Acta Neuropsychiatrica 2015

DOI: 10.1017/neu.2014.26

ACTA NEUROPSYCHIATRICA

The Diagnostic Apathia Scale predicts a dose–remission relationship of T-PEMF in treatment-resistant depression

Bech P, Lunde M, Lauritzen L, Straasø B, Lindberg L, Vinberg M, Undén M, Hellström LC, Dissing S, Larsen ER. The Diagnostic Apathia Scale predicts a dose–remission relationship of T-PEMF in treatment-resistant depression.

Objective: The aim of this study was to evaluate the predictive validity of the apathy subsyndrome in patients with therapy-resistant depression in the dose–remission study with transcranial pulsating electromagnetic fields (T-PEMF).
Methods: The apathy subsyndrome consists of the symptoms of fatigue, concentration and memory problems, lack of interests, difficulties in making decisions, and sleep problems. We evaluated 65 patients with therapy-resistant depression. In total, 34 of these patients received placebo T-PEMF in the afternoon and active T-PEMF in the morning, that is, one daily dose. The remaining 31 patients received active T-PEMF twice daily. Duration of treatment was 8 weeks in both groups. The Hamilton Depression Scale (HAM-D_{17}) and the Bech-Rafaelsen Melancholia Scale (MES) were used to measure remission. We also focused on the Diagnostic Apathia Scale, which is based on a mixture of items from the MINI and the HAM-D_{17}/MES.
Results: In patients without apathy, the remission rate after T-PEMF was 83.9% versus 58.8% in patients with apathy ($p \leq 0.05$). In patients without apathy receiving one active dose daily 94.4% remitted versus 50% for patients with apathy ($p \leq 0.05$). In patients without apathy who received two active doses 69.9% remitted versus 66.7% for patients with apathy ($p \leq 0.05$).
Conclusion: Taking the baseline diagnosis of the apathy syndrome into consideration, we found that in patients without apathy one daily dose of T-PEMF is sufficient, but in patients with apathy two daily doses are necessary. Including the apathy syndrome as predictor in future studies would seem to be clinically relevant.

Per Bech[1], Marianne Lunde[1], Lise Lauritzen[1], Birgit Straasø[1], Lone Lindberg[1], Maj Vinberg[2], Mogens Undén[1], Lone Christina Hellström[3], Steen Dissing[4], Erik Roj Larsen[5]

[1]Psychiatric Research Unit, Psychiatric Centre North Zealand, Copenhagen University Hospital, Hillerød, Denmark; [2]Department of Psychiatry, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark; [3]Psychiatric Research Unit, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Copenhagen NV, Denmark; [4]Department of Cellular and Molecular Medicine, Panum institute, University of Copenhagen, Copenhagen, Denmark; and [5]Department of Affective Disorders, Mood Disorders Research Unit, Aarhus University Hospital, Aarhus, Denmark

Keywords: apathy; depressive disorder; predictive value of tests; transcranial pulsating electromagnetic fields; treatment-resistant depression

Per Bech, Psychiatric Research Unit, Psychiatric Centre North Zealand, University of Copenhagen, Dyrehavevej 48, DK-3400 Hillerød, Denmark.
Tel: +45 38 64 30 95;
Fax: +45 48 26 38 77;
E-mail: Per.bech@regionh.dk

Accepted for publication September 4, 2014

First published online October 2, 2014

Significant outcomes

- The apathy subsyndrome seems to predict the dose–remission relationship in patients with treatment-resistant depression receiving transcranial pulsating electromagnetic fields (T-PEMF).
- When evaluating the dose–remission relationship we used logistic regression analysis for the interaction between the diagnosis of apathy and T-PEMF dose with remission as the dependent variable.

Limitations

- A randomisation at the level of apathy before treatment with T-PEMF has not been done, this might strengthen the findings.

