Efficacy and Safety of Electroconvulsive Therapy in the Treatment of Bipolar Disorder

A Systematic Review

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Objectives: To evaluate the efficacy and safety of electroconvulsive therapy (ECT) in bipolar disorder (BPD).

Methods: Clinical trials on the treatment of BPD with ECT were systematically reviewed. A comprehensive search of MEDLINE, PsycINFO, and ISI Web of Science databases was conducted in March 2010.

Results: A total of 51 articles met our selection criteria. Only 3 controlled or comparative prospective trials addressed the treatment of mania with ECT. In these studies, which had small samples, ECT was superior to simulated ECT, lithium, or the combination of lithium and haloperidol. We did not find any controlled or comparative prospective trial on the efficacy of ECT in bipolar depression. In the 4 retrospective studies that compared ECT with antidepressants, no difference was observed between them. In 9 of 10 trials that compared bipolar with unipolar depressed patients, ECT was equally efficacious for both groups of patients. Of the 6 studies of patients with BPD that performed a comparison between pre-ECT versus post-ECT, only 1 study showed a worsening in cognition after the treatment.

Conclusions: There are no studies with adequate methodology on the treatment of BPD with ECT. The lack of scientific evidence contrasts with broad anecdotal clinical experience that suggests that ECT is an important tool in the treatment of BPD, especially in more severe or refractory cases. The marked stigma associated with ECT and the lack of large financial support may account for the paucity of ECT research.

Key Words: bipolar disorder, electroconvulsive therapy, review

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The value of electroconvulsive therapy (ECT) for the treatment of mental disorders in general, and bipolar disorder (BPD) in particular, still remains a controversial issue. Several therapeutic guidelines for BPD suggest that ECT should be applied only in pharmacotherapy-resistant or very severe cases.[1–8] Accordingly, ECT is not included as one of the first treatment options for either the manic or depressive phase of this illness. However, it has also been suggested that ECT is the most efficacious treatment of both mania[4] and bipolar depression.[9]

The major concern about the use of ECT is the risk of adverse cognitive effects.[10] For example, neuropsychological studies have indicated that patients treated with ECT may present both anterograde and retrograde amnesia.[11] Although memory deficits are usually transitory, remitting within a few weeks or months, a small percentage of patients have long-lasting cognitive dysfunction.[11] Few comparative studies have addressed the effect of ECT on depressed patients' cognition. Accordingly, ECT did not induce more cognitive impairment than simulated ECT,[12] repetitive transcranial magnetic stimulation,[13] or amitriptyline[14] but yielded more memory complaints than imipramine.[15] Although most of these studies have not found differences, few of them have been performed with appropriate methodology. So, it is certainly premature to presume that ECT and transcranial magnetic stimulation, for example, have similar cognitive effects. Moreover, most of the patients assessed in these studies had unipolar depression. Therefore, generalization of these conclusions regarding the effect of ECT on memory processes among patients with BPD must be regarded with caution.[10]

Studies that have investigated the efficacy of ECT in depression treatment have been limited primarily to unipolar patients, again limiting the generalization of these findings to bipolar depression.[16] For example, a meta-analysis of randomized controlled trials[17] found that ECT was significantly more efficacious than simulated ECT or antidepressants in the treatment of depression. However, this meta-analysis reviewed studies that enrolled primarily unipolar patients. Surprisingly, there are no review papers that have examined the impact of ECT exclusively on bipolar depression. The only exception is an article published by Valenti et al.[18] However, this study did not conduct a systematic search for references within this area and did not take into consideration the distinction between unipolar and bipolar depression.

The efficacy of ECT in the treatment of mania was addressed in an extensive review by Mukherjee et al.[19] Because this review was published more than 15 years ago, new evidence has appeared in the literature. Therefore, the purpose of the present work was to carry out a comprehensive systematic review of the published data concerning the efficacy and safety of ECT in the treatment of BPD.

METHODS

Clinical trials describing the use of ECT in the treatment of BPD were identified in MEDLINE, PsycINFO, and ISI Web of Science databases. A search was performed up to March 25, 2010 and used the following terms: "ECT", "electroconvulsive therapy", "electroshock", or "convulsive therapy" in combination with "mania", "manic", "bipolar", "bipolar disorder", or "bipolar depression". Only references with abstracts and original articles were considered. Review articles, case reports, letters to the editor, and book chapters were not included. There was no search for unpublished works. Citations within a paper were also included as an additional source of references. Two of the authors (E.C. and J.L.F.) screened all of the abstracts and made a

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TABLE 1. Clinical Trials That Investigated the Efficacy of ECT in Bipolar Mania

Study	Method	Sample and Design	Diagnostic Criteria	ECT Technique	Outcome Measure	Results
Sikdar et al (1994)[22]	Controlled, prospective	ECT + CPZ (n = 15) vs simulated ECT + CPZ (n = 15)	*DSM-III-R*	Bilateral	BR-MRS (score <6)	ECT > simulated ECT (12 vs 1 patients improved)
					BR-MRS (reduction)	ECT > simulated ECT ($P < 0.001$)
Mukherjee (1989)[21]	Comparative, prospective	ECT (n = 22) vs Li + HAL (n = 5) (medication-resistant patients)	*DSM-III-R* and RDC	Bilateral, left unilateral, or right unilateral	No longer meeting RDC for manic episode	ECT (13 patients improved) > Li + HAL (no patient improved) (59% vs 0%, $P < 0.025$)
Small et al (1988)[23]	Comparative, prospective	ECT (+ AP) (n = 17) vs Li (+AP) (n = 17)	*DSM-III*	Bilateral	BR-MRS (reduction)	ECT > Li (94.9% vs 81.2%, $P < 0.05$)
					CGI (reduction)	ECT > Li (64.4% vs 45.9%, $P < 0.05$)
					BPRS (reduction)	ECT = Li (49.6% vs 33.8%, $P > 0.05$)
McCabe (1976)[25]	Controlled, retrospective	ECT (n = 28) vs nontreatment (n = 28) (patients in a mixed state are included in both groups)	Feighner criteria	Bilateral	Mean duration of hospitalization (in weeks)	ECT: shorter than nontreatment (6.5 vs 15.3, $P < 0.001$)
					Nonoperational clinical criteria	ECT > nontreatment (96% vs 44% of the patients improved, $P < 0.0001$)
Schiele and Schneider (1949)[27]	Controlled, retrospective	ECT (n = 16) vs nontreatment (n = 13)	Not informed	Bilateral	Discharge from hospital (number of patients)	ECT (13 patients) = nontreatment (11 patients) (81% vs 85%, $P > 0.05$)
Black et al (1987b)[24]	Comparative, retrospective	ECT (+AP) (n = 37) vs Li (+AP) (n = 203)	*DSM-III* or RDC	Right unilateral (n = 10), bilateral (n = 8), or mixed (n = 19)	Nonoperational clinical criteria	ECT (29 patients improved) > Li (125 patients improved) (78% vs 62%, $P < 0.05$)
Thomas and Reddy (1982)[28]	Comparative, retrospective	ECT (n = 10) vs Li (n = 10) vs CPZ (n = 10)	By the authors	Bilateral	Mean duration of hospitalization (in days)	ECT = Li = CPZ (60.2 vs 66.8 vs 52.0, $P > 0.3$)
					Mean latency for readmission (in days)	ECT = Li = CPZ (1466 vs 414 vs 373, $P > 0.1$)
McCabe and Norris (1977)[26]	Comparative, retrospective	ECT (n = 28) vs CPZ (n = 28)	Feighner criteria	Bilateral	Mean duration of hospitalization (in weeks)	ECT = CPZ (6.5 vs 7.7, $P > 0.05$)
					Nonoperational clinical criteria	ECT = CPZ (96% vs 96% of the patients improved)
Volpe and Tavares (2003)[29]	Comparative retrospective	ECT + medication (n = 141) vs medication (n = 284) (7.5% of the patients were in a mixed state)	*ICD-10*	Not informed	Mean duration of hospitalization (in days)	ECT + medication group: longer than medication group (18.78 vs 12.51, $P < 0.001$)
Ikeji et al (1999)[30]	Noncomparative, prospective	n = 20 (medication-resistant patients)	*DSM-IV* and *ICD-10*	Bilateral	BPRS (reduction)	46.7 vs 24.8 ($P < 0.001$)

