

Somatic therapies for treatment-resistant psychiatric disorders

Terapias somáticas para transtornos psiquiátricos resistentes ao tratamento

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Abstract

Objective: This paper reviews the current knowledge of somatic treatment in psychiatry, with a focus on treatment-resistant psychiatric disorders. **Method:** A computerized search of the literature was conducted on Medline using the words “electroconvulsive therapy”, “transcranial magnetic stimulation”, “vagus nerve stimulation”, “deep brain stimulation”, and “magnetic seizure therapy”. References from each paper were also screened. **Results:** The development of new non-pharmacological psychiatric interventions in the past decades has renewed the clinical and research interest in somatic therapies. Although electroconvulsive therapy remains the only somatic treatment with undisputed efficacy; transcranial magnetic stimulation, vagus nerve stimulation and deep brain stimulation all offer potential as novel means of psychiatric treatment. **Conclusions:** New treatment modalities still have an insufficient body of data. Notwithstanding, biological strategies continue to hold promise as a safer and more effective approach to psychiatric treatment.

Descriptors: Brain diseases; Electroconvulsive therapy; Transcranial magnetic stimulation; Vagus nerve; Deep brain stimulation

Resumo

Objetivo: O presente artigo é uma revisão do conhecimento atual relativo às terapias somáticas em psiquiatria, com foco em transtornos psiquiátricos resistentes ao tratamento usual. **Método:** Foi realizada uma pesquisa computadorizada da literatura no Medline utilizando as palavras “eletroconvulsoterapia”, “estimulação magnética transcraniana”, “terapia magnética convulsiva”, “estimulação do nervo vago” e “estimulação cerebral profunda”, com todos os termos traduzidos para o idioma inglês. Referências listadas em cada artigo foram também analisadas. **Resultados:** O desenvolvimento de novos tratamentos psiquiátricos não farmacológicos nas últimas décadas renovou o interesse em terapias somáticas. Apesar de a eletroconvulsoterapia continuar a ser o único tratamento somático com eficácia estabelecida, a estimulação magnética transcraniana, a terapia magnética convulsiva, a estimulação do nervo vago e a estimulação cerebral profunda são potencialmente novas modalidades de tratamento psiquiátrico. **Conclusões:** Novas modalidades de tratamento ainda padecem de falta de conhecimento científico adequado. Entretanto, estratégias somáticas ainda representam uma promessa como formas mais eficazes e seguras de tratamento psiquiátrico.

Descritores: Encefalopatia; Eletroconvulsoterapia; Estimulação magnética transcraniana; Nervo vago; Estimulação encefálica profunda

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Introduction

New advances in pharmacotherapy have had a remarkable impact on the course and outcome of psychiatric disorders. However, studies consistently demonstrate that a significant proportion of patients who receive drug treatments achieve minimal or no improvement in their symptoms. To date, electroconvulsive therapy remains the only non-pharmacological treatment with an adequate body of evidence that it is an effective resource for patients with symptoms refractory to pharmacotherapy. Notwithstanding, the continuous growth in the literature on neuromodulation over the past decades has led to an increased interest in research of new somatic treatments such as vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), and deep brain stimulation (DBS). Although these methods are relatively new, we will review here the data to date for each of these treatments.

Electroconvulsive therapy

Convulsive therapy was introduced by Meduna in 1934 as treatment for severe mental illnesses. The technique required the injection of camphor or pentylenetetrazol to induce a generalized grand-mal seizure, which is believed to be the therapeutic component of the treatment. In 1938, Ugo Cerletti introduced electroconvulsive therapy (ECT) by utilizing an electrical stimulus to produce the seizure; a technique proven to be much more reliable and effective than the use of chemicals. Subsequently, ECT has undergone multiple modifications and refinements that have improved the efficacy and tolerability of the treatment.

