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A Feasibility Study of a New Method for Electrically Producing Seizures in Man: Focal Electrically Administered Seizure Therapy [FEAST]

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ABSTRACT

Background: Electroconvulsive therapy (ECT) remains the most effective acute treatment for severe major depression, but with significant risk of adverse cognitive effects. Unidirectional electrical stimulation with a novel electrode placement and geometry (Focal Electrically Administered Seizure Therapy (FEAST)) has been proposed as a means to initiate seizures in prefrontal cortex prior to secondary generalization. As such, it may have fewer cognitive side effects than traditional ECT. We report on its first human clinical application.

Method: Seventeen unmedicated depressed adults (5 men; 3 bipolar disorder; age 53 ± 16 years) were recruited after being referred for ECT. Open-label FEAST was administered with a modified spECTrum 5000Q device and a traditional ECT dosing regimen until patients clinically responded. Clinical and cognitive assessments were obtained at baseline, and end of course. Time to orientation recovery, a predictor of long-term amnestic effects, was assessed at each treatment. Nonresponders to FEAST were transitioned to conventional ECT.

Results: One patient withdrew from the study after a single titration session. After the course of FEAST (median 10 sessions), there was a 46.1 ± 35.5% improvement in Hamilton Rating Scale for Depression ($HRSD_{24}$) scores compared to baseline (33.1 ± 6.8, 16.8 ± 10.9; $P < 0.0001$). Eight of 16 patients met response criteria (50% decrease in $HRSD_{24}$) and 5/16 met remission criteria ($HRSD_{24} \leq 10$). Patients achieved full re-orientation (4 of 5 items) in 5.5 ± 6.4 min (median = 3.6), timed from when their eyes first opened after treatment.

Conclusion: In this feasibility study, FEAST produced clinically meaningful antidepressant improvement, with relatively short time to reorientation. Our preliminary work first in primates and now depressed adults demonstrates that FEAST is feasible, safe, well-tolerated and, if efficacy can be optimized, has potential to replace traditional ECT.

Introduction

Electroconvulsive therapy (ECT) is the most effective acute antidepressant treatment presently available. The cognitive side effects of ECT limit its broader use [1]. Historically, the universal view was that a generalized seizure provided the necessary and sufficient conditions for efficacy. However, based on multiple studies, it is now evident that electrode placement (EP), type of electric stimulus (sine wave, wide or ultrabrief (UB) pulse) and electrical dosage relative to seizure threshold (ST) play critical roles in impacting on efficacy and side effects, and offer an opportunity to optimize efficacy while further reducing side effects. For example, there are clear interactions between electrode placement (EP) and dosage (relative to ST) in influencing efficacy [2–4]. The role that

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these technical variables play in the therapeutic effect of ECT have been large, with remission rates varying between 17 and 70% depending on merely changing these variables. For example, high dosage UB (0.3 ms) right unilateral (RUL) ECT (6 × ST) appears to match the efficacy of a robust form of traditional wide pulse (WP) width bilateral (BL) ECT (2.5 × ST), and has significant advantages in acute, short- and long-term cognitive effects [5]. Nonetheless, some degree of cognitive impairment can occur with the ultrabrief pulse [5].

There is specificity in the neural circuits that may mediate the therapeutic benefit of ECT. ECT produces marked decreases in cerebral blood flow (rCBF) and metabolic rate for glucose (rCMR), and sharp increases in EEG slow wave activity (delta and theta power) during and following the treatment course [6–8]. Consistent with the analysis of current density paths, strong associations have been demonstrated between the magnitude of the prefrontal cortex (PFC) changes caused by ECT and its antidepressant effects [7]. Spatial specificity has also been shown, in that functional changes in other brain regions are independent of efficacy. Instead, rCBF, rCMR, and EEG slow wave changes in temporal areas have been linked to the magnitude of anterograde (AA) and retrograde amnesia (RA) [7,8]. Conversely, as with secondarily generalized, focal seizures in epilepsy, surround inhibition is greatest at the site(s) of seizure initiation rather than in the secondary sites of propagation [9–12]. As such, sites of seizure initiation are more important in modulating efficacy than patterns of seizure propagation [13]. Stronger electric field strength in frontal pole seen with BL and bifrontal compared with RUL ECT [14–17] could explain the poor efficacy of low dose RUL ECT with triggered seizures principally from motor cortex [8,13].