Mohan et al (2009)[33]	Noncomparative, prospective	n = 50 (medication-resistant patients)	*DSM-IV*	Bilateral	CGI ≤2	46 patients (92%) improved
Hiremani et al (2008)[32]	Noncomparative, prospective	n = 36	*DSM-IV*	Bilateral (bifrontal or bitemporal)	YMRS (50% reduction)	29 patients (80.6%) improved
Schnur et al (1992)[34]	Noncomparative, prospective	n = 18	*DSM-III-R* and RDC	Bilateral (n = 11), left unilateral (n = 4), or right unilateral (n = 3)	No longer meeting RDC for manic episode	12 patients (67%) improved
Barekatain et al (2008)[31]	Noncomparative, prospective	n = 28	*DSM-IV*	Bilateral (bifrontal or bitemporal)	YMRS (50% reduction)	18 patients (64.3%) improved
Mukherjee and Debsikdar (1992)[38]	Noncomparative, retrospective	n = 30 (patients in their first affective episode)	*ICD-9*	Bilateral	Nonoperational clinical criteria	30 patients (100%) improved
Hemphill (1942)[43]	Noncomparative, retrospective	n = 19	Not informed	Bilateral	Nonoperational clinical criteria	18 patients (95%) improved
Kalinowsky (1943)[44]	Noncomparative, retrospective	n = 32	Not informed	Bilateral	Nonoperational clinical criteria	30 patients (94%) improved
Gralnick (1946)[42]	Noncomparative, retrospective	n = 14	Not informed	Bilateral	Nonoperational clinical criteria	12 patients (86%) improved
Impastato and Almansi (1943)[35]	Noncomparative, retrospective	n = 184	Not informed	Bilateral	Nonoperational clinical criteria	152 patients (83%) improved
Black et al (1986)[48]	Noncomparative, retrospective	n = 37 (chronic or psychotic patients in general)	*DSM-III* or RDC	Right unilateral (n = 10), bilateral (n = 8), or mixed (n = 19)	Nonoperational clinical criteria	29 patients (78%) improved
Kino and Thorpe (1946)[45]	Noncomparative, retrospective	n = 65	Not informed	Bilateral	Nonoperational clinical criteria	51 patients (78%) improved
Smith et al (1943)[47]	Noncomparative, retrospective	n = 30	Not informed	Bilateral	Nonoperational clinical criteria	23 patients (77%) improved
Medlicott (1948)[46]	Noncomparative, retrospective	n = 41	Not informed	Bilateral	Nonoperational clinical criteria	31 patients (76%) improved
Furst and Stouffer (1942)[36]	Noncomparative, retrospective	n = 12	Not informed	Bilateral	Nonoperational clinical criteria	9 patients (75%) improved
Epstein (1943)[41]	Noncomparative, retrospective	n = 13	Not informed	Bilateral	Nonoperational clinical criteria	9 patients (69%) improved
Bianchi and Chiarello (1944)[40]	Noncomparative, retrospective	n = 51	Not informed	Bilateral	Nonoperational clinical criteria	35 patients (69%) improved
Stromgren (1988)[39]	Noncomparative, retrospective	n = 17 (medication refractory patients or patients with very severe mania)	*ICD-9*	Right unilateral (n = 16) or mixed (n = 1)	Nonoperational clinical criteria	10 patients (59%) improved
Alexander et al (1988)[37]	Noncomparative, retrospective	n = 27 (medication refractory patients; 9 schizomanic patients)	*ICD-8* or *ICD-9*	Bilateral	Nonoperational clinical criteria	13 patients (48.1%) improved

AP indicates antipsychotics; BPRS, Brief Psychiatric Rating Scale; BR-MRS, Bech-Rafaelsen Manic Rating Scale; CGI, Clinical Global Impressions scale; CPZ, chlorpromazine; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAL, haloperidol; ICD, International Classification of Diseases; Li, lithium; RDC, Research Diagnostic Criteria; YMRS, Young Mania Rating Scale; >, more efficacious than.

decision concerning the importance of the work. All studies with a sample of at least 10 patients with BPD treated with ECT were selected. For the purpose of the present review, the diagnosis of schizoaffective disorder (bipolar type) was considered a form of BPD, which is coherent with the view that schizoaffective disorder does not represent a distinct nosological entity.[20]

RESULTS

The initial search retrieved 1229 citations in MEDLINE, 692 in PsycINFO, and 594 in ISI Web of Science. A total of 51 articles met our selection criteria. Most of the excluded articles consisted of case reports, review papers, or letters to the editor. Many studies were excluded because they did not address the efficacy or safety of ECT in the treatment of BPD. Some of these studies addressed epidemiological issues concerning ECT, such as the frequency of its prescription in a particular institution, region, country, or period of time. Other excluded studies described the profiles of patients, psychiatrists, or institutions associated with a more frequent use of ECT. Still, other studies were not considered in the present review because they addressed historical, political, or social issues. Finally, a few clinical studies were excluded because the results from BPD patients were not independent from the results of patients with other diagnoses such as schizophrenia or unipolar depression.

