

Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): A Pragmatic, Randomized, Non-Inferiority Trial

Maria Semkowska, Ph.D., Sabine Landau, Ph.D., Ross Dunne, M.R.C.Psych., Erik Kolshus, M.R.C.Psych., Adam Kavanagh, Ph.D., Ana Jelovac, B.A., Martha Noone, Ph.D., Mary Carton, Ph.D., Sinead Lambe, M.Sc., Caroline McHugh, M.Sc., Declan M. McLoughlin, Ph.D., M.R.C.P.I., M.R.C.Psych.

Objective: ECT is the most effective treatment for severe depression. Previous efficacy studies, using thrice-weekly brief-pulse ECT, reported that high-dose ($6\times$ seizure threshold) right unilateral ECT is similar to bitemporal ECT but may have fewer cognitive side effects. The authors aimed to assess the effectiveness and cognitive side effects of twice-weekly moderate-dose ($1.5\times$ seizure threshold) bitemporal ECT with high-dose unilateral ECT in real-world practice.

Method: This was a pragmatic, patient- and rater-blinded, noninferiority trial of patients with major depression ($N=138$; 63% female; age=56.7 years [$SD=14.8$]) in a national ECT service with a 6-month follow-up. Participants were independently randomly assigned to bitemporal or high-dose unilateral ECT. The primary outcome was change in the 24-item Hamilton Depression Rating Scale (HAM-D) score after the ECT course; the prespecified noninferiority margin was 4.0 points. Secondary outcomes included response

and remission rates, relapse status after 6 months, and cognition.

Results: Of the eligible patients, 69 were assigned to bitemporal ECT and 69 to unilateral ECT. High-dose unilateral ECT was noninferior to bitemporal ECT regarding the 24-item HAM-D scores after the ECT course (mean difference=1.08 points in favor of unilateral ECT [95% CI=-1.67 to 3.84]). There were no significant differences for response and remission or 6-month relapse status. Recovery of orientation was quicker following unilateral ECT (median=19.1 minutes versus 26.4 minutes). Bitemporal ECT was associated with a lower percent recall of autobiographical information (odds ratio=0.66) that persisted for 6 months.

Conclusions: Twice-weekly high-dose unilateral ECT is not inferior to bitemporal ECT for depression and may be preferable because of its better cognitive side-effect profile.

Am J Psychiatry 2016; 173:408–417; doi: 10.1176/appi.ajp.2015.15030372

ECT is used to treat severe mental disorders in 1.4 million people annually worldwide, depression being the most common indication in Western countries (1). ECT is the most acutely effective treatment for treatment-resistant, sometimes life-threatening, depression (2, 3). Nevertheless, its use remains limited, mainly because of cognitive side effects (4), especially concerns about retrograde amnesia (5, 6).

Research on electrode placement has focused on preserving efficacy and minimizing side effects. Based on dosage, right unilateral ECT is less effective than bitemporal ECT (2), the most commonly used electrode placement worldwide (1), but causes less cognitive deficits (7). High-dose is more effective than low-dose ECT but more adversely affects memory (2, 7). However, efficacy trials (8–13) have demonstrated that unilateral ECT can be as effective as bitemporal ECT if delivered in high doses at multiples

(e.g., $5\times$ – $8\times$) of seizure threshold, the minimum charge required to induce the generalized seizure needed for therapeutic effect.

Although unilateral ECT causes fewer cognitive side effects, the higher charges required to achieve comparable antidepressant efficacy might diminish its cognitive advantage. Relevant trials of brief-pulse (i.e., 1.0 msec–1.5 msec pulse width) ECT have obtained inconsistent results: some show comparable cognitive performance following high-dose ($5\times$ – $8\times$ threshold) unilateral ECT with reference to moderate-dose ($1.0\times$ – $1.5\times$ threshold) bitemporal ECT (9, 10, 13), while others demonstrate less cognitive decline following high-dose ($6\times$ threshold) unilateral ECT (8, 11, 12), although the latter studies mostly compared it with higher-dose ($2.5\times$ threshold) bitemporal ECT that increases cognitive side effects (7). None of these studies were designed to determine

See related features: **Clinical Guidance** (Table of Contents) and **AJP Audio** (online)

unilateral noninferiority for antidepressant effect, and most had very limited follow-up. All used thrice-weekly treatment, common practice in the United States where most of these trials originated, even though this does not result in better outcomes than twice-weekly ECT (14) but is associated with increased cognitive side effects (15). This limits their generalizability for populations in which twice-weekly frequency is common practice, as occurs in many European countries (e.g., Belgium, Ireland, the Netherlands, United Kingdom) (16, 17). Additionally, none of the previous trials reflected routine practice in that antidepressants were discontinued before ECT, and all but one (9) required receiving at least eight ECT sessions unless response criteria were met.

To date, no randomized trial has tested whether twice-weekly high-dose ($6\times$ threshold) unilateral ECT is noninferior to reference ($1.5\times$ threshold) bitemporal ECT nor evaluated its superiority in terms of cognition and retrograde memory preservation over a prolonged follow-up period. We aimed to examine short- and long-term effectiveness and cognitive side effects of high-dose unilateral ECT compared with bitemporal ECT for severe depression in routine practice over 6 months.

METHOD

Study Design and Participants

EFFECT-Dep (Enhancing the Effectiveness of Electroconvulsive Therapy in Severe Depression) was a pragmatic, patient- and rater-blinded two-group parallel, randomized, noninferiority trial with a 6-month follow-up (18, 19). Participants were all in-patients recruited between May 2008 and October 2012 from St. Patrick's Mental Health Services (<http://www.stpatricks.ie/>), an independent nonprofit organization that provides national services and runs Ireland's largest ECT clinic, including referrals from public-sector hospitals. Eligible participants were ≥ 18 years old, referred for ECT, met diagnostic criteria for major depressive episode (unipolar or bipolar; Structured Clinical Interview for DSM-IV [20]) and scored ≥ 21 on the 24-item Hamilton Depression Rating Scale (HAM-D) (21). Exclusion criteria were conditions rendering patients unfit for general anesthesia or ECT; ECT in previous 6 months; history of schizophrenia, schizoaffective disorder, or neurodegenerative or other neurological disorder; alcohol/substance abuse in previous 6 months; involuntary status; and inability/refusal to consent. Treatment during the follow-up period was determined by patients in consultation with treating clinicians. This study was approved by the hospital's research ethics committee (approval reference 012/07), and written informed consent was obtained after procedures were fully explained.

