

Depression

Neuroreport. 2005 Nov 7;16(16):1839-42.

Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study.

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Recently, repetitive transcranial magnetic stimulation has evolved as a potential therapeutic tool to interfere with brain changes associated with neurological and psychiatric diseases. Little is known about its mode of action, however. Here, we investigated effects of repetitive transcranial magnetic stimulation on spontaneous magnetoencephalographic activity in patients with major depression. Before treatment, depressed patients showed a significant increase in slow magnetoencephalographic activity (2-6 Hz) over the left prefrontal cortex, compared with healthy controls. This activity significantly decreased during 10 days of repetitive transcranial magnetic stimulation, paralleled by clinical improvement. We conclude that therapeutic repetitive transcranial magnetic stimulation effects can be mirrored by changes of spontaneous magnetoencephalographic activity.

Psychiatry Res. 2005 Nov 15;137(1-2):1-10. Epub 2005 Oct 12.

Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial.

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This 5-week, randomized, double-blind, placebo-controlled trial investigated the efficacy and tolerability of high frequency repetitive transcranial magnetic stimulation (rTMS) directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomly assigned to receive 10 daily applications of either real or sham

rTMS. Subjects assigned to receive active stimulation were divided into two further subgroups according to the intensity of stimulation: 80% vs. 100% of motor threshold (MT). At study completion, the response rates were 61.1% (n=11), 27.8% (n=5) and 6.2% (n=1) for the 100% MT group, 80% MT group and sham group, respectively. A significant difference (Pearson chi(2) test) was found between the 100% MT and sham groups, while the 80% MT group did not differ significantly from the sham group. Between the two active groups, a marginally significant difference was observed. Analysis of variance with repeated measures on Hamilton Depression Rating Scale scores revealed a significantly different decrease over time of depressive symptomatology among the three treatment groups. Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded, and on the whole the technique was well tolerated. The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients.

Prog Neuropsychopharmacol Biol Psychiatry. 2005 Oct 19; [Epub ahead of print]

A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): Therapeutic and cognitive effect in medication free unipolar depression during 4 weeks.

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BACKGROUND: Transcranial magnetic stimulation (TMS) has become a therapeutic tool in psychiatric diseases. **METHODOLOGY:** The objective was to evaluate the efficacy of TMS in unipolar depression: the percentage of responders (>50% HDRS reduction) and remission (HDRS score \leq 8, after four weeks of active TMS treatment in depressed patients free of any antidepressive agent versus placebo-TMS. **RESULTS:** 27 patients were randomized in two groups: rTMS (N=11) versus sham TMS (N=16). Statistical differences were detected between sham and TMS treated groups on remission (0/16 versus 4/11 $p=0.032$, 1/16 versus 6/11 0.028 and 1/16 versus 7/11 $p=0.011$ at day 14, day 21 and day 28, respectively) and on response (2/16 versus 5/11 at day 14 (NS), 2/16 versus 7/11 $p=0.0115$ at day 21 and 1/16 versus 7/11 ($p=0.025$) day 28, respectively, using the exact Fisher test). Significant differences were observed between day 1 versus day 8 ($p<0.01$), day 15, day 21 and day 28 ($p<0.001$) in TMS group and only versus day 21 ($p<0.01$) and day 28 ($p<0.05$) for the sham group. ANOVA comparison between TMS and sham groups was significant at day 14 and day 28 ($p<0.05$). **LIMITATIONS:** The few number of patients. **CONCLUSION:** Our study has shown an efficacy of right rTMS in free medication unipolar depression over a month. Nevertheless, number of patients included is limited and multicentric studies will be necessary to specify the antidepressive action of TMS.

Psychiatry Res. 2005 Nov 15;137(1-2):113-21. Epub 2005 Oct 11.

Chronic repetitive transcranial magnetic stimulation is antidepressant but not anxiolytic in rat models of anxiety and depression.

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Transcranial magnetic stimulation (TMS) has been proposed as a treatment for depression and anxiety disorders. While the antidepressant effect has been modelled in animals, there have been few attempts to examine a possible anxiolytic effect of repetitive TMS (rTMS) in animal models. We administered 18 days of rTMS to male Sprague-Dawley rats. On days 10 through 18, rats were tested in several anxiety models (social interaction, emergence, elevated plus-maze, and predator odor avoidance) and in the forced swim test. No group differences were apparent on any of the anxiety models, while TMS produced an antidepressant effect in the forced swim test. Interestingly, on day 1 of the forced swim test, the home cage control group displayed increased swimming behaviour compared with sham-treated animals, suggesting an observable level of stress may have accompanied sham treatment. The results from the forced swim test suggested that TMS had modest antidepressant properties, but it did not show anxiolytic properties in the models examined. The study also suggested that stress associated with handling should be taken into account in the interpretation of TMS studies in animals.

Curr Psychiatry Rep. 2005 Oct;7(5):381-90.

Transcranial magnetic stimulation for the treatment of depression in neurologic disorders.

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Depression is commonly associated with neurologic disorders. Although depression in neurologic conditions often is associated with a negative impact on quality of life, it frequently is poorly managed. Some factors, such as a multidrug regimen, lack of efficacy, and side effects of antidepressants may explain why depression is not adequately treated in patients with neurologic disorders. Therefore, this population needs new approaches for depression treatment, and repetitive transcranial magnetic stimulation (rTMS) may be one of them because it has been shown to be effective for the treatment of depression alone and depression in certain neurologic diseases such as Parkinson's disease and stroke. rTMS is a noninvasive, focal, and painless treatment associated with few, mild side effects. It may be effective in the treatment of neurologic diseases such as

Parkinson's disease, stroke, and epilepsy. In this paper, we discuss the potential risks and benefits of rTMS treatment for depression in Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. Lastly, a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in neurologic diseases is proposed.

J Psychiatr Res. 2005 Oct 28; [Epub ahead of print]

Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [(123)I] IBZM SPECT study.

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Though there is considerable evidence that prefrontal repetitive transcranial magnetic stimulation (rTMS) exerts antidepressant effects, the neurobiological action of rTMS in patients with depression is poorly understood. Preclinical studies in animals and humans have demonstrated that prefrontal rTMS can induce dopamine release in mesostriatal and mesolimbic regions. We therefore investigated whether rTMS also modulates striatal dopaminergic neurotransmission in depressed patients using a dynamic [(123)I] iodobenzamide (IBZM) single photon emission computed tomography (SPECT) approach. Five patients with a major depressive episode (DSM-IV) underwent an acute 10Hz rTMS challenge with 3000 stimuli over the left dorsolateral prefrontal cortex during an [(123)I] IBZM-SPECT bolus and constant infusion protocol. In four subjects the protocol was repeated after a three week rTMS standard treatment. Striatal IBZM binding to dopamine D(2) receptors was assessed with a region-of-interest (ROI) technique. The change in striatal IBZM binding after the rTMS challenge was regarded as measure of change in endogenous striatal dopamine. Data of nine SPECT investigations showed a significant reduction by 9.6+/-6.2% in IBZM binding to striatal dopamine D(2) receptors after rTMS challenge compared to baseline (p=0.01, Wilcoxon test). In this preliminary study, the reduction of IBZM binding observed after rTMS challenge is suggestive of a release in endogenous dopamine induced by prefrontal rTMS. In future, this approach can be used to differentiate specific and non-specific reward-related effects of rTMS on dopaminergic neurotransmission.

Biol Psychiatry. 2005 Mar 15;57(6):571-6.

Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats.

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BACKGROUND: Evidence suggests that a novel type of magnetic resonance imaging (MRI) scan called echo planar magnetic resonance spectroscopic imaging (EP-MRSI) has mood-elevating actions in humans during the depressive phases of bipolar disorder. We examined whether a low-energy component of EP-MRSI (low-field magnetic stimulation [LFMS]) has antidepressant-like, locomotor-stimulating, or amnesic effects in rats. **METHODS:** We examined the effects of LFMS on immobility in the forced swim test (FST) and activity within an open field in separate groups of rats. After exposure to forced swimming, rats received LFMS (three 20-min sessions at 1.5 G/cm and .75 V/m) before behavioral testing. We also examined the effects of LFMS on fear conditioning (FC), a learning paradigm that also involves exposure to stressful conditions. **RESULTS:** Low-field magnetic stimulation reduced immobility in the FST, an antidepressant-like effect qualitatively similar to that of standard antidepressants. Low-field magnetic stimulation did not alter locomotor activity or FC. **CONCLUSIONS:** Low-field magnetic stimulation has antidepressant-like effects in rats that seem unrelated to locomotor-activating or amnesic effects. These findings raise the possibility that electromagnetic fields can affect the brain biology and might have physiologic consequences that offer novel approaches to therapy for psychiatric disorders. These same consequences might render MRI-based scans more invasive than previously appreciated.