For the purpose of the present review, a study was considered "controlled" when ECT was compared with a placebo equivalent, such as simulated ECT, or to any other nontreatment condition (ie, patients were not treated at all). A study was considered "comparative" when ECT was compared with another type of treatment, such as a pharmacologically active substance. Accordingly, "noncomparative" studies evaluated the effect of ECT through a before-after comparison in a single group of subjects.

The Efficacy of ECT in Bipolar Mania

Table 1 presents 28 clinical trials that investigated the efficacy of ECT in bipolar mania. Only 3 controlled or comparative prospective studies were found, all of which had small samples.[21–23] In a double-blind randomized controlled study,[22] in which patients from both groups were taking chlorpromazine, ECT was superior to simulated ECT. Two comparative randomized nonblind studies[21,23] found that ECT was more efficacious than lithium. In one of them,[21] lithium was used in combination with haloperidol. In the other study,[23] some patients from both groups were taking antipsychotics.

In 6 retrospective studies,[24–29] ECT was compared with nontreatment or medications. None of these studies used clinical scales to evaluate patient outcomes. In 2 controlled studies,[25,27] the files of hospitalized patients with mania in the 1940s were reviewed, and the subjects treated with ECT were compared with those not submitted to any kind of treatment. In 1 study,[25] ECT yielded more positive responses than the nontreatment condition, but in the other controlled study,[27] no statistical differences between ECT and nontreatment groups were found.

Two retrospective trials compared ECT with lithium. In one of them,[24] ECT led to a better outcome, whereas in the other,[28] ECT and lithium yielded equivalent clinical benefits. Two retrospective clinical trials with small samples did not find differences in clinical efficacy between ECT and chlorpromazine.[26,28] From 1996 to 2000, Volpe and Tavares[29] reviewed the records of manic inpatients from a Brazilian institution and divided the sample into 2 groups: 1 group consisting of subjects who received both medication and ECT and another group consisting of subjects who took only medication. The first group had a significantly longer hospitalization. The authors concluded that such results were related to a delay in beginning the ECT course rather than to the therapeutic response speed.

Table 1 also presents 5 noncomparative prospective studies. In one of them,[30] 20 manic patients demonstrated a significant clinical improvement 2 months after ECT treatment. In the other 4 noncomparative prospective studies,[31–34] response rates to ECT ranged from 64.3%[31] to 92%.[33]

Fourteen noncomparative retrospective studies on the efficacy of ECT in mania were found. Sample sizes varied between 184 patients[35] and 12 patients.[36] Response rates ranged from 48.1%[37] to 100%.[38] In all but 2 studies,[37,39] more than two thirds of the patients demonstrated a marked improvement. Of note, 10 of these studies[35,36,40–47] were performed in the 1940s, before the availability of most of the drugs used in the treatment of BPD. The samples of 3 retrospective open-label studies published in the 1980s[37,39,48] consisted of medication refractory or very severe cases. It is important to mention that none of these 14 studies used operational criteria for treatment outcomes.

Although not presented in Table 1, six studies investigated the impact of different ECT techniques on the treatment of mania. Two studies[21,24] did not find a difference in the therapeutic outcome between bilateral and unilateral ECTs. Two other studies[31,32] compared the efficacy of bifrontal and bitemporal ECT. In one of them,[32] bifrontal ECT yielded a faster response than bitemporal ECT; in the other study,[31] both techniques were found to be equally efficacious. In a randomized controlled study,[33] it was observed that higher ECT stimulus intensities did not result in better responses in the treatment of mania. However, in a retrospective study,[49] higher ECT stimulus intensities were associated with a faster response.

The Efficacy of ECT in Bipolar Depression

Table 2 shows 9 clinical trials that investigated the efficacy of ECT in the depressive phase of BPD. No controlled study was found. Four retrospective trials compared ECT with antidepressants.[50–53] These studies indicated that both treatment options resulted in similar outcomes. In 2 of these studies,[50,52] it was also found that ECT combined with antidepressants did not yield a better clinical response when compared with each of these treatments alone.

Three noncomparative prospective trials, presented in Table 2, indicated that the rates of positive responses to ECT ranged from 26%[54] to 91%.[55] Although this last study[54] revealed a low proportion of improved patients, a significant decrease in the mean intensity of depressive symptoms after the ECT course was observed. Finally, Table 2 also presents 2 noncomparative retrospective clinical trials,[56,57] in which approximately three fourths of the patients with bipolar depression improved.

Although not presented in Table 2, three studies performed a comparison between bilateral and unilateral ECT techniques in the treatment of bipolar depression with ECT.[16,48,58] In one of these studies,[16] the bilateral technique yielded a higher response rate; however, in the other 2 studies,[48,58] bilateral and unilateral ECTs were considered comparably efficacious.

Table 3 presents 10 clinical trials that compared bipolar depression and unipolar depression relative to the response to ECT. Half were prospective,[16,58–61] whereas the other half were retrospective.[48,50,52,53,62] In all but 1 study,[60] ECT was as efficacious in bipolar depression as in unipolar depression. In the Medda et al study,[60] unipolar patients presented with higher rates of remission compared with bipolar depressed patients. In 2 of these studies,[16,61] patients with bipolar depression received significantly fewer ECT treatments than those with unipolar depression, indicating that they improved more rapidly. In another study,[58] such a difference was not observed.

TABLE 2. Clinical Trials That Investigated the Efficacy of ECT in Bipolar Depression