ECT remains the only biological treatment among those introduced during the first half of the 20th century that is still utilized in modern clinical practice, while treatments such as fever therapy, insulin coma and frontal lobotomy, introduced during the same era, were abandoned long ago. The primary reason that ECT is still in use is due to its unsurpassed efficacy in treating severe mental disorders when other treatment modalities have failed or when rapid life-saving intervention is necessary.

The scientific literature establishing the efficacy of ECT is among the most robust of any medical treatments. ECT is most commonly used for the treatment of major depression, typically in patients who failed to respond to psychotherapy and/or pharmacotherapy. It is also effective in a variety of conditions such as bipolar states (depressed, mixed and manic), schizophrenia and schizoaffective disorders, catatonia, neuroleptic malignant syndrome, post-partum psychosis, delirium, and some movement disorders.

A recent NIMH sponsored multi-center study by the CORE group illustrates the efficacy of ECT in depression.¹ In this study, the efficacy of continuation ECT and continuation pharmacotherapy (lithium plus nortriptyline) was compared in patients who responded to an acute course of ECT. In the acute phase (Phase I), patients with unipolar major depression referred for ECT received a course of three times weekly, bilateral (bifrontotemporal) ECT. A total of 531 patients were entered into phase 1 from May 1997 to January 2004. Of these, 341 (64.2%) remitted and 137 (25.8%) dropped out. Among completers ($n = 394$), 87% attained remission. Among patients with major depression with psychotic features who completed

the study, remission rates were strikingly high at 96%. Separate analysis of subsamples showed that more than half of the patients had an initial first response by the third ECT treatment.² Additionally, suicidal intent was a symptom particularly amenable to ECT; among patient that reported suicidal thoughts at baseline, 38.2% had no suicidal ideation after three treatments, and 61.1% were free of suicidal intent after six treatments.³ In this sample, history of resistance to pharmacotherapy did not predict poor response to ECT. However, other studies suggest that history of medication resistance is associated with decreased response rates to ECT, ranging from 50% to 60%.^{4,5}

No recent, well-designed, controlled studies evaluate ECT for treatment of mania, but available data indicate that it is a safe and effective option.⁶

The efficacy of ECT in schizophrenia is less clear. Results from nine, double-blind, controlled studies are mixed and difficult to interpret.⁷ Most studies used a limited number of ECT sessions, and did not include treatment resistant patients. Even so, among the six studies that used sham groups, three showed that the combination of ECT with antipsychotics is more effective than antipsychotics alone, while the remaining three studies demonstrated similar efficacy between groups. The possibility that a larger number of ECT sessions might result in further improvement in this population has yet to be determined.

In summary, ECT is the most effective treatment available for major depression, and is probably as useful for bipolar disorder episodes of all types. Schizophrenia is a lesser indication, but ECT could be indicated particularly for patients with treatment-resistant symptoms.

Transcranial magnetic stimulation

The first transcranial magnetic stimulation (TMS) devices, capable of delivering a pulse every 3 seconds, were developed as diagnostic aids for neurologists. In the late 80's, technical developments in the devices made it possible to apply trains of multiple stimuli per second. This form of TMS is called repetitive TMS or rTMS, and it can deliver pulses from 1 to 20 Hz. The magnetic pulse is delivered to the cortex through a hand-held stimulating coil applied directly to the head of the subject. The magnetic pulses pass unimpeded through the skull and induce an electrical current in the underlying tissue which, in turn, is able to depolarize neurons. Low-frequency (≤ 1 Hz) rTMS reportedly decreases neuronal excitability, while high-frequency (10-20 Hz) rTMS increases it. The sessions usually last for 30 minutes and are given 5 days a week. Treatment courses range from 2-4 weeks. The procedure requires neither anesthesia nor seizure induction, and it does not produce disorientation or clinically apparent cognitive side effects. Motor thresholds are used as parameters to determine stimulus intensity, and are defined as the minimum intensity required to elicit a twitch in a target hand muscle in 5/10 trials. Most treatment trials have used intensities between 80 and 120% of motor threshold. In a typical rTMS treatment the patients can return to daily activities immediately following the session. Although the majority of studies use high frequency stimulation (≥ 10 Hz) over the left dorsolateral prefrontal cortex (DLPFC), some authors have suggested that low frequency rTMS on the right DLPFC have similar results.⁸

