Imipramine Is Effective in Preventing Relapse in Electroconvulsive Therapy–Responsive Depressed Inpatients With Prior Pharmacotherapy Treatment Failure: A Randomized, Placebo-Controlled Trial

Walter W. van den Broek, M.D., Ph.D.; Tom K. Birkenhäger, M.D., Ph.D.; Paul G. H. Mulder, Ph.D.; Jan A. Bruijn, M.D., Ph.D.; and Peter Moleman, Ph.D.

Objective: To compare the efficacy of imipramine versus placebo in preventing relapse after successful electroconvulsive therapy (ECT) in depressive inpatients with pharmacotherapy treatment failure prior to ECT.

Method: During a 6-month period, the incidence of relapse was assessed. Two centers, both inpatient units for treatment of depressed patients, participated in this trial. Patients with DSM-IV–diagnosed major depressive disorder resistant to an antidepressant and subsequent lithium addition and/or a monoamine oxidase inhibitor were included. Patients were randomly assigned to double-blind treatment with imipramine with adequate plasma levels (N = 12) or placebo (N = 15) after successful ECT. The mean imipramine dosage was 209 mg/day (standard deviation: 91.7, range: 75–325 mg/day). The main outcome measure was relapse defined as at least "moderately worse" compared with baseline score on the Clinical Global Impressions-Improvement scale. Treatments were compared with survival analysis using the Cox proportional hazards model, including psychotic features and the score on the Hamilton Rating Scale for Depression (HAM-D) at baseline as prespecified covariables. Patients were enrolled in the study from April 1997 to July 2001.

Results: In the placebo group, 80% (12/15) of the patients relapsed compared with 18% (2/11) in the imipramine group. The Cox regression analysis showed a significant reduction in the risk of relapse of 85.6% with imipramine compared to placebo (p = .007; 95% confidence interval [CI] = 24.6% to 97.2%) adjusted for the covariables. There was an 18% increase in the relapse rate (p = .032; 95% CI = 2% to 36%) per unit increase in HAM-D score before the start of the trial; psychotic features had no significant effect (p = .794).

Conclusions: Depressed patients with pharmacotherapy treatment failure may benefit from the prophylactic effect of the same class of drug during maintenance therapy after response to ECT.

(J Clin Psychiatry 2006;67:263–268)

Received May 26, 2005; accepted Aug. 15, 2005. From the Departments of Psychiatry (Drs. van den Broek, Birkenhäger, and Bruijn) and Biostatistics and Epidemiology (Dr. Mulder), Erasmus Medical Centre, Rotterdam; and Moleman Psychopharmacology, Amerongen (Dr. Moleman), the Netherlands.

This study was supported by an unconditional grant from Psychiatric Hospital Parnassia, The Hague, the Netherlands.

Dr. Moleman has been an employee of Eli Lilly and Wyeth; has served as a consultant to Pfizer and Solvay Duphar; has received grant/research support from Lundbeck and AstraZeneca; has received honoraria from Boehringer Ingelheim and Bristol-Myers Squibb; has served on the speakers or advisory boards of GlaxoSmithKline and ICN; is a stock shareholder of Janssen and Synthon; and has received other material support from Organon. Drs. van den Broek, Birkenhäger, Mulder, and Bruijn report no other significant commercial relationships relevant to the study.

We thank the pharmacy department of the Erasmus Medical Centre for the preparation of the medication, determination of the plasma levels, and assistance in dosing the antidepressants.

Corresponding author and reprints: Walter W. van den Broek, M.D., P.O. Box 2040, 3000 CA Rotterdam, the Netherlands (e-mail: w.w.vandenbroek@erasmusmc.nl).

Although electroconvulsive therapy (ECT) is a very effective treatment for patients with a severe depressive episode or a depressive episode with pharmacotherapy treatment failure, a major problem is the high relapse rate after termination of ECT.[1]

Treatment with an antidepressant to prevent relapse is now standard, but controlled studies suggest limited success.[1] Moreover, relapse prevention may be particularly poor in patients with pharmacotherapy treatment failure prior to ECT.[1] None of the currently available studies, however, recruited exclusively medication-resistant patients.[1–6]

This double-blind study in patients responsive to ECT after treatment with an antidepressant, lithium addition, and/or a monoamine oxidase inhibitor (MAOI) had failed investigates the effect of imipramine versus placebo on relapse prevention during a 6-month period.

