Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomised, non-inferiority trial

Supplemental Material

ECT DOSING PROCEDURES

Brief-pulse (1.0 msec pulse width; current amplitude 800 mA) ECT was administered with hand-held electrodes using the Mecta 5000M device (Mecta Corporation, USA; maximum 1200mC). Methohexital (0.75–1.0 mg/kg) was used for anaesthesia and succinylcholine (0.5–1.0 mg/kg) for muscle relaxation. Patients were oxygenated during the procedure with 100% O2 under positive pressure and were monitored for blood pressure, heart rate and rhythm, pulse oximetry and capnography. Seizure duration was measured by observation of motor activity and electroencephalogram (EEG).

Table S1 Stimulus titration and dosing procedures

		Suprathreshold treatment dose (mC)	
Level	Threshold (mC)	Bitemporal (1.5x)	Right unilateral (6x)
1	25	50	150
2	50	75	300
3	75	125	450
4	100	150	600
5	150	225	900
6	250	375	1200
7	350	550	1200
8	500	750	1200
9	750	1000	1200

Empirical dose titration was used to establish the seizure threshold in the first ECT session (1, 2). The seizure threshold was defined as the lowest stimulus charge that produced an adequate seizure, i.e. a generalised tonic/clonic seizure lasting ≥15 seconds from the end of the stimulus, or an electroencephalogram (EEG) record of polyspike followed by 3 Hz spike-and-wave activity lasting ≥25 seconds. The titration procedure is shown in Table S1

and began at the lowest dose of 25 mC. Several factors are known to affect seizure threshold, including older age (>65 years), male gender, use of benzodiazepines and anticonvulsant drugs, and bitemporal electrode placement (3). The presence of any of these factors was incorporated into the dose titration algorithm to tailor the process to the individual patient by beginning at one level higher for each one of these factors when present. For example, in the titration procedure shown in Table S1, the initial stimulus dose for a young adult female undergoing unilateral ECT would be at the lowest level, i.e. 25 mC. However, if she was over 65 years old and taking regular benzodiazepines, the initial stimulus dose would be increased by two levels up to 75 mC.

Patients were stimulated at the appropriate initial level. If an adequate seizure was not produced, then the patient was restimulated one level higher (see Table S1). There was an interval of at least 30 seconds before each restimulation. If an adequate seizure was still not produced after the second attempt, and anaesthetic conditions permitted, the patient was restimulated for the second time at another two levels higher, i.e. one level was skipped. If in the first session a third stimulation was required and resulted in an adequate seizure, the seizure threshold could have been either the dose used or the previous (i.e. skipped) level. Therefore, the second session began with the skipped dose level to clarify the seizure threshold.

Once the seizure threshold was established, subsequent treatments were given at 1.5xthreshold for bitemporal and 6xthreshold for unilateral (d'Elia placement) ECT. Seizure threshold can substantially rise over the course of ECT and this may be manifested in a progressive shortening in seizure duration. The aim of the treatment is to ensure that the dose clearly remains suprathreshold (2). Therefore, if the EEG seizure duration fell by >20% relative to the second session then the initial stimulus dose was raised in the next session by

one level (see Table S1). This new level was adopted as the initial dose for subsequent sessions.

HANDLING OF MISSING DATA

In the presence of missing data, the resulting (maximum likelihood) estimators of group effects on outcome variables are valid provided that missing data-generating mechanisms are Missing At Random (MAR), which here implies that the probability of the outcome being unobserved at the respective post treatment time point depends only on covariates included in the analysis model. Such a MAR assumption might not be realistic and violations of the assumption could lead to biased effectiveness estimates, in particular for non-prioritised secondary outcomes. To base analyses on less restrictive MAR assumptions, we employed multiple imputation (MI). This allowed us to include additional variables (including post randomisation variables) in the imputation step of the MI procedure without having to condition on them in the analysis model. The approach relaxed the MAR assumption to also allow these variables to be predictive of missing outcome and thus avoid bias (4). Specifically, the following types of variables were included in the imputation step: (i) outcome measures at all available time points; (ii) covariates of the analysis model; (iii) known prognostic variables (treatment resistance(5, 6), psychosis(7)); (iv) HDRS-24 at any time point since ability to complete questionnaires may be affected by current depression severity; (v) additional baseline variables detected empirically to predict missingness of respective 6-month outcomes (see later Results); (vi) CAMI-SF at end-of-treatment if this prioritised outcome was found to be predictive of any outcome missingness (8).

Regarding (v) and (vi), we ran a series of binary logistic regressions for observing values of HDRS-24, CAMI-SF, Trail-Making B and FCSRT immediate recall at six-months.

