Efficacy of ECT in Depression:
A Meta-Analytic Review

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This study analyzed the efficacy of electroconvulsive therapy (ECT) in depression by means a meta-analytic review of randomized controlled trials that compared ECT with simulated ECT or placebo or antidepressant drugs and by a complementary meta-analytic review of nonrandomized controlled trials that compared ECT with antidepressants drugs. The review revealed a significant superiority of ECT in all comparisons: ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants in general, ECT versus TCAs and ECT versus MAOIs. The nonrandomized controlled trials also revealed a significant statistical difference in favor of ECT when confronted with antidepressants drugs. Data analyzed suggest that ECT is a valid therapeutic tool for treatment of depression, including severe and resistant forms.

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A clinical reappraisal of electroconvulsive therapy (ECT) was conducted over the last decade after the observation that a proportion comprised between 20% and 40% of either unipolar or bipolar depressions did not respond satisfactorily to antidepressants (1, 2), despite the availability of more effective competitors for treatment of depression, like the selective serotonin reuptake inhibitors (SSRIs). An estimate of ECT efficacy can be obtained through the meta-analytic method that combines information from independent studies. Meta-analyses can use dichotomous or continuous data, with each type of data presenting advantages and disadvantages (3). Meta-analytic reviews that use continuous data produce reliable standardized weight mean differences, however, a decrease in a psychiatric scale does not necessarily means a clinical remission. A dichotomous measure, such as clinical response or no response, has a considerable advantage over derived statistical parameters because it employs raw data from each individual patients, allowing to know, for example, patients' proportions which achieve response with ECT in comparison other therapeutic tools. The objective of our study was to analyze the efficacy of ECT in depression by means a meta-analytic review of controlled clinical trials published between 1956 and 2003, using dichotomous data.

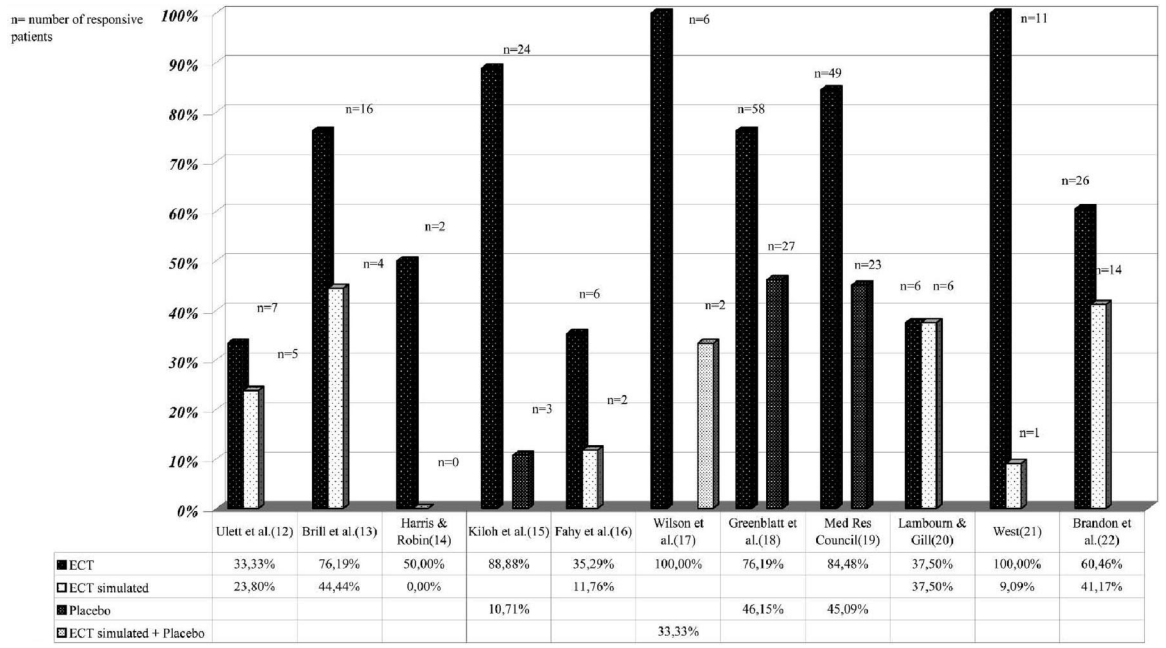
Method

This study reviews, by means of a MEDLINE search procedure using the key words electroconvulsive therapy and depression, all peer-reviewed publications in English from January 1966 to February 2003. We also manually searched articles published prior to 1966 that might be relevant for our purpose. Among these studies, we selected those comparing ECT with simulated ECT, or placebo or antidepressants drugs. ECT trials conducted without comparison group were excluded from our analyses. Selected studies were classified and separated in nonrandomized controlled trials and randomized controlled trials.

