

# Dose-remission of pulsating electromagnetic fields as augmentation in therapy-resistant depression: a randomized, double-blind controlled study

Straasø B, Lauritzen L, Lunde M, Vinberg M, Lindberg L, Larsen ER, Dissing S, Bech P. Dose-remission of pulsating electromagnetic fields as augmentation in therapy-resistant depression: a randomized, double-blind controlled study.

**Objective:** To evaluate to what extent a twice daily dose of Transcranial Pulsating ElectroMagnetic Fields (T-PEMF) was superior to once daily in patients with treatment-resistant depression as to obtaining symptom remission after 8 weeks of augmentation therapy.

**Methods:** A self-treatment set-up of the T-PEMF device was used allowing self-administration by patients in own homes. All patients were treated for 30 min per T-PEMF session. The antidepressant medication the patients were receiving at baseline remained unchanged during the trial. The patients were randomised to either one T-PEMF dose (active dose in the morning and sham in the afternoon) or two T-PEMF doses (active dose both morning and afternoon) in a double-blind procedure. A score of 7 or less on the Hamilton Depression Scale (HAM-D<sub>17</sub>) was the criterion of remission.

**Results:** In total 34 patients received active T-PEMF once a day and 31 patients twice daily. After 5 weeks of therapy remission was obtained in 26.5% and 32.3% on one dose and two doses of T-PEMF, respectively. After 8 weeks the rate of remission was 73.5% and 67.7%, respectively. The side effects as measured by the Udvalget for Kliniske Undersøgelser scale showed a better toleration of the antidepressive medication in both treatment groups, which was reflected by the WHO-5 well-being scale with increased scores in both groups of patients.

**Conclusion:** The high remission rate obtained by the T-PEMF augmentation was not a dose effect (one versus two daily T-PEMF sessions) but was explained by the extension of the treatment period from 5 to 8 weeks.

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## Significant outcomes

- Transcranial Pulsating ElectroMagnetic Fields augmentation resulted in high remission rates (~70%) in patients with therapy resistant depression over a treatment trial of 8 weeks.
- The side effects of antidepressant medication were reduced and the psychological well-being of the patients significantly increased.

## Limitations

- A sham (placebo) Transcranial Pulsating ElectroMagnetic Fields arm was not included, but the dose-remission principle was in a double-blind, controlled approach.

### Introduction

In ~30% of patients with a major depressive episode, antidepressants are ineffective, even after several attempts with well-delivered antidepressant therapy (optimal dose and duration) when remission is defined by a Hamilton Depression Scale (HAM-D<sub>17</sub>) score of 7 or less (1,2). When augmenting with Transcranial Magnetic Stimulation (TMS) (3) or with Transcranial Pulsating ElectroMagnetic Fields (T-PEMF) (4) in these treatment-resistant depressive (TRD) patients we found extremely low rates of placebo-remission (HAM-D<sub>17</sub><8), namely <5% after 5 weeks of therapy. In the active T-PEMF group of patients we obtained a statistically significant higher remission rate (34%) after 5 weeks of therapy (4). The extremely low placebo remission in TRD is in agreement with other studies (e.g. (5)). In the monographs on TRD (1,6), the extremely low placebo-remission rate is insufficiently discussed.

When planning the present dose-remission study with a self-treatment set up of the T-PEMF device to be administered by the patients themselves in their own homes, we decided, on ethical considerations, to exclude sham T-PEMF. Originally, we discussed conducting this dose-remission study as a multi-centre trial within the Danish University Antidepressant Group (DUAG), analogue to our previous study on dose-effect of clomipramine in patients with therapy-resistant depression (7). During our discussion it was actually suggested to include low placebo response to antidepressants as a criterion of the diagnosis of therapy-resistant depression. It was decided to consider the study to be reported here as a pilot trial for such a multi-centre DUAG study.

It was our hypothesis that patients receiving active T-PEMF both morning and afternoon would have a higher remission rate on the HAM-D<sub>17</sub> than patients only receiving active T-PEMF in the morning. According to our protocol the main research question to be answered was to what extent a twice daily T-PEMF dose was superior to once daily, using the HAM-D<sub>17</sub><8 at endpoint as the primary criterion for remission after 8 weeks of therapy.