Thus, it is distinctly possible that an optimal form of ECT would trigger seizures in the PFC with limited propagation to other brain areas. Robust PFC seizure expression would elicit the requisite localized inhibitory process, and the spatial restriction of the ictal process would limit cognitive effects. This could be achieved with improved control over the intracerebral distribution of charge density. However, with traditional ECT high skull impedance and inhomogeneities [14,16,18] result in diffuse current distribution and render poor control over intracerebral charge density [19]. As one potential solution, magnetic seizure therapy (MST) induces eddy currents in neural tissue not otherwise attenuated or distorted by scalp and skull [20–22]. Studies to date suggest that MST offers more precise control over intracerebral charge density and current paths than can be obtained with conventional electrical stimulation and provide evidence of improved safety with relative sparing of cognitive functioning [23]. However, MST has two limitations. First, the energy transfer between current in a coil to current in brain is highly inefficient requiring high power devices to achieve reliable seizure induction in PFC. This may be consequential because MST necessarily delivers a UB pulse and only UB RUL ECT delivered substantially above the seizure threshold has been found to be effective, while lower doses are not. Second, the magnetically induced electrical field has limited penetration, with stimulation restricted to a depth approximately 2–4 cm below the coil depending on the coil's configuration [24–26]. This is an advantage if stimulation of deeper structures contributes to side effects, but could be a disadvantage if deeper stimulation (such as ventromedial or orbitofrontal cortex) could be more effective.

The new stimulation approaches within FEAST promise a fundamental new direction for ECT [27]. FEAST differs from traditional ECT in three respects. First, instead of a bidirectional stimulus, FEAST uses unidirectional stimulation. This creates a positive (anode) and negative (cathode) electrode, with current flow in one direction, which has been reported to be associated with lower seizure threshold [28]. Second, FEAST uses novel electrode geometry, first suggested by Amassian in work maximizing focality of transcranial electrical stimulation. FEAST uses a small anode and large cathode to produce highly focal current flow [21,29–35]. Third, the smaller electrode is placed anteriorly with the lower boundary just above the center of the right eyebrow. This combination concentrates stimulation in the subcallosal cingulate and frontal pole, with less stimulation in temporal lobe compared with bilateral ECT as demonstrated by head modeling of E field distribution [17]. With this theoretical background, and following successful demonstration of FEAST induced seizures in non-human primates [28], we hypothesized that FEAST would be feasible, safe, and potentially effective in treating severely depressed adults. We performed the following pilot open-label trial initially at the New York State Psychiatric Institute/Columbia University and then at the Medical University of South Carolina.

Methods

Study sites and participation

Feasibility research in depressed adults began at New York State Psychiatric Institute/Columbia University and further optimization of the stimulation protocol continued at the Medical University of South Carolina. The general protocol was similar at both sites and approved by the respective Institutional Review Boards and was conducted under an Investigational Device Exemption (IDE) from the United States Food and Drug Administration. All patients signed informed consent prior to enrollment.

Using the Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (with Psychotic Screen), patients met DSM-IV [36] criteria for a major depressive episode (unipolar or bipolar). They scored 21 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item), and treatment with ECT was indicated. Patients were excluded if they had a history of schizophrenia, schizoaffective disorder, non-mood disorder psychosis, neurological illness, alcohol or drug abuse within 6 months, ECT within 6 months, or severe medical illness that presented a risk for undergoing general anesthesia.