1. rTMS for depression

The first study to suggest the efficacy of rTMS in depression was published in 1996 by Pascual-Leone et al.⁹ Based on previous data suggesting hypofunctioning of the left prefrontal cortex, the authors used high frequency rTMS over the left DLPFC in 17 patients with treatment resistant depression, in a within-subject, crossover design. After 5 days of treatment targeting the left DLPFC, patients, including those with psychosis, had marked decreases in depressive symptoms, while stimulation at other sites (i.e. right DLPFC, vertex) and sham had no effect. Since this initial auspicious study, a large number of papers have been published on rTMS and depression. However, studies with rTMS are laborious and expensive, and not surprisingly the vast majority of studies report on small samples. Therefore, the statistical power of the current evidence remains limited.

In a meta-analysis published in 2003, Martin et al. reviewed controlled trials that compared rTMS with sham, irrespective of placement or specific treatment parameters.¹⁰ The authors concluded that the data from 14 trials suggested that rTMS was statistically more effective than sham at treatment endpoint, with a small mean standardized difference of -0.35 for rTMS. However, this difference was not sustained 2 weeks later. The authors concluded that the trials were of low quality and provided insufficient evidence for rTMS use in depression. Other meta-analyses performed have also been limited by a paucity of high-quality studies, and reached comparable conclusions.¹¹⁻¹⁴ In a recent meta-analysis, Herman et al. attempted to address this limitation by using less stringent inclusion criteria.¹⁵ The authors included 33 studies, and found that the rTMS group had a mean reduction of 33.6% on depression scores, compared to 17.4% in the sham group. The effect size was 0.65 (95% CI = 0.51 to 0.79), suggesting a clinical significant effect for rTMS. However, the test for heterogeneity was highly significant ($p < 0.0001$), indicating that the variability in outcomes between studies was not due to chance. This implies that variation in rTMS procedures, as seen in the different studies had a marked impact on treatment efficacy. Since multiple regression analyses including treatment parameters and sample characteristics did not yield significant results, the optimal treatment procedures for rTMS remain unknown.

2. rTMS versus ECT

Initial studies comparing ECT to rTMS suggested that the two treatments had comparable efficacy rates. For instance, Grunhaus et al. randomly assigned 40 inpatients to treatment with up to 4 weeks of daily, left DLPFC rTMS or 2.5 x seizure threshold, right unilateral ECT.¹⁶ Both treatments had similar efficacy among nonpsychotic patients (approximately 60% response rate). However, ECT was strikingly superior among psychotically depressed patients. A later study by the same group used a similar method in 40 patients with severe depression without psychotic features.¹⁷ The initial results were replicated, with an overall efficacy of 58% and no significant difference between treatments. Janicak et al. randomized severely depressed patients to rTMS or ECT, with no significant difference in efficacy between the two treatments in 22 patients (rTMS-55%, ECT-64%).¹⁸ Comparable results were found by Pridmore et al., as ECT had a trend toward superiority (66.4% improvement in depression ratings with ECT as compared to 55.6% for rTMS).¹⁹ It is possible that larger samples would have yielded significant results. Nonetheless, it

is notable that these underpowered studies demonstrated an emerging trend in favor of ECT, albeit not statistically significant or significant only on isolated measures. Also, some authors²⁰ suggest that efficacy rates for rTMS in these studies – around 50% reduction in Hamilton Rating Scale for Depression (HRSD) scores – are higher than other rTMS studies, suggesting a possible bias due to a lack of blinding. In a more recent multi-center, controlled trial, 46 patients were randomized to ECT versus rTMS.²¹ Despite relatively low dose right unilateral ECT and small number of ECT treatments (mean of 6.3), ECT was markedly superior to rTMS. While 59.1% of patients who received ECT remitted, remission rates were only 16.7% in patients treated with rTMS.

