Combination of Pharmacotherapy With Electroconvulsive Therapy in Prevention of Depressive Relapse

A Pilot Controlled Trial

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Objective: Relapse rates after electroconvulsive therapy (ECT) remain high with standard treatments. We aimed to test the efficacy of an early administered continuation pharmacotherapy (c-pharm early) strategy in prevention of post-ECT relapse.

Method: A 20-week, randomized, double-blind, placebo-controlled trial. Patients aged 18 to 65 years diagnosed with *Diagnostic and Statistical Manual of Mental Disorders* major depressive disorder, with or without psychotic features, with initial Montgomery-Åsberg Depression Rating Scale scores higher than 22, underwent 8 bilateral ECT sessions (2 per week). Randomization to c-pharm early, c-pharm late, and placebo groups in 2:2:1, respectively, was performed at the completion of the fourth ECT session. After randomization, subjects in the c-pharm early group were given sertraline at 150 mg/d. Subjects in the c-pharm late group were first given placebo, which was substituted with sertraline at 150 mg/d at the completion of the eight ECT. Relapse was defined as a Montgomery-Åsberg Depression Rating Scale score of 16 or higher.

Results: Seventy-three percent of the patients responded to the given treatment. The relapse rates were 12.5% in the c-pharm early group, 28% in the c-pharm late group, and 67% in the placebo group ($P = 0.09$). The c-pharm early strategy resulted in significantly lower relapse rates and longer well time compared with the placebo ($P = 0.04$). When the trend with the initiation of the c-pharm intervention was investigated in the 3 groups with equally spaced trend weights, the time of initiation was found to have a significant effect on the probability of the remaining well ($P = 0.03$).

Conclusions: Comparative efficacy of c-pharm early and late strategies in providing improved protection against post-ECT relapse of major depressive disorder needs to be further explored.

Key Words: major depressive disorder, electroconvulsive therapy, controlled trial, antidepressants, placebo, relapse

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Electroconvulsive therapy (ECT) has proven efficacy in treatment of major depressive disorder (MDD).[1,2] Remission rates with ECT are in the range of 70% to 90% and exceed that of any other antidepressant treatment.[3,4] However, post-ECT relapse is an important problem.[5–9] Continuation ECT (c-ECT) at biweekly or monthly intervals over 4 to 6 months and continuation pharmacotherapy (c-pharm) after ECT are strategies developed to decrease post-ECT relapse.[10,11] In naturalistic follow-up studies, it has been reported that 51% of MDD patients receiving usual care with continuation antidepressants alone or in combination with lithium experienced relapse within 6 months.[12,13] A prospective naturalistic study found a 64.3% post-ECT relapse rate at 6 months, with a median time to relapse of 8.6 weeks.[14] The Health Technology Assessment Committee reported relapse rates of 33% for c-ECT, 32% with lithium plus a tricyclic antidepressant, 56% with an tricyclic antidepressant, and 72% without treatment at 12 months.[15] A review by Wijkstra et al found 29% and 28% relapse rates with c-ECT and c-pharm, respectively.[16] Depressive relapse rates with c-ECT and c-pharm were reported as 37.1% and 31.6%, respectively, in the Consortium for Research in Electroconvulsive Therapy (CORE).[17]

Research on the mechanism of action of antidepressants focus on synaptic pharmacology, particularly on neurotransmitter turnover and neurotransmitter receptors, and on the regulation of signaling pathways involved in cellular survival and neuroplasticity.[18] It has been reported that chronic adaptations in brain function (rather than increases in synaptic norepinephrine, dopamine, and serotonin per se) underlie the therapeutic effects of antidepressant drugs.[18] Chronic administration of antidepressants modulate intracellular signaling pathways, counteracting cellular death cascades, increasing neurogenesis in adult hippocampus, and mediating long-term persistent adaptations that serve as a form of drug-induced neuroplasticity.[19] The mode of action of ECT remains a mystery, but it seems to be unique. If the modes of action of ECT and antidepressants are not identical, the strategy of classic c-pharm may leave the brain unprotected until the antidepressant drug develops its own adaptive mechanisms. This temporal gap between cessation of ECT and development of antidepressant drug-induced adaptive mechanisms may trigger depression. Using this hypothesis, we developed this prospective pilot study to provide preliminary data on the efficacy and safety of the c-pharm early strategy, in which an antidepressant drug is initiated 2 weeks before termination of ECT.