Randomization and Masking

After baseline assessments and before the first ECT session, patients were allocated (1:1) to bitemporal or unilateral ECT using an online system by the Clinical Trials Unit, King's College London. Minimization with variable block sizes

ensured that group allocation was balanced regarding three stratifiers: age > 65 years (yes/no), previous ECT (yes/no), and referral site (St. Patrick's Mental Health Services/St. James's Hospital/other hospital). Recruiting researchers electronically submitted participants' identifying number, initials, birthdate, history of ECT, and referral site. Treating clinicians received e-mail notification of randomization but were not involved in outcome assessments. Allocation was concealed from patients (prepared for receiving both electrode placements), recovery staff, referring clinicians, assessors, and trial statistician until completion of final analyses. Success of masking was investigated after end-of-treatment assessments by asking patients and raters to guess the treatment used.

Interventions

Brief-pulse (1.0-msec pulse width; current amplitude 800 mA) ECT was administered twice weekly (Mecta 5000M device, Mecta Corp., Portland, Ore.; maximum 1200 mC) according to Royal College of Psychiatrists' guidelines, using methohexital (0.75 mg/kg–1.0 mg/kg) anesthesia, and succinylcholine (0.5 mg/kg–1.0 mg/kg) for muscle relaxation (16, 22). Seizure threshold was established by dose titration at the first session (see the data supplement accompanying the online version of this article). Subsequent treatments were $1.5\times$ -threshold for bitemporal and $6\times$ -threshold for unilateral (d'Elia placement) ECT. Stimulus charge was titrated upward as required during the treatment course (22, 23). In line with regular practice, the number of ECT sessions was determined by referring clinicians in consultation with patients, up to 12 sessions in accordance with recommendations of the Irish Mental Health Commission (http://www.mhcirl.ie/Mental_Health_Act_2001/Mental_Health_Commission_Codes_of_Practice/Use_of_ECT_for_Voluntary_Patients/), who publish annual national data on ECT (<http://www.mhcirl.ie/Publications/Publications/>). Patients continued regular antidepressant treatments. ECT characteristics were recorded: seizure threshold (millicoulomb [mC]); mean stimulus charge (mC) for all sessions and nontitration sessions; motor and EEG seizure durations (seconds); total number of sessions; and number of sessions to establish threshold. Time to recovery of orientation (i.e., ability to answer 4/5 simple orientation questions, such as person, place, age, birthdate, day), once breathing spontaneously post-ECT, was recorded after each session (24).

Common adverse physical effects (nausea, headache, muscle aches) were recorded for each session to measure occurrence (yes/no) within each course. Serious adverse events that required prolonged medical attention or were life-threatening were recorded.

Data were obtained at baseline, within, and soon after (2–4 days) completing the ECT course, as well as during the 6-month follow-up. Baseline assessments included the National Adult Reading Test (premorbid IQ), collection of demographic variables (age, gender, years in education, socioeconomic and marital status), and collection of the following clinical variables: referral reason, treatment resistance

(yes/no; Antidepressant Treatment History Form [25]), current psychotropic medications, number of previous depressive episodes, current episode duration, presence of psychosis, and depression polarity. Baseline Clinical Global Impression (CGI) severity was rated by referring clinicians.

Primary Outcome

The primary outcome was depression severity measured by the 24-item HAM-D after completing the ECT course (end of treatment). Interrater reliability for HAM-D scoring was assessed every 6 months; median intraclass correlation agreement was 0.96 (range: 0.89–0.98). To classify depression status, HAM-D scores were obtained after every second ECT session and 1 week after the final session if indicated.

Secondary Outcomes

Secondary depression outcomes included HAM-D scores at the 3- and 6-month follow-ups, end-of-treatment remission and response status, and relapse status for remitters during the 6-month follow-up. Remission was defined as $\geq 60\%$ decrease from the baseline HAM-D score and a score ≤ 10 for two consecutive weeks; response was defined as $\geq 60\%$ decrease from the baseline HAM-D score and a score ≤ 16 ; and relapse was defined as a HAM-D score ≥ 16 for two consecutive weeks. The majority of patients who relapse following successful ECT do so within 3 months (26). To monitor relapse, HAM-D scores were obtained after the end of treatment at 2, 4, 6, and 8 weeks plus 3, 4, and 6 months.

The post-ECT cognitive secondary outcome of main interest, retrograde amnesia measured by the Columbia University Autobiographical Memory Interview-Short Form (27), was prioritized for data collection. Further non-prioritized cognitive outcomes are summarized in Table S2 in the online data supplement and included standardized measures of global cognition (Mini-Mental State Examination [MMSE]), auditory attention and verbal working memory (digit spans forward and backward), psychomotor speed and executive function (Trail-Making Test, parts A and B), semantic memory (category fluency), verbal learning and delayed recall (Free and Cued Selective Reminding Test), and visuo-spatial functioning and memory (Complex Figures Test). Alternative versions were used where appropriate. Cognitive outcomes were collected at baseline, end of treatment, and 3- and 6-month follow-ups. These outcomes, as well as the HAM-D scores, were similar to ones used to establish efficacy and side effects of bitemporal ECT (7, 8, 11–13, 16).

Subjective symptoms attributable to ECT were assessed with the Columbia ECT Subjective Side Effects Schedule, including six items on memory, concentration, and orientation for self-rating of cognition (total=18) (28).

Sample Size

Based on a large bitemporal ECT series (29), we estimated that 69 patients were required per group to have 80% power to demonstrate, using a one-sided equivalence t test at 5%

level, that the mean reduction in the 24-item HAM-D score following high-dose unilateral ECT was no more than 4 points (i.e., equivalent to 3 points on the 17-item HAM-D, deemed to be clinically relevant [30]) less than that achieved using bitemporal ECT.