Poor end-of-treatment CAMI-SF performance predicted missingness of both HDRS-24 and CAMI-SF at six-months and was included in all imputation models. With regard to non-prioritised outcomes, poorer performance on category fluency and better performance on FCSRT immediate recall at baseline predicted missingness respectively in Trail-Making B and FCSRT immediate recall and these two variables were also included in the imputation models for these outcomes.

Imputation by chained equations was carried out using Stata's ice command with the number of imputations set to 200. Steps were taken to ensure imputed values lay within limited scale ranges and respected the discrete nature of some scales. In addition, distributions of imputed values were always compared with those of respective observed values to check that imputed values appeared realistic. (Further technical information regarding imputation procedures can be requested from the authors.) Where missing values were present in an outcome we always report findings from the multiple imputation analysis. For the prioritised outcomes (HDRS-24, CAMI-SF), where the amount of missingness was relatively small, we also compared MI results with complete-case analysis results and found these to be very similar (details not reported.)

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Table S2 Neurocognitive test battery and associated references	
Test	**Reference**
Mini-mental state examination	Folstein MF, Folstein SE, McHugh PR: "Mini mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198
National Adult Reading Test	Nelson HE, Willison I: National Adult Reading Test (NART). Windsor, NFER Nelson, 1991
Digit Span (WAIS-III)	Wechsler D: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). San Antonio, The Psychological Corporation, 1997
Trails Making Tests A and B	Reitan RM Wolfson, D: The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation. Tucson, AZ, Neuropsychological Press, 1985
Category fluency	Lezak MD, Howieson DB, Biegler ED, Tranel D: Neuropsychological assessment. 5th ed. New York, Oxford Univerity Press, 2012
Free and Cued Selective Reminding Test	Van der Linden M, GREMEM: Memory disorders assessment - four episodic memory tests with normative data. Marseille, Solal, 2004
Complex Figures Test	Strauss E, Sherman EMS, Spreen O: Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York, Oxford University Press, 2006, pp. 811-841 Versions: (1) Rey-Osterrieth, Form A, (2) Rey-Osterrieth, Form B, (3) Medical College of Georgia Complex Figure 1; (4) Medical College of Georgia Complex Figure 2

TABLE S3: Distribution of % autobiographical memory recall consistency scores on the Columbia Autobiographical Memory Interview – Short Form according to treatment allocation

	Bitemporal electrode placement	Right unilateral electrode placement
	End-of-treatment	
Minimum	0	27
Maximum	100	93
25th Percentile	46.25	54.25
50th Percentile	55.00	71.00
75th Percentile	69.00	80.75
	3-months follow-up	
Minimum	11	20
Maximum	100	93
25th Percentile	41.50	59.25
50th Percentile	56.50	68.00
75th Percentile	67.75	76.75
	6-months follow-up	
Minimum	28	13
Maximum	95	92
25th Percentile	42.00	53.5
50th Percentile	50.00	65.00
75th Percentile	64.25	78.50

TABLE S4: Results of analyses of cognitive outcomes by post treatment time point						
Cognitive tasks			**Comparison of randomisation groups[a]**			
	Predicted mean[b] RUL (N=69)	**Predicted mean[b] Bitemporal (N=69)**	**Estimated difference in means**		**Statistical significance test**	
			BT-RUL	**95% CI**	**z**	**p**
Global cognitive status: MMSE						
Baseline (sample average)	27.7 (N=59)	27.7 (N=60)				
EOT	27.8 (N=62)	27.4 (N=63)	-0.4	-1.2 to 0.4	-0.93	0.35
3 months	27.9 (N=45)	28.1 (N=31)	0.2	-0.6 to 1.0	0.44	0.66
6 months	28.2 (N=38)	28.1 (N=32)	-0.1	-1.1 to 1.0	-0.12	0.90
Psychomotor speed: TMT-A[c]						
Baseline (sample average)	51.4 (N=49)	51.4 (N=54)				
EOT	53.1 (N=54)	47.9 (N=59)	0.9	0.8 to 1.0	-1.52	0.13
3 months	44.1 (N=40)	43.8 (N=28)	1.0	0.8 to 1.2	-0.07	0.94
6 months	41.0 (N=34)	43.1 (N=30)	1.1	0.9 to 1.3	0.52	0.61
Auditory attention: Digit span forward						
Baseline (sample average)	8.0 (N=53)	8.0 (N=52)				
EOT	8.8 (N=55)	8.1 (N=58)	-0.7	-1.5 to 0.2	-1.51	0.14
3 months	8.8 (N=41)	7.7 (N=30)	-1.2	-2.1 to -0.2	-2.36	0.02
6 months	9.3 (N=38)	8.4 (N=29)	-0.8	-1.8 to 0.1	-1.76	0.08
Verbal working memory: Digit span backward						
Baseline (sample average)	5.7 (N=53)	5.7 (N=52)				
EOT	5.9 (N=55)	5.8 (N=58)	-0.04	-0.9 to 0.8	0.08	0.93
3 months	6.4 (N=41)	5.6 (N=30)	-0.8	-1.6 to 0.0	2.01	0.05
6 months	7.0 (N=37)	6.3 (N=29)	-0.6	-1.7 to 0.5	-1.16	0.25
Verbal learning: FCSRT immediate recall						
Baseline (sample average)	24.9 (N=47)	24.9 (N=48)				
EOT	25.7 (N=49)	22.5 (N=50)	-3.2	-6.1 to -0.2	-2.15	0.03
3 months	27.3 (N=36)	26.7 (N=31)	-0.6	-3.5 to 2.4	-0.40	0.69
6 months	28.5 (N=33)	27.6 (N=28)	-0.9	-4.9 to 3.0	-0.46	0.65
Verbal delayed memory: FCSRT delayed recall						
Baseline (sample average)	9.6 (N=47)	9.6 (N=47)				
EOT	8.5 (N=49)	7.7 (N=49)	-0.8	-2.1 to 0.5	-1.24	0.22
3 months	9.3 (N=36)	9.2 (N=31)	-0.2	-1.5 to 1.2	-0.23	0.82
6 months	9.6 (N=32)	9.2 (N=28)	-0.4	-1.8 to 1.05	-0.53	0.60
Visuo-spatial functioning: CFT copy						
Baseline (sample average)	26.4 (N=46)	26.4 (N=45)				
EOT	28.9 (N=51)	29.2 (N=54)	0.3	-1.4 to 2.1	0.37	0.71