METHODS

Subjects

Patients aged 18 to 65 years, diagnosed with *Diagnostic and Statistical Manual of Mental Disorders,* (*DSM-IV*) MDD, unipolar type, with or without psychosis, were admitted

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to the psychiatric inpatient unit of Dokuz Eylül University (DEU) Medical Center in Izmir, Turkey, for this single-site trial. Study subjects were recruited between April 2004 and February 2007. The inclusion criteria were (a) diagnosis of MDD on the Structured Clinical Interview for *DSM-IV* (SCID, patient edition)[20]; (b) aged 18 to 65 years; and (c) Montgomery-Åsberg Depression Rating Scale (MADRS)[21] total score higher than 22 at both screening and baseline visit. The exclusion criteria were (a) pregnancy, breastfeeding, or intention to become pregnant; (b) history of bipolar disorder, schizophrenia, schizoaffective disorder, nonmood psychosis, or neurological illness; (d) ECT within the past 6 months; (e) substance abuse at screening, active substance abuse within 2 weeks, or substance dependence within 2 months; and (f) severe medical illness that would increase the risks of ECT (eg, unstable or severe cardiovascular conditions, aneurysm, or vascular malformation susceptible to rupture and severe chronic obstructive pulmonary disease). The study was approved by the Dokuz Eylül University Institutional Ethics Committee. Written informed consent was obtained from all the patients.

Treatment

The trial consisted of 2 distinct phases: phase 1, in which patients with acute depression received bilateral ECT twice weekly for 2 weeks; and phase 2, in which patients were randomized to c-pharm early, c-pharm late, or c-pharm placebo groups in 2:2:1 ratio, respectively. Given that the study was aimed to test additional benefit of early antidepressant administration, which was set at 2 weeks before cessation of ECT in decreasing post-ECT relapse rates, randomization was performed not at the time of response but at the beginning of the drug initiation in the c-pharm early group. Patients in the randomized continuation phase (phase 2) were followed up for 18 weeks. The primary end point was time to relapse, which was determined from time of response to the given treatment to time of relapse.

Electroconvulsive Therapy Procedures

All patients received bilateral ECT (bifrontotemporal placement) with a Thymatron System IV, using age-based dosing by setting Thymatron System IV according to half the age.[22] Seizure duration was determined by using 2-lead single-channel electroencephalography (EEG) and the cuff technique. When seizure duration on electroencephalography was shorter than 20 seconds or failed to show adequate seizure quality, treatments were repeated at 50% higher energy settings under the same anesthetic dose until an acceptable seizure was recorded. Propofol at 1.0 mg/kg and succinylcholine chloride at 1.0 mg/kg were used as anesthetic medications, with intravenous preadministration of an anticholinergic agent (0.4–0.6 mg of atropine). Treatments were performed twice weekly for 4 weeks.

Pharmacotherapy Procedures

On the day scheduled for the fifth ECT session, that is, after completion of 4 ECT sessions, patients were randomized to 1 of 3 study arms in a 2:2:1 ratio; the study arms were the c-pharm early, c-pharm late, and c-pharm placebo groups. Medication was administered as 50-mg film-coated sertraline HCl tablets and identical placebo tablets (both produced by the manufacturer, Pfizer Inc, New York, NY). Patients randomized to the c-pharm early group were administered an initial dosage of 50 mg/d of sertraline HCl, with an increase in dosage to 150 mg/d on the third day of randomization. Patients randomized to the c-pharm late group were given identical placebo tablets; after completion of the eighth ECT session, this was switched to 50-mg sertraline HCl tablets, and dose adjustments such as those of c-pharm early were made. Patients randomized to the c-pharm placebo group received identical placebo tablets throughout the continuation phase. Additional psychotropic medications were prohibited throughout the study, with the exception of lorazepam of up to 7.5 mg/d and clonazepam of up to 4 mg/d for anxiety or insomnia (not given within 12 hours of scheduled ECT sessions).

Clinical Assessment

The treatment team, the outcome assessors, and the patients were blind to the treatment assignments. The primary instrument to rate depressive symptoms was MADRS, which was administered at weekly intervals for the first 4 weeks and at 2-week intervals for the remaining 16 weeks. Clinical outcome evaluators were medical physicians (psychiatrists or psychiatry residents) with prior experience working in clinical and research settings with psychiatric patients. The evaluators underwent an intensive prestudy training period (12 sessions) at the DEU. Before collecting data, evaluators demonstrated high reliability (intraclass correlation coefficient ≥ 0.90) for MADRS ratings. Clinical ratings during the acute (phase 1) and continuation phases (phase 2), were obtained by the same blinded evaluator (continuous rater).