METHOD

The study was performed at the Department of Psychiatry of the Erasmus Medical Centre (Erasmus MC) in

Rotterdam, the Netherlands, and at Parnassia Psychomedical centre in The Hague, the Netherlands. Both inpatient units treat therapy-resistant depressed patients besides treating uncomplicated depressed patients. Patients were enrolled in the study from April 1997 to July 2001.

Included in the study were 27 patients aged 18 to 65 years who had a DSM-IV diagnosis of major depressive disorder (DSM-IV codes 296.2 and 296.3).[7] Eleven of these patients were recruited from a trial in which 6 patients were treated with imipramine with adequate plasma levels during 4 weeks (the predefined blood level for imipramine plus its metabolite, desipramine, was 200–300 ng/mL) and 5 patients were treated with high doses of fluvoxamine (225–350 mg/day),[8] with both groups receiving subsequent lithium addition.[9] Nonresponders had lithium added to the continued double-blind antidepressant. Final evaluation of response was made 3 weeks after the attainment of target lithium level (0.6–1.0 mmol/L). Eight patients were also treated with an MAOI prior to ECT.

Five patients were recruited from a trial in which treatment consisted of a tricyclic antidepressant (TCA) with adequate plasma levels during 4 weeks followed by treatment with either phenelzine or tranylcypromine.[10] Three patients also had lithium treatment prior to ECT. Treatment with 1 of the MAOIs was started at a daily dose of 20 mg, divided into 2 equal dosages given at 8:00 a.m. and 8:00 p.m. After 3, 7, 10, and 14 days, the daily doses could be increased to 40, 60, 80, and 100 mg, respectively, in case of insufficient response (Hamilton Rating Scale for Depression [HAM-D][11] score reduction by less than 50%). The study had a double-blind, flexible-dose design with comparison after 5 weeks.

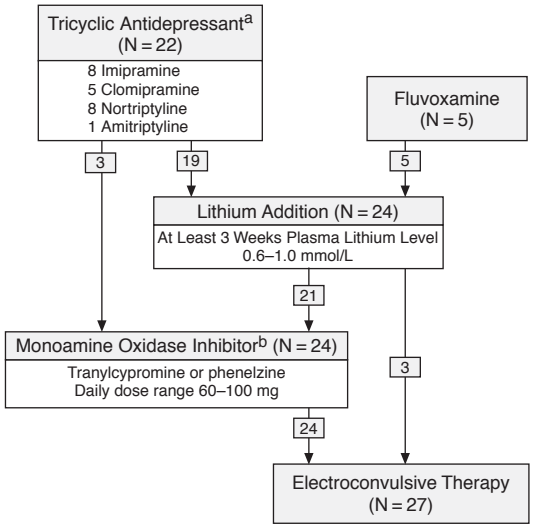
The remaining 11 patients were treated with a TCA with adequate plasma levels of the drugs plus their metabolites (plasma imipramine levels, 200–300 ng/mL for imipramine + desipramine; plasma nortriptyline levels, 50–150 ng/mL; plasma clomipramine levels, 200–300 ng/mL for clomipramine + desmethylclomipramine; and plasma amitriptyline levels, 200–300 ng/mL for amitriptyline + nortriptyline) (10 with lithium addition), and all were treated with an MAOI.

Figure 1 and Table 1 show the medication used by all patients included in this trial before ECT during the index episode.

The diagnosis of major depressive disorder was assessed by W.W.vdB., J.A.B., or T.K.B. after a drug-free period of at least 5 days using the depression part of the Schedule for Affective Disorders and Schizophrenia.[12]

Excluded were patients with schizophrenia, bipolar or schizoaffective disorder, organic brain syndrome, chronic alcohol or drug abuse, or presence of an absolute contraindication for imipramine; pregnancy or the risk to become pregnant; or treatment with ECT during the current episode. To enter the relapse prevention trial, patients had to respond to ECT with at least a 50% reduction in the score on the 17-item HAM-D relative to pre-ECT baseline, with a maximum score of 16 both within 2 days after ECT and at a reassessment 1 week after discontinuation of ECT. All patients were free of psychotropic medication during the post-ECT week.

Figure 1. Flow Chart of the Pretreatment Before ECT for the 27 Patients With Major Depressive Disorder Participating in the Follow-Up Trial



[a] Tricyclic antidepressant with at least 4 weeks of adequate plasma levels of the drugs and their metabolites; imipramine (plasma levels, 200–300 ng/mL for imipramine + desipramine), nortriptyline (plasma levels, 50–150 ng/mL), clomipramine (plasma levels, 200–300 ng/mL for clomipramine + desmethylclomipramine), and amitriptyline (plasma levels, 200–300 ng/mL for amitriptyline + nortriptyline).

