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Research paper

Real-world treatment outcomes of transcranial pulsating electromagnetic fields as augmentation therapy for treatment-resistant depression

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ABSTRACT

Background: Treatment outcomes of patients who had received T-PEMF as an augmenting therapy at Aalborg University Hospital, Aalborg, Denmark, was evaluated.
Methods: Patients diagnosed with unipolar depression or bipolar disorder who had received a self-administered 8-week T-PEMF series between November 2019 and April 2023 were included. Data were retrieved from the patients' records. The primary outcome was the Hamilton Rating Scale for Depression 17-item version (HAM—D_{17}), both as a continuous measure and with proportions of response and remission reported.
Results: A total of 57 patients (65.1 % females, 86.0 % unipolar depression, mean age, 48 ± 14 years) were included. Duration of current depressive episode was almost equally divided for <2 years (38.6 %), 2–5 years (38.6 %) and > 5 years (22.8 %). HAM-D_{17} decreased significantly from baseline (20.8 (SD: 3.3)) to week 8 (14.5 (SD: 6.2), $p < 0.001$). An episode duration of 2–5 years was associated with lower odds of response on HAM-D_6 (adjusted OR = 0.15, 95 % CI: 0.03; 0.96, $p < 0.05$) and self-rated HAM-D_6 (adjusted OR = 0.09, 95 % CI: 0.01; 0.99, $p = 0.05$) when compared to an episode duration <2 years.
Limitations: This study is limited by a lack of a control group, limited controlling of confounders, small sample sizes, and an attrition rate of 29.8 % for the primary outcome.
Conclusion: T-PEMF reduced depressive symptoms in a real-world clinical setting including patients with both unipolar depression and bipolar disorder. Receiving T-PEMF within the first 2 years of the depressive episode was associated with an improved outcome.

1. Introduction

Patients with treatment-resistant depression (TRD) have not responded sufficiently to the first-line antidepressant treatments. Though no standard definition of TRD exists, it is most often defined as an insufficient effect of two or more different antidepressant treatments of an adequate dose and duration (Gaynes et al., 2020). Previous studies have investigated the effect of augmenting with transcranial pulsating, low intensity electromagnetic fields (T-PEMF) in patients with TRD (Larsen et al., 2020; Martiny et al., 2010; Straasø et al., 2014; van Belkum et al., 2021). Stimulation results in a diffuse, multifocal brain stimulation below the neuronal firing threshold (Karabanov and Siebner, 2014). The exact mechanisms behind the clinical effects of T-PEMF have not been identified, a comprehensive summary of different findings is presented in the article by van Belkum et al. (van Belkum et al., 2016). Among other, T-PEMF is known to stimulate intracellular Src kinase activity leading to secretion of growth factors involved in signal pathways controlling cell proliferation, regeneration, angiogenesis, and anti-apoptotic responses (Hyldahl et al., 2023; Rahbek et al., 2004). Additionally, T-PEMF has been found to promote neuronal plasticity in

Abbreviations: CI, Confidence Interval; EEG, Electroencephalography; HAM-D_{17}, Hamilton Rating Scale for Depression 17-item version; HAM-D_6, Hamilton Rating Scale for Depression 6-item version; fMRI, Functional Magnetic Resonance Imaging; MAO-I, Monoamine Oxidase Inhibitor; MID, Minimal Important Difference; MSM, Maudsley Staging Method; NA, Not Available; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; NDRI, Norepinephrine and Dopamine Reuptake Inhibitor; OR, Odds Ratio; Q1, Lower Quartile; Q3, Upper Quartile; RCT, Randomised Controlled Trial; REDCap, Research Electronic Data Capture; SD, Standard Deviation; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant; T-PEMF, Transcranial Pulsating Electromagnetic Fields; TRD, Treatment-Resistant Depression; WHO-5, WHO-5 Well-Being Index.

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dopaminergic MN9D cells (Lekhraj et al., 2014) and to modulate the activity of specific brain regions in depressed patients (van Belkum et al., 2024).

