Electroconvulsive Therapy in Mania: A Review of 80 Years of Clinical Experience

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Resistance to pharmacological agents is commonly encountered in the treatment of acute episodes of mania. In contemporary practice guidelines, electroconvulsive therapy (ECT), once a widely used standalone intervention for mania, is no longer considered a first-line treatment. Stigma, logistics, and ethical factors constrain ECT administration in this condition and lead to its underutilization. However, the past three decades have produced promising research regarding the use of ECT in mania. Randomized controlled trials, albeit in limited numbers, the adoption of ultrabrief ECT, examination of the safety and efficacy of combining ECT with pharmacological agents, including lithium, and use of ECT as a maintenance strategy have enhanced our understanding of how and when to utilize this intervention in mania. In this comprehensive review, the authors summarize the evidence regarding the efficacy and safety of ECT in mania, including related syndromes, such as delirious mania and mixed affective states. The impact of technical parameters, particularly the choice of treatment frequency, electrode placements, and pulse width, are discussed in the light of recent evidence.

Am J Psychiatry 2021; 178:229–239; doi: 10.1176/appi.ajp.2020.20030238

Mania is an acute psychiatric syndrome described since antiquity (1, 2). This syndrome has a lifetime prevalence rate of 0.8% to 1.6% and engenders significant morbidity and mortality (3–6). Prior to the introduction of electroconvulsive therapy (ECT) and psychopharmacological agents, it was estimated that approximately 15% of patients in acute manic episodes died from medical complications resulting from "manic exhaustion," that is, inanition, profound insomnia, and excessive motor activity (6, 7). Currently, the treatment of mania is principally pharmacological. Typically, 40%−60% of manic patients respond to pharmacological monotherapy and another 20% respond to the combination of an antipsychotic medication with lithium or an anticonvulsant, yielding an overall response rate of 80%, at best (8). Combined pharmacotherapy, a norm rather than the exception, is associated with multiple adverse effects. In addition, a long latency to improvement poses significant challenges in patients who are often at risk to themselves or others.

ECT is a rapid and highly effective treatment of manic episodes, and current professional guidelines endorse ECT for pharmacotherapy-resistant mania, but often as second- or third-line treatment (9–12). For example, the APA Task Force on ECT (12) and the National Institute for Health Care and Excellence (NICE) (13) guidelines support its use in mania. However, despite its safety record and robust efficacy, ECT has been underutilized historically in the treatment of mania, presumably because of lack of knowledge regarding its utility, practical issues regarding consent, stigma, and availability, and regulatory barriers. In 1978, the APA Task Force on ECT reported a survey of 3,000 psychiatrists in which 43% of respondents did not consider ECT an appropriate treatment for mania (14). Across the globe, manic episodes typically constitute only 0.2% to 12% of the use of ECT, and in several surveys, no patient with mania received ECT (15–18). In 2018, the U.S. Food Drug Administration placed ECT devices in a less restrictive classification, having determined that the intervention is safe and effective in the treatment of major depressive episodes (unipolar or bipolar) and catatonia (19). Perhaps as a consequence of its relatively low rate of utilization and uncertainty regarding its relative risks and benefits, mania was not included in the labeling of approved indications. In the United States, ECT in mania is now considered "off-label" use, which, like other off-label use of medications or devices, may have implications for the consent process and liability issues.

The most recent major review of the use of ECT in mania was published nearly three decades ago, by Mukherjee et al. (20), in this journal. Examining prospective and retrospective reports across the world literature from 1942 until 1992, Mukherjee et al. found that 80% of 589 manic patients showed substantial clinical improvement or remission following ECT. These findings suggested that ECT was at least as effective in the treatment of mania as in the treatment of depression. However, over the past 30 years, there have been substantial changes in ECT practice, including the widespread adoption of stimulus dose titration to inform

subsequent electrical dosing, the shift from the traditional bifrontotemporal placement to the right unilateral or bifrontal electrode placements, and the abandonment of sine wave stimulation in favor of brief pulse, and now, ultrabrief pulse stimulation (21). Here we present a comprehensive narrative review focusing on the scientific literature over the past 30 years on the use of ECT in mania.