[b] An irreversible monoamine oxidase inhibitor (tranylcypromine or phenelzine) was taken for at least 4 weeks at the dose range mentioned.

The Ethics Committee of the Erasmus MC, Rotterdam, approved the protocol. The protocol was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki. After complete description of the study to the subjects, written informed consent was obtained both before ECT and in the relapse prevention phase.

Electroconvulsive therapy was administered with a brief pulse, constant current apparatus (Thymatron DGx, Somatics, Inc., Lake Bluff, Ill.). Seizure threshold was determined during the first session with stimulus titration.

For right unilateral treatment, the dosage at the subsequent treatment exceeded the initial threshold by at least 250%, and for bilateral treatment by 150%. 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.

Table 1. Data on Randomized Treatment After ECT, Relapse, and Pretreatment Before ECT

Patient	Randomized Treatment After ECT	Relapse?	Pharmacotherapy Before ECT			
			TCA[a]	Fluvoxamine, mg/d	Lithium Addition[b]	MAOI[c] dose, mg
1	Placebo	+	Imipramine		+	90
2	Placebo	+		300	+	100
3	Placebo	+		350	+	60
4	Placebo	+	Imipramine		+	60
5	Placebo	–	Imipramine		+	None
6	Placebo	+	Imipramine		+	60
7	Placebo	+	Clomipramine		–	100
8	Placebo	–	Clomipramine		+	100
9	Placebo	–	Clomipramine		+	100
10	Placebo	+	Clomipramine		+	70
11	Placebo	+	Nortriptyline		+	80
12	Placebo	+	Clomipramine		+	60
13	Placebo	+	Imipramine		+	90
14	Placebo	+	Nortriptyline		+	100
15	Placebo	+	Nortriptyline		+	100
16	Imipramine	Dropout		300	+	100
17	Imipramine	–	Imipramine		+	None
18	Imipramine	–		300	+	100
19	Imipramine	–	Imipramine		+	80
20	Imipramine	+	Imipramine		+	80
21	Imipramine	–		225	+	None
22	Imipramine	–	Nortriptyline		+	80
23	Imipramine	–	Nortriptyline		–	100
24	Imipramine	–	Nortriptyline		–	80
25	Imipramine	+	Nortriptyline		+	100
26	Imipramine	–	Amitriptyline		+	80
27	Imipramine	–	Nortriptyline		+	80

[a]Tricyclic antidepressant with at least 4 weeks of adequate plasma levels of the drugs and their metabolites; imipramine (plasma levels, 200–300 ng/mL for imipramine + desipramine), nortriptyline (plasma levels, 50–150 ng/mL), clomipramine (plasma levels, 200–300 ng/mL for clomipramine + desmethylclomipramine), and amitriptyline (plasma levels, 200–300 ng/mL for amitriptyline + nortriptyline).
[b]Lithium addition with at least 3 weeks of plasma lithium level 0.6–1.0 mmol/L.
[c]An irreversible MAOI (tranylcypromine or phenelzine) was taken during at least 4 weeks at the dosage mentioned.
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.
Symbols: + = yes, – = no.

Anesthesia was achieved during the ECT sessions with intravenous administration of metoclopramide 10 mg and glycopyrrolate 0.002–0.003 mg/kg, then a bolus injection of alfentanil 0.010–0.015 mg/kg and etomidate 0.2–0.3 mg/kg, followed by succinylcholine 0.5–1.0 mg/kg.[13]

Patients were treated twice weekly, and clinical evaluation of treatment was performed each week using the HAM-D and Clinical Global Impressions-Improvement scale (CGI-I).[14] Patients were withdrawn from medication before ECT and were maintained medication free during the course of ECT; in case of severe agitation, pro re nata use of haloperidol was allowed.