Outcome Measures

We defined response as (a) reduction of 50% or more in MADRS scores plus (b) a post-ECT score of 12 or lower. The criterion for relapse was a total MADRS score of 16 or higher that was maintained over 2 consecutive visits. Rate of relapse and survival time were the main outcome measures. Secondary outcome measures were rates of response, changes in absolute ratings of depression, suicide, and global assessment of functioning (GAF).

Data Analysis

The randomized continuation pharmacotherapy groups were compared on baseline categorical and continuous variables using analyses of variance (ANOVA) or χ^2 analyses. The intent-to-treat (ITT) sample comprised all randomized patients who had participated in at least 1 post-ECT symptom status assessment. Relapse-free survival times were compared using Kaplan-Meier survival curves and the log-rank test. In the a priori specified primary analysis, Cox proportional hazards model regression analysis was used to compare time to relapse for the c-pharm early/late versus the placebo in a multivariate model with forward selection of other possible significant predictors of relapse. Presence of suicidal thoughts and acts (score of 3–4 or higher on MADRS item 10) at completion of ECT and incidence of drug- or ECT-induced adverse events were compared using the χ^2 test. Analysis of change in the GAF scores between the study groups was performed using ANOVA. Analysis of weekly change in the total score of MADRS was performed under the ITT principle, based on normal linear mixed effect models for longitudinal data fit by restricted maximum likelihood, including fixed drug, week, and drug-week interaction effects, in which the residual error structure was adjusted for the repeated week effects and other significant covariates. Although $P < 0.05$ was a common threshold for the statistical significance, as indicated on the guideline suggested by the Committee for Medicinal Products for Human Use on clinical trials in small populations, this value may not be adequate. Therefore, we used a less stringent cutoff ($P < 0.10$) for

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overall type 1 error level.[23] All statistical tests were performed using SPSS statistical software, version 13.0 (SPSS Inc, Chicago, Ill). Adverse events are reported as proportions for each group.

RESULTS

Patient Characteristics

A total of 46 patients entered into phase 1. Two patients who were given antipsychotic treatment of psychotic excitation (psychotic agitation or suicidal thoughts) during the first study week were excluded before randomization. Thus, a total of 44 patients entered into phase 2, were randomized, and completed 8 sessions of ECT (Fig. 1). For the study sample (n = 46), 65% were female; the mean (SD) age was 44.5 (11.3) years, which was 12.7 years younger than the mean age reported at the CORE study.[17] It was determined that 17.4% of the patients had psychotic features. The mean (SD) age at illness onset was 34.1 (12.6) years, and the mean number of prior major depressive episodes was 2.8 (1.5) (excluding 6 patients with extremely high number of prior episodes). The MADRS scores at the study entry (phase 1) and at the time of randomization (phase 2) were 38.4 (7.7) and 18.9 (8.9), respectively, considering the whole study population. Except the presence of melancholic features and historical ECT exposure, no statistically significant difference was observed between the treatment groups in demographic or clinical variables (Table 1).

Treatment Effects

Of the ITT sample of 44 patients, 72.7% responded to treatment after 8 sessions of ECT. The response rates in the c-pharm early, c-pharm late, and c-pharm placebo groups were 50% (8/16), 90% (18/20), and 75% (6/8), respectively ($\chi^2_{df=2} = 7.2$, $P = 0.03$). Post hoc comparisons revealed that there was a difference between the c-pharm late and c-pharm early groups with respect to response rates ($\chi^2_{df=1} = 7.09$, $P = 0.008$).

The responders (N = 32) were followed up for the occurrence of relapse. The relapse rates were 12.5% (1/8) in the c-pharm early group, 28% (5/18) in the c-pharm late group, and 67% (4/6) in the c-pharm placebo group ($\chi^2_{df=2} = 4.9$, $P = 0.09$). Post hoc comparisons showed that the relapse rate in the c-pharm early group was significantly lower than the c-pharm placebo group ($\chi^2_{df=1} = 4.4$, $P = 0.04$), whereas the difference between the c-pharm late versus the placebo group failed to reach significance ($\chi^2_{df=1} = 2.9$, $P = 0.09$). The estimated mean (SE) of the mean (SEM) time to relapse of 14 (2) weeks for the c-pharm early group was significantly longer than that of 6.33 (3.2) weeks for the c-pharm placebo group ($\chi^2_{df=1} = 4.09$; $P = 0.04$, for the log-rank). Although, it did not reach the statistical significance level, the estimated mean (SEM) time to relapse of 12.3 (1.5) weeks for c-pharm late group was longer than the c-pharm placebo group ($\chi^2_{df=1} = 3.56$; $P = 0.06$, for the log-rank). In addition, when the trend with the initiation of c-pharm intervention was investigated in the 3 groups (not started, started late, and started early), with equally spaced trend weights, the time of initiation was found to have a significant effect on the probability of remaining well ($\chi^2_{df=2} = 4.6$; $P = 0.03$, for trend with log-rank; Fig. 2).

