Journal of Affective Disorders xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression

Jarosław Sobiś [a,*], Magdalena Jarząb [a], Robert Teodor Hese [a], Aleksander Sieroń [b], Tomasz Zyss [c], Piotr Gorczyca [a], Zbigniew Gierlotka [a], Robert Pudlo [a], Jerzy Matysiakiewicz [a]

[a] Department of Psychiatry, Medical University of Silesia, Zabrze, Poland
[b] Department of Internal Diseases, Angiology and Physical Medicine, Medical University of Silesia, Bytom, Poland
[c] Department of Adult Psychiatry, Jagiellonian University Collegium Medicum, Kraków, Poland

ARTICLE INFO

Article history:
Received 11 March 2009
Received in revised form 23 September 2009
Accepted 23 September 2009
Available online xxxx

Keywords:
Weak variable magnetic fields
Drug-resistant depression
Therapy

ABSTRACT

Background: The aim of this prospective study was to verify whether magnetostimulation with weak variable magnetic fields with low value of induction could enhance the effects of pharmacological therapy in drug-resistant depression.
Materials and methods: Thirty patients, 26 women and 4 men, with drug-resistant depression were enrolled in the study. The subjects from Group No. I (14 patients) were given fluvoxamine and treated with weak variable magnetic field using the VIOFOR JPS device; the subjects from Group No. II (16 patients) were also given fluvoxamine but they were treated with the VIOFOR JPS device in placebo mode. Changes in depressive symptoms were estimated with the 21-point Hamilton Depression Scale (HDRS), Montgomery-Asberg Depression Scale (MADRS) and Beck Depression Inventory (BDI) questionnaire.
Results: After 15 days of treatment highly significant differences were revealed between the patients treated with magnetic field and the patients treated with placebo: the final HDRS score was 53% of the initial value for the group receiving combined treatment, and 86% in the placebo group ($p<0.001$); for MADRS score the values were 51% and 88% ($p<0.001$), respectively, and for BDI 60% and 87% ($p<0.001$). Thus, the average effect of placebo applied with fluvoxamine was a ca. 15% reduction of symptoms, while the concurrent application of magnetic field and SSRI treatment resulted in a 40–50% improvement.
Conclusion: Our study indicates that adding a two-week low-induction variable magnetic field stimulation to a classical pharmacologic therapy reduces the intensity of symptoms in patients with drug-resistant depressive disorders.

1. Introduction

Drug-resistant depressions make up 30% of all depressive disorders, with often unsatisfactory therapeutic effect. Therefore, different non-drug based approaches have been tested, with electroconvulsive therapy (ECT) being the most classic but also the most invasive approach. The use of magnetic field to modify brain activity seems a rational and less burdensome alternative (Carpenter, 2006). Recently, U.S. Food and Drug Administration has approved a device for transcranial magnetic field stimulation (TMS) in the treatment of drug-resistant depression (Repetitive transcranial magnetic stimulation (TMS), 2009). TMS uses strong magnetic fields, often with induction values of 0.5–2 T and repetition rate near 1 Hz (Lopez-Ibor et al., 2008). Optimally, strong magnetic field should be applied by neuronavigation-based approach, but there are some concerns about the feasibility of such procedures (Zyss, 2008).

However, numerous experimental data show that much weaker variable magnetic fields (1 nT–100 μT) may cause changes in the activity of the central nervous system and the behavior of experimental animals. This is the rationale for using

* Corresponding author. Department of Psychiatry, ul. Pyskowicka 49, 42-600 Tarnowskie Góry, Poland. Tel.: +48 322854273; fax: +48 322854358.
E-mail address: jaroslaw.sobis@poczta.onet.pl (J. Sobiś).

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doi:10.1016/j.jad.2009.09.016

weak magnetic fields (often referred to as magnetostimulation, and not to be confused with TMS) in the therapy of drug-resistant depression. One of the therapeutic approaches is to use weak magnetic fields with concomitant drug therapy.

The results of several clinical trials confirmed the potential therapeutic efficacy of magnetostimulation with weak variable magnetic field in the treatment of depressive symptoms in the course of sclerosis multiplex, Parkinson's disease and Alzheimer's disease (Sandyk, 1994a,b, 1995), and this method seems to be of benefit mainly due to its interference with brain function; other applications provide less satisfactory results (see e.g. Wrobel et al., 2008).