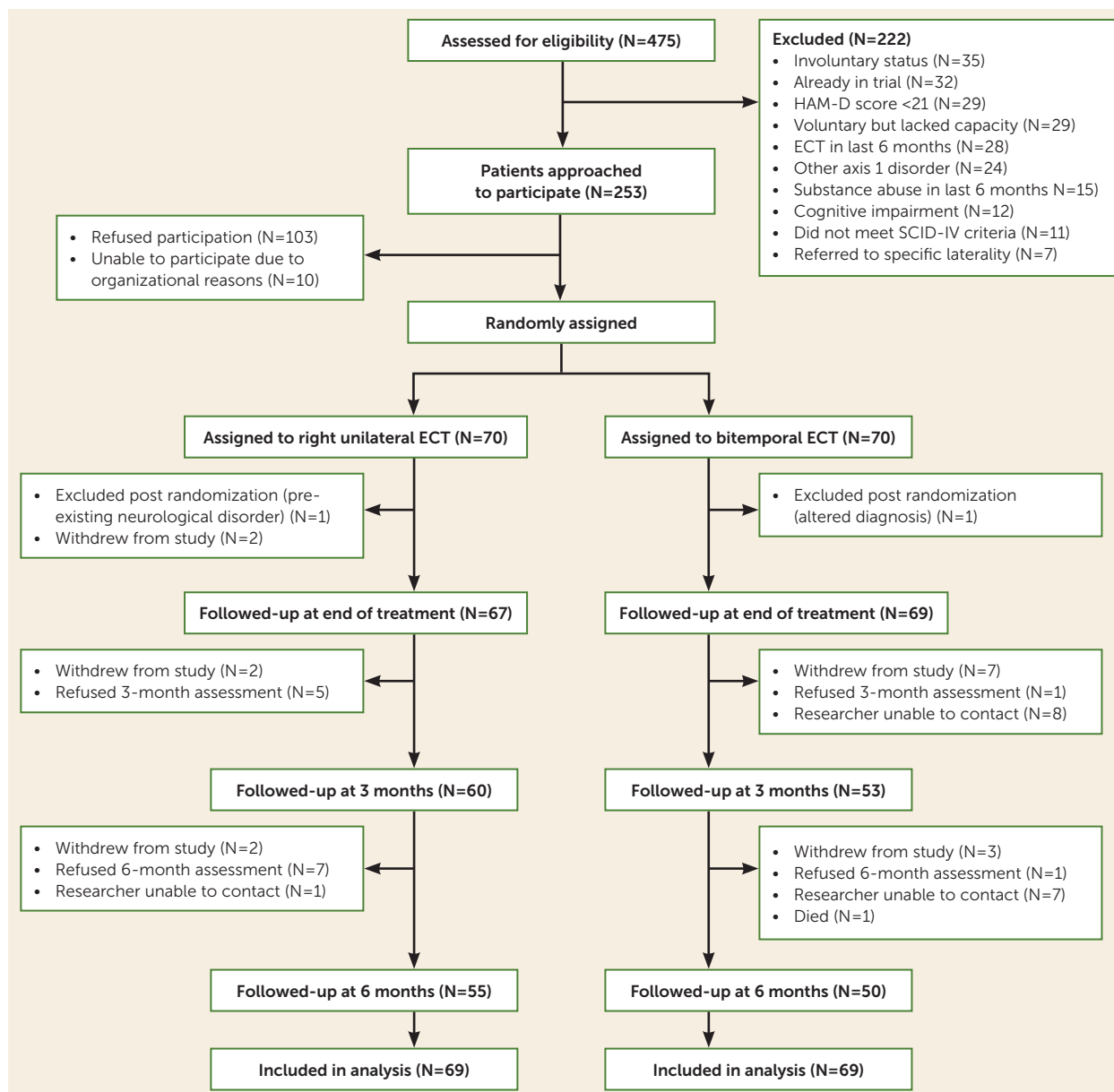
Statistical Analyses

Analyses were on the intention-to-treat principle. ECT measures were summarized by trial arm using relevant descriptive statistics, accompanied by tests of zero group difference where this was not known a priori. We formally compared total numbers of sessions, numbers of sessions to establish seizure threshold (coded “1” or “ ≥ 2 ” sessions), and time to recovery of orientation using regression, logistic regression, and regression of log-transformed times, respectively. In these regression models, randomization stratifiers were included as explanatory variables in addition to trial arm.

The primary statistical analysis was assessment of difference in the 24-item HAM-D scores between arms at the end of treatment. The estimated group difference was supplemented by 95% confidence intervals and this interval compared with the noninferiority threshold (4 points). A regression model was fitted to end-of-treatment HAM-D measures, with prerandomization HAM-D scores, trial arm (unilateral/bitemporal), and randomization stratifiers as covariates. A similar analysis model was assumed for secondary HAM-D outcomes at the 3- and 6-month follow-ups. Among remitters, relapse during the 6-month follow-up was compared between arms using logistic regression as described above.

The main secondary cognitive outcomes of interest (Autobiographical Memory Interview at end of treatment and 3- and 6-month follow-ups) were analyzed using generalized linear models with a binomial distribution and logit-link (31). Posttreatment Autobiographical Memory Interview measures provide the number of baseline items recalled after ECT (27); such “number of items recalled” variables were therefore modeled as arising from binomial distributions, with maximum number of possible recalls set to the number of items obtained at baseline. An overdispersion parameter was introduced to account for recall of individual events being driven by subject characteristics. The covariates of these models were trial arm and randomization stratifiers.

Similar regression models were employed to describe nonprioritized continuous secondary outcomes: other cognitive tasks and subjective side effects (now also including baseline values as a covariate). Time outcomes (i.e., Trail-Making Tests, parts A and B) were log-transformed before analysis to acknowledge positively skewed distributions. The same approach was applied for count outcomes displaying positive skewness (subjective side effects total and cognitive scores). Group effects for these outcomes were therefore quantified by the ratio of outcome in the bitemporal arm to that in the unilateral arm.

FIGURE 1. Trial Profile^a

^a HAM-D=24-item Hamilton Depression Rating Scale; SCID-IV=Structured Clinical Interview for DSM-IV.