Introduction

We have recently performed two controlled clinical trials using T-PEMF as augmentation in patients with treatment-resistant depression, defined as non-response to two different types of antidepressant medication (1,2). In the first trial we used a non-home care model of the T-PEMF apparatus, implying that patients with treatment-resistant depression had to receive the T-PEMF therapy in our clinic. This trial (1) was a sham T-PEMF controlled study over 5 weeks of therapy with one dose daily 5 days a week. Using the MacArthur criterion of remission (3) [a Hamilton Depression Scale ($HAM\text{-}D_{17}$) (4) score of 7 or less at endpoint] we obtained a remission rate of 34% in the active group and 4% in the placebo group ($p < 0.05$).

In the second trial, which was randomised and double blinded, we used a home care model of T-PEMF, implying that we were able to perform a dose–remission study with active T-PEMF all 7 days of the week, in which half of the patients received one active dose morning and sham in the evening and the other half of the patients received an active dose twice daily (2). When using the MacArthur criterion of remission we were not able to demonstrate a dose–remission effect, either after 5 weeks of therapy or at endpoint after 8 weeks of therapy (2). However, in our psychometric analyses of patients with treatment-resistant depression, we have previously identified a subsyndrome present in many of these patients, consisting of such symptoms as fatigue, concentration problems, lack of interests or initiative, and sleep problems (5). This syndrome should be considered as a depression subsyndrome. This in contrast to the recent apathy scale (6), which has been designed with limited overlap with depression scales.

We have now re-analysed our dose–remission trial with focus on this apathy syndrome, which we have identified as an important subsyndrome in treatment-resistant depression. In the analysis to be reported here we have focused on both the Diagnostic Apathia Scale (7) at baseline and the apathy subscale of the Bech-Rafaelsen Melancholia Scale (MES) (8) as one of the outcome scales.

The aims of the present study were to test the following research questions:

1. Does the apathy syndrome have validity in predicting the percentage of remission at end-point using as remission criterion a $HAM\text{-}D_{17}$ of score of 7 or less?
2. Is a dose–remission relationship of the T-PEMF augmentation in operation when using the remission criterion of $HAM\text{-}D_{17}$ score of 7 or less in patients with apathy?
3. Is a dose–remission relationship of the T-PEMF in operation when using the remission criterion of a $HAM\text{-}D_6$ score of 4 or less in patients with apathy?
4. Is a dose–remission relationship of the T-PEMF augmentation in operation when using as remission criterion a MES apathy scale score of 3 or less in patients with apathy?

Materials and method

The study has been comprehensively described in Straasø et al. (2). The study was approved by the Danish Health and Medicines Authority (2013030958) and the Committee on Biomedical Research Ethics (H-L-201-031) and was reported to the Danish Data Protection Agency (PSV-2010-2). The trial was registered at Clinical Trials.gov (ID NCT01353092). Patients were given information as requested by the Biomedical Research Ethics, and all patients signed an informed consent.

The patients all fulfilled the ICD-10 criteria of major depression. They were all classified as having therapy-resistant depression according to the Sackheim criteria (9), with a score of 3 or more.

In the present study we have focused on the following rating scales:

The $HAM\text{-}D_{17}$ in combination with MES (10). From this $HAM\text{-}D_{17}$/MES scale, we have focused on (a) remission as defined by a $HAM\text{-}D_{17}$ score of 7 or less, (b) the $HAM\text{-}D_6$, which is a 6-item subscale consisting of the core symptoms of depression (depressed mood, guilt, work and interests, psychomotor retardation, psychic anxiety, and general somatic symptoms) with a remission cut-off score of 4 or less, and (c) the MES apathy scale (8) including fatigability, concentration or memory problems, introversion, and sleep disturbances, with a remission cut-off score of 3 or less.

We also focused on the Diagnostic Apathia Scale (Fig. 1), which is based on a mixture of items from the MINI and the $HAM\text{-}D_{17}$/MES. This Diagnostic Apathia Scale is based on the Hellström et al. (7) Apathia scale, but modified. Thus, the Hamilton Anxiety Scale item 5 'Concentration and memory' is identical to the MES item 4 (Fig. 1).