Like Janicak et al, (4) we used the studies in which it was possible to individualize each patient's response to treatment, using author's own criterion of response or no response. Basically, the response criterion was defined either as a reduction of at least 50% from baseline to end point on the Hamilton Scale for Depression (HAM-D) or a HAM-D score of 10 or less at the end point or a clinical judgment of "recovered" or "marked improved" depending on which of these 3 outcome measures were used. The category of "moderately improved" was not considered as a response criterion in this review. The diagnostic categories were major depression, bipolar disorder depressed type, schizoaffective disorder depressive type, and other categorizations such as neurotic depression, reactive depression, endogenous depression, involutional depression, primary depression and secondary depression. Only those studies in which we could directly determine each patient's response to treatment were included in the meta-analysis. Therefore, some randomized controlled trials were excluded because they did not reveal the results of patients individually (5–10).

The software used for the meta-analysis was the

Figure 1. Responsive Rate of ECT, ECT Simulated and Placebo in Randomized Controlled Trials



	Ulett et al.(12)	Brill et al.(13)	Harris & Robin(14)	Kiloh et al.(15)	Fahy et al.(16)	Wilson et al.(17)	Greenblatt et al.(18)	Med Res Council(19)	Lambourn & Gill(20)	West(21)	Brandon et al.(22)
ECT	33,33%	76,19%	50,00%	88,88%	35,29%	100,00%	76,19%	84,48%	37,50%	100,00%	60,46%
ECT simulated	23,80%	44,44%	0,00%		11,76%				37,50%	9,09%	41,17%
Placebo				10,71%			46,15%	45,09%			
ECT simulated + Placebo						33,33%					

EasyMA 2001 of the Department of Clinical Pharmacology, Cardiology Hospital, University of Lyon (France) (11). The selected summary statistic and statistical method to our dichotomous end point, response or not response to the treatments, was respectively the odds ratio and the random effect model. The odds ratio has statistical advantages relating to its sampling distribution and its suitability for modeling. The random effects model assumes a different underlying effect for each study and takes this into consideration as an additional source of variation. In the random model, the test of heterogeneity applied was the Cochran Q-test with the objective to examine statistically the degree of similarity in the studies' outcomes. If a test of heterogeneity between trials is statistically significant ($P < 0.05$) then it may not be appropriate to combine the results.

RESULTS

REAL ECT VERSUS PLACEBO EFFECT (SIMULATED ECT OR PLACEBO)

Initially, we did not distinguish the studies that compared the ECT with the simulated ECT and

Table 1. Randomized Controlled Trials of ECT Versus Placebo Effect

Trial	D	Var	W(%)	OR	[OR-	-OR]
Ulett et al (12)	0.454	0.460	0.11	1.575	0.417	5.953
Brill et al (13)	1.341	0.678	0.09	3.824	0.761	19.204
Harris and Robin (14)	2.833	5.124	0.02	17.000	0.201	1437.8
Kiloh et al (15)	4.060	0.696	0.09	57.970	11.293	297.58
Fahy et al (16)	1.326	0.759	0.08	3.765	0.683	20.773
Greenblatt et al (18)	1.034	0.188	0.14	3.684	1.574	8.622
Med Research Council (19)	1.867	0.207	0.14	6.469	2.653	15.778
Lambourn and Gill (20)	0.000	0.515	0.10	1.000	0.245	4.084
West (21)	4.456	1.993	0.05	86.100	5.409	1370.5
Brandon et al (22)	0.771	0.216	0.14	2.162	0.870	5.374

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, Odds ratio.