Rev Med Suisse. 2005 Sep 21;1(33):2162-4, 2166.

[Novel brain stimulation techniques: therapeutic perspectives in psychiatry]

[Article in French]

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Recent advances have allowed the development of new physical techniques in neurology and psychiatry, such as Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), and Deep Brain Stimulation (DBS). These techniques are already recognized as therapeutic approaches in several late stage refractory neurological disorders (Parkinson's disease, tremor, epilepsy), and currently investigated in psychiatric conditions, refractory to medical treatment (obsessive-compulsive disorder, resistant major depression). In Paralell, these new techniques offer a new window to understand the neurobiology of human behavior.

Curr Psychiatry Rep. 2005 Oct;7(5):381-90.

Transcranial magnetic stimulation for the treatment of depression in neurologic disorders.

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Depression is commonly associated with neurologic disorders. Although depression in neurologic conditions often is associated with a negative impact on quality of life, it frequently is poorly managed. Some factors, such as a multidrug regimen, lack of efficacy, and side effects of antidepressants may explain why depression is not adequately treated in patients with neurologic disorders. Therefore, this population needs new approaches for depression treatment, and repetitive transcranial magnetic stimulation (rTMS) may be one of them because it has been shown to be effective for the treatment of depression alone and depression in certain neurologic diseases such as Parkinson's disease and stroke. rTMS is a noninvasive, focal, and painless treatment associated with few, mild side effects. It may be effective in the treatment of neurologic diseases such as Parkinson's disease, stroke, and epilepsy. In this paper, we discuss the potential risks and benefits of rTMS treatment for depression in Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. Lastly, a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in neurologic diseases is proposed.

Exp Neurol. 2005 Sep 26; [Epub ahead of print]

Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex and cortical excitability in patients with major depressive disorder.

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Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex is a relatively non-invasive technique with putative therapeutic effects in major depression. However, the exact neurophysiological basis of these effects needs further clarification. Therefore, we studied the impact of ten daily sessions of left, dorsolateral prefrontal rTMS on motor cortical excitability, as revealed by transcranial magnetic stimulation-elicited motor-evoked potentials in 30 patients. As compared to the non-responders, responders (33%) showed changes in parameters pointing towards a reduced cortical excitability. These results suggest that repetitive transcranial magnetic stimulation of the dorsolateral, prefrontal cortex may have inhibitory effects on motor

cortical neuronal excitability in patients with major depressive disorder. Furthermore, measurement of motor cortical excitability may be a useful tool for investigating and monitoring inhibitory brain effects of antidepressant stimulation techniques like rTMS.

Epilepsy Behav. 2005 Sep;7(2):182-9.

Transcranial magnetic stimulation treatment for epilepsy: can it also improve depression and vice versa?

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Comorbidity with depression is an important determinant of the quality of life for patients with epilepsy. Antidepressant medications can effectively treat depression in epileptic patients, but drug-drug interactions and epileptogenic effects of these drugs pose therapeutic challenges. The mood-stabilizing effects of antiepileptic medications may not be sufficient to treat depression. Therefore, treatments that alleviate the burden of depression without increasing seizure risk or, better yet, with the possibility of improving seizure control are worth exploring. Neuroimaging techniques, such as functional magnetic resonance imaging, are providing novel insights into the pathophysiology of depression in epilepsy. For example, there appears to be prominent brain prefrontal hypoactivity, which may be sustained by the hyperactivity of the seizure focus. If so, neuromodulatory approaches that suppress epileptic focus hyperactivity and concurrently enhance prefrontal activity may be ideally suited. Indeed, vagus nerve stimulation has been shown to yield simultaneous antiseizure and mood effects. Another neuromodulatory technique, transcranial magnetic stimulation (TMS), can also modulate brain activity, but in a noninvasive, painless, and focal manner. Depending on the stimulation parameters, it is possible to enhance or reduce activity in the targeted brain region. Furthermore, TMS has been shown to be effective in treating depression, and preliminary data suggest that this treatment may also be effective for epilepsy treatment. This article reviews these data and explores further the question of whether depression and epilepsy can be simultaneously treated with TMS for optimal therapeutic impact.

J Affect Disord. 2005 Nov;88(3):255-67. Epub 2005 Sep 2.

A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy.

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BACKGROUND: There is a growing interest in extending the use of repetitive transcranial magnetic stimulation (rTMS) beyond research centres to the widespread clinical treatment of depression. Thus it is timely to critically review the evidence for the efficacy of rTMS as an antidepressant treatment. Factors relevant to the efficacy of rTMS are discussed along with the implications of these for the further optimization of rTMS. **METHOD:** Clinical trials of the efficacy of rTMS in depressed subjects are summarized and reviewed, focusing mainly on sham-controlled studies and meta-analyses published to date. **RESULTS:** There is a fairly consistent statistical evidence for the superiority of rTMS over a sham control, though the degree of clinical improvement is not large. However, this data is derived mainly from two-week comparisons of rTMS versus sham, and evidence suggests greater efficacy with longer treatment courses. Studies so far have also varied greatly in approaches to rTMS stimulation (with respect to stimulation site, stimulus parameters etc) with little empirical evidence to inform on the relative merits of these approaches. **LIMITATIONS:** Only studies published in English were reviewed. Many of the studies in the literature had small sample sizes and different methodologies, making comparisons between studies difficult. **CONCLUSIONS:** Current published studies and meta-analyses have evaluated the efficacy of rTMS as given in treatment paradigms that are almost certainly suboptimal (e.g. of two weeks' duration). While the data nevertheless supports positive outcomes for rTMS, there is much scope for the further refinement and development of rTMS as an antidepressant treatment. Ongoing research is critical for optimizing the efficacy of rTMS.

Neuro Endocrinol Lett. 2005 Aug 30;26(4) [Epub ahead of print]

Repetitive transcranial magnetic stimulation in a patient suffering from depression and rheumatoid arthritis: Evidence for immunomodulatory effects.

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Repetitive transcranial magnetic stimulation (rTMS) has been suggested as antidepressive treatment strategy [1]. The mechanism of action by which the antidepressive effect is brought about remains unclear at present. Here, we report findings in a patient suffering from recurrent major depression and rheumatoid arthritis. Improvement of depressive symptoms during 20 Hz rTMS of the left dorsolateral prefrontal cortex was repeatedly associated with a systemic inflammatory reaction, suggesting that rTMS induced an immunomodulatory effect.

Psychiatry Clin Neurosci. 2005 Aug;59(4):425-32.

Clinical application of single-pulse transcranial magnetic stimulation for

the treatment of depression.

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Transcranial magnetic stimulation (TMS) has been recently suggested for the treatment of patients with major depression. Based on the results of the authors' pilot study showing a possible antidepressive effect of single-pulse TMS, a clinical trial was conducted involving patients with major depression. For the present study single-photon emission computed tomography (SPECT) was recorded for six of the target patients to study the effects of TMS on the local blood flow volume. Twenty-three inpatients meeting the Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV) criteria for major depression were invited to participate in the study. Depressive symptoms were rated using the Hamilton Rating Scale for Depression (HAM-D). Patients were given 10 stimuli over the frontal area of both sides for a total of 20 stimuli in a session. The subjects had daily TMS session for 5 days as an add-on therapy. In addition, six patients had their quantitative (99m)Tc-ethyl cysteinate dimer SPECT images measured before and after TMS treatment. Compared with the value 2 days prior to the start of TMS therapy (24.2 +/- 4.9), the average HAM-D scale dropped significantly to 15.3 +/- 6.6 on the day after completion of such therapy. The results of SPECT showed that the regional cerebral blood flow (rCBF) of the bilateral frontal region had increased in four out of six patients when comparing before and after treatment. The present study shows that single-pulse TMS, which is widely used as a neurological test method, possesses a wide range of antidepressive effects without inducing adverse reactions. The results suggest that although repetitive TMS is steadily becoming the mainstay technique today, single-pulse TMS also possesses sufficient antidepressive effects.

Seizure. 2005 Sep;14(6):387-92.

Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy-a pilot study.

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We evaluated the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on seizure frequency in adult patients with medically intractable extratemporal lobe epilepsy (ETLE). Seven patients with medically intractable ETLE received low-frequency rTMS at 0.9 Hz, basically two sets of 15 min stimulation per day for five days in a week, with the stimulus intensity of 90% of resting motor threshold (RMT). The number of seizures during two weeks before and after the stimulation of one week was

compared. Furthermore, RMT and active motor threshold (AMT) were measured before and after rTMS for each daily session. After low-frequency rTMS of one week, the frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures was reduced by 19.1, 35.9 and 7.4%, respectively. The patients with smaller difference between RMT and AMT before rTMS had higher reduction rate of CPSs. A favorable tendency of seizure reduction, though not statistically significant, during two weeks after low-frequency rTMS was demonstrated in medically intractable ETLLE patients. As far as CPSs are concerned, smaller decrease of motor threshold by voluntary muscle contraction was associated with better response to rTMS.