T-PEMF therapy

Coil applicators introduced pulsating electrical fields (E-fields; 50 Hz) of a very low magnitude (0.1–4 mV/cm) into brain tissue. The pulses were constructed to mimic the pulsating E-fields measured outside excitable tissue. The E-fields induced into neural tissue by the coils were five orders of

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press

The Diagnostic Apathia Scale from MINI / Hamilton scales [HAM-D/MES]

1a	Difficulties in concentration and memory The Bech-Rafaelsen Melancholia Scale (MES), Item 4		0 - 4
1b	Difficulties in concentration or decision making MINI International Neuropsychiatric Interview (MINI) version 5.0	A3, item f	0 - 1
2a	Lack of interests MINI International Neuropsychiatric Interview (MINI) 5.0	A2	0 - 1
2b	Work and interests Hamilton Depression Scale (HAM-D) , Item 7		0 - 4
3a	Somatic general (fatigue and muscle pains) Hamilton Depression Scale (HAM-D), Item 13		0 – 2
3b	Tiredness, lack of energy MINI International Neuropsychiatric Interview (MINI) version 5.0	A3, item d	0 – 1
4	Sleep problems (insomnia or hypersomnia) MINI International Neuropsychiatric Interview (MINI) version 5.0	A3, Item b	0 – 1
Total score			0 - 14

Fig. 1. The Diagnostic Apathia Scale from MINI/Hamilton scales (HAM-D/MES).

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. A total of 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 a current was running in coils for treatment in the 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 programs 'double blinding'. Only the GCP unit 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 analysis

The scalability in terms of Mokken's non-parametric item response theory has been found adequate for the HAM-D_6 and the MES apathy subscale (8), as well as for the Diagnostic Apathia Scale (7).

When evaluating the dose–remission relationship, we used logistic regression analysis (SAS version 9.0 2002) for the interaction between the diagnosis of apathy and T-PEMF dose with remission as the dependent variable. The level of statistical significance was $p \leq 0.05$. The intention-to-treat approach was used (last observation carried forward (LOCF)).

Results

In total, 65 patients were included in the study. In total, 34 of these patients received placebo T-PEMF in the afternoon and active T-PEMF in the morning, that is, one daily dose. The remaining 31 patients received active T-PEMF twice daily. During the planned treatment period of 8 weeks, three patients dropped out, one patient at week 4 in the group of one daily dose and two patients (weeks 3 and 4) dropped out in the group receiving T-PEMF twice daily. Intention-to-treat (LOCF) was used.

As seen from Table 1, patients without apathy had significantly higher remission rates than patients with apathy, thus answering the first research question about the predictive validity of the Diagnostic Apathia Scale concerning remission rate (HAM-$D_{17} \leq 7$) at endpoint for all 65 patients. In the group of patients without apathy (a Diagnostic Apathia Scale score < 11), the remission rate was 83.9%

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press

against 58.8% in the group of patients with apathy ($p = 0.032$).

Table 2 concerns our second research question about dose–remission relationship using HAM-$D_{17} \leq 7$ as criterion of remission. The logistic regression analysis obtained a χ^2 value of 3.84 ($p = 0.050$) for the interaction between the diagnosis of apathy (using the Diagnostic Apathia Scale) and the dose of T-PEMF (one versus two active doses daily). As shown in Table 2, the remission rate in the group receiving one active dose daily was 94.4% for patients without apathy but 50% for patients with apathy and the remission rate in the group receiving two active doses daily was 69.2% for patients without apathy and 66.7% for patients with apathy. Our answer to the second research question is therefore that a dose–remission relationship was in operation, so that for patients without apathy one dose of T-PEMF daily is optimal, but in patients with apathy two doses daily are needed. On the other hand, in patients without apathy two doses daily of T-PEMF seemed to flatten the remission rate.

Table 2 shows the third research question about a dose–remission relationship using a HAM-D_6 score of 4 or less as criterion of remission. The logistic regression analysis obtained a χ^2 value of 4.85 ($p = 0.028$) for the interaction between the diagnosis of apathy and the dose of T-PEMF. Again, the remission rate for patients with apathy receiving T-PEMF in a dose once daily was below 50%, whereas it was 72% in those apathy patients who had received T-PEMF twice a day. Therefore, the answer to the third research question is similar to the second.