Table 2. Randomized Controlled Trials of ECT Versus Simulated ECT

Trial	D	Var	W(%)	OR	[OR-	-OR]
Ulett et al (12)	0.454	0.460	0.19	1.575	0.417	5.933
Brill et al (13)	1.341	0.678	0.15	3.824	0.761	19.204
Harris and Robin (14)	2.833	5.124	0.03	17.000	0.201	1437.8
Fahy et al (16)	1.326	0.759	0.14	3.765	0.683	20.773
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Brandon et al (22)	0.771	0.216	0.26	2.162	0.870	5.374

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, odds ratio.

placebo itself (pill), constituting a comparison group denominated placebo effect. As shown in Figure 1, 11 randomized controlled trials were used in the comparison between real ECT and placebo effect (simulated ECT/placebo), involving a total number of 523 patients, with a mean number of 48 patients by trial. A discrepancy in sample sizes among studies was found, with the largest trial involving 109 patients and the smallest 8 patients.

Data from these studies that compared the efficacy of real ECT and placebo effect (Table 1), at the end of the treatment's course, revealed a significant better response of the real ECT (association $\chi^2 = 19.76$, df = 1, $P < 0.001$). The Q Cochran test of heterogeneity revealed that the null hypothesis of homogeneity between these studies is valid ($\chi^2 = 12.13$, df = 10, $P = 0.28$). The probability, in terms of odds ratios (OR), of a positive response with ECT is approximately 5 more times greater than with simulated ECT or placebo (OR 4.77; 95% CI 2.39, 9.49).

Considering the hypothesis that simulated ECT had a greater placebo effect than placebo (pill), due to a possible larger effect of the preparation process to ECT, we separated the comparisons between, respectively, real ECT versus simulated ECT and real ECT versus placebo. Seven randomized controlled trials (Table 2) with a total number of 245 subjects were suitable for meta-analysis of ECT versus simulated ECT and show a significantly greater effect of ECT as compared with simulated ECT (association $\chi^2 = 6.87$, df = 1, $P = 0.0087$). The heterogeneity (Q Cochran) between these 7 studies was not statistically significant ($\chi^2 = 7.35$, df = 6, $P = 0.29$). The chance of response with ECT when compared with simulated ECT is approximately 3 (OR 2.83; CI 95% 1.30, 6.17) more times greater than with simulated ECT.

Only 3 randomized controlled trials (Table 3), involving a total number of 266 patients, made possible a comparison between ECT versus placebo. This comparison revealed a significant more favorable outcome in the ECT group (association $\chi^2 = 13.68$, df = 1, $P < 0.001$). The Q Cochran test revealed no significant statistical heterogeneity between these 3 studies ($\chi^2 = 2.71$, df = 2, $P = 0.26$) and the odds ratio suggested a treatment response chance of approximately 11 (OR 11.083; CI 95% 3.10, 39.65) in favor of ECT when compared with placebo. One trial compared real ECT with simulated ECT plus placebo (pill) (17).

ECT VERSUS ANTIDEPRESSANTS

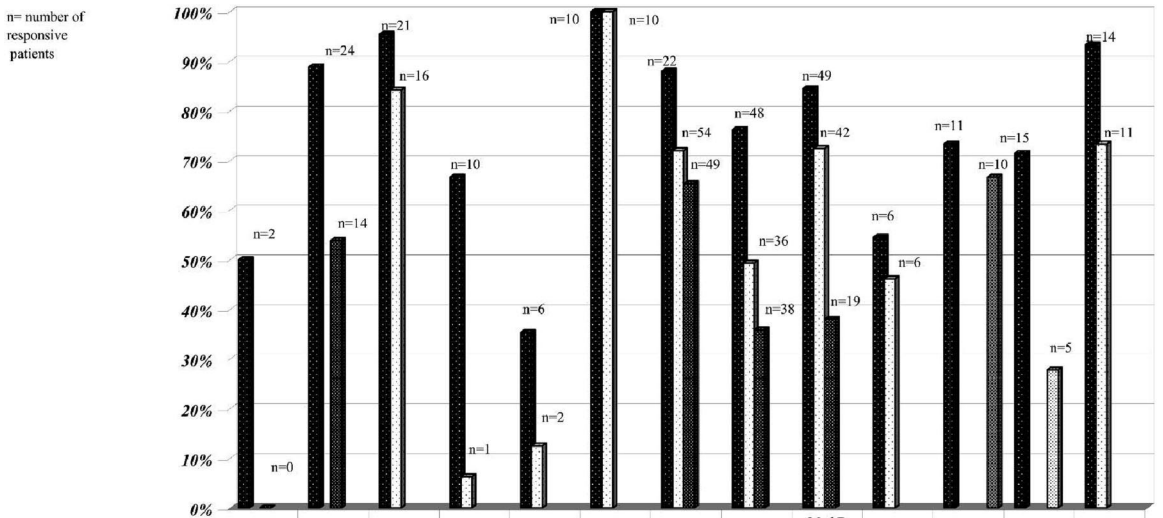
In a first analysis we compared the ECT with the group of antidepressants in an indistinctive manner, including tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOIs), lithium, and SSRIs. This comparison involved 13 randomized controlled trials, with a total number of 892 patients and a mean number of 69 patients for trial; the biggest trial used 242 subjects and the smallest trial involved 8 patients. Of these, 3 studies included 2 comparison groups each of which was an-