Transcranial magnetic stimulation in persons younger than the age of 18.

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OBJECTIVES: To review the use of transcranial magnetic stimulation (single-pulse TMS, paired TMS, and repetitive TMS [rTMS]) in persons younger than the age of 18 years. I discuss the technical differences, as well as the diagnostic, therapeutic, and psychiatric uses of TMS/rTMS in this age group. **METHODS:** I evaluated English-language studies from 1993 to August 2004 on nonconvulsive single-pulse, paired, and rTMS that supported a possible role for the use of TMS in persons younger than 18. Articles reviewed were retrieved from the MEDLINE database and Clinical Scientific index. **RESULTS:** The 48 studies reviewed involved a total of 1034 children ages 2 weeks to 18 years; 35 of the studies used single-pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). Three studies used both single and rTMS. However, the number of subjects involved was not reported. **CONCLUSIONS:** Single-pulse TMS, paired TMS, and rTMS in persons younger than 18 has been used to examine the maturation/activity of the neurons of various central nervous system tracts, plasticity of neurons in epilepsy, other aspects of epilepsy, multiple sclerosis, myoclonus, transcallosal inhibition, and motor cortex functioning with no reported seizure risk. rTMS has been applied to psychiatric disorders such as ADHD, ADHD with Tourette's, and depression. Adult studies support an antidepressant effect from repetitive TMS, but there is only one study that has been reported on 7 patients that used rTMS to the left dorsal prefrontal cortex on children/adolescents with depression (5 of the 7 subjects treated responded). Although there are limited studies using rTMS (in 34 children), these studies did not report significant adverse effects or seizures. Repetitive TMS safety, ethical, and neurotoxicity concerns also are discussed.

Neuron. 2005 Jan 20;45(2):181-3.

Toward establishing a therapeutic window for rTMS by theta burst stimulation.

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In this issue of Neuron, Huang et al. show that a version of the classic theta burst stimulation protocol used to induce LTP/LTD in brain slices can be adapted to a transcranial magnetic stimulation (TMS) protocol to rapidly produce long lasting (up to an hour), reversible effects on motor cortex physiology and behavior. These results may have important implications for the development of clinical applications of rTMS in the treatment of depression, epilepsy, Parkinson's, and other diseases.

Psychiatry Res. 2005 Oct 10; [Epub ahead of print]

Chronic repetitive transcranial magnetic stimulation is antidepressant but not anxiolytic in rat models of anxiety and depression.

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Transcranial magnetic stimulation (TMS) has been proposed as a treatment for depression and anxiety disorders. While the antidepressant effect has been modelled in animals, there have been few attempts to examine a possible anxiolytic effect of repetitive TMS (rTMS) in animal models. We administered 18 days of rTMS to male Sprague-Dawley rats. On days 10 through 18, rats were tested in several anxiety models (social interaction, emergence, elevated plus-maze, and predator odor avoidance) and in the forced swim test. No group differences were apparent on any of the anxiety models, while TMS produced an antidepressant effect in the forced swim test. Interestingly, on day 1 of the forced swim test, the home cage control group displayed increased swimming behaviour compared with sham-treated animals, suggesting an observable level of stress may have accompanied sham treatment. The results from the forced swim test suggested that TMS had modest antidepressant properties, but it did not show anxiolytic properties in the models examined. The study also suggested that stress associated with handling should be taken into account in the interpretation of TMS studies in animals.

Psychiatr Pol. 2004 Mar-Apr;38(2):217-25.

[Estimation of therapeutical efficacy of weak variable magnetic fields with low value of induction in patients with depression]

[Article in Polish]

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AIM: Preliminary results of research on the therapeutical efficacy of weak variable magnetic fields with low value of induction used as magnetostimulation in patients with depression not reacting to two consecutive, correctly applied anti-depressant pharmacological treatment are presented in the paper. **METHOD:** The examined patients (24 persons aged 18-65 years) treated with anti-depressants accessible in Poland were randomly divided into 2 groups. In 1 group (11 persons--9 women and 2 men) magnetostimulation with the use of a weak variable magnetic field with a low value of induction of 15 microT generated by the VIOFOR JPS device (Poland) lasting 12 minutes daily for 15 days was added to pharmacological therapy. Patients from 2 groups (13 persons--11 women and 2 men) were exposed to exposure with the same device. The intensity of depression was estimated with Beck's, Montgomery-Asberg's and Hamilton's scales. **RESULTS:** As a result of a cycle of active magnetostimulation a distinct, statistically significant decrease of intensification of depression, both in the 7th and 15th day exposure was obtained, while in the sham-exposed group only slight, transient decrease of intensification of depression in the 7th day of sham-exposure was observed. **CONCLUSIONS:** It was concluded that adding magnetostimulation to pharmacological therapy results in a progressive, significant reduction of intensification of depression symptoms.

Psychiatry Res. 2005 Oct 11; [Epub ahead of print]

Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial.

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This 5-week, randomized, double-blind, placebo-controlled trial investigated the efficacy and tolerability of high frequency repetitive transcranial magnetic stimulation (rTMS) directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomly assigned to receive 10 daily applications of either real or sham rTMS. Subjects assigned to receive active stimulation were divided into two further subgroups according to the intensity of stimulation: 80% vs. 100% of motor threshold (MT). At study completion, the response rates were 61.1% (n=11), 27.8% (n=5) and 6.2% (n=1) for the 100% MT group, 80% MT group and sham group, respectively. A significant difference (Pearson chi(2) test) was found between the 100% MT and sham groups, while the 80% MT group did not differ significantly from the sham group.

Between the two active groups, a marginally significant difference was observed. Analysis of variance with repeated measures on Hamilton Depression Rating Scale scores revealed a significantly different decrease over time of depressive symptomatology among the three treatment groups. Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded, and on the whole the technique was well tolerated. The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients.

Bipolar Disord. 2005;7 Suppl 5:13-23.

Newer treatment studies for bipolar depression.

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Objective: Depressive symptoms of bipolar disorder have more negative impact on a patient's life than manic symptoms. This review focused on the emerging efficacy data for treatments in bipolar depression. Methods: English-language literature cited in Medline was searched with terms bipolar depression, clinical trial, and trial. Randomized, placebo-controlled trials of newer studies with older agents and all studies with newer or novel agents were prioritized. Open-label studies of novel agents presented at major scientific meetings were also included. Results: Olanzapine, olanzapine-fluoxetine combination (OFC), and quetiapine were superior to placebo in the acute treatment of bipolar depression. Lamotrigine only significantly reduced core symptoms of depression compared with placebo. Pramipexole, a dopamine D2/D3 receptor agonist and omega-3 fatty acids, a polyunsaturated fatty acid, augmentation to mood stabilizer (MS) had superiority to placebo in reducing depressive symptoms. Topiramate augmentation of an MS was equally as effective as Bupropion-SR. Patients treated with an MS responded well to the addition of agomelatine, a melatonin receptor agonist with 5-HT_{2C} antagonist properties. However, inositol and repetitive transcranial magnetic stimulation did not separate from placebo. Lamotrigine and olanzapine, and to a lesser extent, divalproex, are superior to placebo in preventing depressive relapses. All agents were relatively well tolerated. Conclusions: Olanzapine, OFC, and quetiapine are effective in the acute treatment of bipolar depression. Compared with lithium and divalproex, lamotrigine is more effective in preventing bipolar depression. Larger controlled studies of the other agents in the acute and maintenance treatment of bipolar depression are warranted.

Zh Nevrol Psikhiatr Im S S Korsakova. 1999;99(10):26-9.

[Transcranial magnetic stimulation in neurotic depression]

[Article in Russian]

[Stikhina NIa](#), [Lyskov EB](#), [Lomarev MP](#), [Aleksanian ZA](#), [Mikhailov VO](#), [Medvedev SV](#).

Transcranial magnetic stimulation (TMS) was applied in combination with psychotherapy in patients with neurotic depression, including 15 patients of the experimental group and 14 patients of the control one. 10 sessions of daily TMS for the patients from the experimental group (0.015 T, 40 pulses per sec) were performed at the same time for 20 min (twice for 10 min with 5-min interval) in a room which excluded any external stimulation. TMS was performed by contact method: 5 cm coil was applied to the left prefrontal area. The control group received the imitation of TMS-procedure stimulation. The improvement of mental state was in 13 patients of experimental group and in 3 of control one. The course of TMS resulted in a significant attenuation of depression by the Hamilton Depression Rating scale (from 22.9 to 8.6) and the Anxiety Inventory (from 39.4 to 26.6), that was significantly higher in comparison with the control. There weren't found any TMS-related changes in blood pressure and pulse rate as well as any pathological EEG symptoms.