Study design

In this open-label feasibility trial, patients' use of psychotropic medications was discontinued at a minimum of 4 days before starting FEAST, other than lorazepam given as needed (up to 3 mg/d). There was no stipulated minimum or maximum number of treatments for patients to be classified as provisional responders; the aim was to achieve maximal improvement. As a precaution for this preliminary trial, patients who showed less than 40% improvement following 4 treatments (later amended to 6 at MUSC) were either withdrawn from the study and offered traditional ECT (UB RUL ECT) or offered FEAST at 9 times seizure threshold (ST). Patients were oxygenated by mask (100% O_2) prior to anesthesia and until resumption of spontaneous respiration. Methohexital (0.75–1.0 mg/kg) and succinylcholine (0.75–1.0 mg/kg) were used as anesthetic medications with pre-administration of atropine (0.4–0.6 mg) or glycopyrrolate (0.2–0.4 mg).

FEAST was administered with a modified MECTA spECTrum 5000Q device (MECTA Corp, Tualatin, Oregon). It relies on a small (reduced surface area) frontal and large posterior electrode to induce focal seizures. Smaller electrodes however can lead to increased dynamic impedance, and failed treatment delivery if the ECT device voltage limit is exceeded or could produce superficial skin burn. When this clinical study was first proposed with a $^3/_4$ in diameter anode (frontal) electrode, the expectation was that the resulting dynamic impedances would remain in the 200–300 Ω

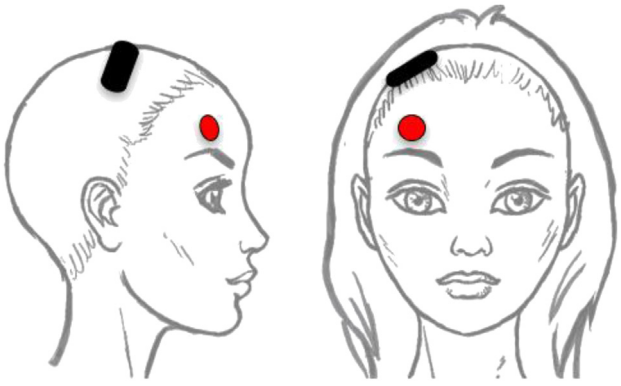

Figure 1. Illustration of FEAST electrode placement.

range, but that the likelihood of skin burns could increase due to reduced electrode surface area. To mitigate this risk, the spECTrum voltage limit was reduced from 400 to 240 V, thus reducing the allowed dynamic impedance upper limit (at 800 mA) from 500 to 300 Ω. The stimulating electrodes initially (NYPI; $n = 7$ and MUSC; $n = 2$) consisted of a small (0.75″ diameter) anterior round stainless steel electrode and a larger posterior oblong stainless steel electrode (1 × 2.5″) (with a concave curve to approximate the roundness of the skull). Subsequent modification to the protocol involved use of larger size anterior electrodes (MUSC; $n = 3$ with 1.0″ and $n = 5$ with 1.25″ diameters) and posterior electrodes (MUSC; $n = 8$ with 2″ × 3″ oblong, similarly curved) to address an unacceptably high rate of stimuli aborted by device impedance limits with the prior electrodes. Electrodes were attached in a standard manner to the MECTA remote-treat stimulus cables that were pre-identified as anode and cathode. The smaller electrode (labeled anode) was placed anteriorly, with the lower boundary just above the center of the right eyebrow (see Fig. 1).

The posterior electrode was placed tangential to the midline and extended across the right supplementary motor cortex. The medial position of this electrode was adjacent to the line connecting the nasion and inion and with the posterior boundary 1.0 “anterior to the vertex, with the lateral portion extending over the right hemisphere.”