In this randomized prospective study we aimed to verify whether weak variable magnetic fields with low value of induction were able to enhance the effects of pharmacological treatment in drug-resistant depression.

2. Materials and methods

Patients (from Psychiatric Department, Medical University of Silesia), with confirmed drug-resistant depression, were prospectively recruited into the study. For the purposes of this investigation drug-resistant depression was defined as two unsuccessful courses of anti-depressive therapy, with at least two anti-depressive drugs from different groups, administered in relatively high doses for at least six weeks.

The study inclusion criteria were as follows:

1. Fulfillment of DSM-IV diagnostic criteria for Major Depressive Disorder, Recurrent (without psychotic symptoms).
2. Drug-resistant depression, as defined above.
3. The score of at least 18 points on the 21-point Hamilton Depression Scale.
4. Age between 18 and 65 years.

The exclusion criteria were as follows: cancer disease, active pulmonary tuberculosis or other severe infection, gastrointestinal tract bleeding, implanted electronic devices such as a pacemaker, a cardioverter-defibrillator, etc. and pregnancy.

The study protocol was approved by the Ethics Committee (Medical University of Silesia, Katowice, Poland). A written informed consent to participate in the study was obtained from the patients; all the procedures were carried out in accordance with the Declaration of Helsinki regulations.

The patients that fulfilled the criteria were randomly assigned into two study groups. The patients from Group No. I (12 women and 2 men) received fluvoxamine, a basic anti-depressive drug (150 mg daily; administration of the drug initiated 14 days before magnetostimulation, at 50 mg/day during week −2 and at 100 mg/day during week −1) and were subjected to magnetostimulation using the VIOFOR JPS device (Med & Life, Komorow, Poland) in active mode. The apparatus is a magnetic field generator, with adjustable magnetic field parameters and different accessory application devices; it also has the option to perform sham exposure (in placebo mode). During magnetostimulation the patient is lying down directly on an application mat. The frequency of basic impulses in the active mode ranged between 180–195 Hz, that of clustered impulses between 12.5–29 Hz, and that of thrustered impulses between 2.8–7.6 Hz and 0.08–0.3 Hz; with the saw tooth-like characteristic of the basic impulse curve. The exposure was carried out with the settings (M2 P2, intensity 6 degrees) corresponding to 15 μT effective induction of the magnetic field.

The patients were exposed to magnetostimulation (with the instrument in either active or placebo mode) once a day over a three-week period, Saturdays and Sundays excluded. Each patient underwent 15 exposures. A single magnetostimulation treatment session lasted 12 min.

In the Group No. II (14 women and 2 men) fluvoxamine was administered in the same regimen as in the Group No. I, but the patients were treated by the VIOFOR JPS device in the placebo mode, i.e. subjected to sham exposure, with no voltage applied to the clamps and no magnetic field generated by the application device (this difference in the operation mode of the apparatus is not perceived by the subject exposed).

The increase of depressive symptoms was estimated with the 21-point Hamilton Depression Scale (HDRS) and the Montgomery-Asberg Depression Scale (MADRS). Also, the patients estimated themselves with the Beck Depression Inventory (BDI) questionnaire. Assessments using these tests were carried out on day 0 and on days 7 and 15 of the exposure (Fig. 1).

The statistical analysis was performed using General Linear Model with repeated measures, using SPSS 13 (Statsoft Inc., Chicago, IL, USA). Additionally, the point values between both groups on a fixed day of observation were compared by Mann–Whitney U test. The results for both groups were shown as median and quartile values by box-and-whisker plot.

3. Results

The assessment of depressive symptoms was carried out at the initial visit (at the randomization) and then after 7 days and 15 days of treatment (Fig. 1). No differences in the depressive symptoms were concluded following a psychiatric evaluation prior to the treatment onset (not shown).

We used a general linear model to compare the repeated measures performed by all three tests applied (repeated measures ANOVA, separately for HDRS, MDRS, BDI) and compared the results between the groups of the magnetic field-treated, and sham-treated patients. We found a statistically significant difference in the results between the two tested groups in all three tests applied, with significant effects attributable to the treatment time and the applied magnetic field. The effect of the magnetic field was most pronounced in BDI (RM ANOVA $F=9.24$, $p<0.005$), highly significant for MADRS ($F=8.08$, $p=0.008$) and HDRS ($F=5.20$, $p=0.03$).

