Efficacy of Continuation/Maintenance Electroconvulsive Therapy in the Treatment of Patients With Mood Disorders
A Retrospective Analysis

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Objective: The aim of the study was to contribute evidence for the efficacy of continuation and maintenance electroconvulsive therapy (c/mECT) going beyond the existing literature by examining longer-term outcomes from a single center.

Methods: We conducted a retrospective observational cohort study for a 14-year period, in which a group of 27 individuals with mood disorders, as defined by International Classification of Diseases-10, were examined and received acute ECT, followed by c/mECT. Mirror-image comparison of individual data sets, 5 years before and after c/mECT, was conducted for the number and mean duration of hospitalizations, as well as inpatient days per year. Statistical analysis was performed using general equation estimation modeling.

Results: In 27 patients (63% female, mean ± SD age = 54.3 ± 11.7 years) experiencing either from bipolar (41%) or unipolar (59%) mood disorder, with most patients presenting with a depressive episode at hospital admission (93%), c/mECT was initiated after a successful course of acute ECT in addition to treatment as usual. In a 5-year period before and after starting c/mECT, we observed a significant decline in the mean number of hospitalizations per year (0.64 vs 0.32, $P = 0.031$), the average number of inpatient days per year (23.7 vs 6.1 days, $P < 0.001$), and the mean duration of hospital stays (41.6 vs 22.1 days, $P = 0.031$).

Conclusions: The findings provide further support for the efficacy of c/mECT as an augmentation therapy to psychopharmacological treatment in patients experiencing mood disorders, who have responded to acute ECT. Further studies, however, using a controlled study design and larger sample sizes are needed.

Key Words: continuation/maintenance ECT, electroconvulsive therapy, retrospective analysis, outcome, affective disorders, depressive disorder, bipolar disorder

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Incidence rates of relapse approximate 0.4 episodes for bipolar disorders and 0.2 episodes for unipolar depression per year.[1] Approximately 30% of patients with mood disorders present with treatment-resistant depression.[2,3]

In severe and chronic forms of mood disorders, electroconvulsive therapy (ECT) has been shown to be a safe and effective treatment.[4,5] In bipolar disorder, acute ECT was significantly more effective than algorithm-based pharmacological treatment.[6] Acute ECT seems to be equally effective in unipolar and bipolar depression.[7] Treatment of acute mood episodes in general is mostly followed by relapse prevention, which usually consists of medication and psychotherapy. However, almost 40% to 50%[8,9] of depressive patients and up to 95% of patients with psychotic depression[10] who responded to a course of ECT relapse within the next 6 to 12 months despite receiving appropriate drug treatment after acute ECT.

So far, we have limited evidence on how to best continue after acute ECT, with ongoing pharmacotherapy, manual-based psychotherapies or continuation ECT (cECT), followed by maintenance ECT (mECT) having the best evidence base.

Continuation ECT refers to the continued administration of ECT sessions in a tapering-down fashion for up to 6 months after initial response, to prevent early relapse and achieve further symptom improvement in cases of incomplete remission. Prolongation of ECT beyond 6 months is defined as mECT with the intention to prevent recurrence. In mECT, a distinction is basically made between (1) fixed regimens with treatments every 1 to 4 weeks, (2) tapered treatment programs that start at higher frequency and gradually decrease in frequency, and (3) demand-oriented approaches where treatment with ECT is initiated as soon as signs of clinical deterioration are observed. Maintenance ECT is typically performed weekly to monthly, with or without concomitant pharmacotherapy; however, the duration of mECT is variable. The literature uses the terms cECT and mECT interchangeably, and boundaries are not clearly defined. To cope with the different nomenclatures, we use the acronym c/mECT.

In a review, cECT and mECT were seen to be valuable treatment modalities to prevent relapse and recurrence of mood disorders in patients who have responded to an index course of disorders.[11] However, the evidence for the efficacy of c/mECT is still sparse and hampered by different methodologies because they are based on case series and retrospective data analyses.[12,13] Only few prospective studies or controlled trials are available to date.

Continuation and mECT seems to be less potent than c/mECT augmentation in addition to ongoing medication.

