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Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression

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ABSTRACT

Major depression is a common mental health problem and associated with significant morbidity and mortality, including impaired social and physical functioning and increased risk for suicide. Electroconvulsive therapy (ECT) is highly efficacious in treatment-resistant depressive disorders, but cognitive side effects are frequently associated with the treatment. Magnetic seizure therapy (MST) is a form of convulsive therapy, using magnetic fields in order to induce therapeutic seizures. First studies suggested that cognitive side effects of MST, including postictal recovery time, are more benign than those resulting from ECT treatment. In this open-label study we tested the hypothesis that MST is associated with clinically significant antidepressant effects in treatment-resistant depression (TRD) as an add-on therapy to a controlled pharmacotherapy.

Twenty patients suffering from TRD were randomly assigned to receive either MST or ECT starting from July 2006 until November 2008. Primary outcome measure was antidepressant response assessed by Montgomery Åsberg Depression Scale. Secondary outcome measures included Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Beck Depression Inventory and 90-Item Symptom Checklist.

Antidepressant response (improvement of 50% in MADRS ratings) was statistically significant and of similar size in both treatment groups. Cognitive side effects were observed in neither group. Characteristics in MST- and ECT-induced seizures were comparable, especially regarding ictal activity and postictal suppression. Thus, MST may be a potential alternative to ECT if efficacy and safety are validated in larger clinical trials.

1. Introduction

Major depression is widely recognized as the world's most burdensome mental health problem in adults (Lopez and Murray, 1998). The disorder is associated with significant morbidity and mortality, including impaired social and physical functioning and increased risk for suicide (Agency for Health Care Policy and Research, 1993; Hirschfeld and Russell, 1997; Wells et al., 1989). Treatment of depressive disorders – especially of treatment-resistant forms - is therefore an important focus of current psychiatric research. Presently available evidence-based treatments lead to symptomatic improvement in most patients. However, up to 40% of patients partially responding to antidepressant therapy suffer from clinically relevant residual symptoms (Fava and Davidson, 1996) and 30% of patient do not respond to four evidence-based treatment steps (Rush et al., 2006). The more treatments fail, and the longer a current depressive episode lasts, the higher is the risk of developing a so-called treatment-resistant depression (TRD) (Rau et al., 2007).

In an effort to find safer and more effective alternatives to antidepressant drugs for treating severe depression, investigators have recently examined a variety of non-pharmacologic modalities, e.g. electroconvulsive therapy (ECT) (Lisanby, 2007), repetitive transcranial magnetic stimulation (rTMS) (O'Reardon et al., 2007), vagus nerve stimulation (VNS) (Schlaepfer et al., 2008), deep brain stimulation (DBS) (Bewernick et al., 2010) and magnetic seizure therapy (MST) (George, 2002).

Electroconvulsive therapy was developed in 1938 and has been demonstrated to be highly efficacious in severely

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treatment-resistant depressive disorders, with more than half of patients achieving remission (Khalid et al., 2008). ECT is the most effective treatment for major depressive disorder (APA., 1994; Ebmeier et al., 2006), but cognitive side effects such as amnesia are commonly reported (Datka et al., 2007; Donahue, 2000; Schulze-Rauschenbach et al., 2005).

Some randomised trials with transcranial magnetic stimulation (rTMS) have suggested similar efficacy as ECT in the treatment of non-psychotic depression (Grunhaus et al., 2000, 2003; Janicak et al., 2002; Schulze-Rauschenbach et al., 2005), although no large comparison trials have been undertaken so far. The feasibility and safety of deliberately induced seizures with the help of repetitive magnetic fields was first demonstrated in non-human primates (Dwork et al., 2004; Kosel et al., 2003b; Lisanby et al., 2001b). One further alternative to ECT is magnetic seizure therapy (MST), a form of convulsive therapy, in which magnetic fields are used to induce therapeutic seizures. In the course of the first human proof-of-concept study, one patient received a course of four MST treatments (Lisanby et al., 2001b). The same group treated another patient successfully with a full course of 12 MST (Kosel et al., 2003a). In contrast to ECT, MST is a more focal form of convulsive therapy (Lisanby et al., 2001b) that targets seizure induction in prefrontal cortex and spares medial temporal structures (i.e. hippocampus), which are involved in the development of cognitive side effects of ECT (Kosel et al., 2003a; Lisanby et al., 2003a; Lisanby, 2002; Moscrip et al., 2006). It has been demonstrated in primate models of MST that magnetically induced seizures are different from seizures induced by electrical convulsive stimulation (ECS) in regard to neurophysiological effects on the hippocampus (Lisanby et al., 2003a).