After 15 days of treatment a highly significant difference appears between the magnetic field-treated group and the group of patients treated with placebo: in the treated group the HDRS score and the BDI result were 40.64% and 38.98% lower, respectively, than in the group receiving placebo ($p<0.001$, Mann–Whitney U test); for MADRS score the difference was almost two-fold (45.98%, $p<0.001$).

The differences in the HDRS, MADRS or BDI scores were less pronounced after 7 days of treatment (p values for between-group comparisons were $p=0.19$, $p=0.28$, and $p=0.22$, respectively, Fig. 2, Mann–Whitney U test); for BDI score the median values were almost identical between the two groups.

In a longitudinal observation, there was a significant decrease in all three measures between time point 0 and 7 (Wilcoxon signed-rank test, $p<0.001$), most prominent in the

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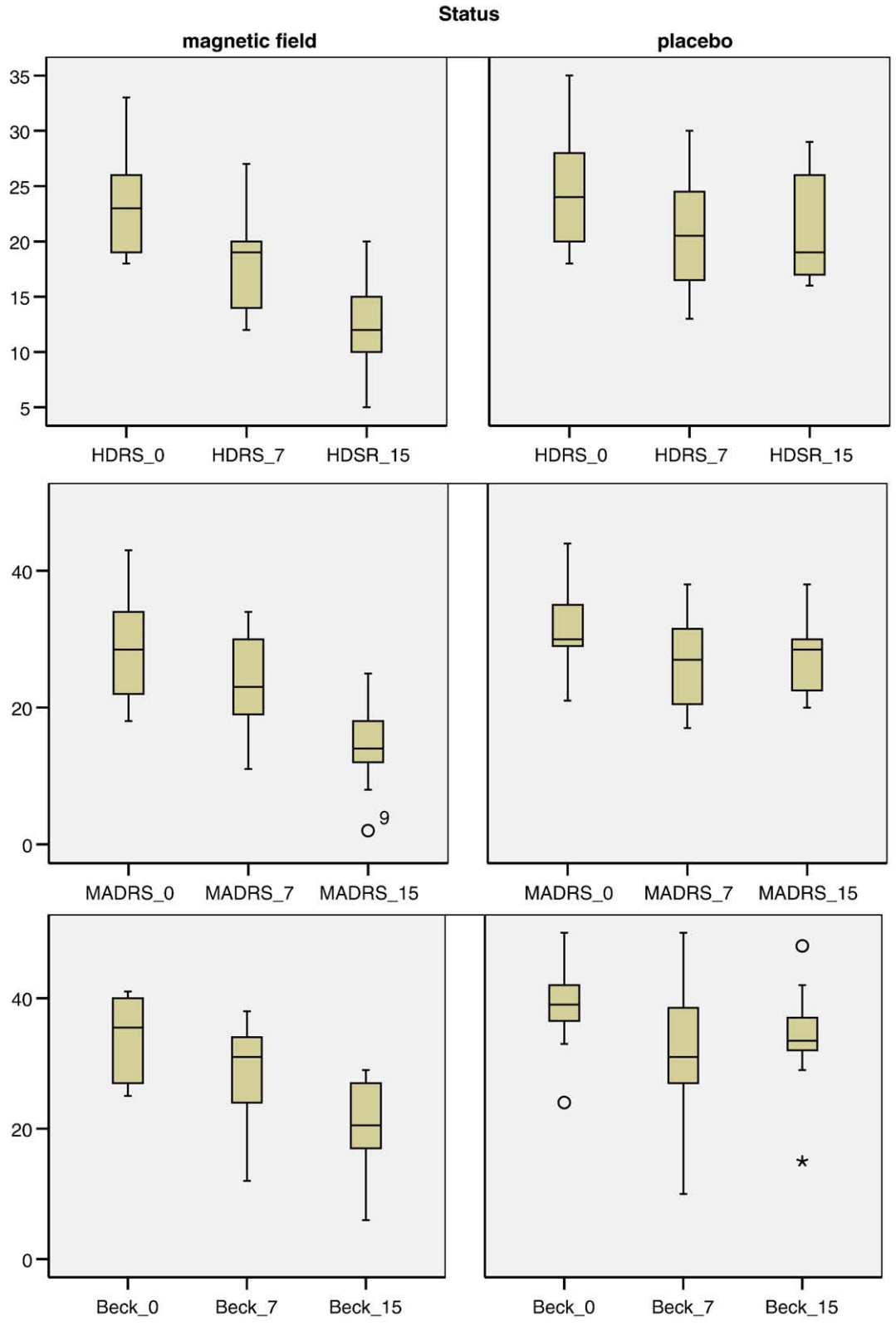