For physical safety analyses, we assessed proportions of patients who had adverse events by treatment group and compared proportions using logistic regression modeling as for ECT measures.

Handling of missing data is described in the online data supplement. We used Stata (version 13) and SPSS 19.0 (IBM Corp., Armonk, N.Y.) for statistical analyses.

RESULTS

Participant Flow

The trial profile is shown in Figure 1. A total of 475 patients (mean age: 62 years [SD=15.1]; 67.7% female) were referred for ECT during the recruitment period (May 2008–October

2012), accounting for 32.9% of all ECT referrals in Ireland (N=1,480; average age: 57.3 years; 66.5% female). Seventy patients, all white Irish, were assigned per group. One patient per trial arm was excluded postrandomization because they were found not to fulfill eligibility criteria. Comparing the 138 participants to the 113 potentially eligible nonparticipants, participants were younger (mean age: 56.7 years [SD=14.8] versus 63.4 years [SD=14.3]; $t=3.64$, $p=0.0001$) but did not differ significantly regarding gender (% female: 63% versus 67%; $\chi^2=0.48$, $p=0.52$), baseline CGI severity (mean: 5.3 [SD=0.7] versus 5.2 [SD=0.9]; $N=101$; U test: $z=0.93$, $p=0.35$), and MMSE scores (mean: 27.7 [SD=2.1]; $N=119$ versus 27.8 [SD=2.5]; $N=85$; $t=-0.27$, $p=0.79$).

All patients adhered to allocated treatment, although five (7.2%) unilateral patients had thresholds >200 mC (225 mC,

TABLE 1. Baseline Clinical and Demographic Characteristics^a

Characteristic	Total Sample (N=138)		Right Unilateral ECT (N=69)		Bitemporal ECT (N=69)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	56.7	14.8	56.6	15.3	56.8	14.4
Education (years)	13.1	3.4	13.7	3.0	12.6	3.8
Hamilton Depression Rating Scale-24 item	29.9	6.2	30.4	6.1	29.5	6.3
Mini-Mental State Examination ^{a,b}	27.7	2.1	28.0	1.8	27.4	2.4
National Adult Reading Test ^{a,c}	108.3	6.8	109.2	5.6	107.4	7.8
Clinical Global Impression-Severity ^d	5.3	0.7	5.4	0.7	5.3	0.7
Number of psychotropic medications	4.2	1.4	4.3	1.3	4.2	1.5
	Median	Range	Median	Range	Median	Range
Episode duration ^e	19.5	2–104	18.0	4–104	21.0	2–104
Number of previous episodes	4.0	0–23	4.0	0–20	3.0	1–23
	N	%	N	%	N	%
Female gender	87	63.0	40	58.0	47	68.1
Socioeconomic group						
Professional	24	17.4	10	14.5	14	20.3
Managerial or technical	23	16.7	15	21.7	8	11.6
Skilled occupations	36	26.1	23	33.3	13	18.8
Partly skilled occupations	22	15.9	8	11.6	14	20.3
Unskilled occupations	31	22.5	11	15.9	20	29.0
Not specified	2	1.4	2	2.9	0	0.0
Marital status						
Married	76	55.1	38	55.1	38	55.1
Single	35	25.4	17	24.6	18	26.1
Widowed/divorced	25	18.1	12	17.4	13	18.8
Not specified	2	1.4	2	2.9	0	0.0
Bipolar depression	32	23.2	16	23.2	16	23.2
Presence of psychosis	29	21.0	16	23.2	13	18.8
Treatment resistance ^f	99	72.8	45	66.2	54	79.4
History of previous ECT	53	38.4	26	37.7	27	39.1
Primary reason for ECT referral ^d						
Refractory to medication	75	54.3	37	53.6	38	55.1
Rapid response required	57	41.3	29	42.0	28	40.1
Acute suicidality	5	3.6	2	2.9	3	4.3
Physical deterioration	1	0.7	1	1.4	0	0.0
Psychotropic medications						
Selective serotonin reuptake inhibitors	29	21.0	15	21.7	14	20.3
Serotonin and noradrenaline reuptake inhibitors	67	48.6	32	46.4	35	50.7
Tricyclic antidepressants	39	28.3	20	29.0	19	27.5
Tetracyclic antidepressants	6	4.3	6	8.7	0	0.0
Mirtazapine	46	33.3	24	34.8	22	31.9
Agomelatine	2	1.4	1	1.4	1	1.4
Lithium	56	40.6	28	40.6	28	40.6
Anticonvulsants ^g	39	28.3	18	26.1	21	30.4
Benzodiazepines	81	58.7	35	50.7	46	66.7
Antipsychotics	97	70.3	48	69.6	49	71.0
Nonbenzodiazepine hypnotics	69	50.0	34	49.3	35	50.7
Tryptophan	2	1.4	1	1.4	1	1.4
Bupropion	4	2.9	2	2.9	2	2.9
Monoamine oxidase inhibitor	1	0.7	0	0.0	1	1.4
Buspirone	1	0.7	0	0.0	1	1.4

^a Data are not available for all participants.

^b N=119 (59 right unilateral, 60 bitemporal).

^c N=112 (54 right-unilateral, 58 bitemporal).

^d As recorded by referring physician.

^e Capped at 104 weeks.

^f Treatment resistance was based on the Antidepressant Treatment History Form (N=136).

^g Anticonvulsants include lamotrigine, sodium valproate, and pregabalin prescribed as mood stabilizers or anxiolytic.

TABLE 2. ECT Session Measures

Variable	Right Unilateral ECT ^a (N=69)		Bitemporal ECT (N=69)		Formal Test ^b		
	Mean	SD	Mean	SD	t	df	p
ECT treatment characteristics							
Anesthesia ^c							
Methohexitone (mg/kg)	1.1	0.2	1.0	0.2			NA
Suxamethonium (mg/kg)	0.8	0.2	0.8	0.2			NA
Stimulus charge (mC), all sessions	620.3	223.5	368.1	192.0			NA
Stimulus charge (mC), nontitration sessions ^d	741.6	275.6	403.5	207.6			NA
Total number of sessions	7.8	2.5	8.3	2.4	1.13	131	0.26
	Median	Range	Median	Range			
Initial seizure threshold (mC)	75	50–500	150	50–500			NA
Motor seizure duration (seconds)	28	12–55	28	14–63			NA
EEG seizure duration	42	17–87	40	16–116			NA
	N	%	N	%	z		p
Number of sessions to establish the seizure threshold					3.07		0.002
1 session	56	81	39	56			
2 sessions	12	18	28	41			
3 sessions	1	1	2	3			
	Median	Range	Median	Range	t	df	p
Recovery of orientation^e							
Time to recovery (minutes), initial titration session	10	5–60	20	5–60	6.82	130	0.001 ^f
Time to recovery (minutes), nontitration sessions ^d	19.1	10–55	26.4	10–60	3.88	130	0.001 ^f

^a Data are not available for all participants (N=67–68).