METHODS AND LIMITATIONS

In conducting this narrative review, we searched PubMed since its inception until May 31, 2020, for publications involving the Medical Subject Headings (MeSH) terms bipolar disorder, mania, mixed state, lithium, or anticonvulsant, each in conjunction with electroconvulsive therapy. This search produced 2,631 references that were screened for relevance by the first two authors. Subsequently, 492 references were retained from this search, and pursual of their bibliographies, earlier classic work, and the general literature regarding mania resulted in identification of 34 additional references. Detailed examination of the 526 references yielded a final group of 115 relevant publications. Potential selection bias in study inclusion is a limitation of narrative review. In addition, the absence in this literature of consistency in treatment methods, outcome measures, and other aspects of study design precluded the use of formal quantitative methods, such as meta-analysis.

EFFICACY AND THE EVIDENCE BASE

Randomized Controlled Trials

In the 80-year history of ECT, there have been seven randomized controlled trials in mania (Table 1). Two trials compared the outcomes of ECT and pharmacotherapy, one trial compared real ECT with sham ECT, and the remaining trials compared different ECT modalities.

In 1959, Lansley et al. (22) reported that in manic patients ECT and chlorpromazine were equivalent in impact on psychosis, mood, and psychomotor symptoms, although the chlorpromazine group had a shorter hospital stay. Both chlorpromazine (N=54) and ECT (N=52) resulted in substantial functional improvement. In 1988, Small et al. (23) compared ECT with lithium in the treatment of manic and mixed episodes. On objective measures, patients who received ECT (N=17) had significantly greater improvement compared with the lithium group (N=17). At the end of 8 weeks, all patients who had ECT were rated as "normal" or "borderline ill," whereas those treated with lithium were rated as "borderline" or "mildly ill." Unlike patients on lithium, the ECT group did not develop depressive symptoms after remission of mania. The average number of treatments with bitemporal ECT was 9.7, whereas unilateral stimulation was deemed largely ineffective after a mean of 5.2 treatments. This work was conducted prior to the recognition that the efficacy of right unilateral ECT is highly sensitive to electrical dosage, at least in major depressive episodes (24–26).

In 1994, Sikdar et al. (27) reported a trial in which 30 patients received either bitemporal ECT and chlorpromazine (N=15) or sham ECT (anesthesia alone) and chlorpromazine (N=15). This was the only sham-controlled trial to test the efficacy of ECT in acute mania. The combination of ECT and chlorpromazine was markedly superior to that of sham ECT and chlorpromazine. After eight treatments, 12 of 15 patients who received active ECT achieved recovery, whereas only one of 15 sham-treated patients did so. Compared with sham ECT, patients treated with active ECT also had far more rapid improvement, and the sham ECT group required higher daily doses of chlorpromazine to achieve a similar clinical outcome several weeks later.

These studies compared ECT with either pharmacotherapy or sham treatment and demonstrated comparable or superior efficacy for active ECT. Mukherjee et al. (28) randomized 25 manic patients to treatment with combined haloperidol (20 mg/day) and lithium (blood levels ≥1.0 mEq/L) or bitemporal, left unilateral, or right unilateral ECT. These patients were recruited based on nonresponse to at least 3 weeks of treatment either with lithium, with documented blood levels ≥1.0 mEq/L, or antipsychotic medication, with oral dosages reaching ≥1,500 mg/day of chlorpromazine equivalents. In this sample with rigorously defined medication-resistant mania, none of the five patients treated with combined and intensive pharmacotherapy met response criteria, whereas 15 of 20 (75%) patients achieved remission with ECT. For the first time, this study also found that unilateral ECT was capable of inducing remission. There was no difference between the bitemporal and unilateral forms of ECT in antimanic effects, but the small sample size limited interpretation.

Subsequent randomized controlled trials examined the impact of electrode placement and stimulus dose on safety and efficacy in mania (29, 30). One trial found that, in comparison to bitemporal ECT (N=19), bifrontal ECT (N=17) resulted in more rapid improvement (30). Another trial suggested that bifrontal ECT (N=14) was equal in efficacy to bitemporal ECT (N=14) but with better cognitive outcomes (29). In the seventh trial, Mohan et al. (31) randomized 50 patients to an electrical dose just above the initial seizure threshold (N=26) or a dose 2.5 times the initial threshold (N=24) when administering twice-weekly bitemporal ECT. The two dosage conditions did not differ in antimanic effects, and both were found to be safe and efficacious, with a combined remission rate of 88%.