Fig. 1. Assessment of depressive symptoms on days 0, 7 and 15 in the magnetic field-treated group (left) and the placebo group (right). HDRS: Hamilton Depression Scale; MADRS: Montgomery-Asberg Depression Scale, BDI: Beck Depression Inventory.

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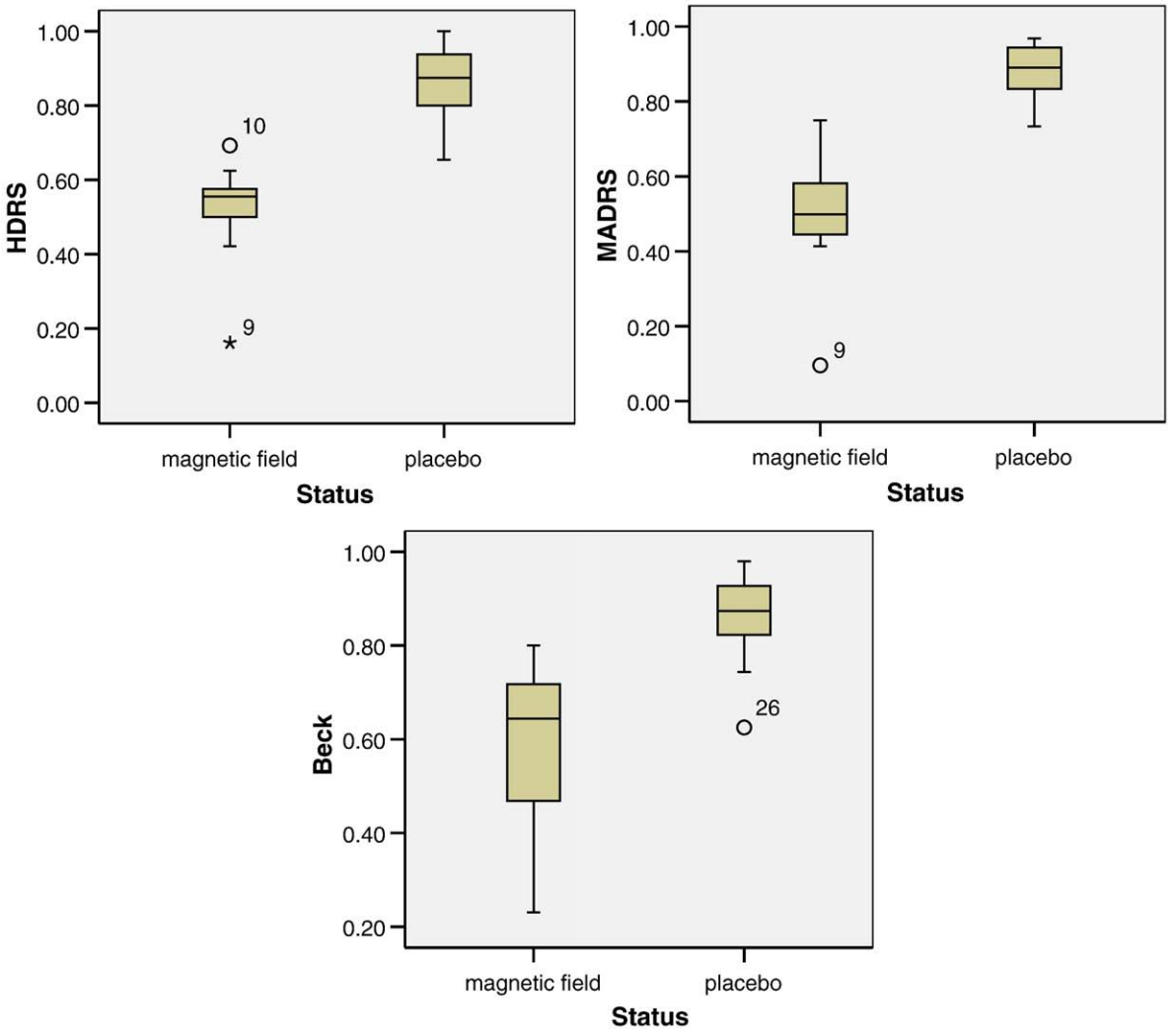