3. rTMS for Mania

Based on observations in healthy subjects that the application of rTMS to left prefrontal cortex increased sadness, in contrast to increased happiness with right prefrontal stimulation, Grisaru et al. tested the hypothesis that the laterality of mania may be opposite to that of depression.²² They enrolled 16 patients on a 14-day double-blind, controlled trial of right versus left prefrontal fast rTMS. They noted that right prefrontal rTMS was significantly more effective than left, and resulted in a 35% reduction in the Young Mania Rating Scale scores. However, a subsequent controlled study from the same group²³ did not replicate the antimanic effect of right active rTMS versus right sham rTMS. The authors argued that the previous results could be due to an effect of left rTMS to worsen mania, as an antidepressant might. Two subsequent reports found that fast rTMS produced a sustained reduction of manic symptoms in 17 bipolar patients.^{24,25} Unfortunately, due to the open case-series design of these reports, no causal relationship between rTMS treatment and reduction of manic symptoms could be clearly established.

4. rTMS for Schizophrenia

Studies of rTMS in schizophrenia struggle with the optimal location of cortical targeting. Most of the methods utilized were based on neuroimaging studies that indicate that negative symptoms are associated with reduced activity in the DLPFC while positive symptoms are associated with the activation of right and left superior temporal cortices and left temporoparietal cortex (TPC). Consequently, treating negative symptoms would require fast rTMS of the DLPFC, while positive symptoms would require slow rTMS over the TPC. Indeed, initial trials that used different methods failed to show any efficacy of the treatment. One open trial with 10 subjects that evaluated fast rTMS over both DLPFC,²⁶ as well as a second that evaluated slow rTMS on left DLPFC on 10 patients²⁷ failed to show any improvement on positive or negative symptoms. However, Cohen et al.²⁸ showed that fast rTMS the left DLPFC caused significant reduction in negative symptoms in six individuals with chronic schizophrenia and similarly, Sachdev et al.²⁹ described good results for negative symptoms with high frequency rTMS on left DLPFC in four patients, which were maintained at the 1-month follow-up.

Results from controlled studies are conflicting. The first study published evaluated slow stimulation of the right DLPFC in 35 subjects with schizophrenia or schizoaffective disorders.³⁰ Patients were randomized to receive active or sham stimulation. At the end of the study, both groups showed a similar mild improvement on the positive and negative syndrome scale (PANSS), without statistical difference between groups. Most subsequent studies used slow rTMS over the left TPC. The data suggest that this method is at least moderately efficacious in reducing hallucinations, but with no impact on overall psychopathology. For example, the largest study with rTMS in schizophrenia evaluated slow rTMS over left TPC in 50 individuals with severe auditory hallucinations.³¹ Patients were randomized to receive active or sham treatment for 9 days. At endpoint, an individualized scale detected significant improvement in hallucinations with the active treatment, but there were no differences between groups in the total scores of the PANSS. Overall, studies repeatedly indicate an effect of slow rTMS over the left TPC on hallucinations. One paper showed no difference between slow rTMS on left or right TPC, with both being effective for hallucinations.³² Only one study on rTMS over TPC failed to show any superiority over sham.³³

Fast rTMS over the left DLPFC was used in four controlled studies. While in two studies active treatment was superior in reducing BPRS scores³⁴ or negative symptoms;³⁵ two other studies with a total of 38 patients failed to detect any significant benefits over sham.^{36,37} Finally, Schonfeldt-Lecuona et al. used stereotactically guided rTMS over Broca's area and over the superior temporal gyrus, but no significant reduction of hallucination severity was noted.³⁸

In summary, research to date has failed to provide unequivocal evidence of rTMS as an effective treatment tool for the treatment of schizophrenia symptoms. However, promising therapeutic effects for the reduction of hallucinations when TPC is targeted using slow-frequency rTMS were noted. Future trials will likely need to address questions regarding optimal cortical targeting and treatment parameters to achieve more convincing results.