Study	Method	Sample and Design	Diagnostic Criteria	ECT Technique	Outcome-Measure	Results
Black et al (1987a)[51]	Comparative, retrospective	ECT (n = 55) vs AD (n = 30)	*DSM-III*, Feighner criteria or RDC	Bilateral, unilateral, or mixed	Nonoperational clinical criteria	ECT = AD (69.1% vs 46.7% of the patients improved, $P > 0.05$)
Perris and d'Elia (1966)[53]	Comparative, retrospective	ECT (n = 40) vs AD (n = 23)	Not informed	Bilateral	Number of patients who relapsed within 3 mos	ECT = AD (1 vs 3, $P > 0.05$)
					Number of patients who relapsed within 2 yrs	ECT = AD (21 vs 13, $P > 0.05$)
Avery and Winokur (1977)[50]	Comparative, retrospective	ECT (n = 14) vs AD (n = 3) vs ECT + AD (n = 17)	*DSM-I* or *DSM-II*	Bilateral	Nonoperational clinical criteria	ECT = AD = ECT + AD (43% vs 33% vs 39% of the patients improved, $P > 0.05$)
Homan et al (1982)[52]	Comparative, retrospective	ECT (n = 30) vs AD (n = 16) vs ECT + AD (n = 7)	Feighner criteria	Bilateral	Nonoperational clinical criteria	ECT = AD = ECT + AD (23% vs 2.5% vs 14% of the patients improved, $P > 0.05$)
Bailine et al (2000)[55]	Noncomparative, prospective	n = 11	*DSM-IV*	Bilateral (6 bifrontal, 5 bitemporal)	HAM-D and CGI (scores: <10 and <3, respectively)	10 patients (91%) remitted
Medda et al (2009b)[63]	Noncomparative, prospective	n = 46 (refractory to medication)	*DSM-IV*	Bilateral	CGI (≤2)	31 patients (67.4%) improved
					CGI (≤1)	19 patients (41.3%) remitted
					HAM-D (50% reduction)	32 patients (69.6%) improved
					HAM-D (≤8)	16 patients (34.8%) remitted
Ciapparelli et al (2001)[54]	Noncomparative, prospective	n = 23	*DSM-IV*	Bilateral	CGI (≤3)	6 patients (26%) improved
					CGI (reduction)	5.0 vs 3.9 ($P < 0.0001$)
					MADRS (reduction)	34.7 vs 15.1 ($P < 0.0001$)
					BPRS (reduction)	32.5 vs 22.2 ($P < 0.0001$)
Devanand et al (2000)[56]	Noncomparative, retrospective	n = 38	*DSM-IV*	Bilateral, unilateral, or mixed	CGI (<3)	76.3% of the patients improved
Kho et al (2005)[57]	Noncomparative, retrospective	n = 11	*DSM-IV*	Bilateral, unilateral, or mixed	HAM-D (<8)	8 patients (73%) remitted

AD indicates antidepressant; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale.

TABLE 3. Clinical Trials That Compared Bipolar Depression With Unipolar Depression Relative to ECT Response

Study	Method	Sample and Design	Diagnostic Criteria	ECT Technique	Outcome-Measure	Results
Daly et al (2001)[16]	Prospective	66 BD vs 162 UD	RDC	Bilateral or right unilateral	HAM-D (60% reduction and score ≤ 10)	BD = UD (48% vs 42% of the patients remitted, $P = 0.65$)
					Number of ECT treatments	BD: less ECT treatments than UD ($p = 0.001$)
Grunhaus et al (2002)[59]	Prospective	20 BD vs 111 UD	Not informed	Bilateral or right unilateral	HAM-D (score ≤11)	BD (10 patients improved) = UD (64 patients improved) (50% vs 57.7%, $P > 0.05$)
					HAM-D (score ≤8)	BD (6 patients remitted) = UD (40 patients remitted) (30% vs 36%, $P > 0.05$)
Sienaert et al (2009)[61]	Prospective	13 BD vs 51 UD	*DSM-IV*	Bifrontal or unilateral	HAM-D (50% reduction)	BD (11 patients improved) = UD (39 patients improved) (84.62% vs 76.47%, $P = 0.72$)
					HAM-D (score ≤7)	BD (7 patients remitted) = UD (18 patients remitted) (53.85% vs 35.29%, $P = 0.22$)
					Number of ECT treatments	BD: less ECT treatments than UD ($P = 0.05$)
Stromgren (1973)[58]	Prospective	26 BD vs 26 UD	"Diagnostic tradition in Denmark"	Bilateral or right unilateral	Depressive symptoms rating scale by the author (mean reduction)	BD = UD (18.5 vs 17.8, $P > 0.05$)
					Number of ECT treatments	BD = UD (8.9 vs 8.8, $P > 0.05$)
Medda et al (2009a)[60]	Prospective	46 BD (type I) vs 17 UD	*DSM-IV*	Bilateral	CGI (score: ≤2)	BD (31 patients improved) = UD (16 patients improved) (67.4% vs 94.1%, $P > 0.05$)
					CGI (score: ≤1)	BD (19 patients remitted) < UD (12 patients remitted) (41.3% vs 70.6%, $P < 0.05$)
					HAM-D (50% reduction)	BD (32 patients improved) = UD (15 patients improved) (69.6% vs 88.2%, $P > 0.05$)
					HAM-D (≤ 8)	BD (16 patients remitted) < UD (12 patients remitted) (34.8% vs 70.6%, $P < 0.01$)
Abrams and Taylor (1974)[62]	Retrospective	15 BD vs 28 UD	Baker's criteria	Bilateral, unilateral, or mixed	HAM-D (reduction)	BD = UD (62.8% vs 58.2, $P > 0.05$)
Avery and Winokur, (1977)[50]	Retrospective	14 BD vs 125 UD	*DSM-I* or *DSM-II*	Bilateral	Nonoperational clinical criteria	BD = UD (43% vs 52% of the patients improved, $P > 0.10$)
Black et al (1986)[48]	Retrospective	55 BD vs 368 UD	*DSM-III*, Feighner criteria or RDC	Bilateral, unilateral, or mixed	Nonoperational clinical criteria	BD = UD (69.1% vs 69.8 of the patients improved, $P > 0.05$)
Homan et al (1982)[52]	Retrospective	30 BD vs 76 UD	Feighner criteria	Bilateral	Nonoperational clinical criteria	BD (7 patients improved) = UD (33 patients improved) (23% vs 43%, $P > 0.05$)
Perris and d'Elia (1966)[53]	Retrospective	40 BD vs 84 UD	Not informed	Bilateral	Number of patients who relapsed within 3 mos	BD (1 patient) = UD (9 patients) (2.5% vs 10.7%, $P > 0.05$)
					Number of patients who relapsed within 2 yrs	BD (21 patients) = UD (33 patients) (52.5% vs 39.3%, $P > 0.05$)

BD indicates bipolar depression; UD, unipolar depression.

The Efficacy of ECT in Mixed States

Table 4 depicts 4 noncomparative clinical trials that addressed the efficacy of ECT in patients with BPD in a mixed state. Half of them were prospective,[54,63] whereas the other half were retrospective.[39,56] In one of the prospective studies,[54] 23 of 41 patients were considered responders. This study also indicated that ECT led to a significant reduction in symptoms. In the other prospective study,[63] the global response rate was 76%. Considering only depressive symptoms, the response rate was 66%. The 2 retrospective studies used small samples and found response rates of 80%[56] and 65%.[39]

The Efficacy of ECT in Samples With Both Manic and Bipolar Depressed Patients

Table 5 presents the results from 3 clinical trials that used both manic and bipolar depressed patients.[64–66] In these studies, all of which were retrospective, the polarity of the bipolar episode was not considered in the analysis of results. The oldest study[66] compared ECT with nontreatment based on the records of 93 BPD inpatients admitted in the 1940s. According to this study, ECT-treated patients had significantly higher rates of home discharged than nontreated patients. However, within 5 years, the patients treated with ECT had more relapses than those who had not been submitted to any kind of treatment. In another comparative study,[65] ECT was better than medication when assessed among 22 adolescents or young adults with a drug-resistant acute bipolar episode. The third study[64] was noncomparative and found that all 12 BPD patients treated with ECT in a Spanish hospital between 1993 and 1998 had full remission of symptoms according to nonoperational clinical criteria.