Fig. 2. Final results of the study: comparison between the magnetic field and the placebo groups using the applied depressive symptoms tests (see Materials and methods). Boxplots show the ratio of measurements done on day 15 vs. day 0. HDRS: Hamilton's Depression Scale; MADRS: Montgomery-Asberg Depression Scale, BDI: Beck Depression Inventory.

results of HDRS and BDI (HDRS: 21.45% and 14.57% reduction in the magnetic field and the placebo groups, respectively, BDI: 16.48% and 16.94% reduction in both groups, resp.). During further observations, we did not notice any significant reductions in any tests applied to the placebo group between time points 7 days and 15 days, while in the magnetic field treatment group there was a significant decrease in the depression symptoms within this time period. For the HDRS test in the magnetic field treatment group, we observed a 33.06% decrease ($p<0.001$) between day 7 and 15, similarly to the results of the MADRS assessment (35.70%).

We summarized the results obtained herein by calculating an index which compares the initial test result (at time point 0) to the result after the treatment (at the time point 15 days). The final HADRS score was 52.58% of the initial value in the treatment group, and 85.68% in the placebo group ($p<0.001$); for MADRS score the values were 51.64% and 87.95% ($p<0.001$), respectively, and for BDI score they were 60.40% and 86.73% ($p<0.001$). Thus, the average effect of placebo applied with fluvoxamine was a ca. 15% reduction of symptoms, while the concurrent application of the magnetic field and SSRI treatment resulted in a 40–50% improvement.

4. Discussion

We found out that the application of weak variable magnetic fields in the patients with drug-resistant depression resulted in a significant reduction of the depressive symptoms, most prominent after 15 days of therapy. The outcome in the patients treated by antidepressant alone was significantly worse than in the subjects exposed concurrently to magnetostimulation. A weak variable magnetic field applied with antidepressive therapy resulted in a 40–50% decrease of the depression symptoms.

It has been demonstrated that low-energy magnetic fields may influence the brain functions in both animals (Carlezon et al., 2005; Rudolph et al., 1985) and humans (Beale et al., 1997). The magnetic field in psychiatric therapy was a modality

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applied as a kind of neurostimulation (Carpenter, 2006), based on positive treatment results in various neurologic disorders (Sandyk, 1994a,b, 1995; Sherman et al., 1998). Therapeutic applications of weak magnetic fields, similar to the induction of natural Earth magnetic fields (30–70 μT) have been studied less thoroughly, compared to higher induction fields. The mechanism of action of the magnetic fields above 100 μT is well-understood: they influence functions of neural tissue, among other things the neuronal conductance and brain electrical activity (Lyskov et al., 1993). Magnetic fields exert also a behavioral effect, e.g. stimulate animal activity (Ossenkopp and Ossenkopp, 1983). Data regarding the influence of low-induction magnetic field on neural tissue are scarce; however, it has been shown that it may influence protein synthesis. The study of low frequency electromagnetic fields in cultured rat astrocytes revealed increased velocity of astrocyte microvesicles, interpreted as adaptation response to cellular stress (Golfert et al., 2001). Some patterns of magnetic fields simulating EEG rhythm were shown to facilitate memory performance and increase the release of neurotransmitters (NE, DA and 5-HT) in the hippocampus of the stimulated animals. Also, morphological changes in nerve synapses were noted (Wang et al., 2004).

In the clinical setting, the most extensive experience in the applications of magnetic fields has been gained thanks to transcranial magnetic stimulation (TMS) with the high induction fields (up to 2 T) applied in very short times (Eitan and Lerer, 2006; O'Reardon et al., 2005). This method has been assessed in several clinical trials and may lead to clinical benefits in the treatment of depression, especially in the therapy-resistant patients (Garcia-Toro et al., 2006; Fregni et al., 2006; Rossini et al., 2005a; Avery et al., 2008, 2007; O'Reardon et al., 2007; Stern et al., 2007; Brakemeier et al., 2008), and also it may show additive effects with the antidepressant treatment (Rossini et al., 2005b; Bretlau et al., 2008); the status of this method has been comprehensively reviewed by Janicak et al. (2008) In our study, we assessed in a similar setting, the therapeutic efficacy of the magnetic field with a low-induction value.