The hypothesis of lowering relapse rates by augmenting c/mECT by pharmacotherapy held true in an open, but randomized Swedish trial.[14] In the methodologically more rigorous "Prolonging Remission in Depressed Elderly" (PRIDE) trial, 120 elderly individuals with major depressive disorder who had remitted after an acute ECT series were randomized to two 6-month treatment arms of either venlafaxine and lithium or c/mECT plus venlafaxine and lithium. At 6-month follow-up, subjects in the c/mECT augmentation group had statistically significantly lower HAM-D scores in comparison with the medication only group. In addition, relapse rates were 1.7 times greater for subjects in the pharmacotherapy alone group.[15] Even in this more vulnerable group of aged patients, c/mECT turned out to be safe in terms of cognitive adverse effects. This study corroborates earlier findings showing that cognitive functioning in patients receiving c/mECT treatment did not differ from that of patients receiving pharmacotherapy alone.[14,16]

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However, all cited studies were of relatively short duration (up to 1 year). Very little is known about safety and efficacy of c/mECT for a prolonged period. This article reports the results of a retrospective analysis of patients with severe, therapy-refractive affective disorders, who were treated with c/mECT at Innsbruck Medical University Hospital for durations of up to more than 6 years.

MATERIALS AND METHODS

Data Collection and Outcome Criteria

Data were collected from all patients diagnosed with a mood disorder, who underwent outpatient c/mECT on at least 4 occasions at our hospital, namely, between January 1998 and July 2016, after a successful ECT series. Individual mirror-image comparisons were conducted. Primary outcome was the number of patients' pre- versus post-c/mECT hospitalizations. Secondary outcomes included mirror-image comparison of inpatient days per year and the mean duration of hospital stays.

Only data that were available in all patients were selected. The data analyzed are therefore limited to general demographic data, diagnoses, medication at the beginning of mECT, and technical ECT parameters. Admission and discharge data from the psychiatric departments in Innsbruck as well as the psychiatric centers in Kufstein and Hall, who refer patients to Innsbruck for ECT, were included in the evaluation of inpatient treatment periods.

After appropriate information and consent, ECT treatment was commenced in patients where indicated. The decision for c/mECT after a successful ECT series was made clinically, depending on the previous therapy resistance and the severity of the current episode successfully treated with ECT. Patients had to renew their informed consent for continuing ECT. Because there are no established guidelines on frequency and duration of mECT, we used the scheme used at our hospital as explained in the Introduction together with concomitant pharmacotherapy, which was only slightly adapted in exceptional cases. To obtain a comparable and sufficiently long observation period, data from 5 five years before and 5 years after commencement of c/mECT were compared. In contrast to our first publication on a smaller sample,[17] we used a more restrictive study design by excluding inpatient days from the pre-c/mECT period whereas the initial ECT series was conducted.

The study was conducted in accordance with the Helsinki Declaration as revised in 1989. The local Institutional Review Board does not require an ethics vote for post hoc evaluations.

Treatment

For the major part of time, namely, ongoing from 2000, a Thymatron IV device with ictal electroencephalogram and electromyography recording was used for c/m ECT. Before 2000, a similar device, the Thymatron DGX, was in use.

A square wave pulse width of 0.5 milliseconds was chosen. Treatment was administered according to the current state of the art by specially trained psychiatrists.[18] Decisions regarding electrode position, stimulus intensity, and duration were made on a case-by-case basis. Initially, seizure threshold was determined using the so-called age method, in which the energy level is chosen as a percentage of the maximum load of 504 mC, which is closest to the patient's age. Because seizure threshold increases with the number of acute ECT sessions, stimulus intensity had to be appropriately adapted during the course of ECT. During c/mECT, the dosage used for the last ECT session was adopted.[19] Seizure quality was defined by the postictal suppression index (PSI) as listed in Table 2. The PSI is a correlate to the so-called central electrical silencing. It describes the ability of the brain to successfully suppress seizure activity and probably correlates to the antidepressant efficacy.

The most commonly used unilateral electrode placement was right unilateral (RUL), even for left-handed patients.[20]

The barbiturates sodium thiopental (3.5–4.0 mg/kg) or methohexital (1 mg/kg) was used for the short general anesthesia, which was administered by anesthesiologists. Suxamethonium (0.5–0.8 mg/kg) was used for short-term muscle relaxation. The dosages of the anesthetics and muscle relaxant remained largely unchanged during c/mECT.

The c/mECT guidelines used in our hospital correspond in modified form to an adaptive fixed pattern,[18] that is, the treatments are administered weekly for the first month and every 2 weeks for the second month. As of the third month, treatment frequency is reduced to once per month and, depending on the clinical symptoms, is then extended to approximately 2- to 3-month intervals.