### Materials and methods

#### Ethics

The study was carried out in accordance with the Declarations of Helsinki and the European Union directive of Good Clinical Practice (8). The study was monitored by an external contract company (Norma, Hørsholm, Denmark). The study was

approved by the Danish Health and Medicines Authority (2013030959) and the Committee on Biomedical Research Ethics (H-1-2010-031) and was reported to the Danish Data Protection Agency (PSV-2010-2). The trial was registered at ClinicalTrials.gov (ID NCT01353092). Patients were given information as requested by the Biomedical Research Ethics, and all patients signed an informed consent.

#### Patient allocation and inclusions

Patients were all treated at our research unit at Psychiatric Centre North Zealand, University of Copenhagen. Inclusion criteria were: older than 18 years of age, patients with TRD as manifested by a score of >3 on the Sackheim Scale (9), major depression according to DSM-IV, a score of 13 or more on the HAM-D<sub>17</sub>, and unchanged antidepressant medication during the previous 4 weeks. Exclusion criteria were suicidal thoughts (a score of >2 on the HAM-D<sub>17</sub> item of suicidal ideations), 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. The randomisation procedure was the same as in our first T-PEMF study (4).

#### Psychometrics

*Diagnostic categories.* The Mini-International Neuropsychiatric Interview (MINI) version 5.0 (10) was used to obtain ICD-10 diagnoses of depression (11).

*Outcome scales.* The HAM-D<sub>17</sub> was used as the primary outcome scale (12–14). We used the HAM-D<sub>17</sub> in combination with the Bech-Rafaelsen Melancholia Scale (MES) as conventionally applied in DUAG studies (13). Within the HAM-D<sub>17</sub> we especially focused on the HAM-D<sub>6</sub> which includes the core symptoms of depressive states (depressed mood, guilt, work and interests, psychomotor retardation, psychic anxiety, and gen somatics). This HAM-D<sub>6</sub> subscale has sufficient transferability, that is the ability to validly measure change in trials of antidepressants (14). The MES contains both the HAM-D<sub>6</sub> and an apathia subscale (fatigability, concentration or memory problems, and sleep disturbances) (15). We focused on the ability of this apathia subscale to predict a dose-remission T-PEMF relation using the baseline scores. In another study we have shown that an apathia scale covering the items of concentration

or memory problems, and sleep or fatigability items from the MINI had predictive validity when following the ability of depressed patients to return to work. This apathia scale was also considered for predicting a dose-remission pattern of T-PEMF.

In the analysis to be reported here, with focus on dose-remission relationship, the remission criterion on the HAM-D<sub>17</sub> was the primary outcome, that is a score at endpoint of 7 or less. In this respect we also focused on the HAM-D<sub>6</sub> in which the remission criterion is a score of 4 or less (14). Other outcome scales for antidepressive effect such as the Major Depression Inventory (MDI\*, (16) or the self-rated version of the HAM-D<sub>6</sub> (14) will be reported elsewhere.

To evaluate side effects we have focused on the clinician administered Udvalget for Kliniske Undersøgelser (UKU) scale (17) and the self-reported Patient Reported Inventory of Side Effects (PRISE) in the version modified by Bech (14).

Finally, the WHO-5 well-being scale (14) was used to assess the patients' own self-reported balance between clinical antidepressive effect and side effects. A score of 20 on the WHO-5 is seen in moderate to severe depression, and a score of 50 in doubtful depression, whereas a score of ~70 is equal to that of the Danish gen population (14).

The MINI as well as clinician assessments on the Hamilton Scale, the MES, and the UKU Side Effects Scale were all performed by experienced raters (B.S., L.L., M.L.) who have participated in the DUAG trials.

*T-PEMF therapy.* Coil applicators introduced pulsating electrical fields (50 Hz) of a very low magnitude (0.1–4 mV/cm) into brain tissue. The pulses were constructed to mimic the pulsating electrical fields (E-fields) measured outside excitable tissue. The E-fields induced into neural tissue by the coils were five orders of magnitude ( $10^{-5}$ ) smaller than the E-field across a biological membrane with a  $V_m$  of  $-70$  mV. Thus, this device distinguishes itself in this regard from rTMS and ECT. Seven coils were applied. The treatment helmet incorporates one pair of coils in the anterior and one pair in the posterior temporal region on both sides, one pair in the upper parietal region and one coil in the centre of the lower occipital region. All patients were treated for 30 min in a session.

