Clinical Applications of Neuromodulation in Psychiatry

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Pedro Shiozawa, Rosamaria Raza, Quirino Cordeiro Jr., and André Russowsky Brunoni

Major Depressive Disorder

Major depressive disorder (MDD) is an incapacitating disorder associated with significant personal, social and economic impairment. Patients with MDD present a "double burden," characterized by a lower quality of life associated with a higher prevalence of medical comorbidities [1]. The main symptoms of MDD include persistent low mood, anhedonia (i.e., diminished pleasure in previous significant activities), impairment in sleep, psychomotor retardation, weight changes, and negative thoughts that range from pessimism to guilt and suicidal ideation (Table 14.1). Moreover, although only the most severe spectrum of depression is associated with suicide, its chronic, incapacitating symptoms make depression one of the most incapacitating conditions worldwide. Thus, MDD has been projected to be the second most disabling condition by 2020 [2]. Since MDD is known to be a recurrent and relapsing psychiatric condition, approximately 50 % of the patients who present a depressive episode shall undergo a new episode further in life [3]. Finally, nearly 30 % of patients present themselves in a refractory state, i.e., when depressive symptoms are observed despite the appropriate psychological and pharmacological treatment [4]. For these reasons, continuous research on MDD in terms of newer treatment techniques presents itself as a mandatory need.

P. Shiozawa (✉)
Laboratory of Clinical Neuromodulation, Santa Casa Medical School, 1 Rua Major Magliano 241, Sao Paulo, Brazil
e-mail: pedroshiozawa@gmail.com

R. Raza • Q. Cordeiro Jr.
Department of Psychiatry, Santa Casa Medical School, São Paulo, Brazil
e-mail: rosamaria.raza@yahoo.com.br; qcordeiro@yahoo.com

A.R. Brunoni
Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil
e-mail: brunowsky@gmail.com; Brunoni@usp.br

Pharmacotherapy

Antidepressant drugs are considered the pillar stone when analyzing treatment approaches for depression. The pharmacological arsenal includes first-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors), SSRIs (serotonin selective reuptake inhibitors, such as sertraline and fluoxetine), serotonin–norepinephrine reuptake inhibitors (SNRIs) ("dual-inhibitors," such as venlafaxine and duloxetine), and others (e.g., bupropion and mirtazapine). A recent meta-analysis suggested that escitalopram and sertraline are the antidepressants that best combine effectiveness with tolerability and therefore should be the first choice for treatment [5]. Given the multiple pharmacological treatments available, the STAR*-D (Sequenced Treatment Alternatives to Relieve Depression), a NIMH-sponsored trial, enrolled almost 3,000 patients to evaluate the efficacy of several antidepressant treatments [4]. STAR*-D highlighted the importance of refractoriness in pharmacotherapy, i.e., remission rates decay as more antidepressant treatments fail—in fact, after four consecutive antidepressant interventions, 30 % of patients still present depression symptoms. Also, different meta-analyses [6–8] observed that dropout rates are relatively high (20–30 %) irrespective of the drug class assessed—the causes of dropouts are multiple and include side-effects, time gap observed from the initial treatment and consequent improvement of depressive symptoms and patient–physician relationship [9] all of each can increase relapse rates in the long-term. These issues reinforce the need for newer interventions in the treatment of MDD.

Neuromodulation Strategies

Noninvasive brain stimulation (NIBS) stands as a general term used to describe techniques that might aid to overcome some of the current challenges that both pharmacological and psychotherapy undergo. Ideally, NIBS techniques

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Table 14.1 Diagnostic criteria for MDD and main clinical symptoms of depressive episode according to DSM-IV [122]

Diagnosis criteria for MDD
A. Presence of two or more Major Depressive Episodes.
B. The Major Depressive Episodes are not better accounted for other psychiatric disorder
C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.
Main clinical symptoms of Depressive Episode
Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others
Markedly diminished interest or pleasure in all, or almost all, activities most of the day
Significant weight loss when not dieting or weight gain
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

MDD major depressive disorder

should not only be as effective as pharmacotherapy but should also present a lower rate of adverse effects, thereby increasing treatment adherence.