Biomed Sci Instrum. 2003;39:466-70.

Autoradiographic evaluation of electromagnetic field effects on serotonin (5HT1A) receptors in rat brain.

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Serotonin (5HT1A) is a chemical mediator of inflammation and the largest single neurotransmitter system of the brain. Its secretion and physiological actions mediate stress and pain, affecting both immune and nervous system functions through the hypothalamic-pituitary-adrenal axis. Serotonin receptor dysfunction is well-characterized in mental disturbances like depression and anxiety. Transcranial magnetic stimulation has been used therapeutically to treat refractory disorders like non-responsive depression and may act in part through its effect on 5HT1A receptors. Previously we have shown that in vitro, 5HT1A receptor binding to a radioactive agonist can be modulated by specific intensity and frequency electromagnetic fields (EMFs). In the present report we have used quantitative receptor autoradiography to evaluate 5HT1A receptor density in rat brain and the impact of pulsed EMF exposure on receptor binding in key brain regions. Rats used in this study had whole body exposures to either a geofield control or to pulsed EMFs to evaluate the treatment for chemically-induced tendinitis. Since the brains were exposed coincidentally as a consequence of the main experiment, we investigated the potential for EMF-induced changes in areas such as the hippocampus. This pilot study should provide a detailed understanding of magnetic field effects on stress-responsive brain regions and will lead to a more coordinated approach to the use of such modalities for therapeutic intervention in humans.

Fortschr Neurol Psychiatr. 2001 Sep;69(9):402-9.

[Which patients with major depression benefit from prefrontal repetitive magnetic stimulation]

[Article in German]

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Antidepressive benefit of prefrontal repetitive magnetic stimulation (RTMS) for one or two weeks varies between 6 % and 60 % (mean 37 %) improvement of the Hamilton depression scale vs. 12 % improvement following sham RTMS. This variance is probably caused by study specific stimulus parameters but also by genetic, psychopathological and neuropsychological characteristics of the patients as well as by the functional state of the cortex area below the stimulation coil. Data from 10 open and 7 sham controlled studies including two own studies comprising more than 300 patients with major depression have been published to date. In synopsis several positive predictors for antidepressive response of prefrontal RTMS become apparent: 1) younger age, 2) somatic signs of anxiety, 3) lack of cortical hyperactivity below the magnetic coil pulsed by 10 Hz stimuli, 4) cortical hypermetabolism below the 1 Hz pulsed coil. Negative predictors of response to prefrontal RTMS were: 1) Advanced age, 2) prefrontal atrophy, 3) cognitive impairment in neuropsychological tasks assigned to the prefrontal cortex, 4) psychotic symptoms, 5) cortical hyperactivity below 10 Hz pulsed coil 6) non-response to electroconvulsive therapy (ECT). While prefrontal RTMS will probably not replace ECT in severe major depression with psychotic symptoms it could be beneficial especially in younger anxious patients without cognitive impairment.

Nord J Psychiatry. 2003;57(3):227-32.

Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence.

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Repetitive transcranial magnetic stimulation (rTMS) is a novel treatment in psychiatry. We reviewed all published evidence on the efficacy of this treatment option in depressive disorders. An extensive electronic and manual search for eligible research reports identified only 12 studies that met the predetermined criteria for inclusion. rTMS was administered differently in most studies, and patient characteristics varied widely. A formal meta-analysis of the studies was thus not possible. Instead, we conducted a

qualitative evaluation of the included studies. The antidepressive efficacy was not consistent, and where efficacy was demonstrated, it was modest in most studies. Some patients had good but transient responses to rTMS. Treatment gains were not maintained beyond the treatment period. Comparisons with electroconvulsive therapy (ECT) indicated the superiority of ECT. More, larger and more carefully designed studies are needed to demonstrate convincingly a clinically relevant effect of rTMS. We conclude that there is insufficient evidence for rTMS as a valid treatment for depression at present.

Int J Neurosci. 1996 Oct;87(1-2):5-15.

Suicidal behavior is attenuated in patients with multiple sclerosis by treatment with electromagnetic fields.

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A marked decrease in the levels of serotonin (5-HT) and its metabolite (5-HIAA) has been demonstrated in postmortem studies of suicide victims with various psychiatric disorders. Depression is the most common mental manifestation of multiple sclerosis (MS) which accounts for the high incidence of suicide in this disease. CSF 5-HIAA concentrations are reduced in MS patients and nocturnal plasma melatonin levels were found to be lower in suicidal than in nonsuicidal patients. These findings suggest that the increased risk of suicide in MS patients may be related to decreased 5-HT functions and blunted circadian melatonin secretion. Previous studies have demonstrated that extracerebral applications of pulsed electromagnetic fields (EMFs) in the picotesla range rapidly improved motor, sensory, affective and cognitive deficits in MS. Augmentation of cerebral 5-HT synthesis and resynchronization of circadian melatonin secretion has been suggested as a key mechanism by which these EMFs improved symptoms of the disease. Therefore, the prediction was made that this treatment modality would result in attenuation of suicidal behavior in MS patients. The present report concerns three women with remitting-progressive MS who exhibited suicidal behavior during the course of their illness. All patients had frequent suicidal thoughts over several years and experienced resolution of suicidal behavior within several weeks after introduction of EMFs treatment with no recurrence of symptoms during a follow-up of months to 3.5 years. These findings demonstrate that in MS pulsed applications of picotesla level EMFs improve mental depression and may reduce the risk of suicide by a mechanism involving the augmentation of 5-HT neurotransmission and resynchronization of circadian melatonin secretion.

Percept Mot Skills. 1996 Oct;83(2):491-8.

Weak, but complex pulsed magnetic fields may reduce depression following traumatic brain injury.

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Many patients who display psychological depression following a traumatic brain injury do not respond completely to antidepressant drugs. We hypothesized that this type of depression is strongly correlated with subclinical, complex partial seizure-activity within the hippocampal-amygdaloid region that continues for months to years after apparent neurological and behavioral "recovery." Four depressed patients who had sustained traumatic brain injuries and who exhibited mild to moderate brain impairment according to standardized tests received 30 min. of weak (1 microT) burst-firing magnetic fields across the temporal lobes once per week for 5 weeks. There was a significant improvement of depression and reduction of phobias while physical symptoms and other complaints were not changed

Pol J Pharmacol. 2002 Nov-Dec;54(6):633-9.

Effect of combined treatment with paroxetine and transcranial magnetic stimulation (TMS) on the mitogen-induced proliferative response of rat lymphocytes.

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Depression is associated with abnormal functions of the immune system. In this study, we investigated how two modern antidepressant therapies, chronic treatment with transcranial magnetic stimulation (TMS) and administration of an antidepressant belonging to selective serotonin reuptake inhibitors (SSRI), paroxetine, affect the proliferative response of thymocytes and splenocytes stimulated in vitro with various mitogens. Paroxetine (10 mg/kg) and TMS (B = 1.2 T, f = 30 Hz, t = 330 s) were applied once daily for 12 consecutive days, while, if given jointly paroxetine was injected 30 min before TMS. The mitogens used were: concanavalin A (Con A), pokeweed mitogen (PWM) or lipopolysaccharide (LPS). While either treatment applied alone had no effect on proliferative response, the joint application of paroxetine and TMS significantly depressed it. The literature data suggest that pulsed magnetic field may directly inhibit mitogen-activated lymphocyte proliferation, which is also inhibited by the presence of high level of serotonin. The present results suggest that both effects are additive, and because of that application of both treatments, whose effects alone are insufficient to prompt the reaction, possibly because adaptive changes during chronic treatment, results in a significant inhibition of lymphocyte proliferation.

Epilepsy Behav. 2003 Oct;4 Suppl 3:S46-54.

Treatment of depression in patients with epilepsy: problems, pitfalls, and

some solutions.

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Many people with epilepsy suffer from comorbid depression. Despite this, there have been few studies addressing the treatment of depression in this population, and the literature on psychiatric management techniques in patients with epilepsy is composed largely of opinions rather than evidence from randomized, controlled trials or other systematic investigations. Antidepressant drugs, including tricyclics and selective serotonin reuptake inhibitors, can be used to treat patients with epilepsy and comorbid depression. Nonpharmacological treatment options include vagus nerve stimulation, transcranial magnetic stimulation, and psychological therapies including cognitive-behavioral therapy, individual or group psychotherapy, patient support groups, family therapy, and counseling. Another important area that remains largely uninvestigated is psychiatric research in patients with epilepsy in non-Western cultures (with the exception of Japan). Factors such as problems with access to and acceptability of therapies in many developing nations have further implications for the treatment of psychiatric disorders in epilepsy.

Depression

Neuroreport. 2005 Nov 7;16(16):1839-42.

Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study.

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Recently, repetitive transcranial magnetic stimulation has evolved as a potential therapeutic tool to interfere with brain changes associated with neurological and psychiatric diseases. Little is known about its mode of action, however. Here, we investigated effects of repetitive transcranial magnetic stimulation on spontaneous magnetoencephalographic activity in patients with major depression. Before treatment, depressed patients showed a significant increase in slow magnetoencephalographic activity (2-6 Hz) over the left prefrontal cortex, compared with healthy controls. This activity significantly decreased during 10 days of repetitive transcranial magnetic stimulation, paralleled by clinical improvement. We conclude that therapeutic repetitive transcranial magnetic stimulation effects can be mirrored by changes of spontaneous magnetoencephalographic activity.

Psychiatry Res. 2005 Nov 15;137(1-2):1-10. Epub 2005 Oct 12.

Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial.

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This 5-week, randomized, double-blind, placebo-controlled trial investigated the efficacy and tolerability of high frequency repetitive transcranial magnetic stimulation (rTMS) directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomly assigned to receive 10 daily applications of either real or sham

rTMS. Subjects assigned to receive active stimulation were divided into two further subgroups according to the intensity of stimulation: 80% vs. 100% of motor threshold (MT). At study completion, the response rates were 61.1% (n=11), 27.8% (n=5) and 6.2% (n=1) for the 100% MT group, 80% MT group and sham group, respectively. A significant difference (Pearson chi(2) test) was found between the 100% MT and sham groups, while the 80% MT group did not differ significantly from the sham group. Between the two active groups, a marginally significant difference was observed. Analysis of variance with repeated measures on Hamilton Depression Rating Scale scores revealed a significantly different decrease over time of depressive symptomatology among the three treatment groups. Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded, and on the whole the technique was well tolerated. The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients.

Prog Neuropsychopharmacol Biol Psychiatry. 2005 Oct 19; [Epub ahead of print]

A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): Therapeutic and cognitive effect in medication free unipolar depression during 4 weeks.

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BACKGROUND: Transcranial magnetic stimulation (TMS) has become a therapeutic tool in psychiatric diseases. **METHODOLOGY:** The objective was to evaluate the efficacy of TMS in unipolar depression: the percentage of responders (>50% HDRS reduction) and remission (HDRS score \leq 8, after four weeks of active TMS treatment in depressed patients free of any antidepressive agent versus placebo-TMS. **RESULTS:** 27 patients were randomized in two groups: rTMS (N=11) versus sham TMS (N=16). Statistical differences were detected between sham and TMS treated groups on remission (0/16 versus 4/11 $p=0.032$, 1/16 versus 6/11 0.028 and 1/16 versus 7/11 $p=0.011$ at day 14, day 21 and day 28, respectively) and on response (2/16 versus 5/11 at day 14 (NS), 2/16 versus 7/11 $p=0.0115$ at day 21 and 1/16 versus 7/11 ($p=0.025$) day 28, respectively, using the exact Fisher test). Significant differences were observed between day 1 versus day 8 ($p<0.01$), day 15, day 21 and day 28 ($p<0.001$) in TMS group and only versus day 21 ($p<0.01$) and day 28 ($p<0.05$) for the sham group. ANOVA comparison between TMS and sham groups was significant at day 14 and day 28 ($p<0.05$). **LIMITATIONS:** The few number of patients. **CONCLUSION:** Our study has shown an efficacy of right rTMS in free medication unipolar depression over a month. Nevertheless, number of patients included is limited and multicentric studies will be necessary to specify the antidepressive action of TMS.

Psychiatry Res. 2005 Nov 15;137(1-2):113-21. Epub 2005 Oct 11.

Chronic repetitive transcranial magnetic stimulation is antidepressant but not anxiolytic in rat models of anxiety and depression.

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Transcranial magnetic stimulation (TMS) has been proposed as a treatment for depression and anxiety disorders. While the antidepressant effect has been modelled in animals, there have been few attempts to examine a possible anxiolytic effect of repetitive TMS (rTMS) in animal models. We administered 18 days of rTMS to male Sprague-Dawley rats. On days 10 through 18, rats were tested in several anxiety models (social interaction, emergence, elevated plus-maze, and predator odor avoidance) and in the forced swim test. No group differences were apparent on any of the anxiety models, while TMS produced an antidepressant effect in the forced swim test. Interestingly, on day 1 of the forced swim test, the home cage control group displayed increased swimming behaviour compared with sham-treated animals, suggesting an observable level of stress may have accompanied sham treatment. The results from the forced swim test suggested that TMS had modest antidepressant properties, but it did not show anxiolytic properties in the models examined. The study also suggested that stress associated with handling should be taken into account in the interpretation of TMS studies in animals.

Curr Psychiatry Rep. 2005 Oct;7(5):381-90.

Transcranial magnetic stimulation for the treatment of depression in neurologic disorders.

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Depression is commonly associated with neurologic disorders. Although depression in neurologic conditions often is associated with a negative impact on quality of life, it frequently is poorly managed. Some factors, such as a multidrug regimen, lack of efficacy, and side effects of antidepressants may explain why depression is not adequately treated in patients with neurologic disorders. Therefore, this population needs new approaches for depression treatment, and repetitive transcranial magnetic stimulation (rTMS) may be one of them because it has been shown to be effective for the treatment of depression alone and depression in certain neurologic diseases such as Parkinson's disease and stroke. rTMS is a noninvasive, focal, and painless treatment associated with few, mild side effects. It may be effective in the treatment of neurologic diseases such as

Parkinson's disease, stroke, and epilepsy. In this paper, we discuss the potential risks and benefits of rTMS treatment for depression in Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. Lastly, a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in neurologic diseases is proposed.

J Psychiatr Res. 2005 Oct 28; [Epub ahead of print]

Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [(123)I] IBZM SPECT study.

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Though there is considerable evidence that prefrontal repetitive transcranial magnetic stimulation (rTMS) exerts antidepressant effects, the neurobiological action of rTMS in patients with depression is poorly understood. Preclinical studies in animals and humans have demonstrated that prefrontal rTMS can induce dopamine release in mesostriatal and mesolimbic regions. We therefore investigated whether rTMS also modulates striatal dopaminergic neurotransmission in depressed patients using a dynamic [(123)I] iodobenzamide (IBZM) single photon emission computed tomography (SPECT) approach. Five patients with a major depressive episode (DSM-IV) underwent an acute 10Hz rTMS challenge with 3000 stimuli over the left dorsolateral prefrontal cortex during an [(123)I] IBZM-SPECT bolus and constant infusion protocol. In four subjects the protocol was repeated after a three week rTMS standard treatment. Striatal IBZM binding to dopamine D(2) receptors was assessed with a region-of-interest (ROI) technique. The change in striatal IBZM binding after the rTMS challenge was regarded as measure of change in endogenous striatal dopamine. Data of nine SPECT investigations showed a significant reduction by 9.6+/-6.2% in IBZM binding to striatal dopamine D(2) receptors after rTMS challenge compared to baseline (p=0.01, Wilcoxon test). In this preliminary study, the reduction of IBZM binding observed after rTMS challenge is suggestive of a release in endogenous dopamine induced by prefrontal rTMS. In future, this approach can be used to differentiate specific and non-specific reward-related effects of rTMS on dopaminergic neurotransmission.

Biol Psychiatry. 2005 Mar 15;57(6):571-6.

Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats.

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BACKGROUND: Evidence suggests that a novel type of magnetic resonance imaging (MRI) scan called echo planar magnetic resonance spectroscopic imaging (EP-MRSI) has mood-elevating actions in humans during the depressive phases of bipolar disorder. We examined whether a low-energy component of EP-MRSI (low-field magnetic stimulation [LFMS]) has antidepressant-like, locomotor-stimulating, or amnesic effects in rats. **METHODS:** We examined the effects of LFMS on immobility in the forced swim test (FST) and activity within an open field in separate groups of rats. After exposure to forced swimming, rats received LFMS (three 20-min sessions at 1.5 G/cm and .75 V/m) before behavioral testing. We also examined the effects of LFMS on fear conditioning (FC), a learning paradigm that also involves exposure to stressful conditions. **RESULTS:** Low-field magnetic stimulation reduced immobility in the FST, an antidepressant-like effect qualitatively similar to that of standard antidepressants. Low-field magnetic stimulation did not alter locomotor activity or FC. **CONCLUSIONS:** Low-field magnetic stimulation has antidepressant-like effects in rats that seem unrelated to locomotor-activating or amnesic effects. These findings raise the possibility that electromagnetic fields can affect the brain biology and might have physiologic consequences that offer novel approaches to therapy for psychiatric disorders. These same consequences might render MRI-based scans more invasive than previously appreciated.

