Rapid Mood-Elevating Effects of Low Field Magnetic Stimulation in Depression

Michael L. Rohan, Rinah T. Yamamoto, Caitlin T. Ravichandran, Kenroy R. Cayetano, Oscar G. Morales, David P. Olson, Gordana Vitaliano, Steven M. Paul, and Bruce M. Cohen

Background: We previously reported rapid mood elevation following an experimental magnetic resonance imaging procedure in depressed patients with bipolar disorder (BPD). This prompted the design, construction, and testing of a portable electromagnetic device that reproduces only the rapidly oscillating (1 kHz, <1 V/m) electromagnetic field of the experimental procedure, called low field magnetic stimulation (LFMS).

Methods: We used a randomized, double blind, sham controlled treatment protocol to study the effects of LFMS in a large group of stably medicated, depressed patients with either BPD ($n = 41$) or major depressive disorder ($n = 22$). Subjects received a single, 20-minute treatment. Change in mood was assessed immediately afterward using a visual analog scale (VAS), the 17-item Hamilton Depression Rating Scale (HDRS-17), and the Positive and Negative Affect Schedule scales.

Results: Substantial improvement (>10% of baseline) in mood was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups for our primary outcomes, the VAS and the HDRS-17. These differences were not statistically significant in primary analyses stratifying by diagnosis but were significant in secondary analyses combining data across the two diagnostic groups ($p = .01$ VAS, $p = .02$ HDRS-17). Rapid improvement in mood was also observed using the Positive and Negative Affect Schedule scales as secondary measures (positive affect scale $p = .02$ BPD, $p = .002$ combined group). A finite element method calculation indicates a broad penetration of the LFMS electric field throughout the cerebral cortex.

Conclusions: Low field magnetic stimulation may produce rapid changes in mood using a previously unexplored range of electromagnetic fields.

Key Words: Bipolar depression, depression, field, electromagnetic field, rapid antidepressant, therapy

Depression is a common and often recurrent disease, with a lifetime prevalence rate in the United States of over 20% (1,2), and is estimated by the World Health Organization to be the leading cause of disease-associated disability in developed countries worldwide (3). Bipolar disorder (BPD) is distinguished from major depressive disorder (MDD) by the presence of episodes of abnormally elevated mood (4). However, it is the depression that is the primary cause of disability and death in both these disorders (5).

Antidepressant drugs are effective in relieving depression in many patients (6) but have limited efficacy overall (7,8); fewer than 40% of patients with MDD in controlled clinical trials have complete remissions (9–11). Even in depressed patients who do experience remissions, relapse rates are very high (37% to 70% within the first year) (12). Many depressed patients are considered treatment resistant, with 33% failing to remit after 3 or more treatment trials (13,14). Patients with BPD often have treatment-resistant depression and risk the induction of mania with treatment (15). There are few effective treatments for these treatment-resistant patients (5,16).

From the McLean Hospital and the Department of Psychiatry, Harvard Medical School, Belmont, Massachusetts; and Departments of Neuroscience (Mind and Brain Institute), Psychiatry, and Pharmacology (SMP), Weill Cornell Medical College of Cornell University, New York, New York.

Address correspondence to Michael L. Rohan, Ph.D., McLean Hospital and Harvard Medical School, Brain Imaging Center, McLean Hospital and the Department of Psychiatry, 115 Mill St, Belmont, MA 02478; E-mail: mrohan@mclean.harvard.edu.

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A limitation of currently available antidepressant therapies, including antidepressant drugs, electroconvulsive therapy (ECT), or repetitive transcranial magnetic stimulation, is that they have little immediate therapeutic effect. Typically, antidepressant drugs require a minimum of 4 to 6 weeks to exert a clinically meaningful improvement in mood (17). Even ECT, which has remission rates ≥65% in many studies, requires two to three treatments per week for 3 to 4 weeks to achieve its full effect (18–20). This time lag to clinical response leaves patients vulnerable to the often disabling symptoms of depression, including a high risk of suicidal behavior during the first weeks of treatment (21). Rapid relief from depression has been reported following intravenous infusion of ketamine (22,23) or scopolamine (24,25), deep brain stimulation (26–29), or sleep deprivation (30). In most cases, these rapid responses are transient, and durable responses have a delay that is more typical of standard antidepressant medications. Few rapid antidepressant treatments have been studied in BPD. These findings of rapid antidepressant responses, even in treatment-resistant patients, have stimulated considerable interest in the potential to develop rapidly acting treatments without the delayed onset of currently available treatments.

Low field magnetic stimulation (LFMS) uses time-varying magnetic fields that are within clinical magnetic resonance imaging (MRI) guidelines but that differ from those used in structural or functional MRI (fMRI) in their waveform, frequency, and strength (31). Low field magnetic stimulation delivers a magnetic field waveform that induces a low, pulsed electric field (≤1 V/m, 1 kHz) in the brain. Following the serendipitous observation of rapid mood improvement in bipolar depressed patients undergoing an experimental magnetic resonance spectroscopic imaging procedure (MRSI) (32), a small sham-controlled study in BPD patients suggested that these dynamic, relatively weak electromagnetic fields could induce rapid improvements in mood (31).

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One of the dynamic components of the gradient field in the MRSI protocol was postulated to mediate this rapid antidepressant effect (see Methods and Materials). A prototype system containing a small MRI-style coil was subsequently used to reproduce these electromagnetic pulses for preclinical studies. Antidepressant-like behavioral effects of LFMS were demonstrated in the forced swim test (33), an animal model sensitive to antidepressant treatments (34).