The ITT assessments of changes in symptom ratings indicated statistically significant differences between the treatment groups per week of trial. Patients randomized to c-pharm early and c-pharm late experienced a mean (SD) decrease of

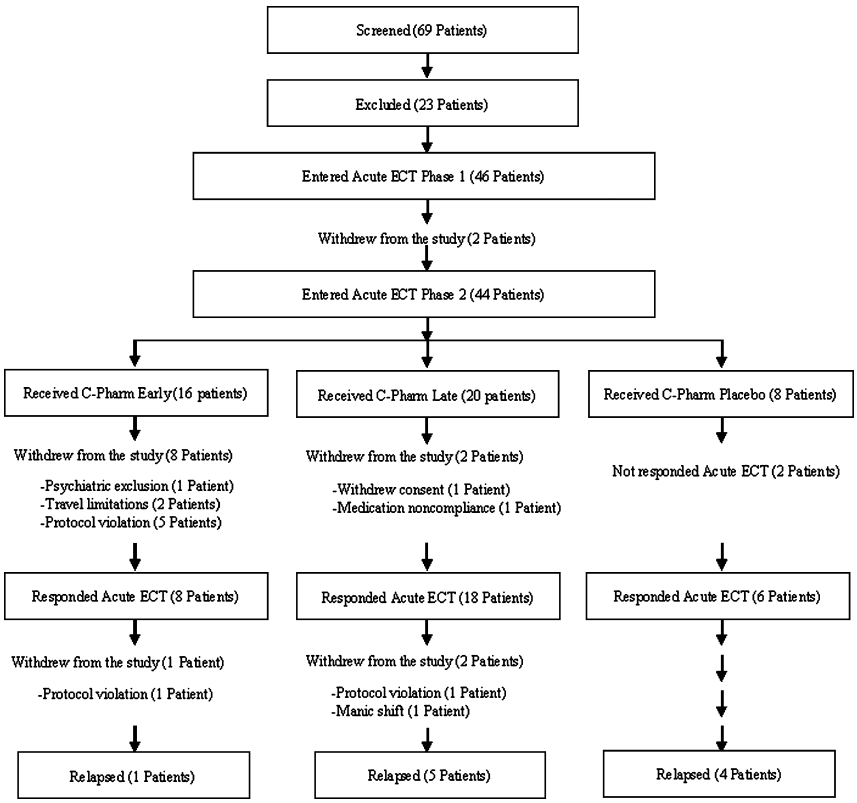

FIGURE 1. Flow of study subjects with *DSM-IV* unipolar depressive states from entry to completion of 20-week randomized double-blind trial of c-pharm early versus c-pharm late versus c-pharm placebo.

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TABLE 1. Characteristics of Subjects Randomized to C-Pharm Early Versus C-Pharm Late Versus C-Pharm Placebo Groups