Neuromodulation techniques include old techniques such as electroconvulsive therapy (ECT) to novel clinical and preclinical techniques, such as transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), and trigeminal nerve stimulation (TNS). Since these techniques are still considered to be unfamiliar to both most of the medical community and to the general public, a cited description of its physiological mechanism is necessary.

Electroconvulsive Therapy

ECT is one of the most effective treatments for acute depression, especially when psychotic features and/or severe acute suicidal ideation are present. ECT was the first neuromodulatory therapy, initially described by Cerletti and Bini (1940), who were in fact investigating safer alternative therapies for therapeutic seizures against the most used strategies at the time (e.g., intramuscular injection of camphor oil, malaric fever, and so forth). In 1938, these two psychiatrists successfully treated one psychotic patient with 11 cycles of ECT [10]. This technique, however, would only become widespread by the end of World War II.

The energy provided by the ECT is approximately 100 J with a peak pulse in the order of 8 A, which lasts from 0.5 to 2 ms. In fact, the induced seizure—and not the electric charge itself—is considered responsible for the observed antidepressant effects [11].

The UK ECT review group [12], in a systematic review and meta-analysis of different ECT protocols, found that active ECT was more effective than (a) sham ECT (difference in Hamilton scores of 9.7; Confidence Interval [CI], 95 % between 5.7 and 13.5), (b) antidepressant drugs (difference 5.2 points, 95 % CI 1.4–8.9); and that bilateral ECT was more effective that the unilateral protocol (reduction of 3.6 points, 95 % CI 2.2–5.2). Currently, ECT is considered the most effective treatment for the acute depressive episode and is particularly suitable for severely ill patients with suicidal ideation and/or psychotic depression [13]. ECT devices, in spite of a vast range of clinical protocols, use preestablished and independent (within certain limits) amplitudes of pulse determined by the impedance found in each electrical circuit. Some devices allow the physician to specify the stimulation parameters (frequency, width, current, and duration) towards a more individual approach. Shorter pulse durations appear to be more effective in inducing seizures, and increases in stimulus duration may be more effective than increases in frequency. The main clinical indications for ECT are summarized in Table 14.2.

Nevertheless, ECT has some important limitations. It requires anesthesia and, therefore, specialized personnel and adequate medical apparatus for advanced life support. When considering cognitive effects, although anterograde amnesia is relatively common and self-limiting, Sackeim and colleagues [14], in an observational study with 751 patients with MDD who underwent ECT, showed significant impairment in several neuropsychological tests, with an emphasis on attention and memory performance worsening. In terms of safety, some possible adaptations have been suggested in different studies: right unilateral stimulation (vs. bilateral), short pulse (vs. sinusoidal), ultrashort pulse, use of smaller doses, and limiting the total number of sessions [15–17]. Other frequent ECT collateral effects include headache and myalgia [18].

Therefore, ECT is a biological alternative in the treatment of MDD, particularly suitable for the most severe cases [19]. Moreover, difficulties inherent in the application of the technique (sedation, number of sessions) associated with the side

Table 14.2 Main clinical indications for ECT

Catatonia or other psychotic symptoms
Severe risk of suicide
History of prior good response to ECT
Need for rapid, definitive treatment response on either medical or psychiatric grounds
Risks of other treatments outweigh the risks of ECT (i.e., comorbid medical conditions make ECT the safest treatment alternative)
History of poor response to multiple antidepressants
Intolerable side effects to all classes of antidepressant medications (e.g., seizures, hyponatremia, severe anxiety)
Patient preference

ECT electroconvulsive therapy

Table 14.3 Summary of rTMS parameters for depression protocols

Parameter	Summary
Stimulation site	Regarding left vs. right stimulation, the accumulated evidence favors the former as more studies were performed stimulating the left DLPFC
Frequency of trains	Most low-frequency protocols use 1 Hz or less; while high-frequency stimulation ranges from 5 to 20 Hz with more recent studies favoring the 10 Hz-frequency
Intensity of stimulus	Vary from 80 to 120 % MT; issue of safety needs to be addressed
Frequency of sessions	Usually delivered daily in weekdays (5 sessions per week) although some studies used different protocols such as three times a week or two times per day
Duration of treatment	Vary from 10 to 30 sessions