In principle, psychopharmacological treatment remained unchanged during c/mECT, but antiepileptics were tapered to not excessively raise the current dosage and lithium was reduced to 0.4 mmol/L for safety reasons.

Statistical Analysis

All statistical analyses were performed using SPSS, Version 24. Statistical testing was performed at a 0.05 level of significance. Psychiatric hospitalizations pre- and post-c/mECT were analyzed by comparing the aspects of hospitalization (number, cumulative duration, and average duration of inpatient stays) in a 5-year period before initiation of c/mECT with the corresponding numbers in a 5-year period thereafter. Because some patients had a follow-up time of less than 5 years after initiation of c/mECT, the analysis was based on rates rather than absolute numbers. Two types of summary measures were reported: measures that can be calculated for each subject individually (number of hospitalizations per year, days hospitalized per year) and sample-based epidemiological measures using the concept of person time at risk: hospitalization rate = total number of hospitalizations/person years at risk and mean annual duration of hospitalization = total number of days spent in psychiatric hospital/person years at risk. The first 2 measures are crude measures in the sense that all patients are given the same weight, irrespective of the duration of follow-up (≤5 years). The latter 2 measures account for this imbalance and hence provide corrected estimates.[21]

Hospitalization rates before and after initiation of c/mECT were compared by means of generalized estimation equation (GEE) models with first-order autoregressive error structure, fitting a model with Poisson distribution and log link to the annual number of hospitalizations. The ratio of the 2 hospitalization rates, post-c/mECT versus pre-c/mECT, was used as a measure of the effect attributable to the intervention. In epidemiological terms, this can be regarded as a ratio of 2 incidence rates (IRRs). The cumulative duration of hospitalizations before and after initiation of c/mECT was also analyzed with GEE models. However, the model was based on a binomial distribution to reflect the fact that each day of the observation period (both pre-c/mECT and post-c/mECT) represents a Bernoulli experiment with 2 possible outcomes, namely, hospitalized or not (binomial distribution $B(n, P)$ with n = days at risk and P = probability of being hospitalized). The ratio of the 2 binomial probabilities, P_{post}/P_{pre}, was used to quantify the effect of the intervention. In addition, cumulative durations of hospitalizations were analyzed on an annual basis to allow year-to-year comparisons, for example, first year before c/mECT versus first year after c/mECT, using the same type of GEE model. Finally, the average duration of each patient's

TABLE 1. Patient Characteristics (N = 27)

Variable	Category/Unit	n (%) or Mean ± SD
Sex	Male	10 (37)
	Female	17 (63)
Age at beginning of mECT	Years	54.3 ± 11.7
Age at first hospitalization	Years	48.9 ± 13.3
Duration of illness at beginning of mECT	Years	5.4 ± 5.3
Diagnosis (ICD-10)	Bipolar disorder (F31)	11 (40.7)
	Unipolar depressive disorder (F33)	16 (59.3)
Depressive episode at initiation of ECT		25 (92.6)
Psychopharmacological treatment	Antidepressants	25 (92.6)
	Antipsychotics	24 (88.9)
	Mood stabilizer and lithium	8 (29.6)

ICD indicates International Classification of Diseases 10th version.

inpatient stays before and after c/mECT was compared by means of a paired *t* test. Durations were log transformed before the analysis to obtain an approximately normal distribution.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. All patients experienced a treatment-resistant depressive episode, except the 2 patients (7.4%) who were referred to our hospital in a manic-psychotic state. Treatment resistance was defined by nonresponse to at least 2 different antidepressants, given sufficiently long and in adequate dosage. Patients received an mean ± SD of 8.21 ± 1.8 acute ECT sessions as part of their inpatient treatment. Of the 27 patients enrolled, eight (29.6%) received cECT (<6 months) only, and the remaining 19 (70.4%) underwent mECT (>6 months).

All patients continued treatment with psychopharmacologic drugs during acute ECT and c/mECT. Almost every patient (92.6%) received antidepressants, a large proportion of patients (88.9%) received antipsychotics, and approximately a quarter (26.9%) were treated with mood stabilizers. Tricyclic antidepressants and monoamine oxidase inhibitors were not used. Most antipsychotics prescribed were second- or third-generation antipsychotic drugs. No patient committed suicide or reported a suicide attempt during the observational period.