Characteristics	C-Pharm Early (n = 16)	C-Pharm Late (n = 20)	C-Pharm Placebo (n = 8)	*P*
Age, median (range), yr				
At randomization	46.0 (25–60)	47.5 (25–64)	39.0 (25–54)	0.40
At onset of illness	33.0 (16–58)	31.0 (21–60)	24.0 (18–42)	0.17
Prior episodes/subject, median (range)*	3 (1–4)	2 (1–7)	3.5 (2–6)	0.39
Sex, n (%)				
Women	9 (56.3)	14 (70)	5 (62.5)	0.69
Men	7 (43.8)	6 (30)	3 (37.5)	
Current episode, n (%)				
Depression	12 (75)	17 (85)	8 (100)	0.28
Psychotic depression	4 (25)	3 (15)	0 (0)	
Current episode, n (%)				
Melancholic features	11 (68.8)	18 (90)	4 (50)	0.07†
No melancholic features	5 (31.3)	2 (10)	4 (50)	
Education, n (%)				
Lower than high school	10 (62.5)	8 (40)	3 (37.5)	0.33
High school or higher	6 (37.5)	12 (60)	5 (62.5)	
Marital status, n (%)				
Married	15 (93.8)	18 (90)	6 (75)	0.38
Single	1 (6.3)	2 (10)	2 (25)	
Comorbid diagnosis, n (%)				
Axis I	5 (31.3)	5 (25)	3 (37.5)	0.79
Axis II	2 (12.5)	2 (10)	1 (12.5)	0.97
Medication resistance, n (%)				
≥1 antidepressant	6 (37.5)	7 (35)	5 (62.5)	0.29
≥2 antidepressant	6 (37.5)	8 (40)	1 (12.5)	
Drugs used in pretrial month, n (%)				
Antidepressant	13 (81.3)	15 (75)	5 (62.5)	0.61
Antipsychotic	8 (50)	6 (30)	1 (12.5)	0.16
≥2 psychotropics	11 (68.8)	9 (45)	3 (37.5)	0.24
Treatment history life-long, n (%)				
Prior ECT	5 (31.3)	1 (5)	0 (0)	0.03†
Prior hospitalization	8 (50)	5 (25)	4 (50)	0.24
Pretrial treatment status				
Medication-free days, median (range)‡	4 (1–30)	5 (2–35)	5 (2–365)	0.11

*Six patients (5 randomized to the c-pharm early group and 1 to the c-pharm late group) were excluded for lack of reliable counts of previous episodes of illness.

†Statistically significant at $\alpha = 0.10$ level.

‡Previously untreated patients were excluded (1 in the c-pharm early group and 4 in the c-pharm late group). Statistics are based on the ANOVA for continuous variables and contingency tables for categorical measures.

−0.64 (0.14) and −0.31 (0.11) MADRS points per week, respectively, whereas among the placebo-treated subjects, the ratings increased slightly by 0.17 (0.17) MADRS points ($P = 0.006$; Table 2). Pairwise comparisons of changes in symptom ratings for the randomized ITT sample yielded a trend for more effective intervention with c-pharm early than with c-pharm late ($P = 0.068$; Table 2). When this analysis was restricted to responders only (N = 32), which was evaluated at the fourth study week, each active treatment strategy was found superior to placebo for symptom improvements per week (Table 2).

Of the 44 patients who entered phase 2 and were randomized, 8 patients (18.1%) from the c-pharm early and 2 patients (4.5%) from the c-pharm late group withdrew from the study. In the c-pharm placebo group, 2 patients (4.5%) did not respond to ECT. Among the 32 responders, 1 patient (3.1%) from the c-pharm early group and 2 patients (4.5%) from the c-pharm late group withdrew from the study. The reasons for the dropouts are presented in Figure 1.

The relapse rates of the patients who completed the study were 14.3% (1/7) for the c-pharm early group (95% confidence interval [CI], 16–27), 31.3% (5/16) for the c-pharm late group (95% CI, 14.2–47.8), and 66.7% (4/6) for the c-pharm placebo group (95% CI, 50–84). The overall relapse rate was 34.5% (10/29). The pre-ECT and prerandomization MADRS scores did not have a significant effect on the event of relapse ($t_{df = 29.5} = 1.51$, $P = 0.143$ and $t_{df = 30} = 0.283$, $P = 0.779$, respectively). Likewise, the patients who relapsed (7.9 [3.9]) did not differ from the patients who did not relapse (7.6 [3.0]) regarding the post-ECT MADRS scores ($t_{df = 30} = -0.21$, $P = 0.84$). The GAF scores of all the 3 study groups increased significantly at the end point compared with the baseline without any significant group differences ($F_{df = 2} = 1.325$, $P = 0.277$).

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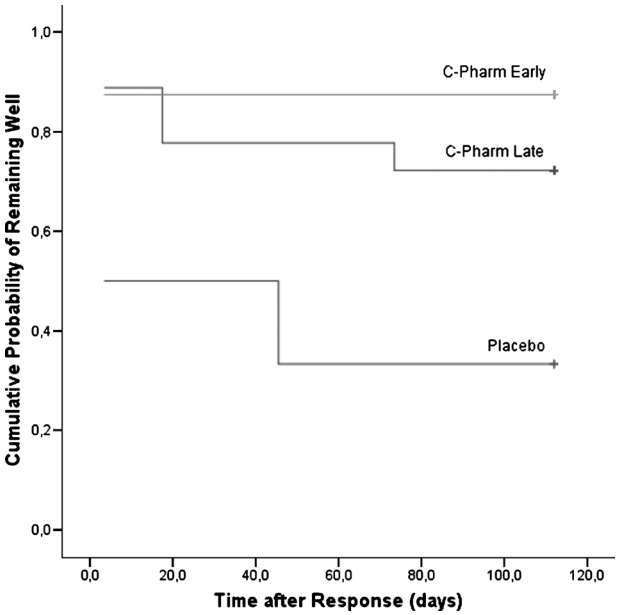