The augmenting antidepressant effect of T-PEMF was studied essentially using two different types of T-PEMF equipment. Re5 Neuro Treatment System T-PEMF apparatus, used also in this study, was evaluated in four previously published studies, including in total 159 patients: one randomised sham-controlled trial (RCT) (Martiny et al., 2010) and three single-arm cohort studies (Straasø et al., 2014; Bech et al., 2015; Larsen et al., 2020). In summary, they show superior effect of 8 vs. 5 weeks of daily treatment, response rates of 28 %–61 %, remission rates of 16 %–68 %, and significantly better antidepressant effect in acute vs. chronic TRD patients. Another RCT (sham-controlled), using a different T-PEMF equipment (different electromagnets number and placement over sculp, and different pulse intensity), did not report a significant difference in antidepressant effect between the active and the control group (van Belkum et al., 2021).

There is still a lack of data reporting T-PEMF treatment outcomes in a real-world clinical setting and examining variables associated with treatment response and remission. Such data are necessary to gain a better understanding of the applicability of the treatment and help guide therapeutic choices. Additionally, no studies have reported separate treatment outcomes of T-PEMF in patients with bipolar disorder experiencing a depressive episode demonstrating a lack of evidence behind its use in this patient population.

Therefore, the aim of this naturalistic cohort study was to evaluate the treatment outcomes of patients who received T-PEMF as an augmenting therapy to pharmacological treatment. Additionally, the study aimed at examining if the treatment outcomes varied between patients diagnosed with unipolar depression and bipolar disorder. Lastly, associations between age, the duration of the depressive episode and response and remission were investigated.

2. Methods

2.1. Study population

Patients who were followed at the Unit for Depression, Aalborg University Hospital, and received a self-administered T-PEMF series between November 2019 and April 2023 were included in the study. Patients who had previously received T-PEMF treatment or received their T-PEMF treatment utilizing a non-standard treatment regimen were excluded. At time of inclusion, all patients were diagnosed with either a depressive episode (F32), recurrent depressive disorder (F33), or bipolar affective disorder (F31), currently experiencing a depressive episode of a moderate or severe degree as defined by the International Classification of Diseases 10th Revision criteria.

2.2. T-PEMF treatment

The T-PEMF treatment series consisted of 56 stimulation sessions of 30 min each using a Re5 Neuro Treatment System (Re5 ApS, Denmark) T-PEMF apparatus. The pulse generator powered the seven electromagnetic coils with alternating bipolar square pulses between +50 and − 50 V and a pulse frequency of 50 Hz. The current changes in the coils created an alternating magnetic field, which induced electrical fields in the brain tissue with an intensity of 2.5 mV/cm at a 2 cm distance from each coil.

The initial treatment sessions were administered at the hospital under supervision of a trained health care professional, where the patients were instructed in the use of the T-PEMF apparatus. Thereafter, the patients received a T-PEMF apparatus to take home and administered the rest of the stimulation sessions by themselves. The patients were instructed to take one stimulation session per day.

2.3. Data collection

Demographic information, disease characteristics, somatic comorbidities and medication at baseline were collected from the patients' records. The duration of the depressive episode was divided into three categories: < 2 years, 2–5 years, and > 5 years. The Maudsley Staging Method (MSM) was used to assess the degree of treatment resistance of the patients at baseline. It is a multidimensional staging method which includes three dimensions: treatment failures (antidepressants, augmentation, ECT), severity of the depressive episode, and duration of the depressive episode. The total score ranges from 3 to 15 with a higher score indicating a higher level of treatment resistance (Fekadu et al., 2009).

Psychometric evaluations of the patients had been made at a consultation at baseline and after 8 weeks of T-PEMF treatment. The results from these were collected from the patients' records. The 8-week evaluations were considered valid and included in the statistical analyses if they were made within ±5 days of the 56. treatment session.

All data were collected using the secure, web-based Research Electronic Data Capture (REDCap) software hosted at the North Denmark Region (Harris et al., 2009; Harris et al., 2019).

2.4. Outcome measures

The primary outcome was the Hamilton Rating Scale for Depression 17-item version (HAM—D_{17}) (Bech, 2012). The Hamilton Rating Scale for Depression 6-item version (HAM—D_6) (Bech, 2012) and the WHO-5 Well-Being Index (WHO-5) (World Health Organization Regional Office for Europe, 1998) were included as secondary outcomes. The primary outcome measure was change in the patients' scores on the HAM-D_{17} between baseline and after eight weeks of T-PEMF. Changes in the patients' scores on the HAM-D_6 and WHO-5 as well as the proportion of patients achieving response and remission were included as secondary outcome measures.

