ARCHIVAL REPORT

Transcranial Low Voltage Pulsed Electromagnetic Fields in Patients with Treatment-Resistant Depression

Klaus Martiny, Marianne Lunde, and Per Bech

Background: Approximately 30% of patients with depression are resistant to antidepressant drugs. Repetitive transcranial magnetic stimulation (rTMS) has been found effective in combination with antidepressants in this patient group. The aim of this study was to evaluate the antidepressant effect of a new principle using low-intensity transcranially applied pulsed electromagnetic fields (T-PEMF) in combination with antidepressants in patients with treatment-resistant depression.

Methods: This was a sham-controlled double-blind study comparing 5 weeks of active or sham T-PEMF in patients with treatment-resistant major depression. The antidepressant treatment, to which patients had been resistant, was unchanged 4 weeks before and during the study period. Weekly assessments were performed using both clinician-rated and patient-rated scales. The T-PEMF equipment was designed as a helmet containing seven separate coils located over the skull that generated an electrical field in tissue with orders of magnitude weaker than those generated by rTMS equipment.

Results: Patients on active T-PEMF showed a clinically and statistically significant better outcome than patients treated with sham T-PEMF, with an onset of action within the first weeks of therapy. Effect size on the Hamilton 17-item Depression Rating Scale was .62 (95% confidence interval .21–1.02). Treatment-emergent side effects were few and mild.

Conclusion: The T-PEMF treatment was superior to sham treatment in patients with treatment-resistant depression. Few side effects were observed. Mechanism of the antidepressant action, in light of the known effects of PEMF stimulation to the brain, is discussed.

Key Words: Hamilton scale, melancholia scale, pulsed electromagnetic fields, randomized controlled trial, transcranial magnetic stimulation, treatment-resistant depression

Approximately 30% of patients with major depressive episodes are resistant to antidepressant drugs (1). In these patients, the risk of developing chronic depression (an episode longer than 24 months) is high. No single treatment modality has been shown to be particularly effective, and patients are often subjected repeatedly to unsuccessful drug trials. There is therefore a great need for new and effective treatment methods for these patients.

The purpose of this study was to investigate the possible antidepressant effect of transcranial application of low-intensity pulsed electromagnetic fields (T-PEMF) in patients suffering from treatment-resistant depression. PEMF stimulation is a technology that uses continuous trains of low-voltage alternating currents running in coils located over the treatment areas. This kind of PEMF treatment has been shown to have efficacy in osteoarthritis (2,3), and we know from in vitro and in vivo studies that PEMF can stimulate angiogenesis in humans and animals (4). PEMF has also been shown to increase microcirculation in arterioles (5) and to enhance in vitro neurite growth in mammalian neurons (6). The PEMF signal used in this study is of exactly the same strength and configuration as that used in osteoarthritis, but the application method is different. In this study patients (Figure S1 in Supplement 1) wear a plastic treatment helmet with the coils placed on the inside to secure contact to the exterior of the human skull. The alternating electromagnetic field that is generated gives rise to discrete alternating electrical currents in the underlying brain tissue.

The electromagnetic properties of the T-PEMF technology, as used in this study, are thoroughly described (7), together with some of the known effects of PEMF on intracellular signaling including the discovery that PEMF stimulation activates animal intracellular Src tyrosine kinase, which is known to influence signal pathways controlling cell growth, metabolism, and survival.

The study was initiated on the basis of a single-arm, open-label pilot study using T-PEMF (8) in which a large antidepressant effect was seen on the Major Depression Inventory (9) as well as on our recent study on repetitive transcranial magnetic stimulation (rTMS) (10) in which we found a clinically and statistically significant effect of active rTMS compared with sham rTMS.

Methods and Materials

Ethics

The study was carried out in accordance with the Declaration of Helsinki and the European Union directive of Good Clinical Practice (11). The study was monitored by an external contract company (Encorium Denmark, Hørsholm, Denmark). The study was approved by the Committee on Biomedical Research Ethics and the Danish Central Data Register. Patients were given information as requested by the Biomedical Research Ethics, and all patients signed an informed consent.