5. rTMS for other psychiatric disorders

Zwanzger et al. demonstrated a reduction in panic symptoms with a marked improvement of anxiety in an open case study of a patient treated for 2 weeks with slow rTMS to the right DLPFC.³⁹ Two other reports report that rTMS can be useful in the reduction of panic symptoms, but in both cases patients presented with comorbid depression, making interpretation of results difficult.^{40,41} Finally, in a recent double-blind study, slow rTMS over the right DLPC was unable to prevent panic response induced by cholecystokinin-tetrapeptide infusion.

rTMS was also evaluated for the treatment of obsessive compulsive disorder (OCD), but results were mixed. Greenberg et al. administered rTMS to a right lateral prefrontal, a left lateral prefrontal, and a midoccipital (control) site.⁴² In this blinded trial compulsive urges decreased significantly for 8 hours after right lateral prefrontal rTMS. Subsequently, in an open trial with 12 OCD individuals, Sachdev et al.⁴³ showed that right or left prefrontal fast rTMS resulted in reduction in some Yale-Brown Obsessive Compulsive Scale (Y-BOCS) subscales, although not in total scores. However, a subsequent double-blind study using right prefrontal 1 Hz rTMS failed to

find significant effects on 18 OCD subjects.⁴⁴

In conclusion, rTMS has raised considerable interest as a potential tool for the treatment of psychiatric disorders. Moderate effects are described in the treatment of depression, some schizophrenia symptoms and possibly mania. However, since pressing questions regarding optimal treatment parameters and cortical targeting are still unanswered, more research is still needed to define the place of rTMS in the psychiatric treatment armamentarium.

Vagus nerve stimulation

VNS has been commercially available for the treatment of resistant partial-onset seizures in epilepsy in Europe since 1994, and in the United States since 1997. The stimulation is delivered through a pulse generator implanted in the left chest wall. The generator's bipolar lead is wrapped around the left vagus nerve near the carotid artery, and is connected to a subcutaneous generator. The procedure for implantation requires two incisions, and is commonly performed under brief general anesthesia. Stimulation parameters are adjusted with a programming wand that communicates with the generator. Patients may turn off the stimulation when needed by holding a magnet over the generator. The most common side effects are voice alteration, dyspnea, and neck pain. The surgical procedure carries very low risks of infection, vocal cord paralysis (temporary), and bradycardia or asystole.

The interest in VNS potential as a treatment for depression was borne from observations of mood improvement in patients originally studied for treatment of partial seizures with the technique, even when the treatment was not effective for seizure therapy. Rush et al. conducted the first study to evaluate VNS efficacy in treatment-resistant depression.⁴⁵ In this multicenter, open-label study, 30 patients had a VNS device implanted. It was turned on after completion of a 2-week, post implantation, single-blind "recovery period". Patients were included if they had failed 2 or more antidepressant medications from differing medication classes within the current depressive episode and had demonstrated no clinical improvement with psychotherapy. Baseline score on the Hamilton Depression Rating Scale was 38 ± 5.5 . Patients were allowed to continue antidepressants and mood stabilizers. After 10 weeks, response rate was 40%, and remained stable after 9 months of follow-up (46%). Furthermore, a significant increase in remission rate from 17% to 29% was noted at follow-up. Of note, only seven patients with history of no response to electroconvulsive treatment were included, and of those only one showed improvement with VNS. The study was extended in a subsequent report, with the addition of 29 patients.⁴⁶ Overall, 30.5% of the patients met criteria of response, i.e. reduction of 50% or more on the Hamilton Rating Scale for Depression (HRSD), and only 15.3% had complete remission ($HRSD \leq 10$). The authors noted that the poor response could be explained by the fact that the additional sample was characterized by patients with a history of resistance to ECT, as well as a significantly higher number of unsuccessful antidepressant trials during the current episode. In a 2-year follow-up study of the sample, response rate had a nonsignificant increase to 44.1% at 12 months, and to 42.4% at 24 months.⁴⁷