It has been stressed that the interactions between magnetic fields and receptor systems stimulated by pharmacologic agents could be as potent as chemical synergism (Whissell and Persinger, 2007). Fields with weak induction were suggested to exert the biological effect by modifying serotoninergic neurons function, stimulating the serotonin synaptic transmission. It has been demonstrated that magnetic field increases the turnover of monoaminergic system in the rat frontal cortex (Sieron et al., 2004). Desensitization of 5-HT1B following the exposure to 50 Hz 2.5 mT magnetic field has been observed and was suggested to be the primary mechanism of the beneficial effect of rTMS on depression (Massot et al., 2000). Other mechanisms, operating by beta-endorphins or substance P also may mediate the effects of low frequency fields, especially the analgesic effect (Bao et al., 2006; Zyss et al., 1999).

As the role and place for TMS in psychiatric therapy are widely discussed (see e.g. Marangell et al., 2007; Ebmeier and Herrmann, 2008; Shah et al., 2008; Rakofsky et al., 2009; Simpson et al., 2009), this could also spur interest in the low-induction magnetic field as an adjuvant therapy in managing patients with drug-resistant depressive symptoms. The preliminary results obtained in our study speak in favor of further exploring this therapeutic modality. In our study the benefit was obtained after a relatively short-time therapy, similarly to the results obtained in rTMS by certain groups (Dell'Osso et al., 2009). This confirms the potential utility of this method from the pharmacoeconomic point of view (Simpson et al., 2009).

The mechanisms by which weak induction magnetic fields act on the neural tissue are not fully understood (such mechanisms, in the case of magnetic fields above 100 μT have been studied far more extensively). It is thus difficult to formulate the criteria for choosing either a low or a high induction magnetic field for the clinical setting. Further research should focus on head-to-head comparison of both methods, with larger patient cohorts and appropriately managed, sham-treated control groups.

5. Conclusions

1. Adding variable weak magnetic field stimulation to classical pharmacologic therapy reduces the intensity of depression symptoms in patients with drug-resistant depressive disorders.
2. The degree of clinical improvement increases with duration of weak magnetic field therapy.
3. At least a two-week magnetostimulation therapy is necessary to obtain clinical benefits.

Role of funding source

Funding for this study was provided by Silesian Medical University; the University authorities had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

Prof. Aleksander Sieron is co-inventor of Viofor JPS instrument. All other authors declare that they have no conflicts of interest.

Acknowledgements

We gratefully acknowledge all the patients, who participated in this study. We thank Dr Aleksander Sochanik, Ph.D. for the thorough language revision of the manuscript.

References

Avery, D.H., Holtzheimer III, P.E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D.L., Haynor, D.R., Claypoole, K.H., Wajdik, C., Roy-Byrne, P., 2007. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. J. Nerv. Ment. Dis. 195 (5), 378–381.

Avery, D.H., Isenberg, K.E., Sampson, S.M., Janicak, P.G., Lisanby, S.H., Maixner, D.F., Loo, C., Thase, M.E., Demitrack, M.A., George, M.S., 2008. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. J. Clin. Psychiatry 69 (3), 441–451.

Bao, X., Shi, Y., Huo, X., Song, T., 2006. A possible involvement of beta-endorphin, substance P, and serotonin in rat analgesia induced by extremely low frequency magnetic field. Bioelectromagnetics 27 (6), 467–472.

Beale, I.L., Pearce, N.E., Conroy, D.M., Henning, M.A., Murrell, K.A., 1997. Psychological effects of chronic exposure to 50 Hz magnetic fields in humans living near extra-high-voltage transmission lines. Bioelectromagnetics 18 (8), 584–594.