3 months	30.9 (N=39)	31.0 (N=31)	0.2	-1.5 to 1.8	0.19	0.85
6 months	30.3 (N=33)	30.2(N=29)	-0.1	-1.8 to 1.6	-0.09	0.93
Visual memory: CFT delayed recall						
Baseline (sample average)	11.3 (N=44)	11.3 (N=40)				
EOT	14.8 (N=50)	14.1 (N=49)	-0.7	-2.9 to 1.5	-0.65	0.52
3 months	19.2 (N=39)	18.0 (N=28)	-1.2	-3.9 to 1.5	-0.89	0.38
6 months	19.2 (N=32)	18.1 (N=28)	-1.1	-4.1 to 2.0	-0.70	0.49
Semantic memory: Category fluency						
Baseline (sample average)	14.0 (N=60)	14.0 (N=59)				
EOT	12.7 (N=65)	12.1 (N=64)	-0.6	-2.3 to 1.0	-0.77	0.44
3 months	14.1 (N=53)	13.8 (N=33)	-0.3	-2.3 to 1.8	-0.28	0.78
6 months	14.4 (N=46)	13.5 (N=36)	-0.9	-2.8 to 1.0	-0.93	0.36
Executive functioning: TMT-B[c]						
Baseline (sample average)	117.9 (N=46)	117.9 (N=50)				
EOT	103.8 (N=47)	107.7 (N=54)	1.0	0.9 to 1.2	0.42	0.67
3 months	87.0 (N=39)	93.1 (N=27)	1.1	0.9 to 1.3	0.66	0.51
6 months	84.1 (N=32)	97.2 (N=27)	1.2	0.9 to 1.5	1.16	0.25
Total side-effects: CSSES total score[c]						
Baseline (sample average)	22.4 (N=50)	22.4 (N=48)				
EOT	14.2 (N=63)	17.3 (N=62)	1.2	0.9 to 1.6	1.44	0.15
3 months	12.5 (N=47)	13.4 (N=32)	1.1	0.7 to 1.6	0.38	0.71
6 months	8.7 (N=39)	12.1 (N=38)	1.4	0.9 to 2.1	1.49	0.14
Cognitive side-effects: CSSES cognitive score[c]						
Baseline (sample average)	5.0 (N=52)	5.0 (N=48)				
EOT	3.8 (N=63)	5.5 (N=62)	1.4	1.1 to 2.0	2.32	0.02
3 months	4.2 N=47)	4.9 (N=32)	1.2	0.8 to 1.6	0.83	0.41
6 months	3.3 (N=39)	4.9 (N=38)	1.5	1.1 to 2.1	2.24	0.03

These scales were not prioritized and hence are subject to missingness.

[a]All analyses were carried out using multiple imputation with 200 imputations (see Supplemental Material).

[b]Means are predicted for patients with average baseline outcome value, who are of younger age (≤65 years), referred from St. Patrick's Mental Health Services and have no previous experience of ECT.

[c]Analysis carried out on the log-scale, means back-transformed and effect estimates representing ratios (Bitemporal/Right unilateral).

RUL=right unilateral ECT. MMSE=Mini-Mental State Examination. TMT=Trail Making Test (versions A and B). FCSRT= Free and Cued Selective Recall Test. CFT=Complex Figure Test. CSSES=Columbia ECT Subjective Side-Effects Schedule.