FEAST treatments were delivered in the morning, 3 times per week. The criterion for an adequate seizure was ≥20 s motor duration assessed with cuffed extremity or EEG. Subconvulsive stimuli, which occurred only during the titration session, were followed 20 s later by restimulation. At the first treatment, the empirical titration procedure was used to estimate ST [37–39]. The titration schedule combined 4 parameters, with a range of charge from 5.4 to 43.2 mC (See Appendix for the titration schedule.) Virtually all modern reports of ECT administration have used either an 800 or 900 mA fixed current amplitude and have then varied the number of pulses or train duration in a stepwise fashion to induce a seizure. Instead this study also explored the feasibility of titration in the current domain [27,40,41]. Titration started with a 200 mA pulse amplitude,[1] and increased in 200 mA steps until 800 mA was reached, holding pulse width (0.3 ms), frequency (30 Hz), and train duration (8 s) constant. If a patient did not have an adequate seizure at the highest titration setting (43.2 mC) they would have exited the protocol and received conventional ECT. However all patients had adequate FEAST induced seizures by this titration step and none exited due to elevated ST. The highest subsequent dosage in this pilot study was 384.0 mC, 66.7% the maximal output of a standard US Spectrum 5000Q (576 mC). Dosing at subsequent treatments was substantially above seizure threshold (6 × ST) as it is now commonly adopted for UB RUL ECT. Given insufficient clinical progress, this dosage was increased in some instances to up to approximately 9 × ST prior to terminating use of FEAST.

[1] MUSC titration started with 400 mA since no seizures occurred at NYPI with 200 mA.

Assessments

The Antidepressant Treatment History Form was completed to quantify medication resistance (i.e., the number of adequate antidepressant trials in the current episode) [42]. Prior to ECT, twice during ECT, and at ECT termination, an experienced clinical rater completed the Hamilton Rating Scale for Depression ($HRSD_{24}$, 24-item). The clinical rater also completed the Clinical Global Impression (CGI) scales (CGI-S indicates severity; CGI-I, improvement), and the Global Assessment of Function scale. Since NYSPI and MUSC cohorts were not recruited during the same period, no inter-rater reliability across sites was established. Patients completed the Beck Depression Inventory-II (BDI) (at NYSPI only) or Inventory of Depressive Symptoms – Self Report (IDS-SR) (at MUSC only) and the Suicide Scale Inventory at the same intervals. Adverse effects were assessed in terms of the frequency of adverse and serious adverse events and the primary cognitive outcome measures from a neuropsychological battery. Adverse events and serious adverse events were defined following standard conventions.

Time to recover full orientation, a putative predictor of long-term amnestic effects, was assessed at each treatment [43]. Correct response to 4 of 5 orientation items (name, place, date of birth, day of week and age) was the criterion for recovery of orientation (Sackeim et al., 1993, NEJM; Sobin et al., AM J Psych, 1995). A neuropsychological battery was administered before the start of ECT and 1–4 days following ECT. Three tests provided primary cognitive outcome measures: total score on the modified Mini-Mental State Examination (MMSE) [44], total recall of unrelated words across 6 trials of the Buschke Selective Reminding Test (SRT) [45], and score on the Autobiographical Memory Interview, Short Form (AMI-SF) [46]. The MMSE assessed global cognitive status, the SRT assessed anterograde amnesia for verbal information, and the AMI-SF assessed retrograde amnesia for autobiographical information. Patients enrolled at MUSC were also administered the Repeatable Battery for Assessment of Neurocognitive Status (RBANS) [28] following the same timeline of cognitive tests presented above. The RBANS is a brief neurocognitive battery with four alternate forms, measuring immediate and delayed memory, attention, language, and visuospatial skills.

Statistical analyses

For this feasibility study, data from NYSPI and MUSC were pooled. Clinical antidepressant response was defined *a priori* as a ≥50% reduction in the mean $HRSD_{24}$ scores at the final assessment 2 days after the last FEAST session relative to the baseline (pre-FEAST) visit or, for secondary analyses, a ≥50% reduction in the mean of baseline IDS-SR score. Remission was defined *a priori* as a $HRSD_{24}$ score of ≤10. We employed a last observation carried forward (LOCF) analysis in the context of missing data for all patients who completed 2 sessions including the initial titration.

All data were quality checked and queries clarified before final analyses were conducted. For clinical and neuropsychological data, paired sample *t*-tests were used to assess for change over time. All statistical tests were two-tailed at 0.05 alpha level.