The HAM-D_{17} is a clinician rated scale, which rates the severity of the depressive symptoms. It consists of 17 items, which are rated on either a five-point scale (0 to 4) or a three-point scale (0 to 2). The total score ranges from 0 to 52 with a higher score indicating a greater severity of the depressive symptoms (Bech, 2012). Remission was defined as an endpoint score ≤ 7, and response was defined as $\geq$50 % reduction from baseline.

The HAM-D_6 is a scale consisting of six items from the HAM-D_{17} describing the core symptoms of depression (depressed mood, guilt, work and interests, psychomotor retardation, psychic anxiety, and general somatic symptoms). It exists in both a clinician rated version and a self-rated version with the total score ranging from 0 to 22 (Bech, 2012). Both versions were used in this study, and the clinician rated version will henceforth be referred to as the HAM-D_6 while the self-rated version will be referred to as the self-rated HAM—D_6. Remission was defined as an endpoint score ≤ 4, and response was defined as $\geq$50 % reduction from baseline.

The WHO-5 scale is a self-rated questionnaire, which measures positive well-being. It consists of five positively phrased items, which are scored based on their presence over the past two weeks from 0 (at no time) to 5 (all the time). The raw score ranges from 0 to 25 and is multiplied by four resulting in a total score ranging from 0 (worst possible quality of life) to 100 (best possible quality of life) (World Health Organization Regional Office for Europe, 1998).

2.5. Statistical analyses

Descriptive statistics were used to describe baseline demographics and disease characteristics as well as the scores on the HAM—D_{17}, HAM—D_6, self-rated HAM—D_6, and WHO-5 scales at baseline and week 8. Categorical variables are presented as percentages with counts. Continuous variables are presented as means with the standard

deviations (SD) if normally distributed and as medians with the lower (Q1) and upper (Q3) quartiles if non-normally distributed.

To compare the patients' scores on the four outcomes between baseline and after 8-weeks of T-PEMF treatment, 2-sided paired *t*-tests or Wilcoxon signed rank tests were used. The proportion of patients who had achieved response or remission was determined using descriptive statistics and are presented as percentages with counts. Fisher's exact tests were used to compare response and remission proportions between patients with unipolar depression and bipolar disorder. To examine whether age and the duration of the depressive episode were associated with response and remission, binary logistic regressions were made. First, a binary logistic regression was made for each of the variables per outcome to determine unadjusted odds ratios. Both variables were hereafter introduced together to get adjusted odds ratios.

A statistical significance level was set at 5 % ($p \leq 0.05$) for all analyses. No adjustment for multiple comparisons was conducted.

Data were exported from REDCap and analysed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY).

2.6. Ethics

Data were retrieved from the patients' records without consent from the patients but with an approval from the psychiatric management at the hospital in accordance with the Danish Health Act. The study was registered at the North Denmark Region (K2022–057). No ethical approval was required for the study.

3. Results

A total of 65 patients were potentially eligible for inclusion, with 57 patients being included, as shown in Fig. 1. Of these, 55 patients (96.5 %) completed their T-PEMF series. One patient discontinued treatment after three T-PEMF sessions due to a sensation of tightness in the chest and nausea while taking the treatment. One patient discontinued treatment after two T-PEMF sessions due to a lack of motivation. The two patients who discontinued the treatment did not differ substantially in the overall clinical presentation and baseline characteristics from the remaining population. Data of the primary outcome fulfilling the study requirements was available for 40 patients.