DLPFC dorsolateral prefrontal cortex, *MT* motor threshold

effects cited previously and the risk of cognitive impairment in the long-term exposure represent a limitation of the technique [20], which is intended to be overruled with newer neuromodulatory therapies.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Transcranial magnetic stimulation (TMS) was first introduced as a neurophysiological technique in 1985, when Anthony Barker and his team developed a compact machine that allowed noninvasive stimulation of the cerebral cortex [21]. TMS is based on the physical property that an electric current can generate a varying magnetic field which in turn induces a new electric current over a conductive material. In humans, the TMS coil is placed over the scalp above the targeted stimulation area. The resulting magnetic field is perpendicular to the electric field. In the case of a circular coil, the magnetic field is stronger near the outer circumference of the coil and weaker near the center. The magnetic field can activate neurons at a depth of 20–30 mm over an area of 30 mm long by 20 mm wide reaching mainly cortical areas.

RTMS for MDD typically involves 10–30 treatment sessions of 15–45 min. duration, administered once a day, 5 days a week on an outpatient basis. For MDD, the dorsolateral prefrontal cortex (DLPFC) is the targeted area; typical protocols apply either high-frequency, excitatory stimulation to the left DLPFC or low-frequency, inhibitory stimulation to the right DLPFC. There are two types of rTMS of interest in MDD: (1) low-frequency rTMS (<1 Hz) that is applied over the right DLPFC to induce a decrease in cortical excitability, and (2) high-frequency (>5 Hz, typically 10–20 Hz) rTMS that is applied on the left DLPC to increase cortical excitability. Both approaches induce neuroplasticity changes in the targeted areas [18] (Tables 14.3 and 14.4).

Table 14.4 Adverse effects related to rTMS

Adverse effects
Seizure and syncope
Cognitive impairment
Headache
Nausea
Pain
Manic episodes
Motor effects
Sleep/tiredness

rTMS repetitive transcranial magnetic stimulation

The rationale for rTMS in the depression treatment is based on the hypothesis that the DLPFC is hypoactive in patients with depression—therefore high-frequency rTMS on this area could restore its activity to physiological levels. The use of low-frequency rTMS over the right DLPFC is based on the prefrontal cortical asymmetry theory that states that the left DLPFC is relatively hypoactive whereas the right DLPFC is relatively hyperactive in MDD [22, 23].

An important phase III study using rTMS for MDD was performed by O'Reardon et al. [24]. In this trial, 301 patients with depressive disorder without concurrent antidepressant therapy were enrolled. RTMS was performed at a 10 Hz frequency (120 % of the motor evoked potential, MEP), 3,000 pulses per session for 4–6 weeks. Active rTMS was statistically superior to sham intervention in terms of improvement in depressive symptoms, which was assessed through the Hamilton Rating Scale for Depression. Despite the positive results obtained, there was only a trend for superior active rTMS efficacy considering the primary outcome that employed the Montgomery–Åsberg Depression Rating Scale (MADRS), which resulted in conflicted doubt regarding rTMS's efficacy. This issue was finally resolved in another multicentric randomized controlled trial [25], which evaluated rTMS effects in 199 depressed patients using a 10 Hz frequency stimulation (120 % MEP), with 3,000 pulses per session for 3–6 weeks. The authors found that patients who underwent active rTMS stimulation had 4.2 times greater chance of meeting remission rates scores than patients receiving sham stimulation (95 % confidence interval, 1.32–13.24), with remission rates of 14.1 % and 5.1 % for active and sham rTMS, respectively. Recent meta-analyses confirmed the efficacy of two rTMS modalities: both high-frequency rTMS over the left and low-frequency rTMS over the right DLPFC are effective for MDD [26, 27].

Long-lasting effects are unclear in medical literature as follow-up studies are still incipient [28]. Cohen and colleagues [29] followed 204 patients performing rTMS every other week. The mean time remission period was of 120 days. Demirtas-Tatlidede et al. [30] followed 16 patients for 4 years performing rTMS protocols when the patients relapsed. The mean period free of depressive symptoms were 5 months. Fitzgerald et al. [31] showed that the time of relapse was 10 months in a sample of 19 patients, who also had clinical response for repetitive rTMS protocols. To some that, O'Reardon and colleagues [32] followed ten patients for a period varying from 6 months to 6 years, with weekly or twice a week maintenance of rTMS sessions. At the end of follow-up, only two patients presented remission of symptoms with exclusive rTMS maintenance therapy. Further studies are necessary to establish the optimal rTMS protocols on the maintenance phase of MDD treatment.