FIGURE 2. Kaplan-Meier survival estimates (n = 32). Kaplan-Meier survival analyses comparing each active treatment condition with placebo in time to relapse yielded a statistically significant effect for c-pharm early ($\chi^2 = 4.1$; $P = 0.04$, for log-rank) but only an observed clinically significant difference for c-pharm late ($\chi^2 = 3.6$; $P = 0.06$, for log-rank). In addition, when the trend with the initiation of c-pharm intervention was investigated in the 3 groups (not started, started late, and started early), with equally spaced trend weights, the time of initiation was found to have a significant effect on the probability of remaining well ($\chi^2 = 4.6$; $P = 0.03$, for trend with log-rank).

Potential Predictors of Relapse

Relapse rates were similar in women (30.4%, 7/23) and men (33.3%, 3/9; $\chi^2_{df=1} = 0.03$, $P = 0.874$).

In the ITT sample, 70.5% (31/44) of the patients had failed to respond to at least 1 and 34.1% (15/44) had failed to respond to 2 or more adequate antidepressant trials. Prior medication resistance was found to have no apparent effect on post-ECT response ($\chi^2_{df=1} = 0.111$, $P = 0.736$). Fifteen percent (5/32) of the responders and 16.7% (2/12) of the nonresponders had psychotic features during the current episode ($\chi^2_{df=1} = 0.07$, $P = 0.933$). Neither the initial response to ECT (71.4% [5/7] vs 73% [27/37]) nor the occurrence of relapse (4% [2/5] vs 29.6% [8/27]) was significantly different in the patients with and those without psychotic features ($\chi^2_{df=1} = 0.07$, $P = 0.933$ and $\chi^2_{df=1} = 0.211$, $P = 0.646$, respectively]. Seventy-five percent of both the study sample (33/44) and the responder sample (24/32) had melancholic features. Among the responders, 37.5% (9/24) of the patients with and 12.5% (1/8) of those without melancholic features relapsed ($\chi^2_{df=1} = 1.745$, $P = 0.186$). Overall, 29.5% (13/44) and 11.4% (5/44) of the patients had comorbid axis I and II diagnosis, respectively. Among the 32 responders, 10 patients had comorbid axis I diagnoses and 3 had axis II diagnoses. A total of 71.4% (5/7) versus 20% (5/25) of the patients with and those without comorbid Axis I diagnoses, respectively, relapsed ($\chi^2_{df=1} = 6.732$, $P = 0.009$). The Cox regression analyses investigating the effect of medication resistance after adjustment with other variables found axis I comorbidity and psychosis as significant variables (Table 3). Because of the small number of events, multivariate effects could only be analyzed by combining the c-pharm early and late groups, where c-pharm therapy remains an important predictor of remaining well (3.6 times protective effect; $P = 0.058$; 95% CI, 0.96–13.5) after adjustment for the presence of axis I comorbidity and psychosis.

TABLE 2. Change per Week in the MADRS Scores

	Change per Week in MADRS Scores, Mean (SEM)	
	After Randomization (All Patients, N)	**After the Fourth Week (Responders, n_R)**
Placebo ($N/n_R = 8/6$)	0.17 (0.17)	0.29 (0.16)
C-pharm early ($N/n_R = 16/8$)	−0.64 (0.14)	−0.23 (0.13)
C-pharm late ($N/n_R = 20/18$)	−0.31 (0.11)	−0.08 (0.09)
P	0.006*†	0.052‡

*C-pharm early versus placebo: $t_{168} = 3.64$, $P < 0.001$; c-pharm late versus placebo: $t_{173} = 2.34$, $P = 0.020$; c-pharm early versus c-pharm late: $t_{172} = 1.84$, $P = 0.068$.

†Statistically significant at $\alpha = 0.10$ level.

‡C-pharm early versus placebo: $t_{86} = 2.45$, $P = 0.016$; c-pharm late versus placebo: $t_{87} = 1.95$, $P = 0.053$; c-pharm early versus c-pharm late: $t_{84} = 0.93$, $P = 0.35$.