Table 1 shows the baseline demographics and disease characteristics for the included patients. The majority of the patients (56.1 %, $n = 32$) were female, and the mean age was 48 years (SD: 14). The median number of previous depressive episodes was 2 (Q1; Q3: 0; 3) and the median MSM score was 9 (Q1; Q3: 8; 10). Most of the patients (86.0 %, $n = 49$) presented with unipolar depression. In 31.6 % ($n = 18$) of the patients, the depressive episode presented with somatic syndrome and 28.1 % ($n = 16$) with the first depressive episode (ever). The duration of the depressive episode was <2 years in 38.6 % ($n = 22$), 2–5 years in 38.6 % (n = 22), and > 5 years in 22.8 % ($n = 13$) of the patients. Somatic comorbidity resulting in treatment was present in 63.2 % ($n = 36$) of the patients with the most common comorbidities being hypertension (17.5 %, $n = 10$), dyslipidaemia (14.0 %, $n = 8$), chronic pain syndrome (12.3 %, $n = 7$), diabetes (10.5 %, $n = 6$), hypothyroidism (8.8 %, $n = 5$), obesity (5.3 %, n = 3), osteoporosis (5.3 %, n = 3), hyperthyroidism (5.3 %, n = 3), asthma (5.3 %, n = 3), rheumatic disease (5.3 %, n = 3), and tinnitus (5.3 %, n = 3). Medication use during the T-PEMF treatment is shown in Table 2. Overall, 61.4 % ($n = 35$) of the patients received somatic medication while 93.0 % ($n = 53$) received psychotropic medication.

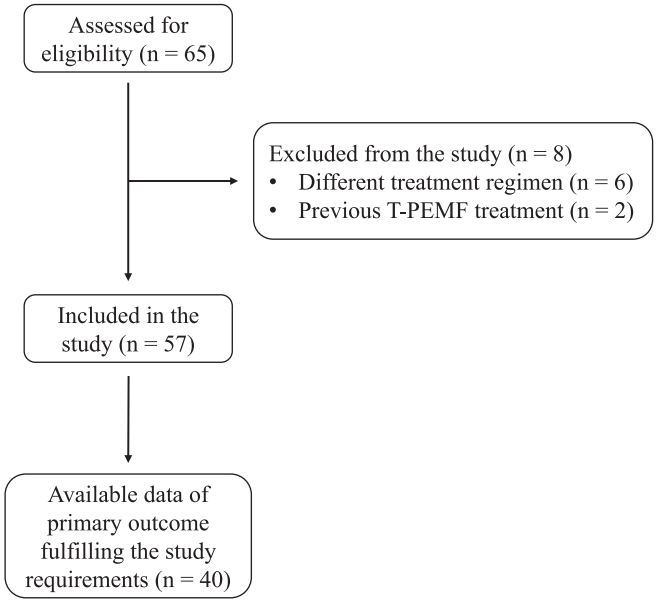

Fig. 1. Flowchart of patient inclusion.
T-PEMF: Transcranial pulsating electromagnetic fields.

Table 1
Demographics and disease characteristics at baseline.

	All patients ($n = 57$)
Duration of depressive episode	
<2 years, % (n)	38.6 (22)
2–5 years, % (n)	38.6 (22)
>5 years, % (n)	22.8 (13)
Female, % (n)	56.1 (32)
Unipolar depression, % (n)	86.0 (49)
Somatic syndrome, % (n)	31.6 (18)
First episode, % (n)	28.1 (16)
Age, mean (SD)	48 (14)
MSM score, median (Q1; Q3)	9 (8; 10)
Number of previous depressive episodes, median (Q1; Q3)	2 (0; 3)
Smoking	
Smoker, % (n)	26.3 (15)
NA, % (n)	14.0 (8)
Somatic comorbidity (resulting in treatment), % (n)	63.2 (36)
Marital status	
Married, % (n)	33.3 (19)
Divorced, % (n)	15.8 (9)
Widow, % (n)	1.8 (1)
Single (living alone), % (n)	29.8 (17)
Single (living with a partner), % (n)	14.0 (8)
NA, % (n)	5.3 (3)
Education	
Elementary, % (n)	10.5 (6)
High school, % (n)	47.4 (27)
Bachelor's degree, % (n)	28.1 (16)
Master's degree, % (n)	8.8 (5)
NA, % (n)	5.3 (3)
Socio-economic status	
Employed, % (n)	14.1 (8)
Retired, % (n)	10.5 (6)
Early retirement, % (n)	17.5 (10)
Sickness benefits, % (n)	38.6 (22)
Other social assistance, % (n)	12.3 (7)
NA, % (n)	7.0 (4)

Note: Specific somatic comorbidities are reported in the Results section. The category Employed includes full-time employed, part-time employed and self-employed. The category Other social assistance includes educational support, cash assistance and unemployment assistance.
MSM: Maudsley Staging Method; Q1: Lower quartile; Q3: Upper quartile; SD: Standard deviation; NA: Not available.