Characteristics of c/mECT

Patients received c/mECT on average 1.5 times a month (1.51 ± 0.86, range = 0.49–4.35 c/mECT per month), the mean ± SD number of c/mECTs was 21.2 ± 18.0 (range = 5–72) for a period of 1.7 ± 1.9 years (range = 0.15–6.15 years). In most patients (81.5%), an RUL electrode position was used; 18.5% of the patients were stimulated bitemporally. The mean ± SD seizure duration was 50.4 ± 18.4 seconds, resulting in a mean ± SD PSI of 80.5% ± 8.0% at 70.4% ± 27.0% stimulus intensity of a maximum charge of 504 mC (Table 2).

In 14 patients (52%), c/mECT was discontinued after achieving euthymia and in agreement with these patients. Because of insufficient clinical improvement or at the patient's request, treatment was discontinued in 5 individuals. Five patients (19%) were still receiving mECT at the time of study closure. In 1 patient, the so far effective treatment had to be discontinued because of cognitive decline. In 3 patients (11%), the reason for stopping c/mECT was not recorded.

Effect of c/mECT on Psychiatric Admissions

Comparison of the 5-year periods before and after initiation of c/mECT indicates a significant reduction in the 3 outcome measures investigated. Hospitalization rates (mean annual number of hospitalizations corrected for duration of follow-up) decreased by approximately 50% from 0.644 to 0.319 ($P = 0.031$). The total number of inpatient days per year was largely reduced from 23.7 to 6.1 days, that is, to about one quarter of its initial value ($P < 0.001$). In addition, the average duration of each patient's psychiatric inpatient stays decreased markedly from 41.6 days before initiation of c/mECT to 22.1 days thereafter ($P = 0.031$) (Table 3).

A breakdown of the cumulative durations of hospitalizations by year is shown in Figure 1. There was a significant increase in the average number of inpatient days per year before initiation of c/mECT (risk ratio per year [RR] = 1.47, Wald $\chi^2 = 9.19$, $P = 0.002$) and a significant decrease thereafter (RR = 0.47, Wald $\chi^2 = 10.45$, $P = 0.002$). Comparison of corresponding years before and after initiation of c/mECT (first year before vs first year afterwards, etc) reveals that the mean number of inpatient days in the individual years before c/mECT was always significantly larger than the corresponding number after initiation of c/mECT.

DISCUSSION

Our data show a statistically significant effect of combined maintenance treatment with c/mECT and medication on the number and duration of hospitalizations. For a 5-year period before starting c/mECT, the number of hospital admissions was reduced by approximately by two thirds and the mean duration of inpatient treatment was almost halved. In addition, the annual number of hospital stays decreased by 77%. These results are largely consistent with the results of previous studies. Similarly, a retrospective cohort analysis (n = 25) showed a 75% reduction in the duration of hospital stays in a comparable 6-year observation period.[22] In another retrospective survey (n = 43), 83% fewer days of inpatient stay were noted during the reference period.[23] In a further

TABLE 2. Characteristics of c/mECT (N = 27)

Variable	Category/Unit	n (%) or Mean ± SD
Total number of c/mECT		21.15 ± 18.0
Frequency of c/mECT	c/mECT per month	1.51 ± 0.86
Duration of c/mECT	Years	1.70 ± 1.85
Position of electrodes	Unilateral	22 (81.5)
	Bilateral	5 (18.5)
Stimulus intensity	% of 504 mC	70.4 ± 27.0
Ictal EEG duration	Seconds	50.4 ± 18.4
Ictal EMG duration	Seconds	33.3 ± 11.8
PSI	%	80.5% ± 8.0

EEG indicates electroencephalogram; EMG, electromyography.

TABLE 3. Number of Hospitalizations and Number of Days Hospitalized Per Year: 5-y Period Before c/mECT Versus 5-y Period After c/mECT (N = 27)—Without Last Hospitalization Before c/mECT

	Pre-c/mECT	Post-c/mECT	Comparison				
Variable	Mean ± SD (Median)	Mean ± SD (Median)	Measure (Post vs Pre)	95% CI	Statistic	*df*	*P*
No. hospitalizations per year (Hospitalization rate)							
Crude measure	0.644 ± 0.60 (0.60)	0.400 ± 0.45 (0.27)					
Corrected for time at risk*	0.644	0.319	IRR = 0.537	0.31–0.94	Wald $\chi^3 = 4.67$	1	0.031
Total number of inpatient days per year							
Crude measure	23.7 ± 22.2 (18.2)	7.5 ± 9.6 (4.4)					
Corrected for time at risk†	23.7	6.1	RR = 0.256	0.16–0.41	Wald $\chi^3 = 31.0$	1	<0.001
Average duration of inpatient stay							
Crude measure	41.6 ± 29.3 (35.0)	21.8 ± 19.7 (18.5)					
Corrected for time at risk‡	41.6 ± 29.3 (35.0)	22.1 ± 20.5 (18.5)	Ratio = 0.533	0.30–0.93	$t = 2.42$	13	0.031

*Total number of hospitalizations/person years at risk.