Patient Allocation and Inclusion

Patients were treated at a psychiatric research unit and a psychiatric specialist practice, both located in the Greater Copenhagen area.

Inclusion criteria were age older than 18, treatment resistance (a score of ≥3 on the Sackheim criteria) (12), major depression according to the DSM-IV, a score of 13 or above on the 17-item version of the Hamilton Depression Rating Scale ($HAMD_{17}$), and unchanged psychotropic medication during the previous 4

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weeks. Exclusion criteria were suicidal thoughts (a score of ≥2 or more on the $HAMD_{17}$ item for suicidal ideation); alcohol or drug abuse; previous treatment with T-PEMF; pregnancy, lactating, or insufficient contraception; antisocial, borderline, schizotypic, and psychotic disorders; dementia; and inability to comply with the planned treatment sessions and assessments.

Psychometrics

The diagnoses of major depression and comorbid conditions were made using the Mini International Neuropsychiatric Interview (MINI) (13). This instrument is based on DSM-IV (14). Because treatment-resistant depression is not a DSM-IV diagnosis, we used the Antidepressant Treatment History Form (ATHF) to assess the level of treatment resistance, as suggested by Sackheim (12), with a score of three or more required for inclusion (range = 0–4, with four signifying the highest level of treatment resistance).

The primary outcome scale was the $HAMD_{17}$ (15). All other scales were secondary outcome scales and included the Hamilton six-item subscale ($HAMD_6$) (16,17) and the Melancholia Scale (MES) (18,19). Furthermore, the clinician-rated Visual Analogue Scale (VAS) was used in which 0 signifies no depression and 100 signifies extreme depression. Remission was defined as a score of 7 or less on the $HAMD_{17}$ and response as a score reduction from baseline of 50% or more on the $HAMD_{17}$. Patients were assessed once weekly for 5 weeks. As patient-rated secondary outcome scales, we used, the Major Depression Inventory (MDI) (9) and the WHO-5 (World Health Organization-Five) Well-Being Index (20) for all visits; for baseline and end point, the Symptom Check List (SCL-90) (21) was used.

The MDI, which covers the DSM-IV criteria for major depression, is scored on a frequency-response scale from "none of the time" (0) to "all of the time" (5). The score range is from 0 to 50. The WHO (Five) Well-Being Index consists of five items that are scored on a frequency response scale from "none of the time" (0) to "all of the time" (5). The score range is from 0 (lowest level of well-being) to 100 (highest level of well-being). The SCL-90 scale measures psychosomatic symptoms; generally nine subscales and total score are analyzed separately. The total item number of the full SCL-90 is 90, and each item is scored on a 5-point scale from 0 = "not at all" to 4 = "extremely." The Preskorn scale, constructed as a VAS scoring from 0 (no depression) to 10 (worst depression ever), was used to monitor mood changes from day to day. The rating period was the previous 24 hours.

The patients completed compliance logs for T-PEMF treatment. Side effects were measured at all visits with the Udvalget for Kliniske Undersøgelser (UKU) scale (22).

At baseline, patients were asked to assess their treatment expectation on a VAS from 0 (no improvement) to 10 (total remission from depression). At end of study, as a measure of blinding, patients were asked to which treatment they believed they had been allocated, active or sham T-PEMF.

Study Randomization and Design

This was a proof of concept study to test whether the T-PEMF method is functional and feasible. The 5 weeks of therapy were designed as a double-blind randomized controlled trial. In total, eight T-PEMF generators were used in this study. Four of these were inactivated internally. All startup and power-down procedures were identical. The pulse generators were labeled with a coded unique identifier that served to identify it as active or inactive. The generators were also labeled consecutively with randomization numbers from the randomization list. The monitoring company provided the randomization list and performed all labeling of the generators. The randomization list was computer-generated as random numbers in blocks of 10. Investigators had no information regarding the randomization list or generator identification numbers or block size. Patients were consecutively allocated to the next randomization number that served as the patient number on the Case Report Form. The psychopharmacological treatment (antidepressants, mood stabilizers, antipsychotics, tranquilizers, and hypnotics) was unchanged during the previous 4 weeks and was maintained on the same dosage throughout the study. T-PEMF treatment was self-administered, with supervision from health staff, on all weekdays for 5 weeks. The T-PEMF condition (sham or active) was blinded for researchers, patients, and health personnel.

Drug Treatment

Zopiclone was permitted to treat emergent sleep disturbances. No other change in ongoing psychopharmacological treatment was allowed.

T-PEMF Therapy

The T-PEMF delivery system consists of a pulse generator, receiving 220 V, which provides pulses to the applicator constructed as a plastic treatment helmet. The dimensions of the Re5 PEMF generator are (width × height × depth) 2.8 × 1.6 × 9.2 inches. The pulses provided by the generator to the coils in the helmet alternate between +50 and −50 V. The treatment helmet incorporates, on the inner side, two coils in the anterior and posterior temporal region on both sides and one coil in the upper parietal region on both sides and one coil in the center of the lower occipital region. Thus, in total, seven coils are connected in parallel with the pulse generator (see Figure S1 in Supplement 1). The Re5 PEMF pulse generator powers the coils with alternating bipolar square pulses, each lasting 3 msec and interspersed by a 12-msec pause, each pulse sequence thus lasting 18 msec, corresponding to a pulse frequency of 55 Hz. The pulse pattern is quite different from the electromagnetic radiation elicited by cell phones that operate in gigahertz frequencies. The pulse patterns of the PEMF generator were designed to mimic, in magnitude and frequency, the electrical fields occurring outside nerves and muscles due to their own propagation of action potentials.

The rapid change in the current in the coils from the pulse generator creates an alternating magnetic field with a calculated maximum of 19 G (corresponding to 1.9 milliTesla) .5 cm from the coil and capable of inducing electrical fields in tissue with a magnitude of 2.2 mV/cm at a distance of .5 cm from the individual coil (7). The imposed electrical field decreases approximately exponentially with distance and amounts to 30 μV/cm 10 cm from the coil. A Fourier analysis revealed that the frequency composition of the PEMF pulse signal in tissue will be below 333 Hz.

The depolarization (35 mV) required for induction of an action potential by opening of Na^+ channels is many orders of magnitude larger than the electrical field imposed by the T-PEMF treatment (7).

Thus, the field induced in the human cortex by the T-PEMF system is much lower than those obtained with rTMS equipment, which uses stimuli approaching neuronal firing level.

In the sham condition, the generator was internally disconnected, and thus no current reached the applicator. When connected to an active generator, the T-PEMF applicator (treat-

Table 1. Socio-Demographics, Treatment Expectancy Ratings at Baseline, and Blinding Data at End Point

Socio-demographics	Active T-PEMF (n = 25)	Sham T-PEMF (n = 25)
Age, Years, Mean (SD)	56.4 (13.7)	49.7 (11.4)
Gender, % Female (n)	68.0 (17)	72.0 (18)
Number of Previous Depressive Episodes, Mean (SD)	6.4 (5.3)	6.4 (5.5)
Duration of Current Depressive Episode, Months, Mean (SD)	31.3 (34.3)	34.7 (55.0)
Somatic Illness, % (n)	56.0 (14)	56.0 (14)
Smokers, % (n)	44.0 (11)	28.0 (7)
Predisposition to Depressive Illness in First- and Second-Degree Relatives, % (n)	76.0 (19)	84.0 (21)
Treatment Expectancy, Rated from 0 (No Improvement) to 10 (Remission), Mean (SD)	5.0 (2.4)	5.4 (1.7)
Correct Guess as to Treatment Allocation, % (n)	56.0 (14)	56.0 (14)

T-PEMF, T-pulsed electromagnetic fields.

ment helmet), produces a faint humming sound, inaudible to most people, but no heat and skin sensation.

Patients came for daily sessions on all weekdays for 5 weeks at the two study centers.

Statistical Analysis

Sample size was calculated on the basis of the results from our recent rTMS study (10) on the assumption that active treatment with T-PEMF would reduce the $HAMD_{17}$ score by 12.5 points from baseline to end point and that sham treatment with T-PEMF would reduce the score by 9 points. With a power of 80%, an expected standard deviation of 4 and a Type I error of 5%, the number of participants was calculated to be a total of 44 (22 in each group). The $HAMD_{17}$ was the sole primary end point, and all other analyses were exploratory. The intent-to-treat principle was applied, and all randomized patients were included in the analyses. Baseline characteristics in each group were compared by use of the Fisher's Exact Test (dichotomized data) or the two-sample t test for means (continuous data). Available data from the scales assessed at each visit ($HAMD_{17}$, $HAMD_6$, MES, MDI, WHO-5, VAS, and Preskorn) were computed within a mixed-model repeated-measures analysis (23). This included for continuous end points (depression scores) a random-effects regression model (RRM) and for dichotomous end point (response and remission) a generalized estimation equation model (GEE). Thus, for RRM, the model included depression score as the output variable and baseline, visit, treatment group, and the interaction between visit and treatment group as covariates. For GEE, the model included response or remission fraction as the output variable and baseline, visit, treatment group, and the interaction between visit and treatment group as covariates. For tables and graphs, adjusted predicted scores are presented. The model gives p values for each post baseline visits. The difference in scores between treatment groups at Week 5 is considered the primary end point, and analyses for the other weeks are post hoc. The SCL-90, assessed only at baseline and end point, was analyzed with the Mann–Whitney test. Effect sizes were calculated as the difference between mean adjusted predicted scores at end point in the two treatment groups divided by the pooled adjusted predicted standard deviation of this mean difference. Numbers needed to treat was performed on response and remission data and calculated as one divided by the difference in adjusted predicted response and remission fractions in the two treatment groups rounded to a whole number. Compliance was calculated as number of treatment sessions in percent of planned treatment sessions. No interim analysis was performed. Analyses were performed by SAS 9.1 software. The level of statistical significance was set at a 5% level.

Results

In total, 50 patients were included in the study from June 2006 to February 2009. Patients were referred from psychiatric specialist practices (n = 41), general practitioners (n = 3), psychiatric outpatient departments (n = 3), the community mental health center (n = 1), and through advertisement (n = 2). All 50 patients were entered into the intent-to-treat analysis.

Table 1 shows socio-demographic data, expectancy ratings before start of T-PEMF treatment, and results from the questionnaire evaluating blinding at end of treatment. Mean age was 56.4 years in the active treatment group and 49.7 years in the sham treatment group. The mean duration of the current episode was more than 2.5 years, and 33% had durations of more than 2 years. At end of treatment, 56% of the patients indicated a correct guess as to treatment allocation in both groups, indicating a random guess and a good blinding. No statistically significant differences were seen between treatment groups for any variable shown in this table.

Table S1 in Supplement 1 shows the number of patients taking different antidepressant drugs separated by treatment group. The most used antidepressants were selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. More patients in the sham-treated group used hypnotics, but this difference did not reach the level of statistical significance; this was also the case for any other drug used.

Table 2 shows results from the diagnostic interview using the MINI instrument. All patients fulfilled the diagnostic criteria for major depression, and melancholic features were prevalent. The most prevalent comorbid disorders were panic disorder and social phobia. More patients in the sham-treated group fulfilled the criteria for social phobia, but this difference did not reach

Table 2. Comorbidity as Assessed by the MINI Instrument According to DSM-IV

Treatment Group MINI Module	Active T-PEMF (n = 25)	Sham T-PEMF (n = 25)
Major Depression (Inclusion Criteria)	25	25
Major Depression with Melancholic Features	21	19
Bipolar Disorder (I and II)	2	0
Panic Disorder (With and Without Agoraphobia)	6	4
Agoraphobia	1	4
Social Phobia	2	7
Obsessive-Compulsive Disorder	1	0
Posttraumatic Stress Disorder	0	0
Psychotic Disorder (Present and Previous)	0	0
Anorexia	0	0
Bulimia	0	0

MINI, Mini International Neuropsychiatric Interview; T-PEMF, T-pulsed electromagnetic fields.

Table 3. Mean Adjusted Predicted Depression Scores on the $HAMD_{17}$, $HAMD_6$, and MES at Baseline and Weekly During the Treatment Period ($n = 50$)

	$HAMD_{17}$		$HAMD_6$		MES	
Week Group	Active T-PEMF ($n = 25$)	Sham T-PEMF ($n = 25$)	Active T-PEMF ($n = 25$)	Sham T-PEMF ($n = 25$)	Active T-PEMF ($n = 25$)	Sham T-PEMF ($n = 25$)
Baseline	21.1 (4.1)	20.9 (3.3)	12.6 (2.1)	12.1 (2.1)	21.6 (3.0)	21.0 (2.7)
Week 1	17.0 (2.4)[a]	19.0 (2.3)	10.5 (1.6)	11.3 (1.6)	17.8 (2.2)[a]	19.8 (2.2)
Week 2	15.5 (2.3)[a]	18.2 (2.3)	9.5 (1.7)[a]	10.9 (1.6)	16.2 (2.3)[a]	19.1 (2.3)
Week 3	14.0 (3.1)[a]	17.5 (3.1)	8.6 (2.1)[a]	10.5 (2.1)	14.7 (3.1)[a]	18.4 (3.1)
Week 4	12.5 (4.3)[a]	16.7 (4.3)	7.6 (2.9)[a]	10.1 (2.8)	13.1 (4.3)[a]	17.6 (4.3)
Week 5	11.0 (5.7)[a]	16.0 (5.6)	6.7 (3.7)[a]	9.8 (3.7)	11.5 (5.6)[a]	16.9 (5.6)

Adjusted predicted standard deviations in brackets. $n = 50$.

$HAMD_6$, six-item subscale of the Hamilton Depression Rating Scale; $HAMD_{17}$, 17-item HAMD; MES, Melancholia Scale; T-PEMF, T-pulsed electromagnetic fields.

[a] $p < .01$.

statistical significance; this was also true for any of the included Axis I DSM-IV disorders.

Table 3 shows adjusted predicted depression scores on the $HAMD_{17}$, the $HAMD_6$, and the MES scales at baseline and at each weekly assessment for the two treatment groups. On $HAMD_{17}$, the primary outcome scale, scores at end point were statistically significantly lower for patients treated with active T-PEMF compared with scores on patients treated with sham T-PEMF, and post hoc analysis showed that this better outcome for the active T-PEMF-treated group was present from Week 1 and at all subsequent weekly assessments. Exploratory analyses on the $HAMD_6$ and MES scale scores showed similar results, but for the $HAMD_6$, the difference between scores was statistically significant only from Week 2 and at subsequent weekly assessments. Effect sizes (based on adjusted predicted end point scores) were as follows: $HAMD_{17}$, .62 (95% confidence interval [CI] .21–1.02); $HAMD_6$, .60 (95% CI .19–1.00); MES, .68 (95% CI .28–1.09); VAS, .83 (95% CI .42–1.23).

Table 4 shows adjusted predicted response and remission rates from weekly assessments after baseline on the $HAMD_{17}$ depression scale. At Weeks 4 and 5, a statistically significantly larger percentage of patients in the active group obtained response compared with the sham-treated group. At Week 5, a statistically significantly larger percentage of patients in the group treated with active T-PEMF attained remission compared with the sham-treated group. These results correspond to a number needed to treat (NNT) to attain a response of two and an NNT to attain remission of 3, both on the $HAMD_{17}$ scale.

Table 4. Adjusted Predicted Response and Remission Rates, in Percent of Number of Patients, for Each Visit After Baseline on the $HAMD_{17}$ Scale

	Response		Remission	
Group	Active T-PEMF ($n = 25$)	Sham T-PEMF ($n = 25$)	Active T-PEMF ($n = 25$)	Sham T-PEMF ($n = 25$)
Week 1	3.6% ($n = 1$)	.8% ($n = 0$)	1.3% ($n = 1$)	1.2% ($n = 0$)
Week 2	8.7% ($n = 0$)	1.7% ($n = 1$)	3.1% ($n = 0$)	1.6% ($n = 1$)
Week 3	19.5% ($n = 4$)	3.4% ($n = 1$)	7.5% ($n = 2$)	2.2% ($n = 1$)
Week 4	38.1% ($n = 12$)[a]	6.7% ($n = 1$)	17.0% ($n = 5$)	3.0% ($n = 1$)
Week 5	61.0% ($n = 12$)[a]	12.9% ($n = 3$)	33.9% ($n = 8$)[b]	4.1% ($n = 1$)

Response a 50% or more reduction of $HAMD_{17}$ baseline scores. Remission a $HAMD_{17}$ score of 7 or less. Actual number of patients with response and remission is shown in parenthesis.

$HAMD_{17}$, 17-item HAMD; T-PEMF, T-pulsed electromagnetic fields.

[a] $p < .01$.

[b] $p < .05$.

Table S2 in Supplement 1 shows treatment-emergent side effects for UKU items and additional patient-generated items. Only items represented in the active group at double the sham rate were reported. No statistically significant differences were seen between treatment groups on any item. One patient (Patient 40) allocated to active T-PEMF treatment developed suicidal ideation lasting 2 days. This occurred between Visits 3 and 4 and was not reflected in the Hamilton suicidality item (Item 3) on which he scored 1 at both visits. The patient contacted the investigator, and an additional meeting was set up. The suicidal ideation coincided with sudden social difficulties and was not thought to be related to treatment; the patient thus continued in the study.

Results from the patient-rated MDI showed that the group treated with active T-PEMF had a larger reduction in adjusted predicted scores compared with the sham-treated group from Week 2 and all subsequent weeks; this difference reached statistical significance from Week 3 ($p < .05$ each week). Score reduction from baseline to end point was 31.7 (6.7) to 16.3 (9.4) in the active-treated group compared with a 33.6 (5.8) to 23.2 (9.2) in the sham-treated group.

Results from the patient-rated WHO (Five) Well-Being Index showed that the group treated with active T-PEMF had an increase in adjusted predicted scores (higher well-being), from baseline to end point, from 18.2 (11.4) to 41.4 (24.3) compared with an increase in the sham-treated group from 19.0 (12.6) to 31.6 (24.1). This difference was not statistically significant ($p = .16$).

Results from the SCL-90 ($n = 44$) showed a greater reduction in scores from baseline to end point on all subscales (e.g., depression subscale $p = .13$, anxiety subscale $p = .06$) and in the total score ($p = .08$) for the group treated with active T-PEMF compared with the group treated with sham T-PEMF. For the interpersonal subscale, the difference reached statistical significance ($p = .01$).

The three panels of Figure S1 in Supplement 1 show the T-PEMF device in use from dorsal, posterior, and side views. The positioning of the seven coils is clearly visible.

Figure 1 shows adjusted predicted daily mood ratings on the Preskorn scale, separately for the two treatment groups. The patients treated with active T-PEMF had a higher, but statistically insignificant, baseline score than the sham-treated group. The adjusted predicted scores for the whole of the 35-day period show a better outcome for the active T-PEMF compared with the sham-treated group, but this difference was statistically insignificant (Week 1: $p = .12$, Week 2: $p = .10$, Week 3: $p = .08$, Week 4: $p = .06$, and Week 5: $p = .052$).