The pulse generator has a card that is inserted into the device once treatment is initiated. All patients received 8×2 chipcards to cover the entire study period. Each card was provided with week number (1–8) and either 'morgen' (morning) or 'aften' (evening). This text was clearly stated on

the cards, and at each visit the patients received two new cards and returned the two used ones.

The device and cards were constructed in such a way that all patients used the device morning and evening but the card that controls the pulses was programmed in such a way that current was running in coils for treatment in morning and evening (treatment twice a day) and only mornings for those treated once a day (placebo evenings). The patient was not able to identify whether or not current was running in a treatment session. The investigators did not have access to the card programmes (double blinding). Only the Good Clinical Practice Unit (GCP) had access to the information on the cards in order to check whether the treatment had been taken as planned. After study completion the codes were broken so as to determine which treatment group the patient had been allocated to.

#### Statistical analyses

Sample size was calculated using % remission (HAM-D<sub>17</sub><8) after 8 weeks of T-PEMF by last observation carried forward. It was assumed that the twice daily dose of T-PEMF (morning and afternoon) would result in a remission rate of 60% whereas only one active dose of T-PEMF daily would result in a remission rate of ~25%. With a power of 80% and an  $\alpha$  of 5% it was calculated necessary to have at least 31 patients in each treatment arm.

When determining significance levels in between group analyses non-parametric statistics were used (18); for categorical data the Fisher exact test was used, and for continuous data the Mann–Witney test or the Wilcoxon test were used. The intention-to-treat approach was used [Last Observation Carried Forward (LOCF)].

#### Results

In total 65 patients were included in the study from April 2011 to June 2013 (Fig. 1 shows the consort diagram of patient flow). All 65 patients were entered into the intention-to-treat analysis. Of these patients, 34 received T-PEMF as a morning dose only, and 31 patients received T-PEMF both morning and afternoon.

The mean age of the group of patients treated once daily was 46.4 (13.6) years and the mean age of the group of patients treated twice daily was 49.9 (11.5),  $p = 0.27$ . In the group treated once daily 22 were females and 12 males. In the group treated twice daily 20 were females and 11 males ( $p = 1.00$ ).