Rev Med Suisse. 2005 Sep 21;1(33):2162-4, 2166.

[Novel brain stimulation techniques: therapeutic perspectives in psychiatry]

[Article in French]

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Recent advances have allowed the development of new physical techniques in neurology and psychiatry, such as Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), and Deep Brain Stimulation (DBS). These techniques are already recognized as therapeutic approaches in several late stage refractory neurological disorders (Parkinson's disease, tremor, epilepsy), and currently investigated in psychiatric conditions, refractory to medical treatment (obsessive-compulsive disorder, resistant major depression). In Paralell, these new techniques offer a new window to understand the neurobiology of human behavior.

Curr Psychiatry Rep. 2005 Oct;7(5):381-90.

Transcranial magnetic stimulation for the treatment of depression in neurologic disorders.

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Depression is commonly associated with neurologic disorders. Although depression in neurologic conditions often is associated with a negative impact on quality of life, it frequently is poorly managed. Some factors, such as a multidrug regimen, lack of efficacy, and side effects of antidepressants may explain why depression is not adequately treated in patients with neurologic disorders. Therefore, this population needs new approaches for depression treatment, and repetitive transcranial magnetic stimulation (rTMS) may be one of them because it has been shown to be effective for the treatment of depression alone and depression in certain neurologic diseases such as Parkinson's disease and stroke. rTMS is a noninvasive, focal, and painless treatment associated with few, mild side effects. It may be effective in the treatment of neurologic diseases such as Parkinson's disease, stroke, and epilepsy. In this paper, we discuss the potential risks and benefits of rTMS treatment for depression in Parkinson's disease, epilepsy, stroke, multiple sclerosis, and Alzheimer's disease. Lastly, a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in neurologic diseases is proposed.

Exp Neurol. 2005 Sep 26; [Epub ahead of print]

Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex and cortical excitability in patients with major depressive disorder.

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Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex is a relatively non-invasive technique with putative therapeutic effects in major depression. However, the exact neurophysiological basis of these effects needs further clarification. Therefore, we studied the impact of ten daily sessions of left, dorsolateral prefrontal rTMS on motor cortical excitability, as revealed by transcranial magnetic stimulation-elicited motor-evoked potentials in 30 patients. As compared to the non-responders, responders (33%) showed changes in parameters pointing towards a reduced cortical excitability. These results suggest that repetitive transcranial magnetic stimulation of the dorsolateral, prefrontal cortex may have inhibitory effects on motor

cortical neuronal excitability in patients with major depressive disorder. Furthermore, measurement of motor cortical excitability may be a useful tool for investigating and monitoring inhibitory brain effects of antidepressant stimulation techniques like rTMS.

Epilepsy Behav. 2005 Sep;7(2):182-9.

Transcranial magnetic stimulation treatment for epilepsy: can it also improve depression and vice versa?

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Comorbidity with depression is an important determinant of the quality of life for patients with epilepsy. Antidepressant medications can effectively treat depression in epileptic patients, but drug-drug interactions and epileptogenic effects of these drugs pose therapeutic challenges. The mood-stabilizing effects of antiepileptic medications may not be sufficient to treat depression. Therefore, treatments that alleviate the burden of depression without increasing seizure risk or, better yet, with the possibility of improving seizure control are worth exploring. Neuroimaging techniques, such as functional magnetic resonance imaging, are providing novel insights into the pathophysiology of depression in epilepsy. For example, there appears to be prominent brain prefrontal hypoactivity, which may be sustained by the hyperactivity of the seizure focus. If so, neuromodulatory approaches that suppress epileptic focus hyperactivity and concurrently enhance prefrontal activity may be ideally suited. Indeed, vagus nerve stimulation has been shown to yield simultaneous antiseizure and mood effects. Another neuromodulatory technique, transcranial magnetic stimulation (TMS), can also modulate brain activity, but in a noninvasive, painless, and focal manner. Depending on the stimulation parameters, it is possible to enhance or reduce activity in the targeted brain region. Furthermore, TMS has been shown to be effective in treating depression, and preliminary data suggest that this treatment may also be effective for epilepsy treatment. This article reviews these data and explores further the question of whether depression and epilepsy can be simultaneously treated with TMS for optimal therapeutic impact.

J Affect Disord. 2005 Nov;88(3):255-67. Epub 2005 Sep 2.

A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy.

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BACKGROUND: There is a growing interest in extending the use of repetitive transcranial magnetic stimulation (rTMS) beyond research centres to the widespread clinical treatment of depression. Thus it is timely to critically review the evidence for the efficacy of rTMS as an antidepressant treatment. Factors relevant to the efficacy of rTMS are discussed along with the implications of these for the further optimization of rTMS. **METHOD:** Clinical trials of the efficacy of rTMS in depressed subjects are summarized and reviewed, focusing mainly on sham-controlled studies and meta-analyses published to date. **RESULTS:** There is a fairly consistent statistical evidence for the superiority of rTMS over a sham control, though the degree of clinical improvement is not large. However, this data is derived mainly from two-week comparisons of rTMS versus sham, and evidence suggests greater efficacy with longer treatment courses. Studies so far have also varied greatly in approaches to rTMS stimulation (with respect to stimulation site, stimulus parameters etc) with little empirical evidence to inform on the relative merits of these approaches. **LIMITATIONS:** Only studies published in English were reviewed. Many of the studies in the literature had small sample sizes and different methodologies, making comparisons between studies difficult. **CONCLUSIONS:** Current published studies and meta-analyses have evaluated the efficacy of rTMS as given in treatment paradigms that are almost certainly suboptimal (e.g. of two weeks' duration). While the data nevertheless supports positive outcomes for rTMS, there is much scope for the further refinement and development of rTMS as an antidepressant treatment. Ongoing research is critical for optimizing the efficacy of rTMS.

Neuro Endocrinol Lett. 2005 Aug 30;26(4) [Epub ahead of print]

Repetitive transcranial magnetic stimulation in a patient suffering from depression and rheumatoid arthritis: Evidence for immunomodulatory effects.

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Repetitive transcranial magnetic stimulation (rTMS) has been suggested as antidepressive treatment strategy [1]. The mechanism of action by which the antidepressive effect is brought about remains unclear at present. Here, we report findings in a patient suffering from recurrent major depression and rheumatoid arthritis. Improvement of depressive symptoms during 20 Hz rTMS of the left dorsolateral prefrontal cortex was repeatedly associated with a systemic inflammatory reaction, suggesting that rTMS induced an immunomodulatory effect.

Psychiatry Clin Neurosci. 2005 Aug;59(4):425-32.

Clinical application of single-pulse transcranial magnetic stimulation for

the treatment of depression.

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Transcranial magnetic stimulation (TMS) has been recently suggested for the treatment of patients with major depression. Based on the results of the authors' pilot study showing a possible antidepressive effect of single-pulse TMS, a clinical trial was conducted involving patients with major depression. For the present study single-photon emission computed tomography (SPECT) was recorded for six of the target patients to study the effects of TMS on the local blood flow volume. Twenty-three inpatients meeting the Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV) criteria for major depression were invited to participate in the study. Depressive symptoms were rated using the Hamilton Rating Scale for Depression (HAM-D). Patients were given 10 stimuli over the frontal area of both sides for a total of 20 stimuli in a session. The subjects had daily TMS session for 5 days as an add-on therapy. In addition, six patients had their quantitative (99m)Tc-ethyl cysteinate dimer SPECT images measured before and after TMS treatment. Compared with the value 2 days prior to the start of TMS therapy (24.2 +/- 4.9), the average HAM-D scale dropped significantly to 15.3 +/- 6.6 on the day after completion of such therapy. The results of SPECT showed that the regional cerebral blood flow (rCBF) of the bilateral frontal region had increased in four out of six patients when comparing before and after treatment. The present study shows that single-pulse TMS, which is widely used as a neurological test method, possesses a wide range of antidepressive effects without inducing adverse reactions. The results suggest that although repetitive TMS is steadily becoming the mainstay technique today, single-pulse TMS also possesses sufficient antidepressive effects.

Seizure. 2005 Sep;14(6):387-92.

Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy-a pilot study.

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We evaluated the effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on seizure frequency in adult patients with medically intractable extratemporal lobe epilepsy (ETLE). Seven patients with medically intractable ETLE received low-frequency rTMS at 0.9 Hz, basically two sets of 15 min stimulation per day for five days in a week, with the stimulus intensity of 90% of resting motor threshold (RMT). The number of seizures during two weeks before and after the stimulation of one week was

compared. Furthermore, RMT and active motor threshold (AMT) were measured before and after rTMS for each daily session. After low-frequency rTMS of one week, the frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures was reduced by 19.1, 35.9 and 7.4%, respectively. The patients with smaller difference between RMT and AMT before rTMS had higher reduction rate of CPSs. A favorable tendency of seizure reduction, though not statistically significant, during two weeks after low-frequency rTMS was demonstrated in medically intractable ETLLE patients. As far as CPSs are concerned, smaller decrease of motor threshold by voluntary muscle contraction was associated with better response to rTMS.