^b All models used to construct inferences were conditioned on stratifiers.

^c Six patients received propofol during their ECT course at standard doses due to temporary shortage of methohexital, four in the bitemporal group and two in the unilateral group.

^d A mean time was estimated for all sessions following the definite establishment of the seizure threshold.

^e Recovery of orientation was defined as correctly answering 4/5 reorientation questions.

^f Formal inferences carried out after log-transformation.

N=1; 250 mC, N=3; 500 mC, N=1) and thus could not be treated at a fully 6× seizure threshold. Nearly all participants (N=136; 98.6%) were assessed for primary outcome at the end of treatment, while 82% and 76%, respectively, were followed up at 3 and 6 months.

Treatment guesses were made by patients (119/138) and raters (118/138): 12 patients could not guess, and 26/56 in the unilateral group and 36/51 in the bitemporal group correctly guessed ($\chi^2=3.27$, $p=0.07$; kappa=0.17 [low coefficient of beyond-chance agreement]). For raters, 30/57 of the guesses for the unilateral group and 36/61 for the bitemporal group were correct ($\chi^2=1.61$, $p=0.21$; kappa=0.12). Thus, masking was successful for patients and raters.

Baseline and Treatment Characteristics

Summaries of baseline characteristics were comparable between trial arms as would be expected under random allocation (Table 1). Age (mean: 56.7 years [SD=14.8]), gender (63% female), psychosis status (21%), bipolarity (23%), baseline 24-item HAM-D scores (mean: 29.9 [6.2]), and depression episode median duration (19.5 weeks) for the total sample were similar to that found in previous relevant trials (8, 9, 11–13) and large observational studies (5, 29).

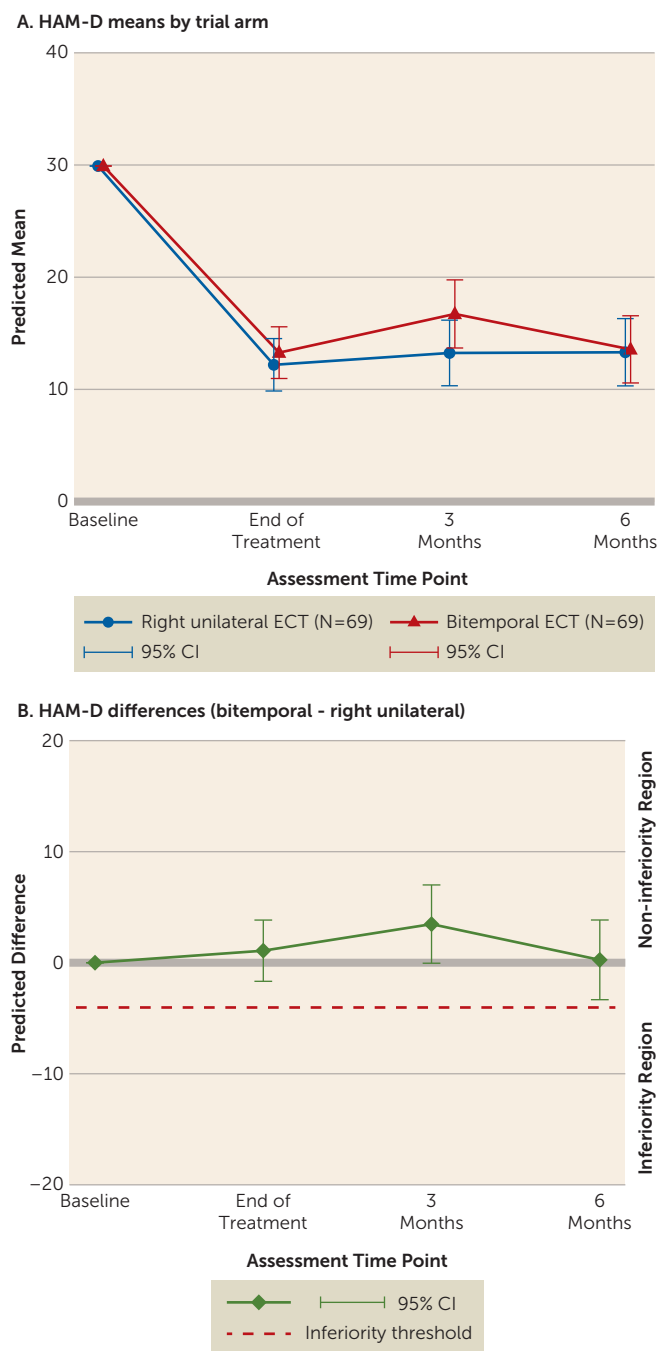
Anesthesia doses were similar for the two groups (Table 2). In line with previous studies (8–12), we found that

threshold was lower with unilateral ECT, and total stimulus charges were higher in the unilateral group, while seizure durations were similar between groups. Ninety-three percent of patients had an adequate seizure in the first session. Although it took fewer sessions to establish threshold in the unilateral group ($p=0.002$), there was no significant difference between groups for total number of ECT sessions ($p=0.26$). Median time to recovery of orientation following the initial titration session in the unilateral group was half that of the bitemporal group ($p<0.001$), and this cognitive advantage was maintained, though to a lesser extent, during the remainder of the course.

Primary and Secondary Mood Outcomes

High-dose unilateral ECT was noninferior to bitemporal ECT at the end of treatment. Changes in the 24-item HAM-D scores are shown in Figure 2A. The prespecified noninferiority margin was no more than a –4-point difference at the end of treatment between the bitemporal and unilateral groups (Figure 2B). The predicted difference at the end of treatment was 1.08 (95% confidence interval [CI]=–1.67 to 3.84; unilateral, N=67; bitemporal, N=69). Noninferiority was evident at both the 3-month (3.48, 95% CI=–0.046 to 7.0; unilateral, N=60; bitemporal, N=53) and 6-month (0.26,

FIGURE 2. Intention-to-Treat Analyses of Primary Outcome^a



^a The top graph (A) shows the predicted mean 24-item Hamilton Depression Rating Scale (HAM-D) (95% CI) scores for the unilateral and bitemporal ECT groups at the end of treatment plus the 3- and 6-month follow-ups. 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. All analyses were carried out using multiple imputation with 200 imputations (see the Statistical Analysis section and the online data supplement). All models used to construct inferences were adjusted for baseline HAM-D scores and conditioned on stratifiers. In the bottom graph (B), the dashed line is the predefined noninferiority margin (-4 points on the HAM-D). The green line shows the predicted mean (95% CI) differences in HAM-D scores at the same time points as shown in graph A.

95% CI= -3.33 to 3.85 ; unilateral $N=55$, bitemporal $N=50$) follow-ups.

These results translated into similar proportions of responders (unilateral: $42/69$ [60.8%]; bitemporal: $35/69$ [50.7%]) and remitters (unilateral: $32/69$ [46.4%]; bitemporal: $29/69$ [42.0%]) in the two groups at the end of treatment. The median number of ECT sessions for both responders and remitters was 7 (range: 3–12), which was less than the median number of 9 (range: 3–12) ECT sessions for both nonresponders and nonremitters (for both Mann-Whitney U test, $p < 0.001$). During the 6-month follow-up, there was no significant difference between the proportion of remitters who relapsed in the unilateral ($8/32$; 25.0%) and bitemporal ($11/29$; 37.9%) groups (odds ratio [unilateral/bitemporal]=0.56, 95% CI=0.17–1.79, $z=0.99$, $p=0.32$).

Cognitive Secondary Outcomes

The cognitive outcome of main interest post-ECT was retrograde amnesia as measured by the Autobiographical Memory Interview. Autobiographical memory scores for the unilateral (46.9 [SD=9.7]; $N=66$) and bitemporal (44.4 [SD=10.3]; $N=64$) groups were similar at baseline. The percent consistency of recall of baseline memories was lower in the bitemporal group at the end of treatment (odds ratio=0.66, 95% CI=0.513–0.85, $p=0.001$; unilateral, $N=64$; bitemporal, $N=64$), and this was maintained at follow-up after 3 months (odds ratio=0.59, 95% CI=0.45–0.78, $p < 0.001$; unilateral, $N=56$; bitemporal, $N=48$) and 6 months (odds ratio=0.59, 95% CI=0.45–0.79, $p < 0.001$; unilateral, $N=49$; bitemporal, $N=42$) (Figure 3). Distributions of individual percent recall consistencies are presented in Table S3 in the online data supplement.

Assessment completion levels varied for nonprioritized secondary outcomes. End-of-treatment completion rates ranged from 93.5% (category fluency) to 71.7% (verbal learning). Three-month completion rates varied from 62.3% (category fluency) to 47.8% (Trail-Making Test, part B) and at 6 months from 59.4% (category fluency) to 42.8% (Trail-Making Test, part B).

There were few differences between groups for the other cognitive tasks (see Table S4 in the data supplement). At the end of treatment, the only statistically significant difference was for better performance in the unilateral group on verbal learning for immediate recall ($p=0.034$), though not delayed recall ($p=0.22$). There were no differences between groups on these verbal learning and memory tasks at the 3- and 6-month follow-ups. At 3 months, performance was better in the unilateral group for both auditory attention ($p=0.021$) and verbal working memory ($p=0.049$), but these cognitive advantages were not evident at the end of treatment or at the 6-month follow-up.

There were no significant differences between groups on the Subjective Side-Effects Schedule for total side effects at any time point (see Table S4 in the data supplement), although the number and severity of side effects declined substantially over time, probably in line with improved

mood (16, 28). However, significantly fewer subjective cognitive side effects were reported by the unilateral group at the end of treatment ($p=0.02$) and after 6 months ($p=0.025$). Thus, there were both objective and subjective cognitive advantages for unilateral compared with bitemporal ECT.

Adverse Events

There were no differences between the unilateral and bitemporal groups for occurrence of headaches (26.5% versus 27.5%; odds ratio=0.93, 95% CI=0.42–2.04; $z=0.20$, $p=0.84$), nausea (16.2% versus 11.6%; odds ratio=1.54, 95% CI=0.56–4.17; $z=-0.84$, $p=0.40$), or muscle pain (11.8% versus 8.7%; odds ratio=1.37, 95% CI=0.44–4.17; $z=-0.55$, $p=0.58$).

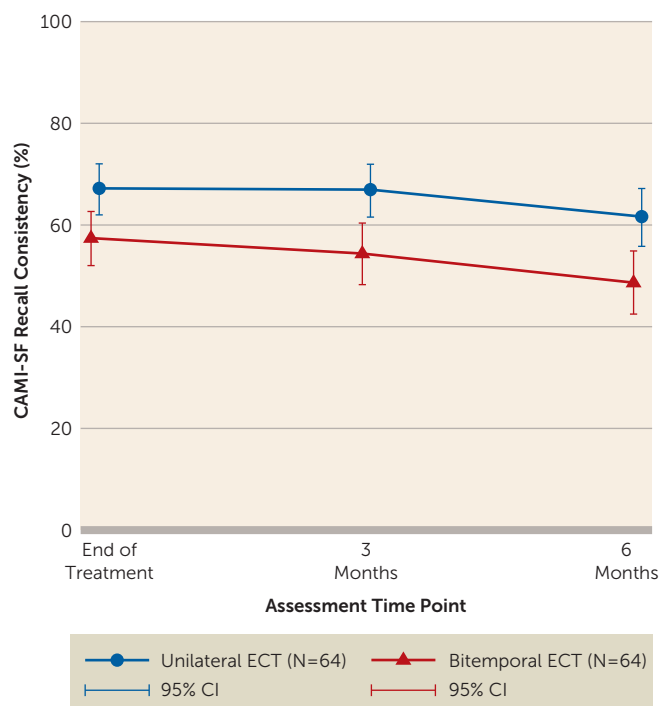
Regarding major adverse events, six patients required β -blockers for ECT-related hypertension (unilateral, $N=4$; bitemporal, $N=2$). In the unilateral group, one patient developed laryngospasm with temporary drop in oxygen saturation, one developed tachyarrhythmia necessitating ECT termination, and one attempted suicide during the course. In the bitemporal group, three patients developed interictal confusion resulting in postponement/termination of ECT, one developed bronchospasm, one required β -blocker treatment for sinus tachycardia, one developed bradyarrhythmia, and one developed a pulmonary embolus after the fifth treatment. None of these events led to trial dropout.

DISCUSSION

Our findings show that twice-weekly high-dose unilateral ECT is noninferior to bitemporal ECT for severe depression in regular clinical practice, which included continued antidepressant pharmacotherapy, and this was maintained over 6 months. The proportions of responders and remitters, as well as relapse rates, are consistent with this. Furthermore, we found high-dose unilateral ECT to be less taxing on autobiographical memory than bitemporal ECT. The unilateral group showed significantly higher autobiographical memory consistency with baseline recall than the bitemporal group at the end of treatment and the 3- and 6-month follow-ups. Other cognitive advantages of unilateral ECT included quicker recovery of orientation following treatments, better verbal learning at the end of treatment, and fewer subjective cognitive side effects. Both forms of ECT were well tolerated. The numbers of common physical side effects and serious adverse events were similar in both groups, in line with previous studies reporting harms (12, 32).

Our findings for the primary outcome, the 24-item HAM-D score, are consistent with results of previous, non-pragmatic, thrice-weekly efficacy trials (8–13). However, the overall remission rate (44.2%) was lower than the rate in some trials (range: 46%–65%) (8, 9, 11–13) but similar to that in a large community study (46.7%) (33), while the overall 6-month relapse rate (31.1%) was at the lower limit reported in a recent meta-analysis of post-ECT relapse (26). These differences most likely reflect the pragmatic nature of our trial,

FIGURE 3. Autobiographical Memory Following ECT: Recall Consistency (%) With Baseline Scores for Unilateral and Bitemporal ECT Groups^a



^a CAMI-SF=Columbia Autobiographical Memory Interview-Short Form.

in which the number of treatments was decided by the patients and referring physicians rather than by the protocol, as well as a naturalistic follow-up, and are unlikely to be related to concomitant use of antidepressants, which may improve ECT efficacy (12). Cognitive outcomes at the end of treatment were consistent with previous thrice-weekly ECT trials (8, 9, 11, 12). Regarding autobiographical memory, as measured by the Autobiographical Memory Interview, our findings differed only from two previous trials (9, 13) that found both treatments to have comparable effects. This might be explained by the higher stimulus charge used for the unilateral group ($8\times$ seizure threshold) for one trial (9) and/or use of thrice-weekly ECT (9, 13), as both result in larger cognitive deficits.

Strengths and Weaknesses

Trial strengths include noninferiority design, pragmatic attitude, relatively large sample size, and adequate power. We showed excellent adherence and end-of-treatment completion rates. Retention at both follow-ups was satisfactory for the primary and main cognitive outcomes and superior to previous relevant trials. Indeed, existing efficacy trials either lacked follow-up (8, 12, 13), had shorter follow-ups (1–2 months) (9, 10), and/or had smaller follow-up samples (19–22 per group) (9, 11). None was designed to test noninferiority of high-dose unilateral ECT compared with bitemporal ECT. The randomized sample was representative of the general population referred for ECT and similar to

potentially eligible nonparticipants. Our findings, therefore, have good generalizability to countries where twice-weekly ECT is normal practice.

Our study has some limitations. First, we did not include involuntary patients who could not consent due to illness severity (7.4% of referrals), for whom bitemporal ECT may be better (13). Second, other than for autobiographical memory, there are high levels (13%–54%) of missing variables for secondary cognitive outcomes at the follow-ups. Nevertheless, this study presents the best available evidence, to our knowledge, of long-term cognitive correlates of high-dose unilateral and bitemporal ECT. A third limitation concerns the Autobiographical Memory Interview. We selected this instrument to situate our trial within existing research evidence, as most previous trials used a variant of it (8, 11–13). However, it does not allow quantification of retrograde amnesia attributable directly to ECT even though it is sensitive in detecting differences between treatment allocations on autobiographical memory recall (6, 7, 34, 35). Nevertheless, the present trial shows that high-dose unilateral ECT affects autobiographical memory less than bitemporal ECT. Fourth, all trial participants were in-patients, but this reflected routine practice. Fifth, the relatively lower remission rate may be due to the pragmatic design when compared with other trials (8–13) performed under more stringent, but less clinically general, conditions.

CONCLUSIONS

Our study has important clinical implications. In terms of harms/benefits ratio, high-dose unilateral ECT was non-inferior to bitemporal ECT but showed a better cognitive profile, especially for preserving retrograde personal memories and fewer subjective cognitive side effects. While there is much interest in other modifications to maintain effectiveness but reduce side effects (e.g., ultrabrief pulse-width ECT), these require further refinement and characterization for optimization (36, 37). Our findings justify considering high-dose unilateral ECT as the preferred ECT option for treating depression and may help improve acceptability and availability of this effective treatment.

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry, Trinity College Dublin, St. Patrick's University Hospital, Dublin, Ireland; Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland; the Department of Psychology, University of Limerick, Castletroy, Co. Limerick, Ireland; and the Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, King's College London.

Address correspondence to Dr. McLoughlin (d.mcloughlin@tcd.ie).

Previously presented in part at the 7th Biennial Congress of The International Society of Affective Disorders, April 29, 2014, Berlin.

Supported by awards from the Health Research Board (grants TRA/2007/5, HPF/2010/17 and TRA/2007/5/R).