In summary, across seven randomized controlled trials in patients receiving ECT for acute mania, rates of substantial improvement or remission were high, and improvement was rapid. The difference in efficacy between real and simulated ECT in the single sham-controlled trial was profound, even though all patients were treated with chlorpromazine. The limited information from these randomized controlled trials suggests that ECT's efficacy in the acute treatment of mania may be superior to lithium alone and superior to, or at least comparable to, antipsychotic medications. All commonly

TABLE 1. Randomized controlled trials of ECT in mania[a]

Study	Treatment Arms	ECT Administration	Outcomes	Comments
Langsley et al. 1959 (22)	Chlorpromazine (N=54), ECT (N=52); blinded outcome ratings, allocation concealment not described	Unmodified ECT; three times a week; number of treatments ranged from 15 to 20	Hickerson-Goodrich Scale of Patient Improvement; 16 items, readiness for discharge; 54 patients (100%) in the chlorpromazine group and 47 (90%) in the ECT group; statistically nonsignificant; side effects were within acceptable range in both groups	ECT and chlorpromazine had equivalent efficacy; mean length of hospital stay was 16 days shorter in the chlorpromazine group; no summative scores used to define dichotomous outcomes such as remission
Small et al. 1988 (23)	ECT (N=17), lithium (N=17); ratings by blind and nonblind observers	Modified ECT; started with right unilateral ECT for six patients and then changed to bitemporal ECT as the starting treatment for remaining patients; three times a week; mean number of bitemporal treatments, 9.7	At 8 weeks, CGI scores were significantly better in the ECT group; up to 10 patients in the ECT group and 12 patients in lithium group required antipsychotics; improvement on CGI: 64.4% with ECT, 45.9% with lithium	Little information about dose titration in right unilateral ECT and doses used; Lancaster placement of electrodes for right unilateral, with shorter interelectrode distance with possible shunting of current
Mukherjee et al. 1988 (28)	Patients nonresponsive to 3-week trial of lithium or antipsychotics; ECT (N=20), pharmacotherapy (combined lithium and haloperidol) (N=5); raters blind to ECT status	ECT three times a week in the pilot study and daily in the subsequent trial; dose titration and 150% above threshold for right unilateral ECT; d'Elia placement	Response defined by MMS; 13 patients (59%) remitted with ECT; no significant difference between right unilateral ECT (54%) and bitemporal ECT (55%)	Stringent definition of response; patient sample resistant to pharmacological monotherapy; limited by small sample size
Sikdar et al. 1994 (27)	Double-blind study; experimental group, ECT and 600 mg of chlorpromazine (N=15); control group, simulated ECT and chlorpromazine (N=15)	Eight bitemporal ECT treatments; three times a week	Outcomes defined by MRS; at the end of 8 weeks, 12 patients (86%) in the ECT group and one (7%) in the control group had complete recovery; the ECT group improved more rapidly than the control group	ECT group required fewer doses of antipsychotics than the control group
Hiremani et al. 2008 (30)	Double-blind trial, patients referred to ECT by psychiatrist; bitemporal ECT (N=19), bifrontal ECT (N=17) (patients free of mood stabilizers during ECT)	Titration method, 1.5 times threshold as the treatment dose; three times a week	Efficacy defined by YMRS; response rate: bifrontal ECT, 87.5%; bitemporal ECT, 72.2%; significantly more patients in the bifrontal ECT group had a rapid response than in the bitemporal group; no difference in cognitive performance	Response achieved with a mean of 7.64 treatments with bifrontal ECT and 7.47 treatments with bitemporal ECT; both groups received concomitant antipsychotics and benzodiazepines, without significant difference
Barekatain et al. 2008 (29)	Double-blind trial, patients with severe bipolar I disorder; bitemporal ECT (N=14), bifrontal ECT (N=14)	Titration method, 1.5 times seizure threshold for bifrontal ECT and 1 times seizure threshold for bitemporal ECT; three times a week	Efficacy defined by YMRS; all patients achieved response; patients in the bifrontal ECT group performed significantly better on the MMSE than those in the bitemporal ECT group	Small sample size; 10 patients dropped out; no concomitant antipsychotics or mood stabilizers; patients received benzodiazepines

continued

TABLE 1, *continued*

Study	Treatment Arms	ECT Administration	Outcomes	Comments
Mohan et al. 2009 (31)	Bitemporal ECT threshold dose (N=26); bitemporal ECT, 2.5 times threshold (N=24)	Twice-weekly treatment	Outcomes measured by YMRS, CGI; the groups fared equally in terms of efficacy (speed of response and remission rate) and safety	Overall remission rate of 88%, comparable to previous randomized controlled trials