3.1. Treatment outcomes after eight weeks of T-PEMF

Table 3 shows the total scores on the four outcomes at baseline and after eight weeks of T-PEMF treatment. Symptom scores on both the HAM—D_{17}, HAM—D_6, and self-rated HAM-D_6 decreased significantly

Table 2
Medication use during the treatment period.

	All patients (n = 57)
Somatic medication (any drug or combination of drugs), % (n)	61.4 (35)
Psychotropic medication (any drug or combination of drugs), % (n)	93.0 (53)
Antidepressants[a], % (n)	82.5 (47)
SSRI, % (n)	14.0 (8)
SNRI, % (n)	17.5 (10)
NDRI, % (n)	1.8 (1)
TCA, % (n)	24.6 (14)
MAO-I, % (n)	3.5 (2)
NaSSA, % (n)	8.8 (5)
Others, % (n)	24.6 (14)
Antipsychotics[b], % (n)	31.6 (18)
Quetiapine, % (n)	17.5 (10)
Aripiprazole, % (n)	5.3 (3)
Olanzapine, % (n)	5.3 (3)
Cariprazin, % (n)	1.8 (1)
Lurasidon, % (n)	1.8 (1)
Chlorprothixen, % (n)	1.8 (1)
Mood stabilisers, % (n)	28.1 (16)
Lithium, % (n)	12.3 (7)
Lamotrigine, % (n)	12.3 (7)
Valproate, % (n)	3.5 (2)
Pregabaline, % (n)	21.1 (12)
Central stimulants, % (n)	7.0 (4)
Benzodiazepines[c], % (n)	3.5 (2)
Melatonine, % (n)	7.0 (4)

SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; NDRI: Norepinephrine and dopamine reuptake inhibitor; TCA: Tricyclic antidepressant; MAO-I: Monoamine oxidase inhibitor; NaSSA: Noradrenergic and specific serotonergic antidepressant; the category Others under Antidepressants includes agomelatine and vortioxetine.

[a] Several patients taking a combination of two antidepressants.

[b] Only regular medication reported. One patient taking a combination of two antipsychotics.

[c] Only regular medication reported.

Table 3
HAM—D_{17}, HAM—D_6, self-rated HAM—D_6, and WHO-5 total scores (mean (SD) or median (Q1; Q3)) at baseline and week 8.

	N	Baseline	Week 8	*p*
HAM-D_{17}	40	20.8 (3.3)	14.5 (6.2)	<.001[a]
HAM-D_6	36	10.0 (9.0; 12.0)	7.5 (5.0; 9.8)	<.001[b]
Self-rated HAM-D_6	29	14.0 (12.0; 16.0)	12.0 (6.5; 14.5)	< 0.01[b]
WHO-5	29	20.0 (12.0; 28.0)	28.0 (16.0; 50.0)	<.001[b]

HAM-D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; Q1: Lower quartile; Q3: Upper quartile; SD: Standard deviation; WHO-5: WHO-5 Well-Being Index.

[a] Paired t-test.

[b] Wilcoxon signed rank test.

from baseline to week eight, and the total scores on the WHO-5 increased significantly from baseline to week eight, as shown in Table 3.

In total, 30.0 % (n = 12) achieved response and 15.0 % (n = 6) achieved remission as measured by the HAM—D_{17}, as shown in Table 4. Response and remission were achieved in 33.3 % (n = 12) and 20.0 % (n = 8) of the patients as measured by the HAM-D_6 and in 24.1 % (n = 7) and 16.1 % (n = 5) of the patients as measured by the self-rated HAM—D_6. There were no differences in the proportions of patients who achieved response or remission between the patients with unipolar depression and bipolar disorder on either of the three outcomes.