Results

Patient characteristics

Seventeen unmedicated depressed adults (7 NYSPI: 10 MUSC) participated. There were 5 men and 3 patients with bipolar disorder, and an average age of 53 ± 2 years. The lengths of the current depressive episode and lifetime depressive illness were 225.7 ± 257.3 weeks and 20.1 ± 11.2 years, respectively. There were no differences in age, gender, diagnosis, length of current depressive illness and baseline $HRSD_{24}$ between the sites.

Titration and seizure duration

The average charge needed to elicit a seizure during titration was 19 ± 10.1 mC, a relatively low value suggesting that FEAST may be especially efficient in seizure induction, as also suggested by nonhuman primate research [28]. As seen in Table 1, seizures were successfully induced in several patients with current intensity as low as 400 mA, supporting the feasibility of titration in the current domain. Dynamic impedance was significantly higher at lower current values ($n = 29$, df = 3, $F = 18.81$ and $P < 0.0001$). Across all treatments, the average duration of motor convulsions was 44.3 ± 33.9 s and the EEG seizure duration was 61 ± 49.7 s. With successive increases in anode size from $^3/_4$ " diameter to 1″ and then 1.25″, the average dynamic impedance also dropped from an average of 353 ± 56.16 to 307.9 ± 20.40 and finally to 278.15 ± 74.82 Ω, respectively.

Clinical outcomes

One patient completed only a titration session and elected to withdraw from the study. This patient's clinical outcomes were not included in the summary below. The average number of FEAST treatment sessions per patient was 8.8, the median was 10, with a range 4–14. Patients averaged a 46.1 ± 35.5% improvement after FEAST compared to baseline on the $HRSD_{24}$ ((33.1 ± 6.8, 16.8 ± 10.9; $P < 0.0001$) and a 53.2 ± 23.4% improvement on the IDS-SR (54.1 ± 6.8, 25.3 ± 13.7, $P = 0.0014$). At the end of the course, 8 of 16 (50%) patients met response criteria and 5 of 16 (31%) met remission criteria. Modifications in stimulation parameters implemented in the MUSC cohort including increased electrode size may have improved efficacy over time, with only 1 of the first 9 patients achieving remission compared to 4 of the last 7 although there is also a confound with site and potentially other patient characteristics. Two patients presented with severe suicidal ideation but had their Suicidal Scale Inventory scores drop from 26 to 31 at baseline, to 7 and 0 at end of FEAST. No switches to mania or hypomania were observed (Fig. 2).

Table 1
Detailed demographics, treatment parameters and clinical outcome scores.

ID	Age	Gender	Length of depressive illness	Baseline $HRSD_{24}$	End $HRSD_{24}$	Percent change in $HRSD_{24}$	Intensity of treatment	Titration in mC
1	43	M	572	32	13	60.94	600	16.2
2	38	F	192	22	20	9.09	400	10.8
3	64	F	74	39	28	28.21	400	10.8
4	79	F	41	32	9	71.88	400	10.8
5	51	F	104	21	23	−9.52	400	10.8
6	51	M	88	36	24	34.72	400	10.8
7	66	F	10	31	10	67.74	400	10.8
8	45	F	540	37	30	18.92	800	21.6
9	76	F	54	35	44	−25.71	800	21.6
10	52	F	27	44	15	65.91	800	21.6
11[a]	55	F	864	26	32	−23.08	800	43.2
12	30	M	162	24	16	33.33	600[b]	16.2
13	48	F	108	40	8	80.00	600	16.2
14	72	M	324	29	5	82.76	800[b]	43.2
15	28	F		34	4	88.24	800[b]	21.6
16	55	M		31	18	41.94	800	21.6
17	55	F		43	4	90.70	600	16.2

[a] Patient #11 exited the study after the titration session.
[b] Patients who were treated at 9 × ST after their 6th FEAST session.

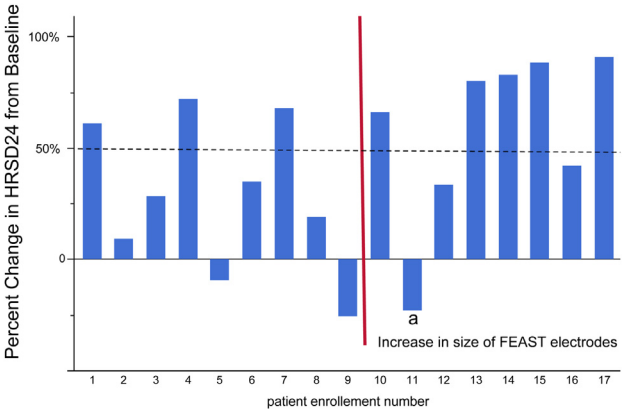

Figure 2. Percent changes in $HRSD_{24}$ from baseline for all 17 patients in the order of their enrollment in the study. Note that the percent improvement and number of FEAST remitters increased with time. The first 9 patients were treated with 0.75″ round anterior and a 1 × 2.5″ posterior electrodes and relatively lower currents. By the 10th patient, the anterior electrode increased to 1 and then 1.25″ diameter. The posterior electrode was also increased to 2 × 3″. Patients who showed less than 40% improvement following 4 treatments (later amended to 6 at MUSC) were offered traditional ECT. [a]Patient #11 exited the study after the titration session. Data was not included in the summary of clinical response.

Cognitive measures

Patients achieved full re-orientation in 5.5 ± 6.4 min (median = 3.6) from when their eyes first opened. One subject exposed to both FEAST and UB RUL ECT had a shorter time to orientation recovery with FEAST (3.8 ± 3.3 min FEAST versus 4.8 ± 4.1). Importantly, other measures of cognition showed no changes after a full course of FEAST. MMSE scores at baseline and end of treatment scores were 28.4 ± 1.2 and 29.1 ± 1.3 ($P = 0.33$), respectively. Similarly, AMI-SF scores were 53 ± 4.9 and 51.5 ± 5.1 ($P = 0.6$); RBANS were 90.3 ± 4.2 and 86.2 ± 14.2 ($P = 0.56$).

Adverse events

There were 2 first-degree burns at the anterior site of stimulation with the smaller 0.75″ electrode. One patient exhibited a drop in RBANS score immediately after the treatment course (11 sessions) but recovered by 2 months follow-up and was back to baseline by 4 months.

Discussion

In this first use of FEAST in 17 depressed adults, we found that we could reliably produce seizures in a manner analogous to traditional ECT. These FEAST treatments produced significant antidepressant effects, with clinically meaningful improvement in this open label feasibility trial. Side effects were minimal and orientation time (5.5 ± 6.4 min) appeared shorter than with conventional methods (10 ± 6 for UB RUL and 33 ± 21 for BL ECT) [5], albeit without formal randomized comparison. And while it is apparent that the efficacy of FEAST (42% response and 29% remission) may be reduced relative to conventional ECT [5], we did

observe an improved efficacy with the changes in electrode size in this the first instantiation of FEAST. More is needed to fully optimize the anatomical target and the size of the neuronal population involved in seizure initiation (degree of facility). Studies are currently underway using functional neuroimaging and high resolution EEG to attend to these important variables.

Spatial distribution and density of current in brain strongly determine ECT efficacy and cognitive side effects. One of the goals in developing FEAST was to avoid seizure initiation in medial temporal lobe structures subserving critical memory functions. Preliminary work first in primates [28] and now depressed adults demonstrates that FEAST is feasible, safe, well-tolerated and has potential for clinical efficacy. Over the 17 subjects there was a trend for better response following the increases in electrode size.

The larger frontal electrode used in the last 4 patients sized at 1.25″ diameter produced dynamic impedances within acceptable and safe ranges for electrical stimulation. This electrode size is substantially larger than what we first explored (0.75″ diameter) and illustrates the importance of the piloting phase to finalize parameters, as we have systematically examined electrical properties of 3 different sized electrodes. The larger size theoretically leads to some reduction in focality [2]. With concurrent EEG recordings from F3, F4, T3 and T4, our impression was that FEAST appears capable of eliciting seizure activity from right PFC areas before propagation to the contralateral hemisphere, motor cortex and the medial temporal lobe, although claims of focality and limited initiation of seizures in the orbitofrontal cortex require empirical demonstration.

This open-label feasibility study has limitations: 2 sites drawing on different patient populations were involved, and because of limited availability, only a subset of the neuropsychological battery was matched across both sites. And while our efficacy appeared to improve over the course of enrollment, possibly due to optimized electrode geometry and treatment delivery, the current report cannot allow a direct testing of such possibilities. Theoretical framework for PFC seizure induction with FEAST is well supported including work in nonhuman primates, yet mechanisms of action studies in patients are still needed to provide direct evidence.

ECT's major adverse effect (memory loss) and its therapeutic properties are dissociable, leading to the possibility of modulating one, without affecting the other. FEAST has potential advantages over traditional ECT methods (BL and UL alike) both in its capacity for spatial targeting and its low dosing needs. Coupling FEAST with UB stimulation (as we have shown) may represent the most precise method at present to target sites for seizure onset and yet retain the capacity to dose at any level above ST needed to maintain efficacy. Changes in electrode geometry can be used to vary the degree of focality.

This study also explored the feasibility of conducting stimulus dose titration in the current domain. In virtually all other brain stimulation technologies, current is one of the primary electrical parameters altered to maximize efficacy or minimize side effects. Theoretical work has long suggested important advantages in manipulating current to adjust dosage in ECT [27,40,41]. For example, individuals vary greatly in the extent to which current is shunted away from brain due to individual differences in scalp and skull anatomy. To account for these individual differences, the standard titration procedure in ECT has involved manipulating the number of pulses patients receive by altering pulse frequency or train duration or both. Directly manipulating current may make individuals more alike in intracerebral patterns of current density. Regardless, this study underscores the feasibility of titration in the current domain and using low current levels through out the treatment course. It is also conceivable that coupling FEAST with the use of lower than usual current values contributed to the limited efficacy. Reductions in current will also produce more focal electrical stimulation by reducing depth of penetration [41]. In future trials of FEAST we plan to use conventional titration procedures with a fixed current to exclude this factor as contributing to reduced efficacy. Nonetheless, the value of titration in the current domain and the use of low current levels should be independently investigated.

An effective antidepressant treatment should not only improve depressive symptoms but also be devoid of serious adverse events. This present FEAST feasibility study posits a new direction for ECT. The extent of clinical improvement in these first 17 patients underscores the need for future refinements in titration strategies, electrode geometry, and choice of anatomic target. Ultimately direct clinical comparison with conventional ECT will test the potential value of FEAST in treating depression. Because of the focal nature of the induced seizure, FEAST might also be useful therapeutically in other brain disorders.

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Appendix I – Titration table.

Pulse frequency (Hz)	Pulse width (ms)	Train duration (s)	Current (mA)	Total charge (mC)	Dose relative to initial ST
Titration schedule					
30	0.3	1.5	200	5.4	–
30	0.3	1.5	400	10.8	–
30	0.3	1.5	600	16.2	–
30	0.3	1.5	800	21.6	–
30	0.3	3	800	43.2	–
Subsequent dosing: 6 × ST					
60	0.3	4.5	200	32.4	6.0
60	0.3	4.5	400	64.8	6.0
60	0.3	4.5	600	97.2	6.0
60	0.3	4.5	800	129.6	6.0
60	0.3	8	800	230.4	5.3
Subsequent dosing: 9 × ST					
60	0.3	7	200	50.4	9.3
60	0.3	7	400	100.8	9.3
60	0.3	7	600	151.2	9.3
60	0.3	7	800	201.6	9.3
60	0.5	8	800	384.0	8.9