ECT in the Prophylaxis of BPD Episodes

We found only 1 clinical trial that investigated the use of ECT as maintenance therapy in BPD. In this retrospective study,[67] the records of 13 BPD patients were examined. In an acute episode of the disorder, all of the patients were refractory to medication but became responders when treated with ECT. As a maintenance therapy, ECT was also administered for a 1- to 3-week interval to all 13 patients. Seven of these patients also received concurrent medication. The results indicated a statistically significant reduction in the number of hospitalizations compared with the period antecedent to ECT maintenance treatment ($P < 0.001$).

The Safety of ECT in BPD

Most of the clinical trials that investigated the efficacy of ECT in BPD did not evaluate eventual adverse effects of this therapeutic modality. However, 2 studies reported anecdotal evidence of cardiac complications, "memory problems and disorientation,"[67] and headaches.[65] There are also 8 prospective studies that systematically evaluated the effect of ECT on cognitive activity among patients with BPD. These studies are presented in Table 6.

As can be observed in Table 6, the first 3 studies compared ECT with pharmacotherapy. A randomized clinical trial with a reduced sample size[68] failed to find differences between ECT and lithium in general intelligence measurements. The other 2 studies[10,69] compared ECT with medications in general. Cognitive assessment was performed several months after the respective treatment to investigate long-term ECT effects. In one of these studies,[69] ECT- and medication-treated groups achieved similar results on 3 cognitive scales. In the other study,[10] both ECT- and medication-treated patients were additionally compared with a normal control group. On 1 cognitive test, no significant

TABLE 4. Clinical Trials That Investigated the Efficacy of ECT in Mixed States

Study	Method	Sample	Diagnostic Criteria	ECT Technique	Outcome-Measure	Results
Ciapparelli et al (2001)[54]	Noncomparative, prospective	n = 41	*DSM-IV*	Bilateral	CGI (score: ≤3)	23 patients (56%) improved
					CGI (reduction)	5.7 vs 3.0 ($P < 0.0001$)
					MADRS (reduction)	33.6 vs 9.7 ($P < 0.0001$)
					BPRS (reduction)	48.3 vs 23.9 ($P < 0.0001$)
Medda et al (2009b)[63]	Noncomparative, prospective	n = 50 (refractory to medication)	*DSM-IV*	Bilateral	CGI (score: ≤2)	76% improved
					CGI (score: ≤1)	34.8% remitted
					HAM-D (50% reduction)	66% improved
					HAM-D (≤8)	30% remitted
Devanand et al (2000)[56]	Noncomparative, retrospective	n = 10	*DSM-IV*	Bilateral, unilateral, or mixed	CGI (score: <3)	8 patients (80%) improved
Stromgren (1988)[39]	Noncomparative, retrospective	n = 20 (medication refractory or very severe)	*ICD-9*	Unilateral or mixed	Nonoperational clinical criteria	13 patients (65%) improved

TABLE 5. Clinical Trials That Investigated the Efficacy of ECT in Samples With Manic and Bipolar Depressed Patients

Study	Method	Sample and Design	Diagnostic Criteria	ECT Technique	Outcome-Measure	Results
Winokur and Kadrmas (1988)[66]	Controlled, retrospective	93 bipolar inpatients (89% in mania and 11% in depression): ECT (n = 60) vs nontreatment (n = 33)	Feighner criteria	Bilateral	Discharged to home	ECT (55 patients improved) > nontreatment (22 patients improved) (92% vs 67%, $P = 0.01$)
					Proportion of patients who relapsed within 5 yrs	ECT: more relapses (87% vs 61%, $P = 0.005$)
Kutcher and Robertson (1995)[65]	Comparative, retrospective	22 drug-resistant young bipolar inpatients (11 in mania and 11 in depression): ECT (n = 16) vs medication (n = 6)	Not informed	Not informed	Nonoperational clinical criteria	ECT: more improved patients than medications ($P < 0.03$)
					Mean duration of hospitalization (in days)	ECT: shorter than medications (73.8 vs 176)
Castel et al (2000)[64]	Noncomparative, retrospective	12 bipolar inpatients	Not informed	Not informed	Nonoperational clinical criteria	12 patients (100%) improved

differences between the 3 groups were observed. However, on the 2 other cognitive tests, bipolar patients treated with ECT performed worse than those who received medication. Finally, both bipolar groups had lower performance compared with the normal control group.

The remaining 5 studies from Table 6 were noncomparative. These studies as well as a comparative study performed by Small et al[68] evaluated the adverse effects of ECT through a before-after comparison in a single group of subjects. In 4 studies,[21,30,31,68] patients were in a manic episode. In 3 of the 4 studies,[21,30,68] ECT treatment was associated with an improvement in neuropsychological tests. However, Barekatain et al[31] observed worse cognitive performance after ECT in comparison with baseline. Two studies with bipolar depression patients[59,61] failed to find cognitive changes after ECT sessions. Finally, Sienaert et al[61] did not observe statistically significant differences in cognitive activity between unipolar and bipolar depressed patients treated with ECT.

Although not presented in Table 6, two prospective studies with patients in a manic episode[31,32] compared bifrontal and bitemporal ECT techniques relative to cognitive adverse effects. In 1 study,[31] bitemporal ECT yielded a worse cognitive performance than bifrontal ECT. However, in the other study,[32] no such differences were found. Another study[33] failed to find an association between worsened cognitive performance and higher ECT stimulus intensity in the treatment of mania.

DISCUSSION

The present study was a systematic review of the clinical trials that have investigated the efficacy and safety of ECT in the treatment of BPD. Since the beginning of the therapeutic use of this technique more than 70 years ago, only 51 studies have been conducted to address these 2 issues. In addition, most of these studies have had important methodological limitations. Very few used a controlled or comparative prospective methodological design or had an adequate sample size.

Of the 28 studies that examined the impact of ECT on the treatment of mania, only 3 were controlled or comparative prospective trials. In these studies, ECT yielded a better clinical response compared with simulated ECT,[22] lithium,[23] or a lithium/haloperidol combination.[21] However, important methodological flaws should be noted. For example, these studies had small sample sizes, and, in 2 of them,[22,23] the patients were allowed to use antipsychotic medication.