3.2. Association of age and duration of the depressive episode with response and remission

The duration of the depressive episode was significantly associated with response as measured by the HAM-D_6 when comparing patients with an episode duration <2 years to a duration of 2–5 years with the OR = 0.15 (95 % CI: 0.03; 0.95, p = 0.044) in the unadjusted model and OR = 0.15 (95 % CI: 0.03; 0.96, p = 0.045) in the adjusted model (see Table 5). The duration of the depressive episode was not associated with response as measured by the self-rated HAM-D_6 in the unadjusted analysis but when adjusting for age, the OR reached statistical significance when comparing the two duration groups mentioned (p = 0.049). Patients with an episode duration of 2–5 years had an OR of 0.09 (95 %

Table 5
Unadjusted and adjusted odds ratios for achievement of response defined as ≥50 % reduction on the HAM-D_{17} or HAM-D_6 from baseline.

	Unadjusted		Adjusted	
	OR (95 % CI)	p^a	OR (95 % CI)	p^a
HAM-D_{17} (n = 40)				
Age	1.02 (0.97; 1.07)	0.543	1.02 (0.97; 1.07)	0.481
Duration: 2–5 years - < 2 years	0.35 (0.07; 1.76)	0.201	0.34 (0.07; 1.73)	0.191
Duration: > 5 years - < 2 years	0.75 (0.13; 4.22)	0.744	0.80 (0.14; 4.61)	0.803
HAM-D_6 (n = 36)				
Age	0.99 (0.94; 1.04)	0.752	1.00 (0.95; 1.06)	0.993
Duration: 2–5 years - < 2 years	0.15 (0.03; 0.95)	0.044	0.15 (0.03; 0.96)	0.045
Duration: > 5 years - < 2 years	0.75 (0.12; 4.66)	0.758	0.75 (0.12; 4.75)	0.761
Self-rated HAM-D_6 (n = 29)				
Age	1.03 (0.96; 1.09)	0.439	1.03 (0.96; 1.11)	0.350
Duration: 2–5 years - < 2 years	0.10 (0.01; 1.06)	0.056	0.09 (0.01; 0.99)	0.049
Duration: > 5 years - < 2 years	0.30 (0.03; 3.63)	0.344	0.34 (0.03; 4.33)	0.404

CI: Confidence interval; HAM—D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; OR: Odds ratio.

[a] Binary logistic regression.

Table 4
Patients with response and remission (% (n)) after 8 weeks of treatment for all patients and stratified according to diagnosis. Remission was defined as HAM-D_{17} ≤ 7 or HAM-D_6 ≤ 4 and response was defined as ≥50 % reduction on the HAM-D_{17} or HAM-D_6 from baseline.

	n	All	n	Unipolar depression	n	Bipolar disorder	p^a
Response							
HAM-D_{17}	40	30.0 % (12)	37	29.7 % (11)	3	33.3 % (1)	1.000
HAM-D_6	36	33.3 % (12)	33	33.3 % (11)	3	33.3 % (1)	1.000
Self-rated HAM-D_6	29	24.1 % (7)	26	23.1 % (6)	3	33.3 % (1)	1.000
Remission							
HAM-D_{17}	40	15.0 % (6)	37	13.5 % (5)	3	33.3 % (1)	0.394
HAM-D_6	40	20.0 % (8)	37	18.9 % (7)	3	33.3 % (1)	0.498
Self-rated HAM-D_6	31	16.1 % (5)	28	14.3 % (4)	3	33.3 % (1)	0.422

HAM-D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6item version.

[a] Fisher's exact test comparing unipolar depression and bipolar disorder groups.

CI: 0.01; 0.99) to achieve response as compared to patients with an episode duration <2 years. Age was not associated with response as measured by either of the outcomes.

Odds ratios for achieving remission are shown in Table 6. No statistically significant associations were found.