[a] CGI=Clinical Global Impressions scale; MMS=Modified Mania Scale; MMSE=Mini-Mental State Examination; MRS=Mania Rating Scale; YMRS=Young Mania Rating Scale.

used electrode placements (bitemporal, bifrontal, and right unilateral) were found to be efficacious, but the role of dose titration and high-dose right unilateral ECT has been unexplored. These reports also suggested that acute manic episodes respond to ECT regardless of baseline severity, but patients who present with anger, irritability, and suspiciousness may have a less favorable outcome (32).

Retrospective Studies

Kalinowsky (33) studied 200 patients and observed comparable rates of improvement in mania (93.8%) and depression (93.2%). In 1945, Bennett (34) also reported that similar proportions of patients with mania and depression improved with ECT. In contrast, others found a more favorable outcome in depression than in mania (35). Detailed reviews of early reports are available elsewhere (20, 36). After 1976, more controlled studies appeared. In one study, patients who had ECT in the pre-antipsychotic era (1945–1949) performed better, with 100% eventual social recovery from mania when compared with untreated patients who acted as a historical control group (1931–1939), with only 44% improvement (37). In one of the largest series, Black et al. (38) found a similar pattern among 438 manic patients, with more marked improvement in patients who received ECT (78%) compared with those who were treated with lithium (62%) or who received no treatment (32%). Furthermore, 69% of the lithium nonresponders improved with ECT. A study that compared ECT, lithium, and chlorpromazine found no significant difference among the groups in efficacy as measured by the length of hospital stay (39). In a naturalistic study, Perugi et al. (40) obtained a response rate of 75% for ECT in pharmacotherapy-resistant mania, which was somewhat higher than that observed in a concurrent depression sample (68.8%).

Thus, numerous retrospective reports, including case series involving hundreds of patients, documented the impressive effectiveness of ECT in acute mania. The rate of marked clinical improvement following ECT was comparable or superior to rates obtained with pharmacotherapy. Furthermore, studies also documented high rates of improvement in patients explicitly identified as having medication-resistant illness.

Safety of ECT in Mania

Cognitive impairment, one of the most worrisome adverse effects of ECT, has been investigated in randomized controlled trials and modern practice with ultrabrief ECT (29, 30, 41, 42). Barekatain et al. (29) found better cognitive outcomes with bifrontal ECT compared with bitemporal ECT, and Wong et al. (42) demonstrated improved cognitive function after ultrabrief ECT. In a randomized controlled trial in mania, time to postictal orientation recovery was significantly shorter with the administration of combined remifentanil and atropine compared with combined saline and atropine (41). In general, ECT has been found to be as safe in mania as it is in depression.

Limitations of the Evidence

The issue of concomitant pharmacotherapy is an important consideration in interpreting the literature on the efficacy of ECT in acute mania. In modern practice, most patients with acute mania who receive ECT are also treated with concomitant antipsychotic medications. It had long been thought that antidepressant medications had no impact on the efficacy of ECT in major depressive disorder, but this view was largely based on randomized controlled trials from the 1960s and 1970s, when ECT was used as a treatment of first choice (43–46). A recent placebo-controlled trial in a sample of patients with largely medication-resistant depression found that the combination of ECT and antidepressant medication resulted in a substantially higher remission rate compared with ECT alone (44). Whether antipsychotic medications also augment the efficacy of ECT in acute mania is a pertinent question, without a clear answer. Reports, particularly from the pre-antipsychotic era, show very high remission rates with standalone ECT, typically between 80% and 100%, but earlier studies did not have control groups. Later results from more rigorously designed studies with control groups indicate comparable response with combined ECT and pharmacotherapy in comparison with historical standalone ECT (27, 30). A possible explanation, as in the case of major depressive episodes, is that combination treatment with antipsychotic medication may be of particular value in patients with pharmacotherapy-resistant illness.

More generally, the literature on the efficacy of ECT in acute mania has several limitations. Methodological standards have significantly evolved over the 80-year time frame.