The authors thank the patients and their families for participating in this study. The authors also thank their nursing (Shane McCarron, Lucy Kealy-Sinclair, Geraldine Ryan) and anaesthetic colleagues (Enda Shanahan,

Sallyann Colbert) at the St. Patrick's University Hospital ECT Clinic for their contributions to this study.

The Health Research Board had no role in the design, data collection, analysis or interpretation, report preparation, review, or decision to submit this study for publication.

Dr. Landau has received salary support from the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr. Noone received a student scholarship to complete a PhD on this research from the Health Research Board, Ireland. All other authors report no financial relationships with commercial interests.

Trial registration: Current Controlled Trials ISRCTN23577151.

Received Mar. 24, 2015; revisions received July 7, Aug. 23, and Sept. 25, 2015; accepted Oct. 16, 2015; published online Feb. 19, 2016.

REFERENCES

- Leiknes KA, Jarosh-von Schweder L, Høie B: Contemporary use and practice of electroconvulsive therapy worldwide. *Brain Behav* 2012; 2:283–344
- UK ECT Review Group: Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003; 361:799–808
- Berlim MT, Van den Eynde F, Daskalakis ZJ: Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depress Anxiety* 2013; 30:614–623
- Semkovska M, McLoughlin DM: Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry* 2010; 68:568–577
- Sackeim HA, Prudic J, Fuller R, et al: The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 2007; 32:244–254
- Semkovska M, McLoughlin DM: Measuring retrograde autobiographical amnesia following electroconvulsive therapy: historical perspective and current issues. *J ECT* 2013; 29:127–133
- Semkovska M, Keane D, Babalola O, et al: Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psychiatr Res* 2011; 45:770–780
- Sackeim HA, Prudic J, Devanand DP, et al: A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 2000; 57:425–434
- McCall WV, Dunn A, Rosenquist PB, et al: Markedly suprathreshold right unilateral ECT versus minimally suprathreshold bilateral ECT: antidepressant and memory effects. *J ECT* 2002; 18:126–129
- Ranjikesh F, Barekattain M, Akuchakian S: Bifrontal versus right unilateral and bitemporal electroconvulsive therapy in major depressive disorder. *J ECT* 2005; 21:207–210
- Sackeim HA, Prudic J, Nobler MS, et al: Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulat* 2008; 1:71–83
- Sackeim HA, Dillingham EM, Prudic J, et al: Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry* 2009; 66:729–737
- Kellner CH, Knapp R, Husain MM, et al: Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry* 2010; 196:226–234
- Charlson F, Siskind D, Doi SAR, et al: ECT efficacy and treatment course: a systematic review and meta-analysis of twice vs thrice weekly schedules. *J Affect Disord* 2012; 138:1–8
- Lerer B, Shapira B, Calev A, et al: Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. *Am J Psychiatry* 1995; 152:564–570

16. Eranti S, Mogg A, Pluck G, et al: A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry* 2007; 164:73–81
17. Rhebergen D, Huisman A, Bouckaert F, et al: Older age is associated with rapid remission of depression after electroconvulsive therapy: a latent class growth analysis. *Am J Geriatr Psychiatry* 2015; 23: 274–282
18. Piaggio G, Elbourne DR, Pocock SJ, et al: Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; 308:2594–2604
19. Zwarenstein M, Treweek S, Gagnier JJ, et al: Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; 337:a2390
20. First MB, Spitzer RL, Williams JBW, et al: Structured Clinical Interview for DSM-IV Diagnoses (SCID-I). New York, Biometrics Research Department, New York Psychiatric Institute, 1995
21. Beckham EE, Leber WR: Hamilton Rating Scale for Depression, ECDEU version used in the Treatment of Depression Collaborative Research Program, in *Handbook of Depression-Treatment, Assessment and Research*. Edited by Beckham EE, Levber WR. Homewood, The Dorsey Press, 1985, pp 992–995
22. Dunne R, McLoughlin DM: ECT prescribing and practice, in *The ECT Handbook*, 3rd ed. Edited by Waite J, Easton A. London, Royal College of Psychiatrists, 2013, pp 28–44
23. American Psychiatric Association: *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging*. Washington, DC, American Psychiatric Publishing, 2001, pp 158–161
24. Sobin C, Sackeim HA, Prudic J, et al: Predictors of retrograde amnesia following ECT. *Am J Psychiatry* 1995; 152:995–1001
25. Sackeim HA: The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001; 62(suppl 16):10–17
26. Jelovac A, Kolshus E, McLoughlin DM: Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology* 2013; 38:2467–2474
27. McElhiney MC, Moody BJ, Sackeim HA: *The Autobiographical Memory Interview-Short Form*. New York, Department of Biological Psychiatry, New York State Psychiatric Institute, 2001
28. Sackeim HA, Ross FR, Hopkins N, et al: Subjective Side Effects Acutely Following ECT: Associations with Treatment Modality and Clinical Response. *Convuls Ther* 1987; 3:100–110
29. Petrides G, Fink M, Husain MM, et al: ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT* 2001; 17:244–253
30. National Institute for Clinical Excellence: *Depression: Management of Depression in Primary and Secondary Care*. London, The British Psychological Society and Gaskell, 2004, pp 41
31. McCullagh P, Nelder JA: *Generalized Linear Models*. London, Chapman and Hall/CRC, 1989
32. Benbow SM, Waite J: Non-cognitive adverse effects of ECT, in *The ECT Handbook*, 3rd ed. Edited by Waite J, Easton A. London, The Royal College of Psychiatrists, 2013, pp 71–75
33. Prudic J, Olfson M, Marcus SC, et al: Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry* 2004; 55:301–312
34. Sackeim HA: Autobiographical memory and ECT - do not throw out the baby. *J ECT* 2014; 30:177–186
35. Semkovska M, McLoughlin DM: Autobiographical memory and electroconvulsive therapy: do not throw out the baby. *J ECT* 2014; 30: 187–188, discussion 189–190
36. Spaans H-P, Kho KH, Verwijk E, et al: Efficacy of ultrabrief pulse electroconvulsive therapy for depression: a systematic review. *J Affect Disord* 2013; 150:720–726
37. Tor P-C, Bautovich A, Wang M-J, et al: A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry* (Epub ahead of print, July 21, 2015)