Table 2 shows the fourth research question about dose–remission relationship using a MES Apathy score of 3 or less as criterion of remission. The logistic regression analysis obtained a χ^2 value of 4.66 ($p = 0.031$) for the interaction between the

Table 1. Remission rates (Ham-$D_{17} < 8$) among patients with and without apathia receiving T-PEMF during 8 weeks

	The Diagnostic Apathia Scale				
	No apathy syndrome < 11 (n = 31)		Apathy syndrome ≥ 11 (n = 34)		p
Remission week 8 HAM-$D_{17} < 8$	Yes	No	Yes	No	
	26	5	20	14	
% remission	83.9		58.8		0.032

T-PEMF, transcranial pulsating electromagnetic fields.
No apathy: Diagnostic Apathia Scale < 11; Apathy: Diagnostic Apathia Scale ≥ 11.

Table 2. Remission rates among patients with and without apathia receiving T-PEMF once or twice daily during 8 weeks

	T-PEMF augmentation				
	One dose daily (n = 34)		Two doses daily (n = 31)		Total (n = 65)
Ham-$D_{17} < 8$*					
No apathy remission week 8	Yes	No	Yes	No	
	17	1	9	4	n = 31
% remission	94.4		69.2		
With apathy remission week 8	Yes	No	Yes	No	
	8	8	12	6	n = 34
% remission	50.0		66.7		
Ham-D6 < 5†					
No apathy remission week 8	Yes	No	Yes	No	
	12	6	6	7	n = 31
% remission	66.7		46.2		
With apathy remission week 8	Yes	No	Yes	No	
	6	10	13	5	n = 34
% remission	37.5		72.2		
MES Apathia Scale < 4‡					
No apathy remission week 8	Yes	No	Yes	No	
	10	8	4	9	n = 31
% remission	55.6		30.8		
With apathy remission week 8	Yes	No	Yes	No	
	5	11	11	7	n = 34
% remission	31.3		61.1		

HAM, Hamilton Depression Scale; MES, Bech-Rafaelsen Melancholia Scale; T-PEMF, transcranial pulsating electromagnetic fields.
No apathy: Diagnostic Apathia Scale < 11; Apathy: Diagnostic Apathia Scale ≥ 11.
* Logistic regression analysis: no apathy versus apathy, p = 0.033; one dose versus two doses, p = 0.338; interaction, p = 0.050.
† Logistic regression analysis: no apathy versus apathy, p = 0.929; one dose versus two doses, p = 0.556; interaction, p = 0.028.
‡ Logistic regression analysis: no apathy versus apathy, p = 0.812; one dose versus two doses, p = 0.845; interaction p = 0.031.

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press

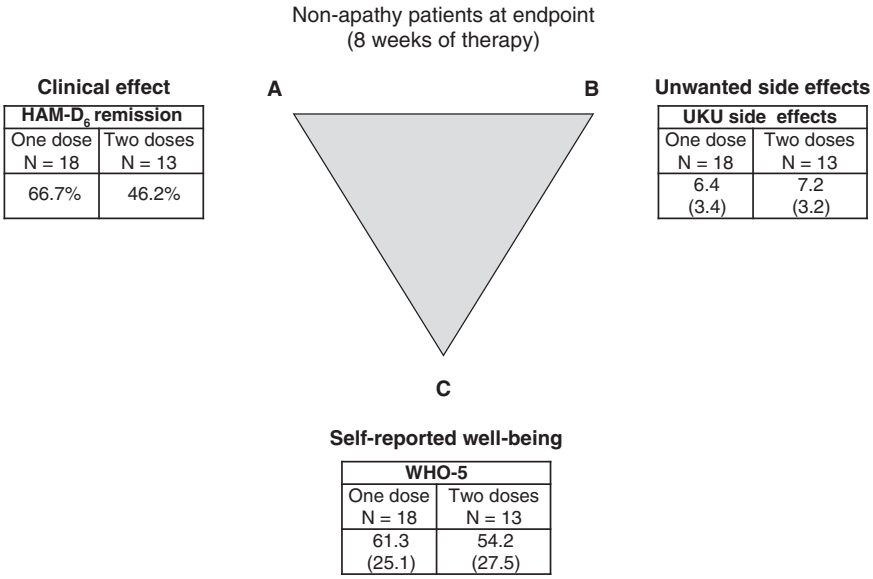

Fig. 2. The pharmacopsychometric triangle and transcranial pulsating electromagnetic fields (T-PEMF) dose relationship.