4. Discussion

This naturalistic cohort study evaluated the treatment outcomes of patients who had received T-PEMF as an augmenting therapy to pharmacological treatment in a real-world clinical setting. Symptom scores as measured by the HAM—D_{17}, HAM—D_6, and self-rated HAM-D_6 decreased significantly between baseline and after eight weeks of T-PEMF treatment while the quality of life as assessed by the WHO-5 increased. The proportion of patients who achieved response and remission varied from 24.1 % to 33.3 % and 15.0 % to 20.0 % across the outcomes, respectively. These findings are in accordance with the previous studies examining the effect of T-PEMF using the same T-PEMF equipment (Re5 Neuro Treatment System) (Larsen et al., 2020; Martiny et al., 2010; Straasø et al., 2014). However, improvements on the outcomes and the response and remission proportions found in this study are lower than those previously reported. Straasø et al. (Straasø et al., 2014) reported a decrease of 13.6 points and a remission proportion of 73.5 % on the HAM-D_{17} after eight weeks of T-PEMF augmentation compared to only 6.3 points and 15.0 % in this study. The median MSM score of 9 (Q1; Q3: 8; 10) in the current study indicates a high degree of treatment resistance in the included patient population. More severely treatment-resistant patients might have lower odds for responding to the treatment. Unfortunately, the previous studies did not include MSM scores or other staging methods, so it is not possible to determine whether the study populations are comparable in this regard. Opposed to the previous studies, no exclusion criteria regarding comorbidities or medication use were applied in the current study, resulting in a not directly comparable case mix. Moreover, since this study was based on real-world data, the patients received the treatment under less controlled conditions. Although inquiries concerning the use of T-PEMF were part of the follow-up protocol, direct data concerning compliance were not collected for the study, so it could not be verified to which degree the patients took the T-PEMF stimulations as intended. These factors might help elucidate why the treatment outcomes found in this study were not as favourable as those previously reported.

Interestingly, these findings contrast with a recent sham-controlled, double-blinded multicentre T-PEMF study (van Belkum et al., 2021) using a different T-PEMF equipment. The study explored the effect of 30 min daily 5 weeks T-PEMF treatment in TRD patients (29 patients in active and 26 patients in sham group) and reported no difference in outcomes between the active and sham groups at different follow-up points (up to 20 weeks). A possible explanation could be related to the differences in technical properties. T-PEMF equipment used in van Belkum's study included 19 electromagnets (placement according to a regular 10/20 electroencephalography (EEG) system) with a pulse intensity of 0.1 mT 1 cm under the coil, whereas all the aforementioned Danish studies used Re5 Neuro Treatment System T-PEMF apparatus with 7 electromagnets (4 (anterior and posterior) temporal, 2 (upper) parietal, and 1 (midline) occipital) with a considerably higher pulse intensity of 2 mT 0.5 cm under the coil. However, the report of functional magnetic resonance imaging (fMRI)-detected changes in brain activation after T-PEMF in the same cohort (van Belkum et al., 2024), suggests a possible normalization in specific brain regulatory regions supposed to be involved in the pathophysiology of depression.

There is no consensus on what the minimal important difference (MID) on the HAM-D_{17} and HAM-D_6 are, but MID estimates across studies range from 3 to 8 points on the HAM-D_{17} and from 2 to 4 points on the HAM-D_6 (Hengartner and Plöderl, 2022). The symptom score reductions reported in the current study all fall below the upper MID estimates indicating that the clinical significance may be doubtful. As for the WHO-5, a clinically relevant change is 10 points, and a score of ≤50 indicates the presence of clinical depression (Topp et al., 2015). Thus, the improved quality of life scores from 20 to 28 points reported in this study fail to reach clinical significance, and the median endpoint score is still below the cut-off score of clinical depression. Though, it should be noted that the dispersion of the symptom and quality of life scores at week 8 is rather large indicating that the improvements experienced by the individual patients varied a lot. Even though the overall estimates of treatment outcomes found in this study do not live up to those previously reported, T-PEMF could still be a valuable treatment option for some TRD patients. TRD is in general difficult to manage. Only few clinical practice guidelines address the treatment of TRD patients, and the recommendations are inconsistent (Gabriel et al., 2023).

To the best of the authors' knowledge, this is the first study examining treatment outcomes of T-PEMF in patients diagnosed with bipolar disorder experiencing a depressive episode as a separate group. No differences in the proportions of patients who achieved response and remission were found between those with unipolar depression and bipolar disorder. However, caution should be taken when generalising these results to populations outside this study due to the very restricted number of patients diagnosed with bipolar disorder in the present study.