TABLE 3. Cox Regression Analyses Investigating the Effect of Medical Resistance After Adjustment for Other Variables

					95% CI Hazards Ratio	
	Wald	***df***	***P***	**Hazards Ratio**	**Lower**	**Upper**
Medical resistance	1.89	1	0.169	4.42	0.53	36.73
Melancholic	1.70	1	0.192	4.27	0.48	37.79
Psychosis	3.22	1	0.073*	0.21	0.04	1.16
Sex (male vs female)	1.61	1	0.205	0.37	0.08	1.71
MADRS (baseline)	0.91	1	0.341	1.06	0.94	1.20
MADRS (post-ECT)	0.01	1	0.912	1.00	0.93	1.08
Axis I comorbidity	8.33	1	0.004*	8.87	2.01	39.05

*Statistically significant at $\alpha = 0.10$ level.

Suicidal Thoughts

This section considers the change in expressed suicidal thoughts, as recorded in item 10 of the MADRS.[24] Thirty of the 46 patients (65.2%) reported suicidal thoughts and acts (score of 3–4 or more) at baseline. Scores decreased to 0 in 56.5% (26/46) at the completion of ECT. Among 4 patients who still had suicidal thoughts and acts at the end of the eighth ECT session, 3 were in the c-pharm early group (3/16) and 1 was in the c-pharm late (1/20) group ($\chi^2_{df=1} = 1.702$, $P = 0.192$).

Adverse Events

Possible adverse effects were reported by 8 (50%) of 16 patients in the c-pharm early group, 7 (35%) of 20 patients in the c-pharm late group, and no patients in the placebo group ($\chi^2_{df=2} = 5.948$, $P = 0.051$). Possible adverse effects reported were increase in anxiety, nausea, vomiting, diarrhea, excessive

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sweating, palpitation, metallic taste, loss of appetite, headache, decrease in libido, tremor, muscle cramps, and dryness of mouth. One patient in the c-pharm late group developed a manic shift in the 16th study week. The shift was considered to be drug induced because it occurred in the 11th week of a new antidepressant treatment. Six patients in the c-pharm early group, 6 patients in the c-pharm late group, and 1 patient in the placebo group reported potential adverse effects related to ECT ($\chi^2_{df=2} = 1.605$, $P = 0.448$), including poor memory, amnesia, confusion, dysarthria, ataxia, headache, nausea, tinnitus, agitation, disorganization, and urinary incontinence. Comparable drug- and ECT-related adverse events were seen in the c-pharm early and (62.5%; 10/16) and late (45%; 9/20) groups ($\chi^2_{df=1} = 1.092$, $P = 0.296$).

DISCUSSION

This is the preliminary report of a double-blind placebo-controlled trial assessing the feasibility and the efficacy of the c-pharm early strategy, in which antidepressant drug treatment was initiated at the midway point in a course of ECT session as a post-ECT relapse prevention strategy in MDD. This strategy is aimed to provide time for the brain to develop antidepressant drug-induced adaptive mechanisms for protection from depression, such as adaptations in the cyclic adenosine monophosphate transduction cascade, the cyclic adenosine monophosphate response element-binding protein, and the brain-derived neurotrophic factor gene expression.[25] If the findings can be replicated in larger study samples, the concept of continuous protection of brain by virtue of its homeostatic adaptive ability may prove effective in minimizing post-ECT relapse.

Given the small sample size, the results of this study should be interpreted with caution. However, 28% relapse rate in our c-pharm late group was identical to the c-pharm result of a prior review[16] and comparable to the reported relapse rate of 31.6% with lithium-nortriptyline combination.[17] The 14% relapse rate for completers in our c-pharm early group with sertraline (95% CI, 16–27) seems better than the 60% previously reported with nortriptyline (95% CI, 41–79) and the 39.1% with nortriptyline-lithium combination (95% CI, 19–59) by Sackeim et al.[7] In the CORE study, the relapse rate with c-ECT was 37.1%.[17] In 2006, van den Broek et al[26] reported a relapse rate of 18% (2/11) with post-ECT administration of imipramine in the MDD patients. In a prospective, randomized, triple-blind, multisite study with 155 ECT remitters, McCall et al[27] found no difference between the post-ECT relapse rates of 4 study groups; 2 were given venlafaxine or nortriptyline throughout and after ECT sessions, whereas the other 2 were given these treatments only after termination of ECT. In the previously mentioned study, post-ECT relapse rates have been reported to exceed 50% in all the 4 treatment conditions.[27] Although our preliminary finding of 12.5% relapse rate with the c-pharm early strategy in a small group of patients in this pilot study requires to be confirmed in studies with larger sample size, it is the lowest relapse rate reported to date, as to our knowledge. Furthermore, the mean (SEM) time to relapse of 14 (2) weeks in our c-pharm early group seems superior to the 9.1 (7.0) weeks reported with c-ECT and the 6.7 (4.6) weeks with c-pharm in the CORE study.[17]

The fixed application of 8 ECT sessions in this study might have limited the number of responders. Nonetheless, the 73% response rate observed in this study is well within the range of previous reports.[3,4] Besides, clinical observations indicate that patients who benefit from ECT often do so during the early courses rather than the later ones.[4]

Although not significantly different, the 4% versus 30% relapse rate observed in this study for psychotic versus nonpsychotic MDD patients, respectively, at 4 months is consistent with the 11% versus 59% relapse rates reported by Birkenhager et al.[28] Although inconsistent, there are reports of an association between higher relapse rates and treatment resistance.[3,6,29,30] In this study, the clinical indication for ECT was determined as in daily clinical practice. A recent naturalistic chart review conducted at the study center (DEU inpatient unit) found an overall ECT application rate of 16.4%; 55.4% of the ECT-treated patients had a diagnosis of unipolar and 10.7% had a diagnosis of bipolar depression.[31] This is comparable to the recently reported 10% rate of ECT administration in US hospitals for recurrent depression.[12] Severity of depression in this study population was indicated by the 70.5% rate of medication resistance, the 65.2% rate of baseline suicidal thoughts and acts, and the mean baseline depression score of 64% of the maximum MADRS score.

Simultaneous application of sertraline with ECT might have influenced response and/or relapse rates by indirect molecular mechanisms or changing the seizure expression in some way. However, among the available antidepressant medications, selective serotonin reuptake inhibitors (SSRIs) would be expected to have minimum effect in that sense. Moreover, our protocol was a priori setting of seizure duration to 20 seconds or longer for all patients. Controlled systematic evaluation of SSRIs in prevention of post-ECT relapse is limited with a study where an SSRI was coadministered with ECT, with a relapse rate of 10% at 6 months.[32] The preliminary findings of this study provide further evidence of the efficacy of SSRIs in prevention of relapse after successful ECT and suggest the administration of SSRIs in the few weeks before cessation of the ECT sessions.

Limitations

The important limitation of the present study is the small sample size resulting in shortage of statistical power to detect significance between the 2 active treatment arms, leaving potential for type 2 error. Our study duration of 20 weeks including phase 1 and postrandomization phase 2 may be shorter than needed for evaluating occurrence of post-ECT relapse. Nevertheless, previous reports, including the CORE study, indicate occurrence of post-ECT relapses within 2 to 4 months.[7,12,17]

Unstratified randomization for presence of psychosis, melancholic features, medication resistance, and especially previous ECT courses in this study is a shortcoming that needs to be considered in future trials. It is difficult to draw a conclusion about whether the coadministration of sertraline or fortuitous inclusion of more patients who had previous ECT decreased the efficacy of ECT in the c-pharm early group. However, when the patients who withdrew from the study were not taken into consideration, the response rates in the c-pharm early and c-pharm late groups were similar.

The actual comparison groups of c-pharm early, late, and placebo not resulting from a randomization process may be considered as a limitation. In this trial, randomization was performed at the initiation of the SSRI, and ECT sessions were fixed at 8 bilateral applications. The fixed application of ECT sessions in this study might have limited the number of responders. However, with an individualized flexible ECT schema where ECT is generally terminated once the patient responds, randomized double-blind incorporation of the c-pharm early arm would not be possible. If we had started randomization at the time of response, we would need to continue ECT sessions for another 2 weeks. This would result in application of 4 extra

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ECT sessions under general anesthesia, which would be ethically unjustifiable, yet still confounding results would be obtained for post-ECT relapse rates because of the unequal number of ECT applications in the study groups.

Besides the small sample size and the unstratified randomization, the use of high-dose benzodiazepines, the lack of biochemical analysis that would confirm medication compliance, the lack of assessment of the integrity of the study blinding, the relatively high dropout rates, and the low response rates in the c-pharm early group in the ITT analysis should be taken into consideration in interpreting the results of the present study.

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