From the same research group came the first randomized study on VNS.⁴⁸ Two hundred and thirty-five patients with

unipolar or bipolar depression were randomized to receive adjunctive VNS or sham. After 10 weeks of treatment, no significant difference on the primary outcomes between active treatment (15.2% reduction on HRSD) and sham (10.0% reduction) was noted. The authors then followed a subsample ($n = 202$) of the acute phase for 12 months in a naturalistic study.⁴⁹ The continued treatment with VNS for 1 year yielded a response rate of 27.2% and a remission rate of 15.8%. The same patients were then compared with a separate cohort of 124 patients with treatment resistant depression, originally enrolled in a unpublished study.⁵⁰ The comparison of these two similar but nonrandomized cohorts followed naturalistically suggested that adjunctive VNS therapy might double the odds for response at 1 year (27% response) as opposed to treatment as usual alone (12%).

Current trends: VNS received approval from the FDA on July, 2005, for "adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode (MDE) and have not had an adequate response to four or more adequate antidepressant treatments." However, it remains a somewhat controversial treatment for refractory depression, mostly due to the absence of unequivocal proof of its efficacy. Also, the relatively high cost associated with the device, the invasive nature of the procedure, and the relative lack of clear parameters of treatment are clear pitfalls in the widespread use of VNS. Therefore, there is a clear need for further controlled trials with long duration and sufficient number of subjects.

Deep brain stimulation

After Benabid et al. showed that electrical stimulation of the brain resulted in clinical benefits comparable to those of surgical ablation, DBS became an established treatment for movement disorders.⁵¹ Due to its adjustability, it has been steadily replacing ablation therapies. In DBS, electrodes with four stimulation sites each are implanted bilaterally under stereotactic guidance. The procedure is performed under local anesthesia. A pulse generator is implanted subcutaneously beneath the clavicle, and connected to the electrodes through an extension. After activation, the stimulator remains active 24 hours a day, and parameters can be adjusted via telemetric wand. The stimulation unit in DBS is a rectangular waveform pulse. Its duration, amplitude and frequency are adjustable. Risks from surgical implantation include symptomatic hemorrhage, infection and seizure, which can occur in about 1% to 4% of cases each. These events usually respond to treatment or resolve without serious sequelae.

1. DBS for obsessive compulsive disorder

Obsessive-compulsive disorder (OCD) seems the most obvious indication for DBS in psychiatry, since some patients with refractory diseases can benefit from stereotactic interventions. The most useful hypothesis is that a dysfunction in the neural circuits that connect frontal lobe and basal ganglia are involved in OCD symptoms.⁵² The fibers of these loops are believed to pass through the anterior limb of the internal capsule.

In 1999 Nuttin et al. reported four cases of patients with severe OCD that were treated with DBS in the anterior limbs of the internal capsules.⁵³ Three patients had some clinical

improvement, and no significant side effects were noted. The three patients were followed for up to 39 months. Two patients had sustained improvement of symptoms, as measured by the Y-BOCS. No side effects and no deleterious impact on neuropsychological measures were noted. Anderson and Ahmed⁵⁴ reported one case of successful DBS on the anterior limbs of the internal capsule for refractory OCD. Aouizerate et al. reported the treatment of a patient with intractable severe OCD and concomitant major depression with DBS.⁵⁵ In this case, the authors implanted the electrodes in the ventral caudate nucleus. Depression and anxiety improved 6 months after the start of stimulation and remission of OCD was observed after 1 year, with a progressive increase in the level of functioning. No neuropsychological deterioration was observed. Further suggestion of the efficacy of DBS in OCD came from a blinded, randomized, crossover study from Nuttin et al.⁵⁶ The authors treated four patients with severe OCD with DBS in both anterior limbs of the internal capsules. Clinical assessments were blinded. Three patients had improvement with the treatment, with at least 35% reduction in Y-BOCS scores. These patients had worsening of symptoms when the stimulator was turned off, with scores returning to baseline level.