## T-PEMF augmentation therapy-resistant depression

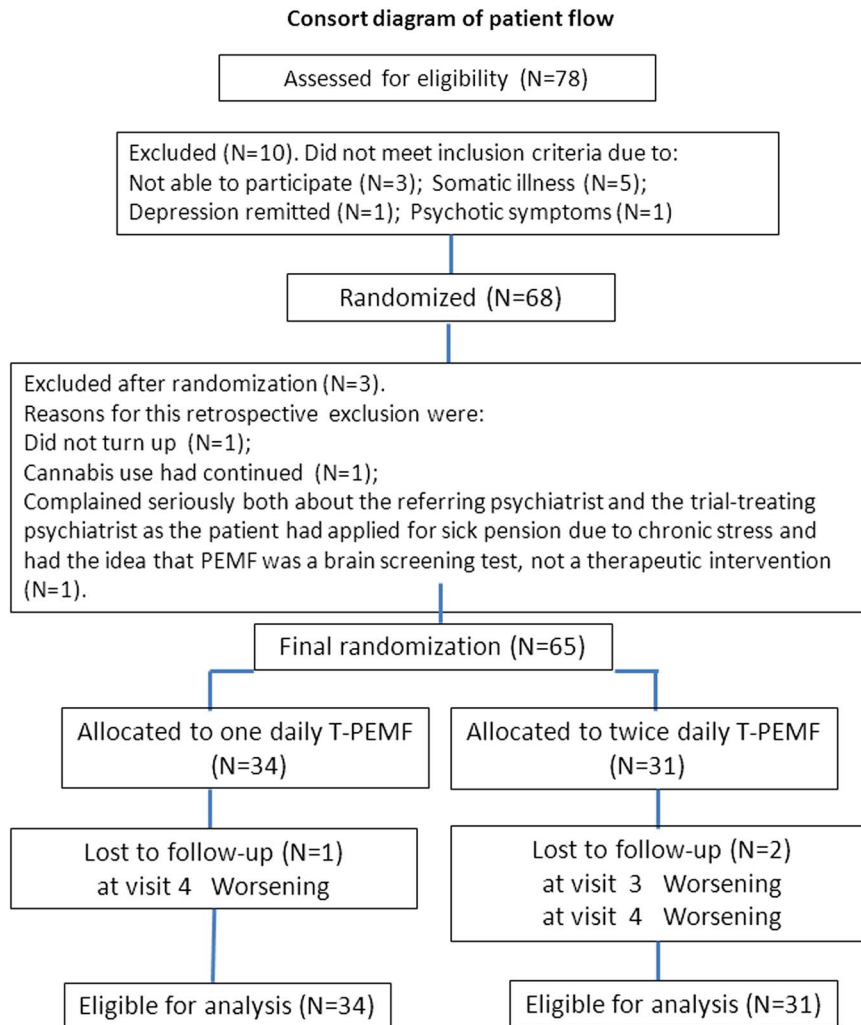


Fig. 1. Consort diagram of patient flow.

The distribution of ICD-10 diagnoses in the two groups of patients is shown in Table 1A. Again no statistically significant difference between the two groups of patients was seen. Table 1B shows the multivariate description of the severity of the TRD in terms of number of previous depressive episodes and the duration of the current episode. No statistical difference was seen between the two groups of patients.

The chip cards registering the date and time of T-PEMF treatment had been taken showed a very satisfying compliance, as 98% of the patients had been >85% compliant. Incorrect administration of the cards (morning therapy on evening card and vice versa) or treatment omitted were errors observed for single days during the 8-week study period. A total of 49 patients (75%) were >90% compliant and the remaining patients made these errors repeatedly, but not evenly distributed.

Table 2 shows the number of patients taking different antidepressants. As indicated, no statistically

Table 1A. The ICD-10 diagnoses according to the Mini International Neuropsychiatric Interview (MINI)

	One dose daily (n = 34)	Two doses daily (n = 31)	p
F 32.1 Moderate depression	3	2	1.00
F 33.0 Recurrent depression (mild)	1	1	1.00
F 33.1 Recurrent depression (moderate)	29	28	0.82
F 33.2 Recurrent depression (severe)	1	0	1.00

Table 1B. Multivariate description of therapy-resistant depression

	One dose daily (n = 34)	Two doses daily (n = 31)	p
Duration in months of the current depressive episode (range)	14 (3–36)	15 (4–38)	0.7371
Number of previous depressive episodes (range)	6 (1–13)	7 (1–15)	0.8534

Table 2. The psychotherapeutic drugs prescribed 4 weeks before the T-PEMF augmentation and during the trial

Psychotherapeutic drugs	One dose daily (n = 34)	Two doses daily (n = 31)	p
Tricyclics	8	6	0.92
SSRI/SNRI	28	20	0.18
Mianserin/mirtazapine	11	11	1.00
Reboxetine	2	3	0.91
Isocarboxazid	2	2	1.00
Moclobemide	2	0	0.54
Agomelatine	7	9	0.43
Lithium	8	6	0.92
Lamotrigine	6	6	1.00
Seroquel	12	4	0.07
Olanzapine	5	3	0.82
Pregabalin	1	2	0.93
Benzodiazepines (Oxazepam, clonazepam)	8	6	0.92
Hypnotics (Zolpidem, Zopiclone)	4	4	1.00

T-PEMF, Transcranial Pulsating ElectroMagnetic Fields.

significant difference between the two groups of patients was seen.

Table 3 shows remission after 8 weeks, last observation carried forward, using the criterion of HAM-D<sub>17</sub><8 and the HAM-D<sub>6</sub><5. On the HAM-D<sub>17</sub> the difference between 73.5% remission in the once daily T-PEMF dose group and 67.7% in the twice daily group after 8 weeks of therapy was not statistically significant (*p* = 0.79). After 5 weeks of therapy, 26.5% and 32.3% obtained a remission (HAM-D<sub>17</sub><8) on one dose and two doses of T-PEMF, respectively.

On the HAM-D<sub>6</sub> (Table 3) the difference in remission rate of 52.9% versus 61.3% after 8 weeks of therapy was not statistically significant (*p* = 0.62). When using the MES apathia scale at baseline to classify patients with an apathia syndrome (a score of 10 or more) versus patients without an apathia syndrome, we found that among the 38 patients with an apathia syndrome, only 58.8% had a remission (HAM-D<sub>17</sub><8) after 8 weeks of therapy against 88.2% in the group of patients without an apathia syndrome for a once daily T-PEMF dose (*p* = 0.118). For a twice daily T-PEMF dose the remission percentage was 71.4% in the apathia syndrome and 60.0% in the non-apatia syndrome (*p* = 0.609). However, on the apathia scale the mean (SD) for all 65 patients at baseline was 9.71 (0.96) and the median = 10. This implied that an apathia syndrome was present for a score of 10 or more. In patients with an apathia syndrome who received T-PEMF once daily, 55.6% obtained a remission after 8 weeks of therapy whereas patients without apathia who received T-PEMF once daily obtained a remission rate of 93.8% (*p* = 0.029.). In the twice