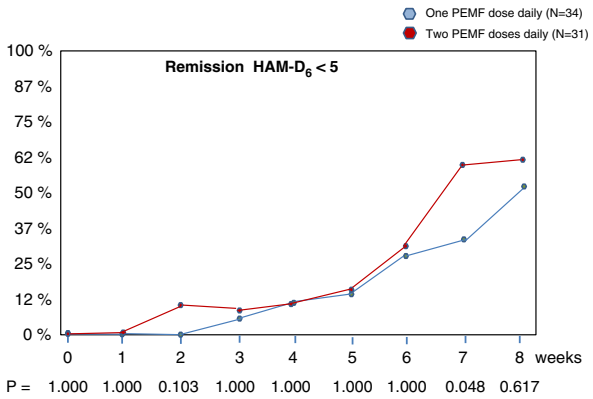

Fig. 3. The week-to-week remission (HAM-D_6) comparing one versus two T-PEMF doses.

diagnosis of apathy and the dose of T-PEMF. The remission rate for patients with apathy receiving T-PEMF in a dose once daily was ~30%, whereas it was 66% in those apathy patients who had received two doses daily (Table 2). Therefore, our answer to the fourth question is similar to our second and third.

The dose–remission pattern in Tables 2A–C seems to indicate that in patients without apathy two daily doses of T-PEMF flattened the remission rate. Because of this, Fig. 2 shows the pharmacopsychometric triangle in the group of patients without apathy at endpoint, that is, after 8 weeks of therapy. In this triangle, A indicates the clinical effect where we show the results from Table 2 concerning HAM-$D_6 < 5$ as criterion of remission. At B in the triangle, the corresponding UKU side-effect total score is indicated, showing a small tendency to a higher side-effect score in patients receiving two daily doses versus one daily dose. In an analysis of the individual UKU side-effect items, such items as concentration difficulties, nausea, and increased sweating were numerically but not statistically (p approximately 0.10) responsible for this tendency. At C in the triangle, the WHO-5 subjective quality of life score indicated a trend towards lower well-being in patients without apathy who received two daily doses versus one dose daily, but again without statistical significance.

In Fig. 3, we have shown the dose–remission relationship without reference to the apathy subsyndrome, using the HAM-D_6 remission criterion of 4 or less week by week throughout the trial. The dose–remission only obtains statistical significance at week 7 ($p = 0.0048$).

Discussion

The ability of the Diagnostic Apathia Scale to differentiate between remission rates after 8 weeks of T-PEMF augmentation using a cut-off score of 7 or less on the full HAM-D_{17} implies that apathy is an important subsyndrome in therapy-resistant depression, and clinically useful. The Apathy Evaluation Scale developed by Marin et al. (11) was designed to focus selectively on motivation items, for example, being interested in things, in persons, or in having new experiences. The apathy syndrome identified with the Diagnostic Apathia Scale covers not only the MINI item of lack of interests, but also the neuropsychological symptoms of concentration or memory problems, decision-making problems, ability to work, lack of energy or fatigue, and sleep problems.

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press

After this positive answer to our first research question, we investigated to what extent a T-PEMF dose–remission relationship was in operation, using three different criteria of remission after 8 weeks of therapy. No matter whether remission was defined by HAM-$D_{17} < 8$, HAM-$D_6 < 5$, or MES apathy subscale < 4, the logistic regression analysis indicated a statistically significant interaction between dose and remission ($p \leq 0.05$). Our answer to the remaining research question is therefore that in therapy-resistant depression without signs of apathy one T-PEMF dose daily for 8 weeks is optimal. However, patients with apathy need to have two T-PEMF doses daily for 8 weeks in order to obtain a remission rate of more than 50%.