2. DBS for depression

Few studies have focused on DBS for the treatment of depression. Recently, based on data that suggests that a decrease in activity of the subgenual cingulate region (Brodmann area 25) is associated with antidepressant response, Mayberg et al. studied whether DBS of BA25 could produce clinical benefit by reducing its activity in six patients with severe medication resistant depression.⁵⁷ After 6 months of treatment, four patients experienced reduction of 50% or more in HRSD scores. Antidepressant effects were associated with a marked reduction in local cerebral blood flow, as well as changes in downstream limbic and cortical sites, as measured with positron emission tomography. More controlled trials in larger samples will be needed to test the utility of this approach, which carries the strength of being able to focally target and chronically stimulate the implicated circuitry. Finally, Kosel et al. presented a case of a patient with treatment refractory depression and tardive dyskinesia treated for 18 months with DBS to the globus pallidus internus bilaterally.⁵⁸ At the end of the treatment, the patient had a 42.3% reduction on HRSD scores and a 35% reduction on the Burke-Fahn-Marsden Dystonia Rating Scale.

The use of DBS is a promising therapeutic tool for the treatment of selected psychiatric disorders resistant to conventional treatment. It has advantages over the more invasive and irreversible ablation techniques and it holds the promise of elaborating the existing neurocircuitry models of depression. However, in light of the lack of large studies, with double-blind methods and strict definitions for treatment-resistant conditions, no conclusions on the efficacy of DBS can yet be reached.

Magnetic seizure therapy

MST is an investigational treatment that consists of an induction of a seizure for therapeutic purposes using repetitive transcranial magnetic stimulation (rTMS). MST is under development as a more focal form of convulsive therapy

proposed as a means of reducing the side effects of ECT, while possibly retaining its efficacy. The rationale is that the alternating magnetic fields produced by rTMS would be able to penetrate the scalp and skull with no resistance, leading to a more precise site of seizure initiation and greater extent of cortical stimulation. This would possibly be an advantage over the high impedance seen in ECT. The first patient to receive MST was a 20 year-old female, with a history of a 3-year episode of depression, refractory to multiple antidepressant trials.⁵⁹ MST was administered three times per week, under the same general anesthetic regimen as used for ECT. MST generated generalized tonic-clonic seizures, and after the fourth treatment the patient presented with a 35% reduction on the HRSD score, with no reduction in the patient's mini mental examination. A second report described a patient with depression resistant to pharmacological treatment who received 12 MST sessions.⁶⁰ The patient experienced remission with an 82% drop in HRSD₂₄ and final HRSD₂₄ = 6. Also, MST was associated with fast posttreatment recovery, and no significant side effects.

To determine if MST has a better side effect profile, Lisanby et al. compared its acute cognitive side effects with those of ECT.⁶¹ Ten inpatients diagnosed with major depressive episode were enrolled in this within-subject, randomized, blinded trial. Each patient received a course of convulsive therapy in which two of the first four treatments were MST and the remaining treatments were conventional ECT. Blinded neuropsychological assessments and side effects ratings were obtained before and after each treatment. MST treatments were associated with fewer side effects, and patients regained orientation more quickly after MST than after ECT. Finally, some neuropsychological measures were superior after MST, notably attention, retrograde amnesia and category fluency.

Unfortunately, no further controlled studies have been published. In summary, MST is a promising strategy for treatment of depression, but its clinical value is still unknown. Most questions regarding the treatment, such as optimal technical parameters for the device, site of stimulation, dosing and schedule of treatment are still to be answered.

Conclusion

While the efficacy of ECT is undisputed, the place for other biological treatments in psychiatry is still unclear. Most treatment modalities still have an insufficient body of data, and basic questions regarding optimal technique and treatment parameters remain to be answered. Notwithstanding, biological strategies continue to hold promise as a safer and more effective approach to psychiatric treatment.

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