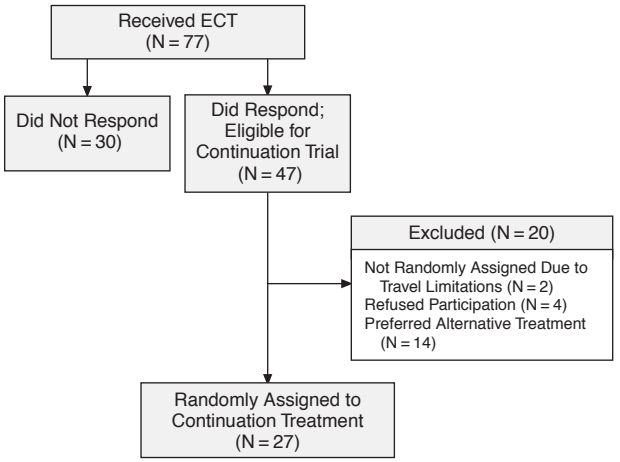
Responders to ECT were then randomly assigned to placebo (N = 15) or imipramine (N = 12). Tablets identical in appearance, weight, and taste containing either imipramine or placebo were administered once a day at 10 p.m., starting with 75 mg. The pharmacist randomized from a random number table. After 2 days, the dose was doubled unless severe side effects were observed. Blood levels were monitored once a week by the pharmaceutical laboratory of the Erasmus MC until discharge from hospital when the patients had a steady dosage and blood level. The hospital pharmacist advised on the dosage on the basis of the targeted blood level according to a predefined dosage table for imipramine and a variable dosing table for the placebo. In order to prevent unblinding, the blood level was communicated to the treating physician in percentages of the target. The treating physicians were not involved in the ratings of this study. The predefined blood level for imipramine + desipramine was 200 to 300 ng/mL (100% = 250 ng/mL).

After inclusion, patients were evaluated every 4 weeks for 6 months by W.W.vdB. and T.K.B., who were blind to the treatment condition. At each visit, the HAM-D and CGI-I were completed.

During the entire study period (1997–2001), interrater sessions with the investigating psychiatrists took place 6 times a year. The sum of all HAM-D items of the 3 research psychiatrists was used to test interrater reliability (kappa = 0.95).

Because relapse rates of 50% with placebo and 20% with imipramine were assumed, the goal was to enroll at least 37 patients in each randomized condition to have

Figure 2. Participant Flow of Patients With Major Depressive Disorder Eligible for Electroconvulsive Therapy (ECT) After Failed Pharmacotherapy



at least an 80% probability of detecting a significant difference.

Relapse was defined as at least "moderately worse" compared with baseline according to the CGI-I. We preferred the CGI-I because the experienced clinician's global judgment for relapse is the most reliable (compared with the HAM-D and MADRS).[15]

The HAM-D score was not included in the definition of relapse since the HAM-D score is a weak index of depression severity; a clear definition of relapse has not been validated with the HAM-D in contrast to the definition of response or remission, and the HAM-D has several alternative versions.[15]

The efficacy of both treatments was compared with survival analysis using the Cox proportional hazards model with duration of treatment until relapse as the survival time variable. An event was scored the first time a patient met the relapse criterion. Dropouts without relapse were censored at the time of dropout. Patients without relapse were censored at the end of the trial. The following prespecified covariables were included along with treatment: psychotic features and HAM-D score at the start of the trial. Statistical significance was defined at $p < .05$ (2-sided); p values were calculated using the likelihood ratio test. Data were analyzed using SPSS version 10 for Windows (SPSS, Inc.; Chicago, Ill.).

RESULTS

After a drug-free period, 77 patients were eligible for ECT. From the 47 patients who responded to ECT, 27 were randomly assigned to treatment with imipramine or placebo (Figure 2); the characteristics of these patients are summarized in Table 2.

Table 2. Characteristics of Patients With Major Depressive Disorder Randomly Assigned to Continuation Treatment Groups After Successful ECT

Characteristic	Placebo (N = 15)	Imipramine (N = 12)
Age, mean (range), y	51.5 (36–64)	51.3 (36–60)
Women, N (%)	10 (71)	10 (83)
Psychotic features, N (%)	4 (27)	5 (42)
Pre-ECT HAM-D score, mean ± SD	28.6 ± 6.4	27.1 ± 6.5
Post-ECT HAM-D score, mean ± SD	5.9 ± 3.8	4.9 ± 2.5
Episode duration < 1 year, N	4	5

Abbreviations: ECT = electroconvulsive therapy, HAM-D = Hamilton Rating Scale for Depression.

Seven of the 27 randomly assigned patients (26%) had been treated with unilateral electrode placement; all others had been started on (N = 13, 48%) or switched to (N = 7, 26%) bilateral ECT. The mean number of treatments was 12.5. None of the patients had previously been treated with ECT. In 1 patient, the benzodiazepine was not discontinued; 2 patients received haloperidol during ECT. None of the responders relapsed in the first week after completion of the ECT course.