Table 3. T-PEMF doses (one vs. two doses daily) in relationship to remission after 5 and 8 weeks of therapy

	One dose daily (n = 34)	Two doses daily (n = 31)	p
HAM-D <sub>17</sub> <8			
After 5 weeks	26.5%	32.3%	0.79
After 8 weeks	73.5%	67.7%	0.79
HAM-D <sub>6</sub> <5			
After 5 weeks	11.8%	12.9%	1.00
After 8 weeks	52.9%	61.3%	0.62

HAM, Hamilton Depression Scale; T-PEMF, Transcranial Pulsating ElectroMagnetic Fields.

Table 4. HAM-D<sub>17</sub> baseline scores and weekly scores (mean and SD) for one vs. two daily doses of T-PEMF

Treatment occasions	HAM-D <sub>17</sub> [mean (SD)]		p
	One dose daily (n = 34)	Two doses daily (n = 31)	
Baseline	20.4 (2.7)	20.9 (2.9)	0.74
Week 1	16.8 (3.5)	16.5 (3.5)	0.79
Week 2	14.5 (4.3)	13.6 (4.2)	0.41
Week 3	12.8 (4.2)	11.9 (4.3)	0.22
Week 4	11.7 (4.1)	11.7 (4.3)	0.92
Week 5	10.2 (4.0)	10.2 (4.7)	0.92
Week 6	9.2 (4.1)	8.8 (4.5)	0.74
Week 7	8.9 (4.7)	7.6 (5.2)	0.11
Week 8	6.8 (4.5)	7.3 (5.8)	0.92

HAM, Hamilton Depression Scale; T-PEMF, Transcranial Pulsating ElectroMagnetic Fields.

daily T-PEMF group the remission rate was 66.7% in the group of patients with apathia and 69.2% in the group without apathia (*p* = 1.00).

Table 4 shows the HAM-D<sub>17</sub> baseline scores (mean and SD) as well as the weekly scores for one versus two daily doses of T-PEMF, last observation carried forward. No statistically significant differences were obtained.

Table 5 shows the HAM-D<sub>6</sub>. No statistically significant differences between one versus two daily doses of T-PEMF doses were obtained.

Table 6 shows the UKU side effect total score from baseline over the weekly ratings, last observation carried forward. No statistically significant differences between one versus two daily doses of T-PEMF doses were obtained. This result was supported by the self-reported side effect scale PRISE.

Table 7 shows the weekly scores on the WHO-5 patient-reported well-being index. At endpoint (week 8) the WHO-5 was 54.5 (27.7) in the group of patients treated with a once daily dose and 52.4 (28.1) in the group treated with two daily doses (*p* = 0.80).

Table 5. HAM-D<sub>6</sub> baseline scores and weekly scores (mean and SD) for one vs. two daily doses of T-PEMF

Treatment occasions	HAM-D <sub>6</sub> [mean (SD)]		<i>p</i>
	One dose daily ( <i>n</i> = 34)	Two doses daily ( <i>n</i> = 31)	
Baseline	12.6 (1.6)	12.7 (1.4)	0.89
Week 1	11.2 (2.2)	10.5 (2.0)	0.26
Week 2	9.7 (2.5)	9.1 (2.7)	0.42
Week 3	8.7 (2.8)	8.0 (2.5)	0.31
Week 4	7.8 (2.7)	7.8 (2.6)	0.83
Week 5	6.9 (2.8)	6.8 (2.5)	0.92
Week 6	6.3 (3.0)	5.9 (2.7)	0.73
Week 7	6.1 (3.1)	5.0 (3.2)	0.09
Week 8	4.6 (3.1)	4.9 (3.5)	0.99

HAM, Hamilton Depression Scale; T-PEMF, Transcranial Pulsating ElectroMagnetic Fields.