The additional evidence that points to the efficacy of ECT in mania is limited to 6 controlled or comparative retrospective trials and 19 noncomparative prospective or retrospective studies. The results from these studies also indicate that ECT results in a significant clinical response in the treatment of manic symptoms. However, small sample sizes in the noncomparative prospective studies and the lack of assessment systematization in the retrospective studies weakens such conclusions about the efficacy of ECT in mania.

We did not find any controlled or comparative prospective trial that investigated the efficacy of ECT in bipolar depression. In the 4 retrospective comparative trials, no difference was observed between ECT and antidepressants in the treatment of bipolar depression. In the noncomparative trials, ECT presented with high response rates in 4 studies,[55–57,63] but a low response rate in 1 study.[54] That only four comparative studies (none of them were prospective) investigated this question suggests that very little attention has been paid to the effect of ECT on bipolar depression.

It is well established that ECT has high efficacy in the treatment of unipolar depression.[17] Because unipolar and bipolar

TABLE 6. Clinical Trials That Investigated the Effects of ECT on the Cognition of Patients With Bipolar Disorder

Study	Method	Sample and Design	Diagnostic Criteria	ECT Technique	Assessment Period	Outcome-Measure	Results
Small et al (1986)[68]	Comparative, prospective	21 patients (in mania or mixed state): ECT (n = 10) vs lithium (n = 11)	*DSM-III* and RDC	Bilateral	8 wks after the beginning of treatment	WAIS (full-scale IQ)	ECT = lithium (96.6 vs 95.4, $P > 0.05$)
							ECT group: increase from baseline (91.0 vs 96.6, $P = 0.031$)
Cohen et al (2000)[69]	Comparative, prospective	20 adolescents (in mania, bipolar depression, or mixed state): ECT (n = 10) vs medications (n = 10)	*DSM-III-R*	Bilateral	3.5 yrs in median after treatment	MMSE	ECT = medications (28.7 vs 29.3, $P = 0.50$)
						WMS	ECT = medications (93.5 vs 93.4, $P = 0.91$)
						CVLT	ECT = medications (57.3 vs 55.7, $P = 0.70$)
MacQueen et al (2007)[10]	Comparative, prospective	40 bipolar patients: ECT (n = 20) vs medications (n = 20) [vs normal controls (n = 20)]	*DSM-IV*	Bilateral	At least 6 mos after treatment (45 mos in median)	CVMT	No differences between the 3 groups (71.1 vs 70.9 vs 74.3, $P = 0.353$)
						CFQ	Both bipolar groups: more memory complaints than normal controls; ECT group: more memory complaints than medication group (58.8 vs 49.3 vs 30.0; $P = 0.001$)
						CVLT	Both bipolar groups: worse performance than normal controls; ECT group: worse performance than medication group in several subtests ($P = 0.001$)
Ikeji et al (1999)[30]	Noncomparative, prospective	20 medication-resistant patients in mania	*DSM-IV* and *ICD-10*	Bilateral	2 and 6 mos after treatment	MMSE	Better performance than at baseline (16.6, 21.0 and 21.7, $P < 0.002$)
Mukherjee (1989)[21]	Noncomparative, prospective	22 patients in mania	*DSM-III-R* and RDC	Bilateral, left unilateral, or right unilateral	At the end of treatment	WAIS and WMS	Responders, but not nonresponders: better performance than at baseline
Barekatain et al (2008)[31]	Noncomparative, prospective	28 severe manic patients	*DSM-IV*	Bilateral (bifrontal or bitemporal)	2 d after the last ECT session	MMSE	Worse performance than at baseline (28.4 vs 25.2, $P < 0.05$)
Grunhaus et al (2002)[59]	Noncomparative, prospective	20 patients in bipolar depression	Not informed	Bilateral or right unilateral	At the end of treatment	MMSE	No difference from baseline scores (25.8 vs 25.3, $P > 0.05$)
Sienaert et al (2009)[61]	Noncomparative, prospective	64 depressed patients (51 UP, 13 BP)	*DSM-IV*	Bifrontal or unilateral	6 wks after treatment	MMSE	BD group: similar performance in comparison with baseline ($P = 0.25$)
							UD = BD ($P = 0.72$)

CFQ indicates Cognitive Failures Questionnaire; CVLT, California Verbal Learning Test; CVMT, Continuous Visual Memory Task; MMSE, Mini-Mental State Examination; WAIS, Weschler Adult Intelligence Scale; WMS, Weschler Memory Scale.

depression share the same symptoms, it is plausible that ECT might have similar therapeutic effects on the treatment of both types of depression. Five prospective and 5 retrospective studies addressed this issue, examining whether ECT would produce comparable therapeutic effects between unipolar and bipolar depression. With a single exception,[60] which found that ECT yielded a somewhat better outcome for unipolar depressive patients, the other 9 studies indicated that ECT was equally efficacious for both groups of patients. However, some of these studies also had methodological problems. For example, in 1 prospective study,[58] the sample size was small, and operational criteria were not used for diagnosis. In 4 retrospective studies,[48,50,52,53] methodological problems were related to the lack of symptom scales in the outcome assessment.

The efficacy of ECT in mixed states was addressed in only 4 noncomparative trials. In these studies, the response rates were more than 50%. Only 1 retrospective study investigated the use of maintenance ECT in the prophylaxis of new BPD episodes.[67] Although these results are promising, this was a noncomparative study with a small sample.

Studies that have addressed the safety of ECT in BPD are restricted to 8 prospective clinical trials with relatively small samples. These studies examined the potential hazardous effects of ECT on the patients' cognitive abilities. Three studies compared ECT with medication among BPD patients. In 2 of these studies,[68,69] no difference was detected between the 2 groups, whereas the other study[10] indicated that the ECT group had higher cognitive deficits compared with the medication group. However, this last result should be viewed with caution, as there was a lack of randomization in the study. Accordingly, it is possible that patients with severe mania or depression (those who are both severe in their symptom profile and who also have intrinsic cognitive deficits) were assigned to the ECT condition. Six studies performed a pre- versus post-ECT comparison. Only one of them[31] found a worsening in cognitive performance. In this study, however, the only neuropsychological assessment conducted was carried out too early: that is, only 2 days after the last ECT session. Because there is evidence showing that cognitive impairment caused by ECT may be reversible,[11] it is possible that these adverse cognitive effects remitted later on.

It is clear from the present review that the efficacy and adverse effects of ECT in patients with BPD have been poorly investigated. This scenario contrasts with broad anecdotal clinical experience that suggests that ECT is an important tool in the treatment of the manic and depressed phases of BPD. Indeed, some investigators[70,71] hold that ECT should be used in the early stages of treatment rather than after a long series of failures with several medications.