†Total number of days spent in a psychiatric ward/person years at risk.

‡Weighted by total time at risk.

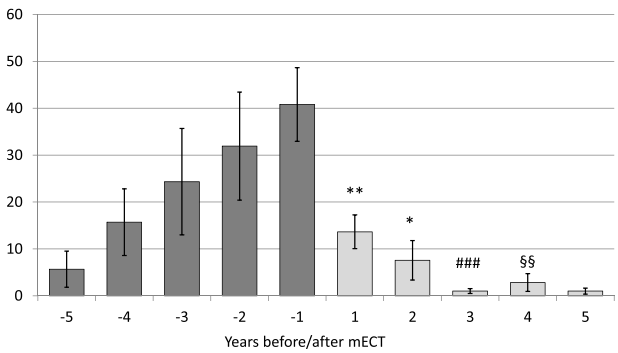
Abbreviations: CI, confidence interval; *df*, degrees of freedom; IRR, incidence rate ratio.

retrospective analysis, the number of inpatient treatment days was also halved after or during c/mECT.[24]

Nevertheless, our results should be interpreted with caution. Data were retrospectively collected. In addition, a positive selection bias, in the sense of an "enriched sample" of patients, can be expected. Another bias might be that closer follow-up necessitated by c/mECT reduced more effectively hospital admissions than did c/mECT itself.

In addition to a delayed onset of the effect of psychopharmaceutical treatments, spontaneous remissions or the simultaneous effect of psychotherapeutic or sociotherapeutic interventions cannot be ruled out. One patient, for example, was discharged to an assisted living setting at the start of c/mECT and has been mentally stable since then, without relapse or hospital admission.

Reasons for discontinuation of treatment as well as adverse effects, such as impairment of cognitive functions, headache and muscle pain, cardiovascular side effects or "tipping" into (hypo)manic episodes could not be determined from the records. Decisions to switch from RUL to bitemporal ECT were based on clinical judgment and not on an evaluated algorithm.



** First year after c/mECT vs. last year before c/mECT: $\chi^2 = 20.6$, p = 0.002
* Second year after vs. second to last year before c/mECT: $\chi^2 = 4.95$, p=0.026
Third year after vs. third to last year before c/mECT: $\chi^2 = 13.4$, p < 0.001
§§ Fourth to fifth year after vs. fourth to fifth year before c/mECT: $\chi^2 = 7.64$, p=0.006

FIGURE 1. The mean number of days per year spent in a psychiatric ward: pre- versus post-mECT.

Although no evidence-based guidelines are currently available for patient-oriented flexible scheduling of ECT, a symptom-driven, algorithm-based longitudinal ECT study (STABLE) has been proposed as a patient-focused approach to individualized c/mECT schedules.[25]

Comparison with other studies with regard to these clinically important methodological aspects is therefore problematic. In the only randomized controlled trial conducted to date, the drop-out rate was 17% in the c/mECT arm compared with 22% in the pharmacotherapy arm.[26] As already mentioned, the literature shows no evidence of lasting cognitive impairment during c/mECT.[16] However, temporary cognitive impairment may occur and an increased risk of falls within the first 3 days after a single ECT session has been described.[27]

Similar to other c/mECT studies, only a relatively small number of patients was included.[24,28,29] As patients with unipolar and bipolar disorder were analyzed together, the study population is heterogeneous.

Nevertheless, this article has some strengths as compared with previous investigations. Because most c/mECT studies have a relatively short duration with a maximum of 12 months, this study was designed to examine longer-term outcomes to address this gap. The length of the comparison period (5 years before and 5 years after c/mECT) is a duration that has not yet been investigated.

Despite methodological concerns, our results show that medication-augmented c/mECT treatment in patients with severe, recurrent, and treatment-resistant mood disorders is able to reduce the number of hospital stays and their duration. This is in line with the majority of the reports available in the literature[30] as well as with our own preliminary data from a smaller sample.[17]

Based on our results and the current literature, we suggest that after a successful ECT series, c/mECT is more frequently considered, especially in patients with a high risk of relapse.

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