Table 6. UKU side effect scale baseline total scores and weekly total scores (mean and SD) for one vs. two daily doses of T-PEMF

Treatment occasions	UKU side effect total score [mean (SD)]		<i>p</i>
	One dose daily ( <i>n</i> = 34)	Two doses daily ( <i>n</i> = 31)	
Baseline	12.8 (3.7)	13.3 (3.7)	0.53
Week 1	11.0 (2.8)	10.9 (3.4)	0.67
Week 2	10.6 (3.3)	10.1 (2.9)	0.52
Week 3	9.7 (3.4)	9.5 (3.2)	0.67
Week 4	9.5 (2.6)	9.2 (4.0)	0.20
Week 5	8.5 (2.4)	8.7 (3.6)	0.64
Week 6	8.6 (3.4)	8.5 (3.7)	0.56
Week 7	8.0 (3.6)	7.4 (4.5)	0.15
Week 8	7.1 (3.6)	6.8 (4.2)	0.58

T-PEMF, Transcranial Pulsating ElectroMagnetic Fields; UKU, Udvalget for Kliniske Undersøgelser.

Table 7. WHO-5 baseline scores and weekly scores (mean and SD) for one vs. two daily doses of T-PEMF

Treatment occasions	WHO-5 [mean (SD)]		<i>p</i>
	One dose daily ( <i>n</i> = 34)	Two doses daily ( <i>n</i> = 31)	
Week 0	22.7 (12.1)	18.1 (10.7)	0.22
Week 1	28.0 (13.2)	30.7 (19.5)	0.92
Week 2	31.5 (16.2)	32.1 (20.4)	0.78
Week 3	34.6 (20.9)	38.9 (21.9)	0.40
Week 4	41.4 (19.7)	38.7 (24.0)	0.50
Week 5	42.1 (19.9)	44.8 (21.9)	0.66
Week 6	45.9 (23.2)	44.8 (25.6)	0.77
Week 7	46.0 (24.7)	50.0 (26.9)	0.55
Week 8	54.5 (27.7)	52.4 (28.1)	0.80

T-PEMF, Transcranial Pulsating ElectroMagnetic Fields.

**Discussion**

The answer to our primary research question: ‘In patients with treatment-resistant depression will augmentation with T-PEMF twice daily be superior to one daily dose in obtaining remission after 8 weeks

of therapy?’ is no. However, the rate of remission in the group of patients receiving one daily dose was much higher (73%) than the expected rate of 25% that was based on our results from our first T-PEMF study (4), which was completed after 5 weeks of therapy. A major outcome of our present study is therefore that the extension of the trial from 5 to 8 weeks has doubled the remission rate.

When using the weekly mean HAM-D<sub>6</sub> scores we found the same pattern, namely a 50% reduction of the baseline scores after 5 weeks of therapy (from 12 to 6, Table 5) and a doubling of the rate of remission (HAM-D<sub>6</sub><5) from week 5 to week 8.

In the present study we have on ethical grounds not included a placebo or sham T-PEMF arm. Both in our first T-PEMF study and in our rTMS study (3) the remission rate in the sham arm after 5 weeks of therapy was below 5% when using the HAM-D<sub>17</sub><8 criterion of remission. After 8 weeks of therapy the Bretlau et al. rTMS study (3) had a remission rate of 8%. In a randomised placebo-controlled trial with vagus nerve stimulation in TRD the remission rate on placebo after 10 weeks of therapy was 3.6% (19).

In major depression the improvement seen in placebo-controlled trials of antidepressants is that of an early steep drop in the HAM-D mean scores, typically in the first 2 weeks. This is the background for the pattern analysis suggested by Quitkin et al. (20) in which the true drug response to antidepressants is considered after 3 weeks of therapy. The weekly HAM-D<sub>17</sub> as well as HAM-D<sub>6</sub> mean scores in our study followed a rather straight line from baseline to week 8. In our previous T-PEMF analysis (4) the weekly HAM-D<sub>17</sub>/HAM-D<sub>6</sub> scores in the active T-PEMF arm followed an improvement line over the 5 weeks of therapy. However, we certainly need a fully blinded study to verify these findings. We are actually planning a randomized, double-blind sham (placebo) controlled multi-centre study in the DUAG.

The weekly mean scores on the UKU side effects scale showed that the baseline level of ~12 decreased by nearly 50% over the 8 weeks of therapy, with no difference between the T-PEMF doses of one versus two daily.