That most of the studies that investigated the effects of ECT on BPD had major methodological problems should not cast a shadow on the high response rates observed in these studies. It is also important to note that in all but 4 studies,[21–23,68] the ECT trials failed to use a randomization design. It has been pointed out that patients with the most severe BPD, including those who are at a high risk for suicide[72] or who are refractory to medication,[73] are more prone to be referred for ECT treatment. Therefore, the lack of a randomization design probably led to the allocation of patients with BPD and these clinical profiles to ECT.

There is a marked stigma associated with ECT,[19] which was strongly attacked by the antipsychiatry movement during the 1960s and 1970s.[70] Electroconvulsive therapy is still viewed by the lay public as an abusive instrument for punishing or controlling unruly patients.[74] This fact may account, in part, for the paucity of research on ECT. Moreover, in contrast with medications, ECT does not have large financial sponsors.

REFERENCES

1. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry.* 2002;159(suppl 4):1–50.
2. Goodwin GM, Young AH. The British Association for Psychopharmacology guidelines for treatment of bipolar disorder: a summary. *J Psychopharmacol.* 2003;17(suppl 4):3–6.
3. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. *World J Biol Psychiatry.* 2002;3:115–124.
4. Grunze H, Kasper S, Goodwin G, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders. Part II: Treatment of mania. *World J Biol Psychiatry.* 2003;4:5–13.
5. Kusumakar V, Yatham LN, Haslam DR, et al. Treatment of mania, mixed state, and rapid cycling. *Can J Psychiatry.* 1997;42(suppl 2): 79S–86S.
6. Malhi GS, Mitchell PB, Salim S. Bipolar depression: management options. *CNS Drugs*. 2003;17:9–25.
7. Sachs GS, Printz DJ, Kahn DA, et al. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med*. 2000; Spec. No. 1–104.
8. Suppes T, Rush AJ, Dennehy EB, et al. Texas Medication Algorithm Project, phase 3 (TMAP-3): clinical results for patients with a history of mania. *J Clin Psychiatry.* 2003;64:370–382.
9. Zornberg GL, Pope HG. Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol*. 1993;13:397–408.
10. MacQueen G, Parkin C, Marriott M, et al. The long-term impact of treatment with electroconvulsive therapy on discrete memory systems in patients with bipolar disorder. *J Psychiatry Neurosci*. 2007;32:241–249.
11. Reisner AD. The electroconvulsive therapy controversy: evidence and ethics. *Neuropsychol Rev.* 2003;13:199–219.
12. Johnstone EC, Deakin JF, Lawler P, et al. The Northwick Park electroconvulsive therapy trial. *Lancet*. 1980;2(8208–8209):1317–1320.
13. Eranti S, Mogg A, Pluck G, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry.* 2007;164:73–81.
14. McDonald IM, Perkins M, Marjerrison G, et al. A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. *Am J Psychiatry.* 1966;122:1427–1431.
15. Gangadhar BN, Kapur RL, Kalyanasundaram S. Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. *Br J Psychiatry.* 1982;141:367–371.
16. Daly JJ, Prudic J, Devanand DP, et al. ECT in bipolar and unipolar depression: differences in speed of response. *Bipolar Disord*. 2001;3:95–104.
17. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003;361(9360):799–808.
18. Valenti M, Benabarre A, Bernardo M, et al. Electroconvulsive therapy in the treatment of bipolar depression. *Actas Esp Psiquiatr*. 2007;35:199–207.
19. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry.* 1994;151:169–176.