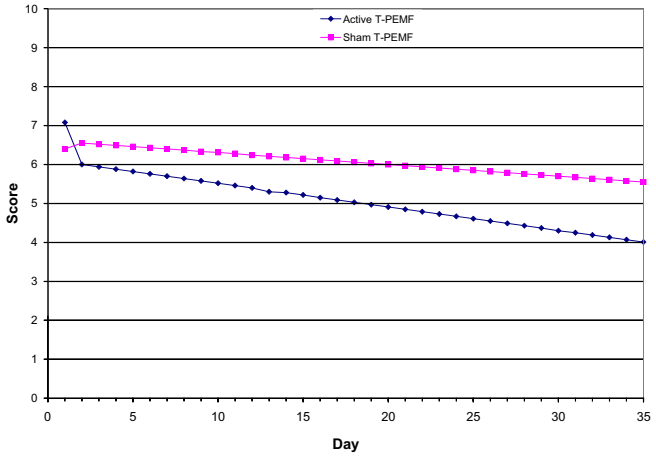

Figure 1. Adjusted predicted daily Preskorn scores shown for the group treated with active T-pulsed electromagnetic fields (T-PEMF; $n = 25$) and the group treated with sham T-PEMF ($n = 25$). Score ranges from 0 (no depression) to 10 (worst depression ever).

Figure 2 shows adjusted predicted scores on the clinician-rated VAS for all weekly assessments shown separately for the two treatment groups. The patients treated with active T-PEMF had a larger score reduction than the sham-treated group from Week 2 and at all the following weekly assessments. This difference reached statistical significance from Week 2 and at all following weekly assessments ($p < .01$ all weeks).

Figure S2 in Supplement 1 shows the waveforms of pulses of current through the coils and of the E-field induced in the tissue. The induced electrical field appears because of the fluctuating voltage (+50 V followed by −50 V) applied to the coils.

At end point, 97.7% percent of the patients expressed their willingness to try T-PEMF treatment again. Compliance with T-PEMF treatment was 95.6% in the active group and 93.7% in the sham group. No patients started on hypnotics during the study period.

Discussion

The observed positive effect of the T-PEMF was present on all clinician rated scales used, and the calculated effect sizes are above what is usually found for any antidepressant. The patient-rated questionnaires also showed better outcomes for the group treated with active T-PEMF but were only statistically significant on the MDI and the SCL-90 interpersonal sensitivity subgroup. It has been shown that the registration of antidepressant effect is delayed by 2 weeks when using self-assessment scales compared with observer rating scales (24), and this could explain the differences in discriminative power between observer rating scales and self-assessment scales.

Taken together, the early onset of antidepressant action and efficacy in patients already receiving combination antidepressant therapy indicates that T-PEMF technology might work through modes of action different from antidepressant drugs or may act as an enhancer of antidepressants.

Clearly, there is a large gap in our knowledge that must be filled before we can link these behavioral findings from a randomized controlled clinical trial to the basic physiologic findings of alteration in intracellular functioning of cells exposed to low-voltage PEMF.

Our technique is based on imposing pulsed electrical fields on tissue. It has previously been shown that PEMF stimulation, using the same parameters as in our study, induces intracellular signaling related to receptor tyrosine kinase activity (7). The biological sensor for pulsed electrical fields has been suggested to include the tyrosine kinases of the Src family (25) that are closely associated with receptor tyrosine kinases and thereby facilitate their function, causing mitogen protein kinase signaling and transcription. In addition, selective serotonin reuptake inhibitors have also been implicated in cellular signaling, causing an enhanced mRNA synthesis for growth factors such as brain-derived neurotrophic factor (BDNF) (26) and fibroblast growth factor (27). Kozisek (26) emphasized that results from clinical and basic studies have demonstrated that stress and depression decrease BDNF expression and neurogenesis and that antidepressant treatment reverses or blocks these effects. Clinical studies have demonstrated an association between BDNF levels and several disorders, including depression, epilepsy, bipolar disorder, Parkinson's disease, and Alzheimer's disease. Electroconvulsive therapy has also been shown to increase the mRNA levels for BDNF and its receptor TrkB in the hippocampus and cortex in rats (26). In conclusion, PEMF might be both an activator of intracellular signaling and an enhancer of the action of antidepressant drugs.