Transcranial magnetic stimulation in persons younger than the age of 18.

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OBJECTIVES: To review the use of transcranial magnetic stimulation (single-pulse TMS, paired TMS, and repetitive TMS [rTMS]) in persons younger than the age of 18 years. I discuss the technical differences, as well as the diagnostic, therapeutic, and psychiatric uses of TMS/rTMS in this age group. **METHODS:** I evaluated English-language studies from 1993 to August 2004 on nonconvulsive single-pulse, paired, and rTMS that supported a possible role for the use of TMS in persons younger than 18. Articles reviewed were retrieved from the MEDLINE database and Clinical Scientific index. **RESULTS:** The 48 studies reviewed involved a total of 1034 children ages 2 weeks to 18 years; 35 of the studies used single-pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). Three studies used both single and rTMS. However, the number of subjects involved was not reported. **CONCLUSIONS:** Single-pulse TMS, paired TMS, and rTMS in persons younger than 18 has been used to examine the maturation/activity of the neurons of various central nervous system tracts, plasticity of neurons in epilepsy, other aspects of epilepsy, multiple sclerosis, myoclonus, transcallosal inhibition, and motor cortex functioning with no reported seizure risk. rTMS has been applied to psychiatric disorders such as ADHD, ADHD with Tourette's, and depression. Adult studies support an antidepressant effect from repetitive TMS, but there is only one study that has been reported on 7 patients that used rTMS to the left dorsal prefrontal cortex on children/adolescents with depression (5 of the 7 subjects treated responded). Although there are limited studies using rTMS (in 34 children), these studies did not report significant adverse effects or seizures. Repetitive TMS safety, ethical, and neurotoxicity concerns also are discussed.

Neuron. 2005 Jan 20;45(2):181-3.

Toward establishing a therapeutic window for rTMS by theta burst stimulation.

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In this issue of Neuron, Huang et al. show that a version of the classic theta burst stimulation protocol used to induce LTP/LTD in brain slices can be adapted to a transcranial magnetic stimulation (TMS) protocol to rapidly produce long lasting (up to an hour), reversible effects on motor cortex physiology and behavior. These results may have important implications for the development of clinical applications of rTMS in the treatment of depression, epilepsy, Parkinson's, and other diseases.

Psychiatry Res. 2005 Oct 10; [Epub ahead of print]

Chronic repetitive transcranial magnetic stimulation is antidepressant but not anxiolytic in rat models of anxiety and depression.

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Transcranial magnetic stimulation (TMS) has been proposed as a treatment for depression and anxiety disorders. While the antidepressant effect has been modelled in animals, there have been few attempts to examine a possible anxiolytic effect of repetitive TMS (rTMS) in animal models. We administered 18 days of rTMS to male Sprague-Dawley rats. On days 10 through 18, rats were tested in several anxiety models (social interaction, emergence, elevated plus-maze, and predator odor avoidance) and in the forced swim test. No group differences were apparent on any of the anxiety models, while TMS produced an antidepressant effect in the forced swim test. Interestingly, on day 1 of the forced swim test, the home cage control group displayed increased swimming behaviour compared with sham-treated animals, suggesting an observable level of stress may have accompanied sham treatment. The results from the forced swim test suggested that TMS had modest antidepressant properties, but it did not show anxiolytic properties in the models examined. The study also suggested that stress associated with handling should be taken into account in the interpretation of TMS studies in animals.

Psychiatr Pol. 2004 Mar-Apr;38(2):217-25.

[Estimation of therapeutical efficacy of weak variable magnetic fields with low value of induction in patients with depression]

[Article in Polish]

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AIM: Preliminary results of research on the therapeutical efficacy of weak variable magnetic fields with low value of induction used as magnetostimulation in patients with depression not reacting to two consecutive, correctly applied anti-depressant pharmacological treatment are presented in the paper. **METHOD:** The examined patients (24 persons aged 18-65 years) treated with anti-depressants accessible in Poland were randomly divided into 2 groups. In 1 group (11 persons--9 women and 2 men) magnetostimulation with the use of a weak variable magnetic field with a low value of induction of 15 microT generated by the VIOFOR JPS device (Poland) lasting 12 minutes daily for 15 days was added to pharmacological therapy. Patients from 2 groups (13 persons--11 women and 2 men) were exposed to exposure with the same device. The intensity of depression was estimated with Beck's, Montgomery-Asberg's and Hamilton's scales. **RESULTS:** As a result of a cycle of active magnetostimulation a distinct, statistically significant decrease of intensification of depression, both in the 7th and 15th day exposure was obtained, while in the sham-exposed group only slight, transient decrease of intensification of depression in the 7th day of sham-exposure was observed. **CONCLUSIONS:** It was concluded that adding magnetostimulation to pharmacological therapy results in a progressive, significant reduction of intensification of depression symptoms.

Psychiatry Res. 2005 Oct 11; [Epub ahead of print]

Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial.

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This 5-week, randomized, double-blind, placebo-controlled trial investigated the efficacy and tolerability of high frequency repetitive transcranial magnetic stimulation (rTMS) directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomly assigned to receive 10 daily applications of either real or sham rTMS. Subjects assigned to receive active stimulation were divided into two further subgroups according to the intensity of stimulation: 80% vs. 100% of motor threshold (MT). At study completion, the response rates were 61.1% (n=11), 27.8% (n=5) and 6.2% (n=1) for the 100% MT group, 80% MT group and sham group, respectively. A significant difference (Pearson chi(2) test) was found between the 100% MT and sham groups, while the 80% MT group did not differ significantly from the sham group.

Between the two active groups, a marginally significant difference was observed. Analysis of variance with repeated measures on Hamilton Depression Rating Scale scores revealed a significantly different decrease over time of depressive symptomatology among the three treatment groups. Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded, and on the whole the technique was well tolerated. The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients.

Bipolar Disord. 2005;7 Suppl 5:13-23.

Newer treatment studies for bipolar depression.

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Objective: Depressive symptoms of bipolar disorder have more negative impact on a patient's life than manic symptoms. This review focused on the emerging efficacy data for treatments in bipolar depression. Methods: English-language literature cited in Medline was searched with terms bipolar depression, clinical trial, and trial. Randomized, placebo-controlled trials of newer studies with older agents and all studies with newer or novel agents were prioritized. Open-label studies of novel agents presented at major scientific meetings were also included. Results: Olanzapine, olanzapine-fluoxetine combination (OFC), and quetiapine were superior to placebo in the acute treatment of bipolar depression. Lamotrigine only significantly reduced core symptoms of depression compared with placebo. Pramipexole, a dopamine D2/D3 receptor agonist and omega-3 fatty acids, a polyunsaturated fatty acid, augmentation to mood stabilizer (MS) had superiority to placebo in reducing depressive symptoms. Topiramate augmentation of an MS was equally as effective as Bupropion-SR. Patients treated with an MS responded well to the addition of agomelatine, a melatonin receptor agonist with 5-HT_{2C} antagonist properties. However, inositol and repetitive transcranial magnetic stimulation did not separate from placebo. Lamotrigine and olanzapine, and to a lesser extent, divalproex, are superior to placebo in preventing depressive relapses. All agents were relatively well tolerated. Conclusions: Olanzapine, OFC, and quetiapine are effective in the acute treatment of bipolar depression. Compared with lithium and divalproex, lamotrigine is more effective in preventing bipolar depression. Larger controlled studies of the other agents in the acute and maintenance treatment of bipolar depression are warranted.

Zh Nevrol Psikhiatr Im S S Korsakova. 1999;99(10):26-9.

[Transcranial magnetic stimulation in neurotic depression]

[Article in Russian]

[Stikhina NIa](#), [Lyskov EB](#), [Lomarev MP](#), [Aleksanian ZA](#), [Mikhailov VO](#), [Medvedev SV](#).

Transcranial magnetic stimulation (TMS) was applied in combination with psychotherapy in patients with neurotic depression, including 15 patients of the experimental group and 14 patients of the control one. 10 sessions of daily TMS for the patients from the experimental group (0.015 T, 40 pulses per sec) were performed at the same time for 20 min (twice for 10 min with 5-min interval) in a room which excluded any external stimulation. TMS was performed by contact method: 5 cm coil was applied to the left prefrontal area. The control group received the imitation of TMS-procedure stimulation. The improvement of mental state was in 13 patients of experimental group and in 3 of control one. The course of TMS resulted in a significant attenuation of depression by the Hamilton Depression Rating scale (from 22.9 to 8.6) and the Anxiety Inventory (from 39.4 to 26.6), that was significantly higher in comparison with the control. There weren't found any TMS-related changes in blood pressure and pulse rate as well as any pathological EEG symptoms.