20. Cheniaux E, Landeira-Fernandez J, Lessa TL, et al. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. *J Affect Disord*. 2008;106:209–217.
21. Mukherjee S. Mechanisms of the antimanic effect of electroconvulsive therapy. *Convuls Ther*. 1989;5:227–243.
22. Sikdar S, Kulhara P, Avasthi A, et al. Combined chlorpromazine and electroconvulsive therapy in mania. *Br J Psychiatry*. 1994;164:806–810.
23. Small JG, Klapper MH, Kellams JJ, et al. Electroconvulsive treatment compared with lithium in the management of manic states. *Arch Gen Psychiatry*. 1988;45:727–732.
24. Black DW, Winokur G, Nasrallah A. Treatment of mania: a naturalistic study of electroconvulsive therapy versus lithium in 438 patients. *J Clin Psychiatry*. 1987b;48:132–139.
25. McCabe MS. ECT in the treatment of mania: a controlled study. *Am J Psychiatry*. 1976;133:688–691.
26. McCabe MS, Norris B. ECT versus chlorpromazine in mania. *Biol Psychiatry*. 1977;12:245–254.
27. Schiele BC, Schneider RA. The selective use of electroconvulsive therapy in manic patients. *Dis Nerv Syst*. 1949;10:291–297.
28. Thomas J, Reddy B. The treatment of mania: a retrospective evaluation of the effects of ECT, chlorpromazine, and lithium. *J Affect Disord*. 1982;4:85–92.
29. Volpe FM, Tavares A. Impact of ECT on duration of hospitalizations for mania. *J ECT*. 2003;19:17–21.
30. Ikeji OC, Ohaeri JU, Osahon RO, et al. Naturalistic comparative study of outcome and cognitive effects of unmodified electro-convulsive therapy in schizophrenia, mania and severe depression in Nigeria. *East Afr Med J*. 1999;76:644–650.
31. Barekatain M, Jahangard L, Haghighi M, et al. Bifrontal versus bitemporal electroconvulsive therapy in severe manic patients. *J ECT*. 2008;24:199–202.
32. Hiremani RM, Thirthalli J, Tharayil BS, et al. Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. *Bipolar Disord*. 2008;10:701–707.
33. Mohan TS, Tharyan P, Alexander J, et al. Effects of stimulus intensity on the efficacy and safety of twice-weekly, bilateral electroconvulsive therapy (ECT) combined with antipsychotics in acute mania: a randomised controlled trial. *Bipolar Disord*. 2009; 11:126–134.
34. Schnur DB, Mukherjee S, Sackeim HA, et al. Symptomatic predictors of ECT response in medication-nonresponsive manic patients. *J Clin Psychiatry*. 1992;53:63–66.
35. Impastato DJ, Almansi RJ. A study of over two thousand cases of electrofit-treated patients. *NY State J Med*. 1943;43:2057–2063.
36. Furst W, Stauffer JF. The electrical shock treatment of psychoses. *J Nerv Ment Dis*. 1942;96:499–506.
37. Alexander RC, Salomon M, Ionescu-Pioggia M, et al. Convulsive therapy in the treatment of mania: McLean Hospital 1973–1986. *Convuls Ther*. 1988;4:115–125.
38. Mukherjee S, Debsikdar V. Unmodified electroconvulsive therapy of acute mania: a retrospective naturalistic study. *Convuls Ther*. 1992;8:5–11.
39. Stromgren LS. Electroconvulsive therapy in Aarhus, Denmark, in 1984: its application in nondepressive disorders. *Convuls Ther*. 1988;4:306–313.
40. Bianchi JA, Chiarello CJ. Shock therapy in the involutional and manic-depressive psychoses. *Psychiatr Q*. 1944;18:118–126.
41. Epstein J. Electrical shock therapy in the psychoses: a study of 100 cases. *J Nerv Ment Dis*. 1943;98:115–129.
42. Gralnick A. A three-year survey of electroshock therapy. *Am J Psychiatry*. 1946;102:583–593.
43. Hemphill RE. Electrical convulsion therapy. *Lancet*. 1942;243: 152–154.
44. Kalinowsky LB. Electric convulsive therapy, with emphasis on importance of adequate treatments. *Arch Neurol Psychiatry*. 1943;50:652–660.
45. Kino FF, Thorpe FT. Electrical convulsion therapy in 500 selected psychotics. *J Ment Sci*. 1946;92:138–145.
46. Medlicott RW. Convulsion therapy: results and complications in four hundred cases. *NZ Med J*. 1948;47:338–348.
47. Smith LH, Hastings DW, Hughes J. Immediate and follow up results of electroshock therapy. *Am J Psychiatry*. 1943;100:351–354.
48. Black DW, Winokur G, Nasrallah A. ECT in unipolar and bipolar disorders: a naturalistic evaluation of 460 patients. *Convuls Ther*. 1986;2:231–237.
49. Thirthalli J, Kumar CN, Bangalore RP, et al. Speed of response to threshold and suprathreshold bilateral ECT in depression, mania and schizophrenia. *J Affect Disord*. 2009;117:104–107.
50. Avery D, Winokur G. The efficacy of electroconvulsive therapy and antidepressants in depression. *Biol Psychiatry*. 1977;12: 507–523.
51. Black DW, Winokur G, Nasrallah A. The treatment of depression: electroconvulsive therapy vs antidepressants: a naturalistic evaluation of 1,495 patients. *Compr Psychiatry*. 1987a;28:169–182.
52. Homan S, Lachenbruch PA, Winokur G, et al. An efficacy study of electroconvulsive therapy and antidepressants in the treatment of primary depression. *Psychol Med*. 1982;12;615–624.
53. Perris C, d'Elia G. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. IX: Therapy and prognosis. *Acta Psychiatr Scand Suppl*. 1966;194:153–171.
54. Ciapparelli A, Dell'Osso L, Tundo A, et al. Electroconvulsive therapy in medication-nonresponsive patients with mixed mania and bipolar depression. *J Clin Psychiatry*. 2001;62:552–555.
55. Bailine SH, Rifkin A, Kayne E, et al. Comparison of bifrontal and bitemporal ECT for major depression. *Am J Psychiatry*. 2000;157:121–123.
56. Devanand DP, Polanco P, Cruz R, et al. The efficacy of ECT in mixed affective states. *J ECT*. 2000;16:32–37.
57. Kho KH, Zwinderman AH, Blansjaar BA. Predictors for the efficacy of electroconvulsive therapy: chart review of a naturalistic study. *J Clin Psychiatry*. 2005;66:894–899.
58. Stromgren LS. Unilateral versus bilateral electroconvulsive therapy. Investigations into the therapeutic effect in endogenous depression. *Acta Psychiatr Scand Suppl*. 1973;240:8–65.
59. Grunhaus L, Schreiber S, Dolberg OT, et al. Response to ECT in major depression: are there differences between unipolar and bipolar depression? *Bipolar Disord*. 2002;1(suppl 4):91–93.
60. Medda P, Perugi G, Zanello S, et al. Response to ECT in bipolar I, bipolar II and unipolar depression. *J Affect Disord*. 2009a; 118:55–59.
61. Sienaert P, Vansteelandt K, Demyttenaere K, et al. Ultra-brief pulse ECT in bipolar and unipolar depressive disorder: differences in speed of response. *Bipolar Disord*. 2009;11:418–424.
62. Abrams R, Taylor MA. Unipolar and bipolar depressive illness: phenomenology and response to electroconvulsive therapy. *Arch Gen Psychiatry*. 1974;30:320–321.
63. Medda P, Perugi G, Zanello S, et al. Comparative response to electroconvulsive therapy in medication-resistant bipolar I patients with depression and mixed state. *J ECT*. 2010;26:82–86.
64. Castel B, Chamorro L, Olivares D, et al. Utilizacion de la terapia

electroconvulsiva en una unidad de agudos de hospital general / ECT (electroconvulsive therapy) in a general hospital psychiatric inpatient unit. *Actas Esp Psiquiatr*. 2000;28:88–95.

65. Kutcher S, Robertson HA. Electroconvulsive therapy in treatment-resistant bipolar youth. *J Child Adolesc Psychopharmacol*. 1995;5:167–175.
66. Winokur G, Kadrmas A. Convulsive therapy and the course of bipolar illness, 1940–1949. *Convuls Ther*. 1988;4:126–132.
67. Vaidya NA, Mahableshwarkar AR, Shahid R. Continuation and maintenance ECT in treatment-resistant bipolar disorder. *J ECT*. 2003;19:10–16.
68. Small JG, Milstein V, Klapper MH, et al. Electroconvulsive therapy in the treatment of manic episodes. *Ann NY Acad Sci*. 1986;462:37–49.
69. Cohen D, Taieb O, Flament M, et al. Absence of cognitive impairment at long-term follow-up in adolescents treated with ECT for severe mood disorder. *Am J Psychiatry*. 2000;157:460–462.
70. Fink M. Convulsive therapy: a review of the first 55 years. *J Affect Disord*. 2001;63:1–15.
71. Grunze H, Erfurth A, Schafer M, et al. Electroconvulsive therapy in the treatment of severe mania: case report and a state-of-art review. *Nervenarzt*. 1999;70:662–667.
72. Munk-Olsen T, Laursen TM, Videbech P, et al. All-cause mortality among recipients of electroconvulsive therapy: register-based cohort study. *Br J Psychiatry*. 2007;190:435–439.
73. Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Res*. 1990;31:287–296.
74. Runck B. NIMH report: consensus panel backs cautious use of ECT for severe disorders. *Hosp Community Psychiatry*. 1985;36:943–946.