Few studies were prospective, and fewer still used a randomized design with blinding. Only one study used a form of sham ECT to truly mask treatment conditions and to assess the intrinsic efficacy of ECT (27). The sample sizes of randomized controlled trials were small, leading to studies that were underpowered in detecting group differences, and the vast majority of studies used retrospective designs that may be subject to bias. Among the randomized controlled trials, there is little consistency in outcome measures, comparison conditions, and the type of ECT administered. Such heterogeneity inhibits the pooling of data and the conduct of a formal meta-analysis. Nonetheless, across the 80-year time span of this treatment, clinicians from various countries have been uniform in reporting that ECT has impressive therapeutic properties in acute mania.

MANIC SUBGROUPS

Mixed Episodes

Bipolar manic, hypomanic, or major depressive episodes may be characterized as presenting mixed features, where, in the case of a manic episode, significant depressive symptoms are manifest (47). Mixed episodes are widely thought to be more resistant to pharmacological treatment than manic or depressive episodes without mixed features (48, 49), and ECT has often been considered an effective alternative for this subgroup (50–53).

In one series, ECT resulted in an 80% response rate, comparable to a concurrent group with a major depressive episode (76%), but with longer hospital stays and greater numbers of treatments (53). Ciapparelli et al. (52) and later Medda et al. (51) reported better response rates in patients with mixed episodes (56% and 76%, respectively) than in patients with major depressive episodes without mixed features (26% and 67%, respectively). In both studies, twice-weekly bitemporal ECT was administered, with a mean of seven treatments in pharmacotherapy nonresponders. Strömgren (18) reported a 70% remission rate with right unilateral ECT after a mean of 11 treatments in patients who did not respond to antipsychotics, lithium, or carbamazepine. In a recent study, 72.9% of patients with mixed episodes achieved response with bitemporal ECT (40).

ECT is one of the few interventions in psychiatry with established efficacy in treating both depressive and manic syndromes. These findings suggest that ECT retains this efficacy when episodes are mixed in presenting both manic and depressive symptoms. Furthermore, there is a substantial concern that antidepressant medication can result in symptomatic worsening in mixed episodes (54, 55), but the ECT literature documents strong efficacy, especially in pharmacotherapy-resistant mixed episodes. Nonetheless, inferences from these studies are limited in the absence of prospective randomized controlled trials comparing ECT to pharmacological alternatives in the treatment of mixed episodes.

Delirious Mania and Catatonia

Delirious mania, although once thought to be rare, is now recognized as a life-threatening neuropsychiatric syndrome characterized by manic symptoms, psychosis, and disorientation (56). It represents between 15% and 35% of acute manic presentations and is associated with acute onset, rapid progression, and potential mortality from severe physical exhaustion and metabolic derangements. Catatonia is often a feature of delirious mania. Given concerns about precipitation of a neuroleptic malignant syndrome in delirious mania, expert opinion is to avoid antipsychotics, especially first-generation medications.

Given the difficulties of conducting prospective research in such a population, controlled data are lacking on the use of ECT. However, numerous reports unambiguously demonstrate its efficacy in this condition. Symptomatic improvement is typically quite rapid, with a substantial resolution of delirium usually after the first or second treatment session, of psychomotor excitement after two to four sessions, and a full resolution in six treatments (56, 57). The evidence exists mostly for bitemporal treatment. Contrary to the historical view of catatonia as a subgrouping of schizophrenia, catatonia is commonly linked to mood disorders, particularly mania (58, 59). ECT provides rapid relief of symptoms of catatonia with a compelling efficacy indicated by 80% to 100% response rates (59, 60).

MAINTENANCE TREATMENT

To date, there have been no randomized controlled trials testing the efficacy of maintenance ECT in bipolar disorder. Naturalistic studies suggest that the use of maintenance ECT may produce significant reductions in the number of episodes, with prolongation of interepisode euthymic intervals in patients with treatment-resistant bipolar disorder, mostly rapid cycling (61–63). Partial or full remission that extended up to 2 years with maintenance ECT has been observed in 100% of a sample with rapid-cycling bipolar disorder (62). This study used the bitemporal placement, once a week for most patients, but up to once a month, for a maximum of 3 years. Santos Pina et al. (63) documented a significant diminution in mean number of days of full hospitalization during maintenance ECT. The mean duration of maintenance ECT was 705 days, and the frequency varied from fortnightly to once in 6 weeks, on an as-needed basis. Other studies on maintenance ECT had samples with mixed diagnoses, and the data are insufficient to draw firm conclusions about the differential impact of ECT on bipolar disorder, let alone on mania.