Prompted by our preliminary clinical findings in depressed BPD patients, as well as the forced swim test data in rats, we hypothesized that an LFMS device that produced this waveform would rapidly improve depressed mood in patients with either BPD or MDD. We designed and constructed this LFMS device and calculated the estimated distribution and penetration of the LFMS-induced electromagnetic fields in the brain using the finite element method (FEM). We then conducted a randomized, double blind, sham-controlled study of LFMS using this new device in a large group of stably medicated, but still symptomatically depressed, BPD and MDD patients and observed rapid (within 20 minutes) elevation of mood.

Methods and Materials

Subjects

Sixty-three patients ages 18 to 65 who met DSM-IV criteria for either BPD or MDD (35) and who were in a current episode of depression, defined as having a score greater than or equal to 17 on the 17-item Hamilton Depression Rating Scale (HDRS-17) (36), contributed data to the analysis. All patients contributing data (mean baseline HDRS-17 score = 22.4 $\pm$ 4.2) were on a stable regimen of antidepressant or mood-stabilizing medications for at least 6 weeks before randomization. Eligible patients were randomly assigned in a 1:1 ratio to either active LFMS or sham treatment in permuted blocks of 10 within diagnostic strata (MDD and BPD). All procedures were reviewed and approved by the McLean Hospital Institutional Review Board, and all subjects provided informed consent before enrollment.

Potentially qualifying subjects participated in a screening visit. They provided informed consent, had their diagnosis confirmed, and were interviewed by a physician to determine eligibility, including ability to give consent. Eligible subjects received a physical exam and had their mood rated using the HDRS-17 and Young Mania Rating Scale (for BPD subjects). Qualified subjects then had a treatment visit scheduled. During their treatment visit, subjects had their pretreatment mood assessed with the HDRS-17, visual analog scale (VAS), and Positive and Negative Affect Schedule (PANAS), followed by either 20 minutes of active or sham LFMS. Following the treatment, subjects were observed for 10 to 15 minutes, after which the HDRS-17, VAS, and PANAS were administered again for posttreatment mood ratings. Subjects were asked about any sensation or discomfort after treatment and were contacted 1 week after the treatment visit by telephone, for safety purposes only, not for clinical ratings. Detailed clinical procedures are presented in Supplement 1.

Characteristics of the sample at baseline, including medication details, are presented in Table 1 and were compared using the Wilcoxon rank-sum tests (ordinal and continuous variables) and Fisher's exact tests (categorical variables). There were no significant differences in demographic characteristics, medication usage, or baseline clinical ratings between the active and sham groups, either for BPD, MDD, or the combined sample. Most subjects were taking multiple medications during the study. Safety data, including reported adverse events, were collected on all subjects. There was one report of hypomania the day following treatment in a BPD subject that was determined to be unlikely to be related to treatment because this subject received a sham treatment. There were two reports of dizziness during the venipuncture at the initial physical exam. Forty-four additional patients were treated with LFMS in an exploratory group. These subjects did not satisfy the study enrollment criteria, due to either subthreshold HDRS-17 scores (less than 17) or comorbid psychiatric conditions such as posttraumatic stress disorder or obsessive-compulsive disorder. As these additional patients were treated for exploratory, primarily safety, purposes and fell under separate institutional review board approval, they were excluded from the data analysis of this report.

Table 1. Subject Demographics, Medication Profiles, and Baseline Clinical Ratings for the Patients Entered in the LFMS Trial

	Bipolar Disorder			Major Depression			Combined Sample		
	Active	Sham	*p*	Active	Sham	*p*	Active	Sham	*p*
n	21	20		13	9		34	29	
Demographics									
Female	15	10	.21	9	4	.38	24	14	.12
Age	42.5 (12.1)	43.6 (12.6)	.64	47.1 (13.5)	48.8 (10.0)	.97	44.2 (12.7)	45.3 (11.9)	.68
Medication									
Antidepressants	14	14	.74	12	9	1.00	26	23	.76
Antipsychotics	13	11	1.00	6	5	1.00	19	16	1.00
Anticonvulsants	16	15	1.00	5	3	1.00	21	18	1.00
Benzodiazepines	11	8	.55	7	6	.67	18	14	1.00
Baseline Clinical Ratings									
HDRS-17	23.8 (5.1)	22.2 (3.7)	.36	20.6 (2.6)	22.4 (4.2)	.33	22.6 (4.5)	22.3 (3.8)	.93
VAS	6.3 (1.6)	6.3 (1.7)	.98	5.1 (2.0)	6.9 (2.3)	.07	5.8 (1.9)	6.4 (1.9)	.22
PA (PANAS)	18.9 (4.7)	21.1 (7.0)	.41	21.4 (10.1)	19.6 (6.1)	1.00	19.8 (7.3)	20.6 (6.6)	.52
NA (PANAS)	26.4 (9.1)	22.7 (7.8)	.30	21.7 (8.8)	22.6 (6.0)	.48	24.6 (9.2)	22.6 (7.2)	.67

Values are mean (SD) or *n*. Medications are reported according to current prescription; many subjects had multiple prescriptions. *p* values are from Wilcoxon rank-sum test (continuous and ordinal variables) or Fisher's exact test (categorical variables) comparing active treatment with sham treatment. Age and medication data are missing for one patient with BPD.

BPD, bipolar disorder; HDRS-17, 17-item Hamilton Depression Rating Scale; LFMS, low field magnetic stimulation; NA, negative affect; PA, positive affect; PANAS, Positive And Negative Affect Schedule; VAS, visual analog scale.