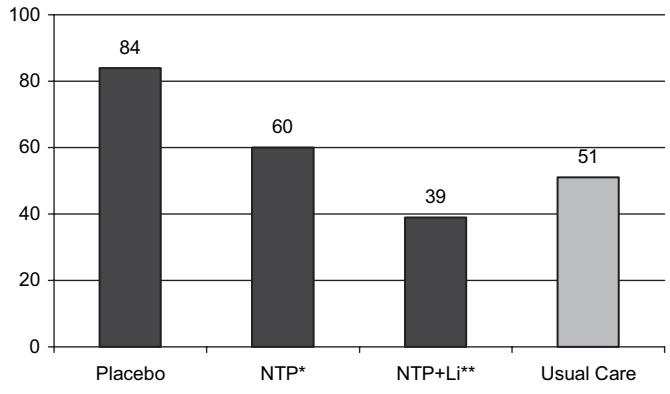

Figure 1 Percentage of Patients Relapsing in 6 Months.

*NTP = nortriptyline
**NTP + Li = nortriptyline with lithium augmentation

DISCUSSION

In this naturalistic study, 51% of "usual care" patients who had responded to acute ECT relapsed within 6 months. This relapse rate was intermediate to the one associated with protocolized administration of nortriptyline alone (60%) and nortriptyline plus lithium (39%). All but one "usual care" patients received continuation pharmacotherapy, including 13 (25%) who received lithium augmentation of an antidepressant. This high rate and intensity of pharmacologic treatment may explain the lower relapse rate under "usual care" than among patients who received placebo in the continuation protocol (84%) (7).

Like those patients receiving protocolized pharmacotherapy, most "usual care" patients that relapsed did so within 2 months, and all but one within 4 months following ECT. This confirms that patients are at greatest risk for depression relapse immediately following ECT, regardless of whether they are receiving care in a highly structured study environment or care as usual. The consistency of results between the patients in the pharmacotherapy protocol and the usual care group underscores the magnitude of the relapse risk for ECT responders entering continuation treatment. ECT remains one of the few acute treatments for depression that is typically discontinued soon after patients respond. This study adds to the evidence that patients who get well on ECT should consider continuation ECT, particularly if they have a history of previous relapse following ECT despite adequate continuation pharmacotherapy. In this naturalistic study, despite the high rate of medication resistance, only one patient in usual care received ECT as a first-line continuation treatment, suggesting that use of continuation ECT as a first line treatment following acute response is still relatively uncommon.

This study has several limitations. First, since patients were not randomized to the pharmacotherapy protocol or to "usual care," there may have been a selection bias: one half of the "usual care" patients had refused participation in the randomized protocol and the other half was not eligible. Thus, our two groups may have had intrinsically different relapse risks. Also, assessments were more frequent in the pharmacotherapy protocol

(weekly to once a month) than in the naturalistic study (every two months). This sparse follow-up schedule prevented us from conducting a survival analysis to compare the relapse rates. In addition, the naturalistic follow-up may have missed some relapses if a patient relapsed and recovered between two assessment points. Furthermore, more than a quarter of patients eligible for naturalistic follow-up were unreachable for all or some of the follow-up assessments. It is possible that these non-completers were more likely to relapse. Both of these factors could have artificially lowered the overall detection of relapse in the usual care group. Indeed, the rate of relapse observed in our study under "usual care" conditions is lower than the one reported in a recent naturalistic study by Prudic and others in which 347 depressed patients were followed for 6 months after ECT (10). In the Prudic study, 64% of the ECT responders experienced depression relapse within the 6-month follow-up period.

This study, although quite limited in its methods, suggests that the relapse rate associated with usual care following ECT may be similar to protocolized pharmacotherapy. If further studies confirm this, then the high relapse rate following ECT is probably not due to "an efficacy-effectiveness gap" alone.

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