Brakemeier, E.L., Wilbertz, G., Rodax, S., nker-Hopfe, H., Zinka, B., Zwanzger, P., Grossheinrich, N., Varkuti, B., Rupprecht, R., Bajbouj, M., Padberg, F., 2008. Patterns of response to repetitive transcranial magnetic stimulation (rTMS) in major depression: replication study in drug-free patients. J. Affect. Disord. 108 (1–2), 59–70.

Please cite this article as: Sobiś, J., et al., Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression, J. Affect. Disord. (2009), doi:10.1016/j.jad.2009.09.016

Bretlau, L.G., Lunde, M., Lindberg, L., Unden, M., Dissing, S., Bech, P., 2008. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. Pharmacopsychiatry 41 (2), 41–47.

Carlezon Jr., W.A., Rohan, M.L., Mague, S.D., Meloni, E.G., Parsegian, A., Cayetano, K., Tomasiewicz, H.C., Rouse, E.D., Cohen, B.M., Renshaw, P.F., 2005. Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats. Biol. Psychiatry 57 (6), 571–576.

Carpenter, L.L., 2006. Neurostimulation in resistant depression. J. Psychopharmacol. 20 (3 Suppl), 35–40.

Dell'Osso, B., Mundo, E., D'Urso, N., Pozzoli, S., Buoli, M., Ciabatti, M., Rosanova, M., Massimini, M., Bellina, V., Mariotti, M., Altamura, A.C., 2009. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. Bipolar Disord. 11 (1), 76–81.

Ebmeier, K.P., Herrmann, L.L., 2008. TMS—the beginning of the end or the end of the beginning? Psychol. Med. 38 (3), 319–321.

Eitan, R., Lerer, B., 2006. Nonpharmacological, somatic treatments of depression: electroconvulsive therapy and novel brain stimulation modalities. Dialogues Clin. Neurosci. 8 (2), 241–258.

Fregni, F., Marcolin, M.A., Myczkowski, M., Amiaz, R., Hasey, G., Rumi, D.O., Rosa, M., Rigonatti, S.P., Camprodon, J., Walpoth, M., Heaslip, J., Grunhaus, L., Hausmann, A., Pascual-Leone, A., 2006. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int. J. Neuropsychopharmacol. 9 (6), 641–654.

Garcia-Toro, M., Salva, J., Daumal, J., Andres, J., Romera, M., Lafau, O., Echevarria, M., Mestre, M., Bosch, C., Collado, C., Ibarra, O., Aguirre, I., 2006. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. Psychiatry Res. 146 (1), 53–57.

Golfert, F., Hofer, A., Thummler, M., Bauer, H., Funk, R.H., 2001. Extremely low frequency electromagnetic fields and heat shock can increase microvesicle motility in astrocytes. Bioelectromagnetics 22 (2), 71–78.

Janicak, P.G., O'Reardon, J.P., Sampson, S.M., Husain, M.M., Lisanby, S.H., Rado, J.T., Heart, K.L., Demitrack, M.A., 2008. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J. Clin. Psychiatry 69 (2), 222–232.

Lopez-Ibor, J.J., Lopez-Ibor, M.I., Pastrana, J.I., 2008. Transcranial magnetic stimulation. Curr. Opin. Psychiatry 21 (6), 640–644.

Lyskov, E.B., Juutilainen, J., Jousmaki, V., Partanen, J., Medvedev, S., Hanninen, O., 1993. Effects of 45-Hz magnetic fields on the functional state of the human brain. Bioelectromagnetics 14 (2), 87–95.

Marangell, L.B., Martinez, M., Jurdi, R.A., Zboyan, H., 2007. Neurostimulation therapies in depression: a review of new modalities. Acta Psychiatr. Scand. 116 (3), 174–181.

Massot, O., Grimaldi, B., Bailly, J.M., Kochanek, M., Deschamps, F., Lambrozo, J., Fillion, G., 2000. Magnetic field desensitizes 5-HT(1B) receptor in brain: pharmacological and functional studies. Brain Res. 858 (1), 143–150.

O'Reardon, J.P., Blumner, K.H., Peshek, A.D., Pradilla, R.R., Pimiento, P.C., 2005. Long-term maintenance therapy for major depressive disorder with rTMS. J. Clin. Psychiatry 66 (12), 1524–1528.

O'Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., McDonald, W.M., Avery, D., Fitzgerald, P.B., Loo, C., Demitrack, M.A., George, M.S., Sackeim, H.A., 2007. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry 62 (11), 1208–1216.