Table 3. Randomized Controlled Trials of ECT Versus Placebo

Trial	D	Var	W(%)	OR	[OR-	-OR]
Kiloh et al (15)	4.200	0.748	0.26	66.667	12.229	363.42
Greenblatt et al (18)	1.317	0.191	0.37	3.733	1.586	8.778
Med Research Council (19)	1.891	0.211	0.37	6.628	2.695	16.300

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, odds ratio.

Figure 2. Responsive Rate of ECT and Antidepressants in Nonrandomized Controlled Trials.



	Harris & Robin(14)	Kiloh et al.(15)	Bruce et al.(24)	Robin & Harris (25)	Fahy et al.(16)	Wilson et al.(17)	Huntchinson(23)	Green blatt et al.(18)	Med R Council (19)	Gangadahar(26)	Dinan & Barry(27)	Folkerts et al.(28)	Janakiramaiah (29)
ECT	50,00%	88,88%	95,45%	66,66%	35,29%	100,00%	88,00%	76,19%	84,48%	54,54%	73,33%	71,42%	93,33%
TCA			84,21%	6,25%	12,50%	100,00%	72,00%	49,31%	72,41%	46,15%			73,33%
MAOI	0,00%	53,86%					65,33%	35,84%	38,00%				
SSRI												27,77%	
Lithium + TCA											66,66%		

alyzed separately (18, 19, 23). Therefore, we had 9 trials comparing ECT versus TCA (531 patients), 5 trials ECT versus MAOIs (438 patients), 1 trial of ECT versus SSRIs (39 subjects), and 1 trial of ECT versus the combination lithium-TCA (30 patients; Figure 2).

Overall, the comparison of ECT versus antidepressants in general demonstrated a significant superior effect of ECT (association $\chi^2 = 51.88$, df = 1, $P < 0.001$). The test of heterogeneity (Q Cochran) demonstrated the homogeneity between these studies ($\chi^2 = 11.45$, df = 12, $P = 0.49$). The chance of response with ECT was about 4 times greater than with the antidepressant drugs (OR 3.72; CI 95% 2.60, 5.32; Table 4).

Table 4. Nonrandomized Controlled Trials of ECT Versus Antidepressants

Trial	D	Var	W(%)	OR	[OR-	-OR]
Bruce et al (24)	1.224	1.216	0.03	3.400	0.391	29.542
Harris and Robin (14)	2.833	5.124	0.01	17.000	0.201	1437.8
Kiloh et al (15)	1.859	0.501	0.07	6.414	1.602	25.681
Robin and Harris (25)	3.170	1.154	0.03	23.819	2.901	195.60
Fahy et al (16)	0.174	0.528	0.06	1.190	0.286	4.949
Wilson et al (17)	0.000	2.211	0.02	1.000	0.054	18.443
Huntchinson et al (23)	1.142	0.383	0.09	3.133	0.931	10.549
Greenblatt et al (18)	1.501	0.109	0.30	4.485	2.346	8.574
Med Research Council (19)	1.413	0.166	0.20	4.107	1.848	9.127
Gangdahar et al (26)	0.323	0.648	0.05	1.381	0.285	6.695
Dinan and Barry (27)	0.304	0.612	0.05	1.356	0.292	6.286
Folkerts et al (28)	1.818	0.492	0.07	6.158	1.558	24.341
Janakiramaiah et al (29)	1.460	1.194	0.03	4.307	0.505	36.694

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, odds ratio.