Only few results have been published since the first application of MST in the year 2000 (Lisanby et al., 2001b). Preliminary studies suggest that MST possesses antidepressant efficacy (Kayser et al., 2009; White et al., 2006), good feasibility and better tolerability in comparison to ECT (Lisanby et al., 2003a). First studies have suggested a more benign cognitive side effects profile of MST as compared to ECT (Kayser et al., 2009; Kosel et al., 2003a; Lisanby et al., 2003b), including faster postictal recovery time (Kirov et al., 2008), reductions in attention deficits and anterograde and retrograde amnesia (Dwork et al., 2004; Khalid et al., 2008; Lisanby et al., 2003a; Moscrip et al., 2006).

In this study twenty patients were assigned to receive either complete courses of treatment with either MST or ECT. We hypothesized that MST would lead to clinically significant antidepressant effects in treatment-resistant depression (TRD), as an add-on treatment to a controlled drug therapy.

2. Methods

2.1. Patients

The study was approved by the Institutional Review Boards (IRBs) of the University Bonn. The protocol has been registered at ClinicalTrials.gov with the identifier NCT00770783. Ten patients received MST (experimental) and ten other patients ECT (active comparator) at the University Hospital Bonn, Department of Psychiatry and Psychotherapy, from July 2006 to November 2008 (see Table 1 for demographic data). All patients met the diagnostic criteria for a major depressive disorder and were in a current episode as diagnosed with Structured Clinical Interview for DSM IV (Diagnostic and Statistical Manual of Mental Disorders IV) (APA, 1994). No patient suffered from a psychotic depression. Treatment resistance was defined as failure to respond to at least two treatments from different treatment categories during the current major depressive episode (MDE). For study inclusion, patients had to receive a score $\geq$20 on the 28-item Hamilton Rating Scale of Depression. Furthermore, convulsive therapy had to be clinically indicated. The exclusion criteria were a secondary diagnosis of, or signs of delirium, dementia, amnesia or other cognitive disorders and/or diagnosis of non-affective psychotic disorders. Further exclusion criteria were alcohol or substance dependence within the previous twelve months or abuse within the previous six months and a history or diagnosis of clinically relevant cardiac disease. Diagnosis of clinically relevant injury, disease of the central nervous system, magnetic material in the head or implanted medical devices (i.e. cardiac pacemaker, vagus nerve stimulator, medical pumps) also lead to exclusion.

Table 1
Patients' Demographic and Clinical Characteristics.

	MST	ECT
	Mean (SD)($n = 10$)	
DSM IV diagnosis	8 MDD, 1 BPI, 1 BPII	8 MDD, 2 BPII
Gender	60% f	70% f
Current Age (years)	48.80 (8.35)	52.8 (11.43)
Age MDD/BP onset (years)	32.80 (8.61)	37.1 (7.64)
Length of current Episodes (years)	6.01 (10.42)	3.5 (4.12)
Number of Lifetime Episodes	6.10 (7.56)	6.7 (7.8)
Number of Medications	18.40 (7.53)	17.9 (8.17)
Psychotherapy	90%	90%
Number of Hospital stays	3.70 (1.89)	4.1 (2.18)
Attempted Suicides	3/10 [0.80 (1.62)]	2/10 [0.3 (0.67)]
Pension/Unemployment	60%	70%
Family History	60%	50%

Diagnostic and Statistical Manual of Mental Disorders, DSM IV; Mean, Standard Deviation (SD); Major Depression Disease, MDD; Bipolar Disorder, BP.

Generally, patients with depression are judged as being able to give informed consent. Nonetheless, we required – without stipulation by the IRBs – in addition to the patient's own consent the agreement of the closest caregiver and requested a waiting period before signing the informed consent form of two weeks after the information meeting. The randomization to the treatment groups was carried out according to CONSORT (Consolidated Standards of Reporting Trials) (Moher et al., 2001a, 2001b) (see Fig. 1). Patients were recruited from their treating psychiatrist, responded to contributions in media, or were referred from the University Hospital outpatient clinic.

2.2. Magnetic seizure therapy (MST)

MST was performed using a MagPro MST device (MagVenture A/S, Denmark). Biphasic waveform stimulation, pulse width 370 μs, was delivered using a twin coil, containing two individual coils, each of a diameter of 13 cm. The pulse had a dampened cosine waveform. During the stimulation, the center of the coil was placed at the vertex. The peak magnetic field induced about 2 Tesla at the coil surface. At the beginning of each trial we treated with 100, 200, 300, etc. pulses in train (reflecting approximately 3x seizure threshold in ECT), afterwards we chose stimulation depending of the seizure threshold up to 600 pulses in a train. MST seizure threshold was defined as the minimum number of pulses required to induce a tonic-clonic seizure. Stimulation amplitude (i.e. an expression for power output level) was 100%. Stimulation frequency was 100 Hz and train duration up to 6 s. Repetition Rate was from 0.1 to 250 pps. To obtain comparability between all MST patients, the stimulation parameters were kept constant throughout the whole study.

2.3. Electroconvulsive therapy (ECT)

ECT was delivered with a Thymatron IV, ECT device (Somatics LLC, USA & Canada). Stimulus parameters are the following: