A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT

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Abstract

An important goal in electroconvulsive therapy (ECT) research is to minimize associated cognitive side-effects while maintaining its high efficacy. This study explored the use of a novel approach, right unilateral (RUL) ECT with an ultrabrief pulsewidth (0.3 ms) (RUL-UB), in comparison with standard RUL ECT. Seventy-four depressed in-patients received RUL-UB ECT at six times seizure threshold, and 22 patients received standard RUL ECT (1.0 ms pulsewidth) at five times seizure threshold. Formal, prospective evaluations of mood and cognitive functioning over the treatment course were done by a rater blinded to treatment condition. Efficacy was maintained using the ultrabrief pulsewidth, with equivalent numbers of responders and remitters to the standard RUL ECT group, although the speed of response was slower. Cognitive outcomes were superior in the RUL-UB ECT group, particularly in the retention of verbal and visual information, as well as in retrograde autobiographical memory.

Introduction

Electroconvulsive therapy (ECT) is the most effective treatment for severe depression but its use is often limited by concerns over cognitive side-effects. A range of strategies to achieve similar efficacy with fewer adverse effects have been proposed (MacPherson and Loo, 2008; Pigot et al., 2008; Prudic, 2008). Manipulation of the pulsewidth of the electrical stimulus during ECT is one such prominent technique currently under investigation.

Since its inception in 1938, a key advance in ECT technique was the modification of the electrical stimulus, from a long pulsewidth (8 ms), sine-wave stimulus, to a brief pulsewidth (0.5–1.5 ms), square-wave stimulus. With this development efficacy was preserved (Kho et al., 2003), while cognitive side-effects (confusion, retrograde amnesia) were markedly reduced (Carney et al., 1976; Valentine et al., 1968; Weiner et al., 1986). Thus, brief pulsewidths of 0.5–1.5 ms are commonly used in modern ECT machines and in clinical ECT practice. Neurophysiological observations however, suggest that the optimal pulsewidth for neuronal stimulation is even shorter at 0.1–0.2 ms, which avoids unnecessary stimulation during the refractory period of the neuron, and results in neuronal depolarization at lower electrical doses (Ranck, 1975). Unfortunately, reductions of pulsewidths to this extent are not practical in the context of ECT due to the difficulty of achieving sufficient charge, within the dosage range used in typical clinical practice. Consequently, attention has turned to the use of a pulsewidth of 0.3 ms (known as 'ultrabrief' in contrast to 'brief') in ECT. Theoretically, it has been suggested that a narrower band of tissue would be stimulated with reduction of the pulsewidth, minimizing the stimulation of adjacent, non-targeted brain areas, and thus associated side-effects (Sackeim, 2004). However, the exact differences in brain stimulation outcomes (current pathway, charge density) with reduction of the pulsewidth to 0.3 ms are unknown, and should be examined, e.g. using computer modelling techniques.

Thus far clinical research involving the ultrabrief pulsewidth in ECT has been limited. The main

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evidence comes from two double-blind, randomized-controlled trials [Sackeim et al., 2008; Sienaert et al., 2006 (conference abstract)], and a retrospective report (Loo et al., 2007).

Sackeim et al. (2008) randomized 90 depressed patients to one of four treatment groups: right unilateral (RUL) ECT at six times seizure threshold, or bilateral (bitemporal) ECT at 2.5 times seizure threshold, given at a standard (1.5 ms) or ultrabrief (0.3 ms) pulsewidth. For RUL ECT, both the ultrabrief and standard pulsewidth approaches were found to be very effective, with no significant difference in final remission rates [Hamilton Depression Rating Scale (HAMD)-24 score ⩽10, 1 wk after ECT] of 73% and 59% respectively. Analysis of cognitive outcomes revealed patients treated with the ultrabrief pulsewidth showed significantly less impairment of anterograde and retrograde memory than patients receiving standard pulsewidth stimulation, for both RUL and bilateral ECT.

In a double-blind study, Sienaert et al. (2006) randomized 64 depressed patients to receive RUL ECT at six times seizure threshold or bifrontal ECT at 1.5 times seizure threshold, both given with an ultrabrief pulsewidth (0.3 ms). Efficacy was similar for both groups with the remission rate of 44% (defined as final HAMD-17 score ⩽7) for RUL-ultrabrief (UB) ECT being clinically significant, although less than that of the Sackeim et al. (2008) study. Consistent with the Sackeim et al. study, RUL-UB (and ultrabrief bifrontal) ECT appeared to have minimal effect on cognitive functioning, with no change found on the Mini Mental State Examination (MMSE; Folstein et al., 1975), and some significant improvements in verbal memory, attention, executive functioning and autobiographical memory (Sienaert et al., 2008).

Together, these studies suggested that the reduction of the pulsewidth in ECT to 0.3 ms can be effective in maintaining efficacy while minimizing cognitive side-effects. The present study tested these assertions in a larger sample, drawn from patients referred for ECT in a typical clinical service. All patients were prospectively evaluated for mood and cognitive outcomes over a course of treatment with RUL-UB ECT at 0.3 ms pulsewidth, or the standard form of RUL ECT used at the clinic (1.0 ms pulsewidth).

Method

Study design

All in-patients at a Sydney psychiatric hospital who were beginning an acute course of RUL ECT, from 2005 to 2008, were screened for inclusion in the trial. The trial was approved by the Human Research Ethics Committees of the University of New South Wales and Ramsay Sydney Psychiatric Hospitals. Prospective data was gathered from patients who met inclusion criteria and gave written informed consent. The trial followed a naturalistic design whereby the type of RUL ECT (standard: RUL; or ultrabrief pulsewidth: RUL-UB) given, the number of ECT treatments and the decision to switch to bilateral ECT were determined by the patient's treating psychiatrist, based on clinical observations, i.e. the decision to switch to bilateral ECT was based on inadequate clinical response to unilateral ECT, as judged by the treating psychiatrist. Mood and cognitive functioning were assessed by a rater blind to the patient's treatment category.

Participants

All participants met the following inclusion criteria: DSM-IV-TR major depressive episode, no other Axis I disorder (except for bipolar disorder, non-rapid cycling), score ⩾25 on Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), score ⩾20 on MMSE, age ⩾18 yr, no ECT in the last 3 months, no drug or alcohol abuse in the last 6 months, and no significant neurological disease. Clinical and demographic data were collected in detailed assessments conducted by a psychiatrist (see Table 1).

Antidepressant medications taken by the patients were either discontinued prior to commencing ECT or were continued at a stable dose during the ECT course. Anticonvulsant medications were withdrawn. All decisions regarding medication status were made clinically by the patient's psychiatrist.

ECT procedure

ECT was administered three times per week with a Mecta Spectrum 5000 Q machine (Mecta Corp., Lake Oswego, OR, USA). Thiopentone (3–5 mg/kg) and succinyl choline (1 mg/kg) were used for anaesthetic induction and muscle relaxation. At the first session, seizure threshold was determined by titration. Standard RUL ECT was given at five times seizure threshold [as it was not considered feasible to consistently treat all subjects at six times seizure threshold, given the relatively higher seizure thresholds with a standard pulsewidth, and maximum dose available of 1152 milliCoulombs (mC)], 1.0 ms pulsewidth, and RUL-UB ECT was given at six times seizure threshold, 0.3 ms pulsewidth. Treatment procedures for both groups were otherwise identical. The ictal EEG was

Table 1. Demographic, clinical and ECT treatment characteristics of the two treatment groups [mean (standard deviation)]

Scale	RUL	RUL-UB	t test	χ^2	Sig.
Age	50.4 (12.8)	47.7 (15.5)	0.74		0.459
Gender: male	9	34		0.17	0.677
Diagnosis					
MDD	15	43		0.51	0.475
Bipolar	7	29			
Melancholic features	11/22	50/72		2.80	0.094
Psychotic features	0/22	10/72		3.42	0.064
Current episode duration (wk)	41.9 (39.3)	72.1 (72.3)	−2.42		<0.05
No. of adequate courses failed	3.3 (2.0)	3.2 (1.8)	0.20		0.840
Previous depressive episodes	19/22	69/72		2.53	0.112
Previous ECT	10/22	23/72		1.35	0.245
Antidepressant taken during ECT	19/22	52/72		1.82	0.177
Onset age (yr)	36.0 (14.7)	30.3 (14.0)	1.65		0.103
MADRS score pre-ECT	36.1 (5.3)	35.7 (7.9)	0.19		0.853
MMSE score	29.1 (1.0)	29.0 (1.2)	0.30		0.767
NART errors	16.2 (8.3)	14.5 (8.0)	0.81		0.425
Initial seizure threshold (mC)	73.5 (28.2)	36.0 (29.6)	5.25		<0.001
Dose (mC) first treatment	354.9 (161.1)	219.3 (140.6)	3.83		<0.001
Dose (mC) final treatment	468.6 (237.5)	419.4 (271.6)	0.75		0.455
No. of ECT treatments[a]	7.6 (2.8)	10.3 (3.2)	−2.46		<0.05
Switch rate to bilateral ECT	8/22	41/74		4.05	0.132
No. of ECT treatments prior to switching to bilateral ECT[b]	6.4 (2.5)	6.4 (2.1)	0.001		0.991
Response after unilateral ECT[c]	11/22	32/74		0.26	0.611
Remission after unilateral ECT[c]	8/22	20/74		0.65	0.419

ECT, Electroconvulsive therapy; EEG, electroencephalogram; MADRS, Montgomery–Asberg Depression Rating Scale; mC, milliCoulombs; MDD, major depressive disorder; MMSE, Mini Mental State Examination; NART, National Adult Reading Test; RUL, right unilateral; RUL-UB, right unilateral ultrabrief.

[a] Based on patients who finished the ECT course with one electrode placement (i.e. did not switch to bilateral ECT).

[b] Based on patients who switched to a bilateral electrode placement.

[c] Note results do not include outcomes after switching to bilateral ECT.

monitored through two prefrontal-mastoid channels. ECT doses were increased during the course of treatment, by 50% each time, when there was a significant decline in EEG seizure quality (according to the indices described by Krystal *et al.*, 1998).

Testing materials and procedure

Mood ratings

The patient's mood was assessed by a psychologist using the MADRS prior to commencing ECT, after each week of ECT, and at the end of the treatment course. Response was defined as ⩾50% improvement in MADRS scores from pre-ECT baseline, and remission as a final MADRS score <10.

Cognitive assessments

Patients were assessed by a psychologist prior to commencing ECT, after six ECT treatments and at

the end of the treatment course using the following tests: Rey–Osterrieth and Taylor Complex Figure Tests (CFT); Rey Auditory Verbal Learning Test (RAVLT); Controlled Oral Word Association Task (COWAT); Digit Span forwards; Stroop Test; Autobiographical Memory Interview – short form (AMI-SF; McElhiney *et al.*, 2001). For the first 67 subjects, an abbreviated 10-item version of the AMI was used, prior to the introduction of the AMI-SF. For the CFT, RAVLT and COWAT, alternative forms were used across the different testing occasions, to minimize practice effects.

Statistical analysis

The two ECT treatment groups were compared for differences in baseline demographic and clinical variables, and in ECT treatment indices and outcomes, using t tests (continuous data) and χ^2 (categorical data) tests. A repeated-measures analysis of covariance

(ANCOVA) was conducted on the MADRS scores with ECT treatment group as the between-subjects factor and time-point (before ECT, after each week of ECT, end of the treatment course) as the repeated-measures factor, controlling for the effects of the number of ECT treatments in each group. The analysis accounted for missing data (e.g. subjects withdrawing and/or switching to bilateral ECT) by an intention-to-treat approach, in all cases where there had been at least one further rating after the baseline rating.

Neuropsychological test scores were examined using ANCOVAs with baseline scores and MADRS scores at week 2 as the covariates (for scores after six treatments), and baseline scores, the number of ECT treatments, and final MADRS scores as covariates (for final scores after ECT). For the RUL-UB group, paired *t* tests were conducted on the cognitive data to assess for significant changes from the pre-ECT baseline. All *p* values were calculated in two-tailed tests with the significance level set at $p < 0.05$.

Results

Clinical and demographic characteristics, and ECT treatment indices

The two ECT treatment groups did not differ in most clinical and demographic characteristics at baseline. The RUL-UB group had lower seizure thresholds and initial treatment doses and a higher number of ECT treatments (see Table 1).

Mood scores

There was a significant reduction in MADRS scores over the ECT treatment course [$F_{(3, 231)} = 2.87$, $p < 0.05$]. There were no significant differences in MADRS scores between the RUL and the RUL-UB ECT groups across the treatment course ($p > 0.05$); however, the interaction between time-point and ECT group was significant [$F_{(3, 231)} = 2.97$, $p < 0.05$], indicating the rate of decline in MADRS scores was slower for the RUL-UB group than the RUL group (see Figure 1).

Cognitive assessments

The RUL-UB group performed better than the RUL group on several measures after six ECT treatments and at the end of the ECT course (see Table 2).

Analysis of the RUL-UB group alone showed significant decline in functioning in some tests over the course of ECT: RAVLT total learning [$t_{(58)} = 4.8$, $p < 0.001$], immediate recall [$t_{(58)} = 7.9$, $p < 0.001$] and delayed recall [$t_{(57)} = 8.4$, $p < 0.001$]; COWAT
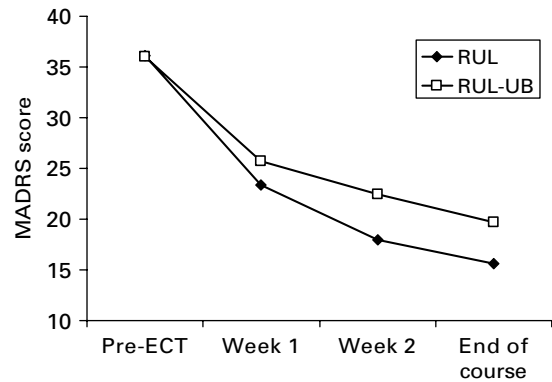
Figure 1. Mean Montgomery–Asberg Depression Rating Scale (MADRS) scores for the standard right unilateral (RUL) and ultrabrief (RUL-UB) electroconvulsive therapy (ECT) groups. Time-points shown are pre-ECT, after 1 and 2 wk treatment, and at the end of unilateral ECT treatment.

letters [$t_{(58)} = 6.1$, $p < 0.001$] and category [$t_{(58)} = 4.9$, $p < 0.001$]; AMI [$t_{(59)} = 3.2$, $p < 0.01$]; and AMI-SF [$t_{(26)} = 3.6$, $p < 0.001$].

Discussion

Consistent with Sackeim et al. (2008), in the present study seizure thresholds were markedly lower with ultrabrief pulsewidth stimulation than with a standard pulsewidth. This difference reflects the more physiological and hence, more efficient nature of the ultrabrief stimulus.

In contrast, the remission rates observed here after both RUL and RUL-UB ECT (36% and 27% respectively) were lower than rates reported in the Sackeim et al. (2008) and Sienaert et al. (2006) studies. This is despite the fact that both forms of RUL ECT were given at higher relative and absolute doses than in the Sackeim et al. study (details of actual doses were not reported in the conference abstract and poster by Sienaert et al., 2006). Mean actual doses quoted in the Sackeim et al. study indicated that RUL and RUL-UB ECT were given at approximately 4.5 and 5 times seizure threshold respectively, with absolute doses (mC) being less than half those used in this study. The latter is partly accounted for by the lower seizure thresholds found in their study, and is probably attributable to the use of methohexital (which is not available in Australia) rather than the more anticonvulsant thiopentone as the anaesthetic induction agent. Furthermore, in the present study, treatment doses were typically increased over the course of ECT, whereas doses were unchanged in the Sackeim et al. study. Thus, the poorer outcomes in our study did not arise from insufficient dosage.

Table 2. Neuropsychological test scores for the two treatment groups

Assessment	RUL Mean (S.D.)	RUL-UB Mean (S.D.)	F	p
Complex Figure Task				
Pre-ECT				
Copy	32.8 (6.5)	35.4 (1.2)	9.43	<0.01
Immediate recall	19.4 (8.9)	20.8 (8.1)	0.45	0.502
Delayed recall	18.4 (7.2)	21.0 (8.4)	1.49	0.226
% forgotten[a]	−2.7 (23.1)	0.4 (19.6)	0.35	0.555
After 6 treatments[b]				
Copy	33.6 (0.5)	34.9 (0.3)	4.45	<0.05
Immediate recall	17.5 (1.6)	19.8 (0.9)	1.58	0.214
Delayed recall	14.2 (1.3)	19.3 (0.7)	11.38	<0.01
% forgotten[a]	17.6 (8.5)	−4.5 (4.5)	5.29	<0.05
After ECT[c]				
Copy	34.0 (0.5)	34.9 (0.3)	2.0	0.163
Immediate recall	17.8 (1.7)	20.1 (0.9)	1.42	0.235
Delayed recall	14.5 (1.6)	19.9 (0.7)	9.58	<0.01
% forgotten[a]	18.2 (9.3)	−5.7 (4.5)	5.28	<0.05
Rey Auditory Verbal Learning Task				
Pre-ECT				
Total learning	49.9 (12.3)	48.5 (10.1)	0.25	0.616
Immediate recall	10.2 (3.6)	9.8 (3.2)	0.24	0.629
Delayed recall	10.4 (3.8)	10.0 (3.2)	0.28	0.595
After 6 treatments[b]				
Total learning	39.6 (2.4)	41.9 (1.3)	0.68	0.412
Immediate recall	5.2 (0.7)	6.7 (0.4)	3.68	0.059
Delayed recall	4.7 (0.7)	6.8 (0.4)	6.32	<0.05
After ECT[c]				
Total learning	40.9 (2.7)	42.8 (1.4)	0.39	0.536
Immediate recall	5.8 (0.8)	6.7 (0.4)	0.92	0.340
Delayed recall	5.0 (0.8)	6.8 (0.4)	3.91	0.052
Controlled Oral Word Association Task				
Pre-ECT				
Letters	40.6 (14.1)	42.0 (12.8)	0.17	0.681
Category	19.9 (5.6)	19.8 (4.8)	0.00	0.956
After 6 treatments[b]				
Letters	35.6 (2.3)	33.5 (1.3)	0.63	0.429
Category	16.2 (1.4)	16.5 (0.8)	0.02	0.877
After ECT[c]				
Letters	34.6 (2.5)	32.4 (1.3)	0.57	0.453
Category	15.9 (1.5)	15.4 (0.8)	0.09	0.765
Digit Span				
Pre-ECT	7.7 (1.8)	8.7 (2.5)	2.61	0.110
After 6 treatments[b]	9.0 (0.4)	8.4 (0.2)	1.44	0.233
After ECT[c]	9.3 (0.5)	8.6 (0.2)	1.44	0.235
Stroop task				
Pre-ECT				
Interference ratio[d]	2.0 (0.9)	2.0 (0.6)	0.00	0.972
Median RT	18.7 (5.8)	18.1 (5.7)	0.14	0.708
After 6 treatments[b]				
Interference ratio[d]	2.1 (0.2)	1.9 (0.1)	1.92	0.170
Median RT	17.9 (1.1)	18.1 (0.6)	0.03	0.855

[*continues overleaf*

Table 2 (*cont.*)

Assessment	RUL Mean (S.D.)	RUL-UB Mean (S.D.)	F	p
Stroop task (*cont.*)				
After ECT[c]				
Interference ratio	2.1 (0.2)	1.8 (0.1)	3.65	0.060
Median RT	18.1 (1.3)	18.7 (0.7)	0.15	0.700
Autobiographical Memory Interview (10-item)				
Pre-ECT	11.8 (1.2)	12.0 (1.1)	0.54	0.464
After 6 treatments[b]	11.2 (0.2)	11.5 (0.1)	0.99	0.322
After ECT[c]	11.1 (0.3)	11.5 (0.1)	1.95	0.167
Autobiographical Memory Interview – Short Form[e] (30-item)				
Pre-ECT	42.6 (14.5)	44.0 (9.2)	0.19	0.667
After 6 treatments	36.0 (19.1)	42.0 (9.4)	2.95	0.097
After ECT	22.7 (8.1)	41.1 (9.9)	11.1	<0.01

ECT, Electroconvulsive therapy; RT, Reaction time; RUL, right unilateral; RUL-UB, right unilateral ultrabrief.

[a] % forgotten = [(immediate recall – delayed recall)/immediate recall] × 100. Positive scores indicate a drop off from immediate to delayed recall, whereas negative scores indicate more was recalled at delayed than immediate recall.

[b] After six treatments: analysis of covariance with baseline scores as covariate. RUL ($n = 18$), RUL-UB ($n = 59$).

[c] After ECT: analysis of covariance with baseline scores and number of ECT treatments as covariates. RUL ($n = 16$), RUL-UB ($n = 59$).

[d] Interference ratio = time incongruent/time dots.

[e] RUL ($n = 5$ pre-ECT, $n = 3$ after six treatments, after ECT); RUL-UB ($n = 27$ pre-ECT, after six treatments, after ECT).

Differences between the study populations used in our study and the Sackeim et al. (2008) study may account for the lower response and remission rates observed here. Specifically, the present sample was derived from a typical clinical ECT service, whereas the Sackeim et al. study was conducted at a research centre. Although there were minimal differences in the inclusion criteria used, this sample included a lower proportion of psychotic patients and may have been more treatment resistant, having failed a larger number of antidepressant trials prior to ECT (mean 3.2 compared with 2). Both these factors have been reported to be associated with poorer ECT response (Dombrovski et al., 2005; Petrides et al., 2001).

It is also important to note that the response and remission rates quoted (Table 1) are based on mood outcomes after unilateral ECT treatment only (i.e. not including outcomes after the switch to bilateral ECT). Thus, of those who completed treatment with unilateral ECT only, response and remission rates were in fact 79% and 57% (RUL group), and 97% and 61% (RUL-UB group) respectively. Patients were switched to bilateral ECT treatment based on clinical judgements of inadequate response, after a mean of six unilateral treatments (both groups). However, insufficient time may have been given for response to RUL-UB ECT,

given that the average number of treatments required by the 33 RUL-UB patients who did not switch (of which 32 were responders) was ten.

Unfortunately, data on final response and remission rates (after all unilateral and bilateral ECT) are not available, but would be expected to be substantially higher than the initial response and remission rates quoted in Table 1, judging from reports by others (Sackeim et al., 2008).

Amongst patients who did not switch to bilateral ECT, the RUL-UB group required more ECT sessions than the RUL ECT group, suggesting the speed of response may be slower with an ultrabrief stimulus. However, the two treatment groups did not differ in overall efficacy outcomes, in terms of the final rates of response and remission. The RUL-UB group had a significantly longer duration of the current episode of depression, a factor reported to be associated with poorer treatment response (Dombrovski et al., 2005). It is possible that this may have contributed to the slower speed of response observed.

In line with previous investigations, these results showed less impairment of anterograde and retrograde memory after RUL-UB ECT than RUL ECT. The differences between the two groups appeared to mainly reflect a deficit in retaining information over a

delay, rather than learning or immediate recall, which were equivalent for the RUL and RUL-UB groups. The lesser retrograde amnesia for the RUL-UB group became apparent when the more sensitive 30-item AMI-SF was used, despite the relatively small subsample in which this version was used.

In contrast to the findings presented by Sienaert et al. (2006) and Sackeim et al. (2008), some impairment in neuropsychological function (verbal memory, frontal functioning, and retrograde memory) was apparent after the course of RUL-UB ECT. In the present study a higher number of ECT treatments was given (mean 10.3 compared with 8.7 in the Sackeim et al. study), ECT was given at a higher dosage (relative to seizure threshold and in absolute terms), and doses were further increased over the course of treatment, such that absolute doses at the end of the ECT course were similar to those used for standard RUL ECT. It is probable that these factors accounted for the greater cognitive impairment with RUL-UB in the present study. Taking these considerations into account, the cognitive outcomes reported here are not inconsistent with previous studies.

Several important limitations should be considered when interpreting these results. As patients were not randomly allocated to the two ECT groups, it is possible that bias may have been introduced. For example, the treating psychiatrists may have tended to assign more severely ill patients to RUL ECT or patients at greater risk of cognitive impairment to RUL-UB ECT. However, detailed clinical data collected prior to ECT, found there were no significant differences between the groups on clinical and demographic variables (apart from episode duration) or baseline mood and cognitive scores. Additionally, the previously mentioned assignment bias would have tended to overestimate the cognitive impairment associated with RUL-UB ECT, whereas our study found that it was reduced. The unequal sample sizes of the two groups may also have resulted in a loss of power to detect more subtle differences. Strengths of the study included the testing of RUL-UB ECT in a typical ECT clinical population, using formal, prospective assessments of mood and cognitive outcomes by a rater blinded to the type of ECT, in a larger sample than hitherto reported.

These findings support previous reports of reduced cognitive impairment with reduction of the pulsewidth to 0.3 ms for RUL ECT. However, the results also suggest that this cognitive advantage may be accompanied by a slower speed of response, with a greater number of treatments required to achieve equivalent response. Further, more than six treatments may be required for an adequate trial of RUL-UB ECT, prior to any decision to switch to another form of ECT. These issues require further investigation. Overall, the results support the further development of RUL-UB ECT as a major advance in ECT technique, and its cautious adoption into clinical practice, with the caveat that a larger number of treatments may be required, and that response may be slower.

Acknowledgements

Statement of Interest

None.

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