The WHO-5 well-being scale, which might be considered as the patients’ own self-reported outcome, taking both wanted (HAM-D) and unwanted (UKU) side effects into account, showed a mean score steady increase from ~20 to 50 over the 8 weeks of therapy with no difference between the two T-PEMF doses. However, to obtain an optimal effect, the WHO-5 mean scores should reach the level in the Danish gen population of 69. Trials of 12 weeks or more are often needed to obtain this goal of therapy (14).

We have recently shown in a trial with depressed patients (submission process on-going) that an apathia syndrome scale (containing such items as concentration or memory problems, fatigability, and sleep problems) had predictive validity in identifying, at baseline, those patients who were later on unable to return to work. In patients with an apathia syndrome at baseline (a score of 10 or more) the remission rate after 8 weeks of therapy was 56% whereas in patients without an apathia syndrome the remission rate was 93% in the group of patients receiving one daily T-PEMF dose ( $p < 0.05$ ). The respective remission rates in the group of patients receiving T-PEMF twice daily were 69% versus 68% ( $p = 1.000$ ).

The antidepressive medication prescribed during the T-PEMF study covered serotonin or noradrenaline reuptake inhibitors (unspecific as TCA's or specific as SSRIs or SNRIs or reboxetine) most predominating, as only two patients in each group of patients received isocarboxazid (an irreversible mono-amino-oxidase inhibitor). The serotonin receptor 2 inhibitors (the unspecific mianserin/mirtazapine and the specific agomelatine) were typically prescribed in combination with the serotonin/noradrenaline reuptake inhibitors. The patients included in the T-PEMF study were all resistant to these drugs but were considered to have obtained a sufficient partial response to justify a continuation, often because the side effects to the antidepressants were found acceptable by the patients, that is were tolerated.

It has now become evident that reuptake inhibitors that act as antidepressants have additional effects such as upregulating mRNA for brain-derived neurotrophic factor (BDNF) and also its receptor TrkB. BDNF was thus reported to play a role in the long-term effects of antidepressants, and it has been shown that acute as well as chronic antidepressant administration activates neurotrophin signalling in a BDNF-dependent manner in prefrontal cortex (21). In animal studies increased BDNF mRNA levels were found after chronic antidepressant administration (22) and BDNF signalling thus appear to be required for the typical behavioural effects produced by these drugs in experimental animals studies. There is now wide consensus that SSRI classes of drugs may act at least partially by activating endogenous BDNF signalling.

We have found that (23) that T-PEMF upregulates the cytoplasmatic tyrosin kinase Src in human endothelial cells. Moreover it has been found (24) that T-PEMF upregulates mRNA for BDNF. In human-derived endothelial cells both the SSRI antidepressant sertraline and T-PEMF upregulate mRNA in such a pattern that T-PEMF has a clear additive effect on the sertraline results. We therefore propose that the additive effect of T-PEMF demonstrated in patients with only a very partial

response to antidepressants such as sertraline is an induced cellular signalling leading to an upregulation on mRNA for BDNF and to its secretion from endothelial cells and neural tissue.

In conclusion, a twice daily T-PEMF dose was not superior to once daily, using the HAM-D<sub>17</sub> < 8 at endpoint as the primary criterion for remission after 8 weeks of therapy. In future studies it therefore seems appropriate to use T-PEMF once daily. The high remission rates found in this study of T-PEMF as augmentation in patients with TRD were thus not explained by a dose effect (one versus twice daily applications), but rather by the extension of the treatment time from 5 to 8 weeks. During this trial the baseline side effects of the antidepressant medication, which remained unchanged over the 8 weeks, were reduced by ~50%. This outcome of high remission rates and reduced side effects was reflected by the patients' self-reported WHO-5 well-being scale scores which increased significantly during the trial.

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#### Author Contributions

Birgit Straasø and Lise Lauritzen: Involvement in planning the study, methodological design and performing patient ratings. Marianne Lunde: Active in performing the patient ratings. Maj Vinberg and Erik Roj Larsen: Active in clarification of the theoretical part of the study and the recruitment of patients. Lone Lindberg: Supervision of use of T-PEMF device, including helping the patients in this respect throughout the study. Steen Dissing: Formulation of the scientific problem and the theoretical background of T-PEMF treatment and actual device. Per Bech: Involvement in planning the study, methodological design as well as selection of rating instruments and supervision of rating procedures. Responsible for the statistical analysis.