One patient in the imipramine group refused further participation immediately after randomization. The mean imipramine dosage was 209 mg/day (standard deviation: 91.7, range: 75–325 mg/day) during follow-up.

In the placebo group, 12 (80%) of 15 patients relapsed compared with 2 (18%) of 11 in the imipramine group ($p = .004$, Fisher exact test, 2-sided; relapse was defined as at least "moderately worse" compared with baseline according to the CGI-I). The Cox regression analysis showed a significant reduction in the risk of relapse of 85.6% with imipramine compared to placebo ($p = .007$; 95% confidence interval [CI] = 24.6% to 97.2%) adjusted for the covariables. There was an 18% increase in the relapse rate ($p = .032$; 95% CI = 2% to 36%) per unit increase in HAM-D score before the start of the trial; psychotic features had no significant effect ($p = .794$). Analysis after removal of the 5 patients pretreated with fluvoxamine showed a similar reduction in relapse rate of 80.3% ($p = .033$). Hamilton Rating Scale for Depression scores at continuation trial entry and endpoint are shown in Table 3.

DISCUSSION

Imipramine prevented relapse after successful ECT. This is surprising, since all our patients were treated unsuccessfully with an antidepressant (22/27 with a TCA) and 24 of the 27 patients were subsequently treated with lithium addition and the remaining 3 patients with an MAOI before ECT treatment. In total, 21 of the 27 patients were treated with an antidepressant, lithium addition, and an MAOI before ECT (Figure 1).

Five patients were not pretreated with a TCA drug, which theoretically could explain the efficacy of imipra-

Table 3. Hamilton Rating Scale for Depression (HAM-D) Scores at Baseline and Endpoint for Patients With Major Depressive Disorder Randomly Assigned to Imipramine or Placebo for Relapse Prevention After Successful Electroconvulsive Therapy

Treatment Group	HAM-D Score at Baseline, Mean (SD)	HAM-D Score at Endpoint, Mean (SD)
Placebo (N = 15)	5.9 (3.81)	14.7 (9.69)
Imipramine (N = 11)	4.9 (2.53)	8.0 (9.21)

mine in the preventive phase. However, analysis of the results when omitting the patients treated with fluvoxamine showed a similar efficacy of imipramine in preventing relapse.

Imipramine prevented relapse after ECT in patients not responsive to a TCA in the acute phase and, in addition, not responsive to lithium addition and/or an MAOI.

During the inclusion of patients in our trial, results of another placebo-controlled trial by Sackeim et al. were published.[5] Nortriptyline was significantly more efficacious for relapse prevention (60% relapse) compared to placebo (84% relapse), with the combination of nortriptyline and lithium being even more effective (39% relapse) in that trial.[5] It is surprising that the relapse rate with nortriptyline plus lithium in their trial appears to be higher than the relapse rate with imipramine alone in the present trial, particularly because the Sackeim et al. sample had been treated less rigorously during the acute episode. However, different relapse criteria could explain the difference in outcome.[5] The sensitive relapse criteria in the Sackeim and colleagues study[5] could have accounted for the high rate of relapse. Relapse was defined as a mean score of at least 16 on the HAM-D 24-item version that was maintained over at least 2 consecutive visits (1 week) and a mean absolute increase of 10 points at 2 consecutive visits relative to continuation trial baseline.[5] Another difference exists in study population. Our patients were ECT naive; none of our patients had been treated with ECT during an earlier episode compared to 40% to 50% of patients in this recent study. Their study[5] also included mostly women with an average age of around 50 years, and a third or more patients were diagnosed with a depressive disorder with psychotic features; these characteristics are comparable to the characteristics of patients in our trial (Table 2).

In the present study, the risk of relapse was significantly higher for patients with a higher HAM-D score at baseline; this result is in agreement with the findings of Sackeim et al.[1,5] This higher relapse risk emphasizes the need for rigorous treatment with ECT. Maximal symptomatic improvement with ECT can diminish the chance of relapse.