Biomed Sci Instrum. 2003;39:466-70.

Autoradiographic evaluation of electromagnetic field effects on serotonin (5HT1A) receptors in rat brain.

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Serotonin (5HT1A) is a chemical mediator of inflammation and the largest single neurotransmitter system of the brain. Its secretion and physiological actions mediate stress and pain, affecting both immune and nervous system functions through the hypothalamic-pituitary-adrenal axis. Serotonin receptor dysfunction is well-characterized in mental disturbances like depression and anxiety. Transcranial magnetic stimulation has been used therapeutically to treat refractory disorders like non-responsive depression and may act in part through its effect on 5HT1A receptors. Previously we have shown that in vitro, 5HT1A receptor binding to a radioactive agonist can be modulated by specific intensity and frequency electromagnetic fields (EMFs). In the present report we have used quantitative receptor autoradiography to evaluate 5HT1A receptor density in rat brain and the impact of pulsed EMF exposure on receptor binding in key brain regions. Rats used in this study had whole body exposures to either a geofield control or to pulsed EMFs to evaluate the treatment for chemically-induced tendinitis. Since the brains were exposed coincidentally as a consequence of the main experiment, we investigated the potential for EMF-induced changes in areas such as the hippocampus. This pilot study should provide a detailed understanding of magnetic field effects on stress-responsive brain regions and will lead to a more coordinated approach to the use of such modalities for therapeutic intervention in humans.

Fortschr Neurol Psychiatr. 2001 Sep;69(9):402-9.

[Which patients with major depression benefit from prefrontal repetitive magnetic stimulation]

[Article in German]

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Antidepressive benefit of prefrontal repetitive magnetic stimulation (RTMS) for one or two weeks varies between 6 % and 60 % (mean 37 %) improvement of the Hamilton depression scale vs. 12 % improvement following sham RTMS. This variance is probably caused by study specific stimulus parameters but also by genetic, psychopathological and neuropsychological characteristics of the patients as well as by the functional state of the cortex area below the stimulation coil. Data from 10 open and 7 sham controlled studies including two own studies comprising more than 300 patients with major depression have been published to date. In synopsis several positive predictors for antidepressive response of prefrontal RTMS become apparent: 1) younger age, 2) somatic signs of anxiety, 3) lack of cortical hyperactivity below the magnetic coil pulsed by 10 Hz stimuli, 4) cortical hypermetabolism below the 1 Hz pulsed coil. Negative predictors of response to prefrontal RTMS were: 1) Advanced age, 2) prefrontal atrophy, 3) cognitive impairment in neuropsychological tasks assigned to the prefrontal cortex, 4) psychotic symptoms, 5) cortical hyperactivity below 10 Hz pulsed coil 6) non-response to electroconvulsive therapy (ECT). While prefrontal RTMS will probably not replace ECT in severe major depression with psychotic symptoms it could be beneficial especially in younger anxious patients without cognitive impairment.

Nord J Psychiatry. 2003;57(3):227-32.

Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence.

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Repetitive transcranial magnetic stimulation (rTMS) is a novel treatment in psychiatry. We reviewed all published evidence on the efficacy of this treatment option in depressive disorders. An extensive electronic and manual search for eligible research reports identified only 12 studies that met the predetermined criteria for inclusion. rTMS was administered differently in most studies, and patient characteristics varied widely. A formal meta-analysis of the studies was thus not possible. Instead, we conducted a

qualitative evaluation of the included studies. The antidepressive efficacy was not consistent, and where efficacy was demonstrated, it was modest in most studies. Some patients had good but transient responses to rTMS. Treatment gains were not maintained beyond the treatment period. Comparisons with electroconvulsive therapy (ECT) indicated the superiority of ECT. More, larger and more carefully designed studies are needed to demonstrate convincingly a clinically relevant effect of rTMS. We conclude that there is insufficient evidence for rTMS as a valid treatment for depression at present.

Int J Neurosci. 1996 Oct;87(1-2):5-15.

Suicidal behavior is attenuated in patients with multiple sclerosis by treatment with electromagnetic fields.

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A marked decrease in the levels of serotonin (5-HT) and its metabolite (5-HIAA) has been demonstrated in postmortem studies of suicide victims with various psychiatric disorders. Depression is the most common mental manifestation of multiple sclerosis (MS) which accounts for the high incidence of suicide in this disease. CSF 5-HIAA concentrations are reduced in MS patients and nocturnal plasma melatonin levels were found to be lower in suicidal than in nonsuicidal patients. These findings suggest that the increased risk of suicide in MS patients may be related to decreased 5-HT functions and blunted circadian melatonin secretion. Previous studies have demonstrated that extracerebral applications of pulsed electromagnetic fields (EMFs) in the picotesla range rapidly improved motor, sensory, affective and cognitive deficits in MS. Augmentation of cerebral 5-HT synthesis and resynchronization of circadian melatonin secretion has been suggested as a key mechanism by which these EMFs improved symptoms of the disease. Therefore, the prediction was made that this treatment modality would result in attenuation of suicidal behavior in MS patients. The present report concerns three women with remitting-progressive MS who exhibited suicidal behavior during the course of their illness. All patients had frequent suicidal thoughts over several years and experienced resolution of suicidal behavior within several weeks after introduction of EMFs treatment with no recurrence of symptoms during a follow-up of months to 3.5 years. These findings demonstrate that in MS pulsed applications of picotesla level EMFs improve mental depression and may reduce the risk of suicide by a mechanism involving the augmentation of 5-HT neurotransmission and resynchronization of circadian melatonin secretion.

Percept Mot Skills. 1996 Oct;83(2):491-8.

Weak, but complex pulsed magnetic fields may reduce depression following traumatic brain injury.

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Many patients who display psychological depression following a traumatic brain injury do not respond completely to antidepressant drugs. We hypothesized that this type of depression is strongly correlated with subclinical, complex partial seizure-activity within the hippocampal-amygdaloid region that continues for months to years after apparent neurological and behavioral "recovery." Four depressed patients who had sustained traumatic brain injuries and who exhibited mild to moderate brain impairment according to standardized tests received 30 min. of weak (1 microT) burst-firing magnetic fields across the temporal lobes once per week for 5 weeks. There was a significant improvement of depression and reduction of phobias while physical symptoms and other complaints were not changed

Pol J Pharmacol. 2002 Nov-Dec;54(6):633-9.

Effect of combined treatment with paroxetine and transcranial magnetic stimulation (TMS) on the mitogen-induced proliferative response of rat lymphocytes.

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Depression is associated with abnormal functions of the immune system. In this study, we investigated how two modern antidepressant therapies, chronic treatment with transcranial magnetic stimulation (TMS) and administration of an antidepressant belonging to selective serotonin reuptake inhibitors (SSRI), paroxetine, affect the proliferative response of thymocytes and splenocytes stimulated in vitro with various mitogens. Paroxetine (10 mg/kg) and TMS (B = 1.2 T, f = 30 Hz, t = 330 s) were applied once daily for 12 consecutive days, while, if given jointly paroxetine was injected 30 min before TMS. The mitogens used were: concanavalin A (Con A), pokeweed mitogen (PWM) or lipopolysaccharide (LPS). While either treatment applied alone had no effect on proliferative response, the joint application of paroxetine and TMS significantly depressed it. The literature data suggest that pulsed magnetic field may directly inhibit mitogen-activated lymphocyte proliferation, which is also inhibited by the presence of high level of serotonin. The present results suggest that both effects are additive, and because of that application of both treatments, whose effects alone are insufficient to prompt the reaction, possibly because adaptive changes during chronic treatment, results in a significant inhibition of lymphocyte proliferation.

Epilepsy Behav. 2003 Oct;4 Suppl 3:S46-54.

Treatment of depression in patients with epilepsy: problems, pitfalls, and

some solutions.

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Many people with epilepsy suffer from comorbid depression. Despite this, there have been few studies addressing the treatment of depression in this population, and the literature on psychiatric management techniques in patients with epilepsy is composed largely of opinions rather than evidence from randomized, controlled trials or other systematic investigations. Antidepressant drugs, including tricyclics and selective serotonin reuptake inhibitors, can be used to treat patients with epilepsy and comorbid depression. Nonpharmacological treatment options include vagus nerve stimulation, transcranial magnetic stimulation, and psychological therapies including cognitive-behavioral therapy, individual or group psychotherapy, patient support groups, family therapy, and counseling. Another important area that remains largely uninvestigated is psychiatric research in patients with epilepsy in non-Western cultures (with the exception of Japan). Factors such as problems with access to and acceptability of therapies in many developing nations have further implications for the treatment of psychiatric disorders in epilepsy.