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#### Conflicts of Interest

Birgit Straasø, Lise Lauritzen, Marianne Lunde, Lone Lindberg, Erik Roj Larsen, and Per Bech: none

to declare. Maj Vinberg: has been consultant for Eli Lilly, Lundbeck A/S, AstraZeneca and Servier. Steen Dissing: first author on two patents describing the technology and the physiological implications of the T-PEMF method. The patents are owned by the company Re5. Steen Dissing's percentage of ownership in the above company is 0.5.

**Ethical Standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008.

**References**

1. GREDEN JF, RIBA MB, McINNIS MG, eds. Treatment Resistant Depression: A Roadmap for Effective Care. Washington, DC: American Psychiatric Publishing, 2011.
2. SCHÄPFER TE, KAYSER S. The role of nonpharmacological interventions in treatment-resistant depression. In: Kasper S, Montgomery S, eds. Treatment-Resistant Depression. Chichester: Wiley-Blackwell, 2013, p. 159–182.
3. BRETLAU LG, LUNDE M, LINDBERG L, UNDEN M, DISSING S, BECH P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry* 2008;**41**:41–47.
4. MARTINY K, LUNDE M, BECH P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol Psychiatry* 2010;**68**:163–169.
5. HERESCO-LEVY U, GELFIN G, BLOCH B et al. A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression. *Int J Neuropsychopharmacol* 2013; **16**:501–506.
6. AMSTERDAM JD, HORNIG M, NIERENBERG AA, eds. Treatment-Resistant Mood Disorders. Cambridge: Cambridge University Press, 2001.
7. DUAG. Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. Danish University Antidepressant Group (DUAG). *Clin Pharmacol Ther* 1999;**66**:152–165.
8. EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS. Note for guidance on Good Clinical Practice. CPMP/ICH/135/95. London: European Agency for the Evaluation of Medicinal Products, 1997.
9. SACKEIM HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001;**62**(Suppl. 16):10–17.
10. SHEEHAN DV, LECRUBIER Y, SHEEHAN KH et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.):

the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(Suppl. 20):22–33; quiz 34–57.

11. WORLD HEALTH ORGANIZATION. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Diagnostic Criteria for Research. Geneva: World Health Organization, 1993.
12. BECH P, KASTRUP M, RAFAELSEN OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, and schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatr Scand Suppl* 1986;**326**:1–37.
13. BECH P, GRAM LF, KRAGH-SORENSEN P, REISBY N. DUAG: standardized assessment scales and effectiveness of antidepressants. *Nord J Psychiatry* 1988;**42**:511–515.
14. BECH P. *Clinical Psychometrics*. Oxford: Wiley Blackwell, 2012.
15. BECH P, LAURITZEN L, LUNDE M et al. Psychometric analysis of the Melancholia Scale in trials with non-pharmacological augmentation of patients with therapy-resistant depression. *Acta Neuropsychiatrica* 2013:1–6.
16. BECH P, RASMUSSEN NA, OLSEN LR, NOERHOLM V, ABILDGAARD W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord* 2001;**66**:159–164.
17. LINGJAERDE O, AHLFORS UG, BECH P, DENCKER SJ, ELGEN K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987;**334**:1–100.
18. SIEGEL S. *Nonparametric Statistics for the Behavioural Sciences*. New York: McGraw Hill, 1956.
19. RUSH AJ, MARANGELL LB, SACKEIM HA et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry* 2005;**58**:347–354.
20. QUITKIN FM, RABKIN JG, ROSS D, STEWART JW. Identification of true drug response to antidepressants. Use of pattern analysis. *Arch Gen Psychiatry* 1984;**41**:782–786.
21. SAARELAINEN T, HENDOLIN P, LUCAS G et al. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J Neurosci* 2003;**23**:349–357.
22. NIBUYA M, MORINOBU S, DUMAN RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 1995;**15**:7539–7547.
23. RAHBK UL, TRITSARIS K, DISSING S. Interactions of low frequency, pulsed electromagnetic fields with living tissue: biochemical responses and clinical results. *Oral Biosci Med* 2005;**2**:29–40.
24. DISSING S, TRITSARIS K, HANSEN AJ. Pulsed electrical fields cause activation of tyrosin kinase related cellular signalling in endothelial cells leading to transcription processes and angiogenesis. *FASEB* 2012;**26**:1129.29.