In this study, an episode duration <2 years was associated with higher odds for achievement of response as measured by the HAM-D_6 and self-rated HAM-D_6 when compared to an episode duration of 2–5 years. Larsen et al. have previously reported higher remission proportions in patients with an episode duration ≤2 years compared to patients with an episode duration >2 years (Larsen et al., 2020).

The present study is not without limitations. The study merely reports a descriptive evaluation of the outcomes from the included treatment group. It cannot be determined to which degree the improved treatment outcomes were due to the T-PEMF treatment, the underlying pharmacological treatment, a placebo effect, or spontaneous improvement over time as no control group is present. Some of the statistical analyses made in this study were based on small sample sizes, which increases the risk of type II errors. Additionally, controlling of confounders was limited, and the study had an attrition rate of 29.8 % for the primary outcome.

Future studies with an optimized study design and larger sample sizes should aim to further investigate, which patient populations would

Table 6
Unadjusted and adjusted odds ratios for achievement of remission defined as HAM-D_{17} ≤ 7 or HAM-D_6 ≤ 4.

	Unadjusted		Adjusted	
	OR (95 % CI)	p^a	OR (95 % CI)	p^a
HAM-D_{17} (n = 40)				
Age	0.97 (0.91; 1.03)	0.253	0.96 (0.90; 1.03)	0.231
Duration: 2–5 years - < 2 years	0.57 (0.08; 4.01)	0.573	0.59 (0.08; 4.29)	0.599
Duration: > 5 years - < 2 years	0.50 (0.04; 5.70)	0.577	0.41 (0.03; 4.99)	0.480
HAM-D_6 (n = 40)				
Age	1.02 (0.97; 1.08)	0.447	1.03 (0.97; 1.10)	0.302
Duration: 2–5 years - < 2 years	0.15 (0.02; 1.44)	0.099	0.13 (0.01; 1.32)	0.085
Duration: > 5 years - < 2 years	0.73 (0.11; 4.99)	0.751	0.90 (0.12; 6.63)	0.918
Self-rated HAM-D_6 (*n* = 31)				
Age	1.04 (0.97; 1.13)	0.280	1.07 (0.98; 1.16)	0.160
Duration: 2–5 years - < 2 years	0.39 (0.03; 4.87)	0.461	0.29 (0.02; 4.09)	0.359
Duration: > 5 years - < 2 years	3.33 (0.32; 34.8)	0.315	4.99 (0.35; 71.6)	0.236

CI: Confidence interval; HAM—D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; OR: Odds ratio.

[a] Binary logistic regression.

benefit most from T-PEMF treatment. Additionally, the "one-size-fit-all" approach currently used with T-PEMF has been questioned as the optimal stimulation parameters and dose might vary between patients (Karabanov and Siebner, 2014). For instance, extending the T-PEMF series from five to eight weeks more than doubled the remission proportions in the study by Straasø et al. (Straasø et al., 2014), raising the question whether further extension of the treatment could increase the number of patients achieving response and remission. Moreover, TRD patients with an apathy subsyndrome (defined as the presence of symptoms of fatigue, concentration and memory problems, lack of interests, difficulties in making decisions, and sleep problems) have been found to benefit more from a twice daily dose of T-PEMF than a once-daily dose (Bech et al., 2015). Thus, a more personalised treatment approach might be helpful to improve treatment outcomes.

In conclusion, this study found that eight weeks of augmenting therapy with T-PEMF reduced depressive symptoms and increased the quality of life in a real-world clinical setting in both patients with unipolar depression and bipolar disorder. Patients with a short duration of the depressive episode had higher odds for achieving response on both the clinician and self-rated HAM—D_6. Further investigations of predictors of response and remission should be made to provide more guidance for therapeutic choices in the future.

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CRediT authorship contribution statement

Rikke Hedegaard Jensen: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **René Ernst Nielsen:** Writing – review & editing, Supervision. **Gustav Bizik:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

R.E.N. has, within the past 3 years, been an investigator for Compass Pharmaceuticals, Janssen-Cilag, Sage and Boehringer-Ingelheim for clinical trials; has received speaking fees from Lundbeck, Teva Pharmaceuticals, Janssen-Cilag and Otsuka Pharmaceuticals; and has acted as advisor to Lundbeck and Janssen-Cilag. R.H.J. and G.B. declare that they have no conflicts of interest.

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