The influence of PEMF on cortical excitability has been investigated (28). Healthy subjects treated with low-frequency and low-voltage PEMF, quite similar to the parameters used in the T-PEMF in this study, were investigated by the use of conventional TMS measuring the threshold of motor-evoked potentials. The authors found that active PEMF treatment, but not sham treatment, increased cortical excitability as measured by the intracortical facilitation test and proposed that PEMF exposure produces a selective enhancement of glutaminergic neurotransmission in the brain. Because this parameter is supposed to be involved in the pathophysiology and treatment of mood disorders, this represents another possible explanation for the antidepressant effect of T-PEMF.

Several therapies using electromagnetic stimulation are in current use in the treatment of depression. For rTMS, using powerful magnetic fields approaching the neuronal seizure threshold, there is accumulated evidence of an antidepressant effect (29).

Transcranial direct current stimulation (tDCS) has received more interest in recent years. This method applies a weak

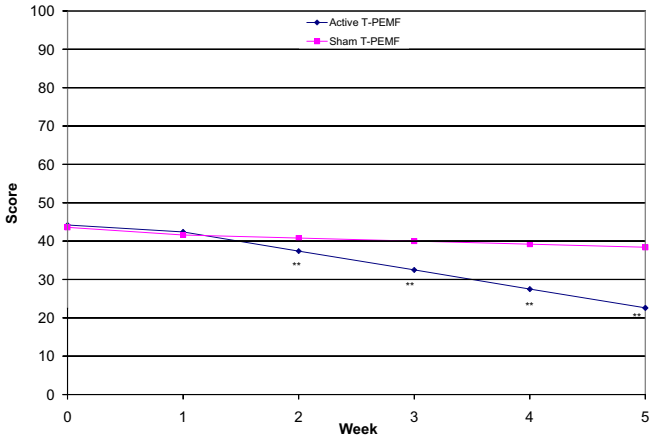

Figure 2. Adjusted predicted visual analog scores shown for active ($n = 25$) and sham ($n = 25$) groups receiving T-pulsed electromagnetic fields (T-PEMF). Score ranges from 0 (no depression) to 100 (extreme depression). Clinician rated. $^{**}p < .01$.

constant current via scalp electrodes. Studies have shown this to induce changes in cortical excitability, and there is evidence of an antidepressant effect of prefrontal tDCS (30).

It is well documented that animal neuronal cells are able to sense electrical fields as low as 5 nV/cm (31). The electrical field from the individual T-PEMF coil is expected to be on the order of 30 μV/cm at a 10-cm distance from the coil rim, and some animals would thus easily detect this field. A number of studies have shown that low-frequency environmental-strength electromagnetic fields produce measurable effects in the activity of the human brain (32), pointing toward the possibility that clinical effects can be produced by much lower electromagnetic fields than those generated by rTMS.

Limitations of this study include the fact that the patients included were somewhat older than is normally seen in depression studies, probably because the inclusion criteria required patients to be treatment refractory. The applicator emits a faint humming sound not noticed by the patients as demonstrated by their inability to guess treatment allocation. We therefore believe that blinding was acceptable.

We suggest that a dose–response study be performed with a study using an extended study period of 8 or 10 weeks.

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ClinicalTrials.gov: PEMF Treatment in Patients with Treatment-Resistant Major Depression in Ongoing Pharmacological Treatment of Depression; http://clinicaltrials.gov/ct2/show/NCT00287703?term=pemf&rank=3; NCT00287703.

Supplementary material cited in this article is available online.

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