Table 5. Randomized Controlled Trials of ECT Versus TCA

Trial	D	Var	W(%)	OR	[OR-	-OR]
Bruce et al (24)	1.371	1.443	0.04	3.938	0.374	41.506
Robin and Harris (25)	3.401	1.367	0.04	30.000	3.033	296.77
Fahy et al (16)	1.340	0.829	0.06	3.818	0.641	22.753
Wilson et al (17)	0.000	4.211	0.01	1.000	0.018	55.849
Huntchinson et al (23)	1.048	0.445	0.12	2.852	0.771	10.545
Greenblatt (18)	1.191	0.142	0.37	3.289	1.570	6.890
Med Research Council (19)	0.730	0.218	0.24	2.074	0.831	5.178
Gangadahar et al (26)	0.336	0.676	0.08	1.400	0.279	7.018
Janakiramaiah et al (29)	1.627	1.412	0.04	5.091	0.495	52.312

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, odds ratio.

Separated comparisons between, respectively, ECT and TCA and between ECT and MAOIs were also performed. The analysis of ECT trials versus TCA trials revealed a significant greater efficacy of ECT than TCAs (association $\chi^2 = 22.81$, df = 1, $P < 0.001$). The Q Cochran test of heterogeneity between the trials was not significant ($\chi^2 = 6.04$, df = 8, $P = 0.64$). Patients receiving real ECT had nearly 3 more chance of a positive response than a patient that used TCA (OR 2.99; 95% CI 1.91, 4.71; Table 5).

As compared with MAOIs, the ECT showed a significant greater efficacy (association $\chi^2 = 56.55$, df = 1, $P < 0.001$) and the likelihood of a positive response with ECT was approximately 6 greater than with MAOIs (OR 6.13; 95% CI 3.82, 9.83; Table 6). A statistical homogeneity was present between the studies of this subgroup [heterogeneity χ^2 (Q Cochran) = 1.47, df = 4, $P = 0.83$].

ECT versus Antidepressants in Nonrandomized Controlled Trials

We also made a systematic review of the nonrandomized controlled trials that compared ECT versus antidepressants. Seven nonrandomized controlled trials were used in this meta-analysis, revealing a large total number of patients (n = 2275) and a large mean number of patients by trial (n = 325; Figure 3).

Two nonrandomized controlled trials compared ECT with imipramine (30, 31) and the other 5 studies compared ECT with various antidepressants (TCA and MAOIs) in adequate doses. These studies confirmed the superiority of ECT in comparison with antidepressants even in clinical settings (association $\chi^2 = 26.77$, df = 1, $P < 0.001$), with a similar common odds ratio (OR 2.84) and statistical homogeneity between the trials [heterogeneity χ^2 (Q Cochran) = 7.77, df = 6, $P = 0.26$; Table 7]. The nonrandomized controlled trials results fell within the confidence interval of the randomized controlled trials (95% CI 1.91, 4.21).