TECHNICAL PARAMETERS

Frequency of Treatment, Electrode Placement, Electrical Stimulus Dosing, and Pulse Width

Historically, ECT for mania was often administered over a longer time period and with multiple daily treatments

(33–35). This practice did not produce additional benefits compared with one treatment per day, three times a week. Retrospective data support the efficacy of twice-weekly treatment as well (39, 40). In the early reports, it is unknown whether patients continued to receive treatment after remission either as continuation treatment or simply until the point of discharge. In either case, the average number of treatments administered did not give an accurate estimate of the number required for remission. Given that improvement with ECT is cumulative and time dependent, a larger number of treatments within a short time span—for example, multiple treatments a day—may be not only therapeutically unnecessary but also misleading in terms of the number of treatments needed to achieve remission. Prospective controlled studies in the latter part of the 20th century provided the data supporting fewer treatments and shorter duration of the acute treatment period.

The long-running debate about the relative merits of bitemporal and right unilateral ECT in major depressive episodes also found its place in the treatment of mania. Bitemporal ECT was the traditional treatment for mania, often justified by the severity of the symptoms and the heightened need for rapid and definitive improvement (64, 65). However, the findings of randomized trials, naturalistic studies, and anecdotal reports have challenged this view. In their randomized trial, Mukherjee et al. (28) used rigorous criteria for remission, and demonstrated a comparable remission rate for bitemporal and unilateral ECT, using the d'Elia placement, albeit in a small sample (N=20). As in the case in major depression, scientific evidence accumulated to suggest comparable efficacy of right unilateral and bitemporal ECT in mania (28, 38, 42, 66–68). Unsuccessful use of right unilateral ECT reported by Small et al. (23) may have been due to technical issues in the choice of electrode positioning and the dosing of the electrical stimulus. Small et al. (23) used the Lancaster right unilateral electrode placement, which has a shorter interelectrode distance (temple to above the ear), resulting in more shunting of the current away from the brain than the d'Elia placement (69–71) (temple to scalp midline), which has become the standard for right unilateral ECT (12). Thus, with the Lancaster placement, electrical stimulus dosing with right unilateral ECT may have been close to the seizure threshold (23, 70).

In major depressive episodes, there is consistent evidence that dose relative to seizure threshold affects efficacy (24–26, 71–73). In view of the emerging reports on the effectiveness of ultrabrief right unilateral ECT, dose titration followed by at least six times the threshold stimulus intensity, two or three times a week, may be appropriate in mania. One randomized controlled trial (30) suggested superior efficacy of moderate-dose bifrontal ECT (1.5 times seizure threshold) over bitemporal ECT, but this finding has not been replicated. Indeed, others have shown more favorable cognitive outcomes with bifrontal compared with bitemporal ECT, but no difference in efficacy (29).

Ultrabrief ECT in Mania

Several recent reports indicate burgeoning interest in the use of the ultrabrief pulse width when administering ECT in mania and mixed episodes (42, 66–68, 74), and available data suggest 70% to 100% remission rates with the use of ultrabrief ECT. The mean number of treatments in one treatment series (N=11) was 6.9 (66). A retrospective study replicated the beneficial role of ultrabrief right unilateral ECT in mania, and after comparing different electrode placements, found that ultrabrief right unilateral ECT (N=13) led to remission in 100% of patients, as defined by changes in score on the Young Mania Rating Scale (42). The mean number of treatments with ultrabrief right unilateral ECT (mean=7.4) was lower than with right unilateral brief pulse ECT (mean=8.6) and dose-titrated bitemporal ECT (mean=9.8). These findings support the effectiveness of ultrabrief ECT in manic episodes. Randomized controlled trials in major depressive episodes have shown that the use of an ultrabrief pulse (0.25 or 0.3 ms) compared with a brief pulse (1.0 or 1.5 ms) results in overall lower electrical dosing and substantially less severe short-term and long-term cognitive side effects (73, 75).

ECT AND CONCURRENT PHARMACOTHERAPY IN MANIA

ECT and Concomitant Anticonvulsant Mood Stabilizers

There is conflicting guidance on the use of concomitant anticonvulsant medications during an ECT course. Since anticonvulsants may raise the threshold for seizure induction and interfere with seizure expression, it has been frequently recommended that anticonvulsant dosage should be reduced or the medications stopped when administering ECT, if these medications are used in the management of the psychiatric disorder (12). However, some empirical data suggest otherwise. Continuation of anticonvulsants during ECT has been found to be safe and free from the detrimental impact on efficacy in a few investigations (76–79). A retrospective chart review reported equivalent efficacy between patients who had ECT alone and ECT and concomitant anticonvulsants, although patients on the concomitant therapy required a larger number of treatments and had longer hospitalizations and a higher incidence of seizure failure (77). Subsequent randomized trials did not support such apprehension, however, and demonstrated no significant difference in number of treatments or length of hospital stay between ECT alone and ECT plus sodium valproate or carbamazepine (78, 79). In a recent randomized controlled trial, patients randomized to receive the full dosage of anticonvulsants, most commonly sodium valproate and carbamazepine, had a shorter time to remission compared with patients randomized to receive half the dosage of anticonvulsants, without differences in the overall remission rate or adverse cognitive effects (79). Combining lamotrigine with ECT has also been found to be safe and free from interference with seizure expression and impact on stimulus dosing (80). The use of stimulus dose titration to determine individually electrical

dosing relative to seizure threshold may at least partially offset the impact of anticonvulsants on seizure induction.

ECT and Lithium

The literature on the combination of ECT and lithium is replete with conflicting reports. While these studies document divergent outcomes, there have been no reports of death directly attributable to combining lithium with ECT (81). A detailed review of the safety of lithium during ECT has been published elsewhere (82). The reported adverse reactions include prolonged apnea, prolonged or tardive seizure, postictal delirium, increased cognitive impairment, and serotonin syndrome (83–85). On close examination, the generalizability of the findings is often limited because of the presence of other factors that could influence the outcomes besides concomitant lithium. These patients were often receiving treatment with complex pharmacological regimens, with preexisting medical conditions. Adverse reactions often occurred when lithium blood levels were relatively high, typically close to or above 1.0 mEq/L (83, 86). It is difficult to ascertain whether the lithium-ECT combination resulted in persistent postictal confusion or prolonged seizure, because such adverse reactions can occur with ECT in the absence of lithium. However, this issue was examined in a recent medical database study of a nationally representative sample of adult psychiatric inpatients across the United States (87). The study found a substantially higher number of diagnoses of delirium and cognitive impairment in patients treated with the combination of ECT and lithium (N=422) compared with patients treated with ECT alone (N=64,148) or lithium alone (N=158). A negative interaction was observed in 7.8% of patients with major depressive disorder, 3.4% of patients with bipolar depression, and none of the patients with mania (87). The study was limited, however, by retrospective chart review and the absence of information on lithium level or electrode placement.

Data from a controlled prospective study and a large retrospective study did not reveal serious adverse effects emanating from combining ECT and lithium (81, 88). In a nonrandomized prospective study (88), patients on lithium (intervention group) and not on lithium (control group) received bitemporal ECT. Although sessions with ECT and lithium showed a nonsignificant trend toward prolonged time to recover from anesthesia and increased duration of apnea, these effects were related to higher lithium levels, near or above 1.0 mEq/L (88). There was no incidence of postictal delirium or significant differences in seizure parameters attributable to lithium. In a large retrospective study, there was no significant difference in the number of ECT sessions or post-ECT length of hospital stay between patients receiving ECT and lithium (N=90) and ECT with other psychotropic medications, such as antipsychotics (N=51) (81). These reports are consistent with a previous chart review that failed to observe prolonged recovery from anesthesia while receiving concomitant lithium and ECT (89). Overall this literature suggests that the adverse effects seen with this combination are relatively infrequent, rapidly reverse with lithium discontinuation, and may be linked to higher lithium blood levels (83, 87, 88). When ECT is used as a continuation therapy in patients receiving lithium, a common practice is to hold the medication the day before the ECT treatment (90). Much of the information on the potential risks of combining ECT and lithium come from reports of patients treated for major depressive episodes, and applicability to mania is not certain.

Many patients with bipolar disorder are treated with lithium and may need additional treatment with ECT. Lithium discontinuation may create several challenges, including increased waiting time for the washout and delaying ECT. Some reports document the development of rapid cycling during ECT after lithium discontinuation and its resolution with the restoration of lithium and continuation of ECT (91, 92).