We have shown that the E-fields cause activation of the Scr kinase (12), which in turn leads to mRNA upregulation and secretion of proteins, which lead to angiogenesis in animal models. Our working hypothesis is that secretion of growth factors from various cell types causes angiogenesis and activation of neurons and astrocytes and thus an enhanced neural plasticity, and leads to the reported remission by patients. Duration of treatment (30 min) was determined from biological data obtained from the time dependency of the Src kinase activation. This kinase becomes inactivated after 30 min in spite of continued stimulation with E-fields. Since our mode of action is based on secretion of growth factors and paracrine activation processes, which are limited by the Src kinase activity, we would assume that there is a limit to the effective daily dose. Further investigation is needed to clarify how T-PEMF treatment should be optimised, including the observation that in depressed patients without apathy the high dose of T-PEMF twice daily is inferior to only one dose daily.

In conclusion, we have demonstrated a dose–remission relationship of T-PEMF augmentation when taking the baseline diagnosis of the apathy syndrome into account. However, no statistically significant dose relationship concerning side-effects was seen as the level of T-PEMF-induced side-effects was very low.

Acknowledgements

Per Bech was involved in planning the study, methodological design as well as selection of rating instruments and supervision of rating procedures; responsible for the statistical analysis. Marianne Lunde was active in performing the patient ratings. Lise Lauritzen was involved in planning the study, methodological design, and performing patient ratings. Birgit Straasø was involved in planning the study, methodological design, and performing patient ratings. Lone Lindberg was involved in the supervision of use of T-PEMF device, including helping the patients in this respect throughout the study. Maj Vinberg was active in clarification of the theoretical part of the study and the recruitment of patients. Mogens Undén was active in clarification of the theoretical part of the study and the recruitment of patients. Lone Hellstrôm was active in the clarification of the concept of apathy and in the formulation of the Diagnostic Apathia Scale. Steen Dissing was involved in formulation of the scientific problem and the theoretical background of T-PEMF treatment and the actual T-PEMF device. Erik Roj Larsen was active in clarification of the theoretical part of the study and the recruitment of patients.

Financial Support

The T-PEMF-II study was financially supported by a grant from the Lundbeck Foundation (Grant R54-A5567).

Conflicts of Interest

Maj Vinberg has been consultant for Eli Lilly, Lundbeck A/S, AstraZeneca, and Servier. Steen Dissing is 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. The remaining authors have none to declare.

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. Martiny K, Lunde M, Bech P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. Biol Psychiatry 2010;**68**:163–169.
2. Straasø B, LauritZen L, Lunde M et al. Dose-remission of pulsating electromagnetic fields as augmentation in therapy-resistant depression: a randomized, double-blind controlled study. Acta Neuropsychiatrica 2014: doi:10.1017/neu.2014.5.
3. Frank E, Prien RF, Jarrett RB et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;**48**:851–855.

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press

4. 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.
5. Andreasson K, Liest V, Lunde M et al. Identifying patients with therapy-resistant depression by using factor analysis. Pharmacopsychiatry 2010;**43**:252–256.
6. Radakovic R, Abrahams S. Developing a new apathy measurement scale: Dimensional Apathy Scale. Psychiatry Research 2014;**219**:658–663.
7. Hellström LC, Eplov LF, Nordentoft M, Ostergaard SD, Bech P. The Apathia Scale predicts the ability to return to work. Acta Neuropsychiatrica 2014. doi:10.1017/neu.2014.23.
8. 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 Neuropsychiatr 2014;**26**:155–160.
9. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;**62**(Suppl. 16):10–17.
10. Bech P. The Bech-Rafaelsen Melancholia Scale (MES) in clinical trials of therapies in depressive disorders: a 20-year review of its use as outcome measure. Acta Psychiatr Scand 2002;**106**:252–264.
11. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 1991;**38**:143–162.
12. Rahbek 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.

https://doi.org/10.1017/neu.2014.26 Published online by Cambridge University Press