Discussion

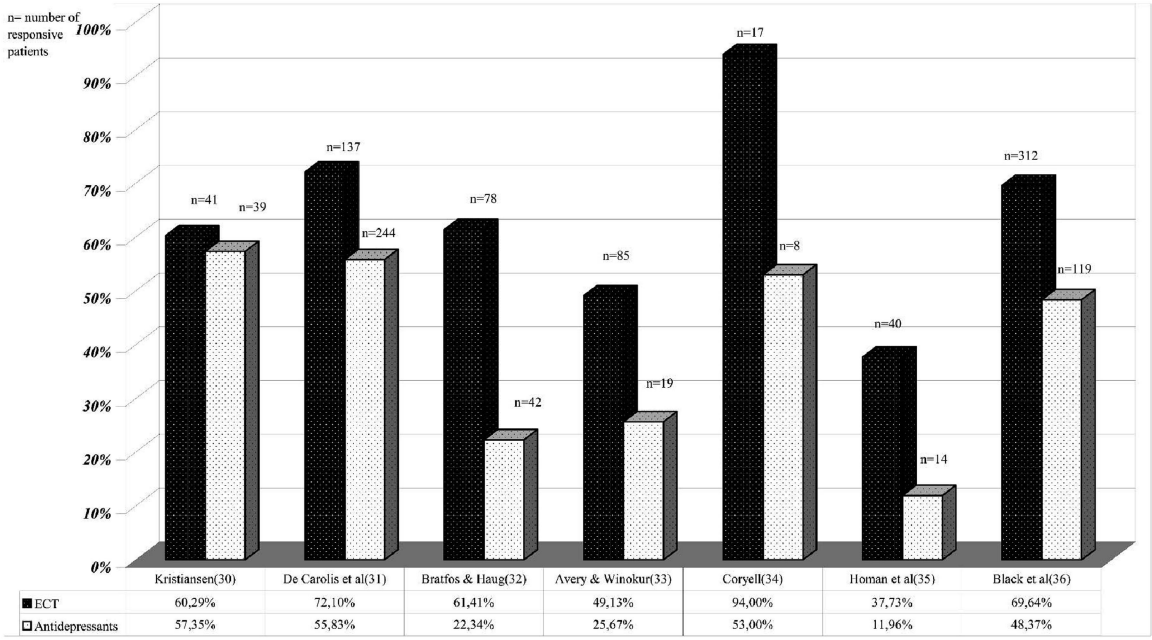
In the present meta-analysis, as compared with the recent review of The UK ECT Review Group, (37) we used a different statistical strategy identifying each patient's response to treatment. Depressive symptoms were assessed by a dichotomous end point. Furthermore, we adopted more stringent criteria than those used by Janicak et al. (4). In fact, we considered as responsive only those patients who

Table 6. Randomized Controlled Trials of ECT Versus MAOI

Trial	D	Var	W(%)	OR	[OR-	-OR]
Harris and Robin (14)	2.833	5.124	0.01	17.000	0.201	1437.8
Kiloh et al (15)	1.859	0.501	0.12	6.414	1.602	25.681
Huntchinson et al (23)	1.294	0.411	0.14	3.649	1.038	12.824
Greenblatt (18)	1.731	0.127	0.46	5.645	2.807	11.356
Med Research Council (19)	2.157	0.212	0.27	8.643	3.502	21.332

D, size of the treatment effect; Var, variance of d; W%, relative weight as a percentage; OR, odds ratio.

Figure 3. Responsive Rate of ECT and Antidepressants in Randomized Controlled Trials.



presented "marked improvement" or "recovery," whereas we excluded from the analyses those who were reported to have "moderate improvement." Additionally, we conducted a large meta-analysis of observational studies that compared ECT versus antidepressants, which included 2272 patients.

RANDOMIZED AND NONRANDOMIZED CONTROLLED TRIALS

The results of our meta-analytic review of the randomized controlled trials revealed a significant superiority of the ECT in all comparisons: ECT versus placebo effect, ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants, ECT versus TCA and ECT versus MAOIs. Additionally, the meta-analysis of the observational studies that compared ECT versus antidepressants presented similar results, reinforcing the assumption that systematic reviews of observational studies and randomized controlled trials usually produce similar conclusions (38). The fundamental criticism toward observational studies is that they have inherent biases. On the other hand, the approach that includes only randomized controlled trials not always ensures relevancy in the reviews even though it minimizes biases (39).

Inside the group of randomized controlled trials we increased the relevancy of the meta-analysis combining all anti-depressants in a single group and the simulated ECT and the placebo itself (pill) in another group.

Table 7. Randomized Controlled Trials of ECT Versus Antidepressants

Trial	D	Var	W(%)	OR	[OR	-OR]
Kristianscn (30)	0.121	0.122	0.14	1.129	0.570	2.237
De Carolis et al (31)	0.715	0.035	0.19	2.045	1.414	2.957
Bratfos and Haug (32)	1.711	0.064	0.17	5.534	3.371	9.082
Avery and Winokur (33)	1.028	0.094	0.15	2.796	1.533	5.099
Coryell (34)	2.700	1.327	0.03	14.875	1.555	142.26
Homan et al (35)	1.495	0.121	0.14	4.459	2.253	8.825
Black et al (36)	0.895	0.027	0.20	2.448	1.776	3.376

D, size of the treatment effect; Var, variance of D; W%, relative weight as a percentage; OR, odds ratio.