MECHANISMS OF ECT IN MANIA

One of the proposed mechanisms of ECT in mania focuses on its anticonvulsant properties (93). While originally introduced to account for ECT's antidepressant effects, this hypothesis may be even more relevant in mania and is based on several observations. First, the seizure threshold progressively increases during ECT, and the seizure duration and the intensity of seizure expression decrease with repeated treatments. These phenomena demonstrate that ECT has strong anticonvulsant properties. Second, the rise in seizure threshold has been associated with the degree of improvement in manic symptoms, and, in turn, relapse has been linked to a return to baseline seizure threshold values (94). A related mechanism may be reflected in the post-ECT reduction in regional cerebral blood flow (rCBF) and regional cerebral metabolic rate for glucose (rCMRglu) in prefrontal cortical regions, including anterior cingulate cortex (95). The effects of ECT on seizure threshold, rCBF, and rCMRglu, as well as the regionally increased slow-wave activity observed on EEG (96), suggest that inhibitory effects on membrane excitability may be key to ECT action in mania (97). At a neurochemical level, ECT increases γ-aminobutyric acid (GABA) concentration, the most abundant inhibitory neurotransmitter in the mammalian brain (98, 99). GABA level is found to be decreased in bipolar disorder, and this is believed to play a role in the increased membrane excitability (100). It is interesting to note that antimanic drugs such as lithium and valproate also increase GABA levels (101, 102). Whether alterations in GABA level occur during an acute manic episode and normalize during ECT warrants further study (103).

IS ECT MORE ANTIMANIC THAN ANTIDEPRESSANT?

There is evidence that remission rates following ECT are higher for patients in a manic episode than for patients in a major depressive episode (40, 53). Although a retrospective study (104) suggested that seizure threshold was higher in

mania than in depression, a prospective controlled trial showed the opposite (28). Recent reports of successful use of dose-titrated ultrabrief ECT treatment suggest that mania is so sensitive to ECT that marked benefit occurs with the form of treatment with the mildest cognitive effects, perhaps with a smaller number of sessions than that required for remission of depression (42, 66–68, 74). Moreover, during a study of maintenance ECT, a 36% relapse rate into a depressive episode was observed, but no relapse into a manic episode (105). These lines of evidence converge in supporting the proposition that ECT has stronger antimanic than antidepressant properties.

This review would not be complete without mention of ECT-induced mania. Varying rates of a switch into mania have been reported during the treatment of a depressive episode with ECT. The reported rates have varied from 6% to 38.6%, and the phenomenon may be less common than switching induced by antidepressant medications (106–110). The change typically involves a hypomanic presentation, and when manic episodes emerged, they were transient and often followed by spontaneous resolution (106, 107, 109). The switching rate is higher in bipolar than unipolar depressive episodes (107, 110). Bitemporal ECT has been associated with a higher rate of switching than right unilateral ECT (110). As described above, concurrent administration of lithium has the potential to prevent manic switch during ECT (91, 92).

ETHICAL AND SOCIAL ASPECTS OF ECT IN MANIA

Ethical issues in the administration of ECT are more challenging in mania than in depression, given the greater likelihood of severe impairment of judgment and insight, and catatonic or delirious presentation. ECT treatment on a voluntary basis may be unrealistic in a considerable number of patients with mania. Involuntary ECT requires a judicial process in most parts of the world, including the United States (111). At least in the context of major depressive episodes, clinical outcomes following ECT appear to be equivalent among patients treated on a voluntary or involuntary basis (112, 113). However, lack of capacity to provide informed consent presents a practical barrier to receiving ECT, and such patients are frequently treated in public facilities, where there is often limited access to ECT (114, 115).

CONCLUSIONS

In comparison with ECT in major depressive episodes, its application in mania has been far less documented. Many practitioners are unaccustomed to the use of ECT in mania, and consequently it is underutilized. An important difference in the pharmacotherapy between major depression and mania is the long latency for remission in depression, while manic symptoms respond quite rapidly. This difference may explain the reduced need for ECT in mania. Prospective studies contrasting the efficacy of ultrabrief ECT in acute mania with a pharmacotherapy comparator group can expand the horizons. Furthermore, predictors of response to ECT in mania have received little attention. Increased educational campaigns among both professionals and the lay public are important to enhance awareness of the beneficial, and at times, the life-saving role of ECT in mania. The combined use of ECT and mood stabilizers, including lithium, requires further clarification. Guidelines should reconsider their position regarding the role of ECT in mania based on the best available evidence, as well as the interests of this patient community.

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Received March 1, 2020; revisions received July 31 and August 19, 2020; accepted September 8, 2020; published online Nov. 10, 2020.

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