Another follow-up trial[6] compared paroxetine with imipramine and placebo after successful ECT. Medication was started before ECT; patients were allocated to the placebo versus paroxetine group if there was a contraindication for the use of imipramine (N = 87). Patients knew to which group they were assigned (placebo vs. paroxetine or paroxetine vs. imipramine). After the last ECT treatment, both the HAM-D and Melancholia Scale scores were significantly lower in the group of patients treated with ECT plus imipramine. Patients who had responded to ECT (HAM-D score of < 13) were admitted to the continuation therapy (N = 74). Relapse was defined as a HAM-D score of > 17 and/or a Melancholia Scale score of > 14 on 2 occasions with an interval of 1 week. The survival curves for paroxetine and placebo differed significantly only after 3 months; this significant difference disappeared after 6 months. The survival curves for paroxetine and imipramine differed significantly after 3 and 6 months in favor of paroxetine; the authors conclude that paroxetine is superior to imipramine in preventing relapse. The relapse rate in the continuation phase was high with placebo (65%), and lower with imipramine (30%), but lowest with paroxetine (10%). In the paroxetine versus imipramine group, more than 50% were pretreated with a TCA before inclusion in the study; in the paroxetine versus placebo group, this rate was 16% to 35%. The imipramine dose and plasma levels were suboptimal in this trial; this could account for the difference in relapse prevention with imipramine between this trial and ours, and, also, this trial used different relapse criteria.[6]

The most important limitation of the present study is probably the small study population, which restricts the generalizability of the results. Replication of this study in a larger population would help address this problem. However, this replication seems unfeasible because we would need to include a large group of patients into a rigorously controlled treatment protocol for unipolar depression before reaching the stage to be treated with ECT. Owing to this limitation, we could not include 37 patients in each treatment group as estimated with the previously mentioned power analysis.

With respect to generalizability, it is important to be aware that our patients were ECT naive and were treated with an antidepressant (mostly a TCA) with adequate plasma levels for 4 weeks, lithium addition, and/or an MAOI prior to ECT. Depression was (moderately) severe; about 30% of the patients were psychotic, and, in about 60%, the duration of the depression was longer than 1 year.

The fact that a TCA was not effective in the acute phase, but did prevent relapse, seems to have implications for the mechanism of action of imipramine and similar antidepressants. If both actions have to be explained by the same (pharmacologic) mechanism of action, the prevention of relapse would imply that the state of the brain in the patients responding to ECT has been changed such that it became susceptible to the action of a TCA after ECT treatment. The state of the brain after response to ECT provides interesting ideas for future research.

For clinical practice, the present results imply that preventive treatment with imipramine with blood level control should be applied after successful ECT.

Drug names: alfentanil (Alfenta and others), clomipramine (Anafranil and others), etomidate (Amidate and others), glycopyrrolate (Robinul and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), metoclopramide (Reglan and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), succinylcholine (Quelicin, Anectine, and others), tranylcypromine (Parnate).

REFERENCES

1. Sackeim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 1990;10:96–104
2. Seager CP, Bird RL. Imipramine with electrical treatment in depression: a controlled trial. J Ment Sci 1962;108:704–707
3. Imlah N, Ryan E, Harrington J. The influence of antidepressant drugs on the response to electroconvulsive therapy and on subsequent relapse rates. Neuropsychopharmacology 1965;4:438–442
4. Kay DW, Fahy T, Garside RF. A seven-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. Br J Psychiatry 1970;117:667–671
5. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001;285:1299–1307
6. Lauritzen L, Odgaard K, Clemmesen L, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. Acta Psychiatr Scand 1996;94:241–251
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
8. van den Broek WW, Birkenhäger TK, Mulder PGH, et al. A double-blind randomized study comparing imipramine with fluvoxamine in depressed inpatients. Psychopharmacology (Berl) 2004;175:481–486
9. Birkenhäger TK, van den Broek WW, Mulder PG, et al. Comparison of two-phase treatment with imipramine or fluvoxamine, both followed by lithium addition, in inpatients with major depressive disorder. Am J Psychiatry 2004;161:2060–2065
10. Birkenhäger TK, van den Broek WW, Mulder PG, et al. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. J Clin Psychiatry 2004;65:1505–1510
11. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
12. Spitzer RL, Endicott J. Schedule for Affective Disorders and Schizophrenia (SADS), Third Edition. New York, NY: Biometric Research, New York State Psychiatric Institute; 1978
13. van den Broek WW, de Lely A, Mulder PGH, et al. Effect of antidepressant medication resistance on short-term response to electroconvulsive therapy. J Clin Psychopharmacol 2004;24:400–403
14. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
15. Mulder RT, Joyce PR, Frampton C. Relationships among measures of treatment outcome in depressed patients. J Affect Disord 2003;76:127–135