However, more specific comparisons between ECT versus other treatments taken singly (TCA, MAOIs, simulated ECT, placebo itself), even with minor relevancy, revealed significantly greater chance of treatment response with ECT as compared with MAOIs, placebo and, to a less extent, TCA. The larger effect of simulated ECT as compared with placebo (pill) suggested that the process of ECT preparation might have a greater impact on patient's outcome than placebo itself; however, definitive conclusions cannot be obtained because only 3 studies comprised a group of patients treated with placebo (pill).

Since 1985, few controlled trials compared the ECT with others treatments or placebo. The only study that compared ECT versus SSRIs in patients with treatment resistant depression showed a significant higher response rate of ECT (28). Nevertheless, more studies with larger samples are needed to confirm the superiority of ECT over SSRIs in general for the treatment of resistant depression. No studies, to our knowledge, compared ECT with other classes of antidepressants (SNRI, NASSA, NRI).

LIMITATIONS

Some limitations inherent the meta-analytic method must be acknowledged: problems in the randomization processes used in controlled trials, publication biases, variation of standard treatments over time and heterogeneity of studies (39,40). Second, ECT studies were in general heterogeneous for multiple aspects. For example, we did not take into account possible variations in the ECT techniques and procedures adopted in the various studies. In fact, most studies did not specify electrical parameters and type of equipment adopted. Furthermore, we did not discriminate between studies using unilateral ECT from those using bilateral ECT.

The reason why we did not distinguish between unilateral and bilateral ECT stays in some controversies regarding which of the 2 techniques is most efficient method of electrical induction of the ECT (41–43). Some studies pointed out that the efficacy of unilateral ECT is simply a question of adequate dosage levels; with high-dose unilateral ECT and bilateral ECT present equivalents response rate, with the advantage that unilateral ECT produces less anterograde and retrograde memory deficits (44–49).

Another consideration regarding the variation of standard treatments is the use of traditional ECT (constant-voltage modified sine-wave stimuli) or modern ECT (constant current brief-pulse). The physiological efficiency of the brief-pulse device is more optimal than the sine wave, but comparisons between the traditional sine-wave ECT and the bilateral suprathreshold modern ECT revealed that the clinical improvement were virtually identical for the 2 methods (50–52).

Another caveat for interpreting data on ECT, regards the diagnostic heterogeneity of samples used in the various studies, which included diagnoses such as neurotic depression (22, 31, 53), depression with psychotic symptoms (20, 22), melancholic depression (29), treatment-resistant major depression (28), and schizoaffective disorders, depressed type (33–36). There are contradictions in the analysis of the association of specific symptom profiles with ECT outcome. Early observational studies found that endogenous or melancholic depression were predictive of greater response to ECT than "neurotic depression"; however, subsequent trials did not reveal a difference in ECT response between patients with versus without melancholia (54). A combined analysis of randomized controlled trials of ECT versus simulated ECT showed that real ECT had a therapeutic advantage, specifically among patients with delusions and/or retardation (55). Nevertheless, in 2 randomized controlled trials, involving 143 patients, Sobin et al (56) investigated the utility of depression subtypes in predicting ECT response and concluded that ECT is a treatment option for patients with major depression regardless of the presence of psychotic features, retardation and/or agitation. More responsible of the variation of results among studies on ECT can be, respectively, the different instruments used to measure the reduction of the depressive symptoms, the difficulties to maintain some research team blind to this therapeutic method, the number of ECT sessions applied and the methodological weakness of some studies that did not specify the electrical parameters of the bilateral ECT and/or unilateral ECT. Moreover, the proportion of patients who previously failed adequate antidepressant medication trials could impact on rates of response to ECT (57–59).

CONCLUSION

In conclusion, by this meta-analysis we tried to analyze systematically available scientific information on ECT trials to provide a reliable estimate of ECT efficacy for depression. Data analyzed suggest that ECT is a valid therapeutic tool in the armamentarium for depression, including severe and resistant forms. Future studies are needed to clarify whether and when such an intervention can be a first choice treatment of some patients.

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