Ossenkopp, K.P., Ossenkopp, M.D., 1983. Geophysical variables and behavior: XI. Open-field behaviors in young rats exposed to an elf rotating magnetic field. Psychol. Rep. 52 (2), 343–349.

Rakofsky, J.J., Holtzheimer, P.E., Nemeroff, C.B., 2009. Emerging targets for antidepressant therapies. Curr. Opin. Chem. Biol. 3 (3), 291–302.

Repetitive transcranial magnetic stimulation (TMS) for medication-resistant depression: Med Lett Drugs Ther 2009; 51(1305):11–12.

Rossini, D., Lucca, A., Zanardi, R., Magri, L., Smeraldi, E., 2005a. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. Psychiatry Res. 137 (1–2), 1–10.

Rossini, D., Magri, L., Lucca, A., Giordani, S., Smeraldi, E., Zanardi, R., 2005b. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. J. Clin. Psychiatry 66 (12), 1569–1575.

Rudolph, K., Krauchi, K., Wirz-Justice, A., Feer, H., 1985. Weak 50-Hz electromagnetic fields activate rat open field behavior. Physiol. Behav. 35 (4), 505–508.

Sandyk, R., 1994a. The effects of external picotesla range magnetic fields on the EEG in Parkinson's disease: a follow up study. Int. J. Neurosci. 76 (3–4), 227–229.

Sandyk, R., 1994b. Alzheimer's disease: improvement of visual memory and visuoconstructive performance by treatment with picotesla range magnetic fields. Int. J. Neurosci. 76 (3–4), 185–225.

Sandyk, R., 1995. Long term beneficial effects of weak electromagnetic fields in multiple sclerosis. Int. J. Neurosci. 83 (1–2), 45–57.

Shah, D.B., Weaver, L., O'Reardon, J.P., 2008. Transcranial magnetic stimulation: a device intended for the psychiatrist's office, but what is its future clinical role? Expert Rev. Med. Devices 5 (5), 559–566.

Sherman, R.A., Robson, L., Marden, L.A., 1998. Initial exploration of pulsing electromagnetic fields for treatment of migraine. Headache 38 (3), 208–213.

Sieron, A., Labus, L., Nowak, P., Cieslar, G., Brus, H., Durczok, A., Zagzil, T., Kostrzewa, R.M., Brus, R., 2004. Alternating extremely low frequency magnetic field increases turnover of dopamine and serotonin in rat frontal cortex. Bioelectromagnetics 25 (6), 426–430.

Simpson, K.N., Welch, M.J., Kozel, F.A., Demitrack, M.A., Nahas, Z., 2009. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv. Ther. 26 (3), 346–368.

Stern, W.M., Tormos, J.M., Press, D.Z., Pearlman, C., Pascual-Leone, A., 2007. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. J. Neuropsychiatry Clin. Neurosci. 19 (2), 179–186.

Wang, M., Guo, M., Wang, X., Ma, S., Liu, B., 2004. Study on effect and mechanism of magnetic fields simulating EEG rhythm upon memory. Conf. Proc. IEEE Eng. Med. Biol. Soc. 6, 4451–4453.

Whissell, P.D., Persinger, M.A., 2007. Emerging synergisms between drugs and physiologically-patterned weak magnetic fields: implications for neuropharmacology and the human population in the twenty-first century. Curr. Neuropharmacol. 5 (4), 278–288.

Wrobel, M.P., Szymborska-Kajanek, A., Wystrychowski, G., Biniszkiewicz, T., Sieron-Stoltny, K., Sieron, A., Pierzchala, K., Grzeszczak, W., Strojek, K., 2008. Impact of low frequency pulsed magnetic fields on pain intensity, quality of life and sleep disturbances in patients with painful diabetic polyneuropathy. Diabetes Metab. 34 (4 Pt 1), 349–354.

Zyss, T., 2008. Magnetotherapy. Neuro Endocrinol. Lett. 29 (Suppl 1), 161–201.

Zyss, T., Mamczarz, J., Roman, A., Vetulani, J., 1999. Comparison of effectiveness of two schedules of rapid transcranial magnetic stimulation on enhancement of responsiveness to apomorphine. Pol. J. Pharmacol. 51 (4), 363–366.

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