The adverse effects of rTMS procedures are generally well tolerated. Although discomfort and facial pain are common symptoms, only a small percentage of patients discontinued treatment due to these symptoms [33]. Another concern is the risk of seizures, which is, in fact, very low for healthy subjects [33]. There are other potential adverse effects, represented by a more rare incidence, which includes: syncope due to a vasodepressor related mechanism, headache, and acute psychiatric changes such as induced mania for bipolar patients (0.84 % mania for active rTMS vs. 0.73 % for sham rTMS) [34].

Currently, rTMS can be considered an interesting therapeutic tool due to its mild side effects and potentially satisfactory clinical outcomes [28]. However, the relatively high-cost for rTMS application remains as an important limitation. In a study carried by Simpson and colleagues, the cost-effectiveness of the technique in question, was analyzed. They concluded that therapy through rTMS had a satisfactory cost-effectiveness when compared to standard antidepressant regimens [35].

In conclusion, rTMS is a safe, well-tolerated strategy, which has been recently approved in several countries as a treatment for Major Depressive Disorder. Given the high-costs, the need of specialized staff for delivering rTMS and the uncertainty regarding its long-term effects, these current limitations still reinforce the need for further research.

Transcranial Direct Current Stimulation

The rationale behind the use of tDCS for depression is based on its properties for increasing (anode) and decreasing (cathode) cortical excitability [36]. Some initial clinical trials showed significant depression improvement. Fregni et al. in a sham-controlled, randomized clinical trial, found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active stimulation with 1 mA for 20 min once a day [37]. The mean reduction in the depression scores were between 60 and 70 % for active tDCS group when compared to the baseline values. Similar results were demonstrated in a posterior study with antidepressant-free patients [38].

Rigonatti et al. [39] compared the clinical effects of active prefrontal tDCS vs. a 6-week treatment protocol with 20 mg/day fluoxetine finding that the effects of both therapies were similar.

Another study investigated the long-lasting antidepressant effects of tDCS. The authors evaluated a protocol of ten tDCS sessions with 2 mA [40]. A total of 40 patients with moderate to severe major depression without current use of antidepressants were included and randomly assigned to prefrontal (21 patients), occipital (9 patients), or sham stimulation (10 patients). Depressive symptoms were assessed before, immediately after, 15 and 30 days after stimulation. Only prefrontal tDCS reduced depressive symptoms significantly—reaching approximately 40 % of baseline ratings, and these effects were stable 30 days after the last stimulation session. Loo et al. [41] did not find significant differences between active tDCS and sham stimulation in a double-blind randomized study including 40 outpatients with depression. Treatment was provided for five treatment sessions, 3 days per week, with anodal stimulation over the left DLPFC at 1 mA for 20 min. In a more recent trial, this same group enrolled 64 participants with current depression to

receive active or sham anodal tDCS to the left prefrontal cortex (2 mA, 15 sessions over 3 weeks), followed by a 3-week open-label active treatment phase. There was a significant improvement in mood after active compared to sham treatment ($p < 0.05$).

Ferrucci and colleagues [42] used tDCS in patients with severe depression applying 2 mA per day, twice a day for five consecutive days demonstrating an improvement that reached near 20 % on diminishing depressive symptoms. Brunoni et al., in a study with 31 patients, found that the same protocol was effective in patients with bipolar depression [43], with a mean reduction of 18 % in clinical symptoms. Another recent open study [44], demonstrated the efficacy of the same protocol in a group of 23 patients with refractory depression reducing symptoms in 25 %. Finally, Martin et al. [45] performed tDCS sessions consecutively for 20 days, with 2 mA for 20 min, in 11 patients with depression. In this open study, which placed the cathode on the right deltoid muscle, the reduction of symptoms was around 44 %.

Recently, a systematic review and meta-analysis [46] reviewed the efficacy of tDCS for MDD treatment, showing that active vs. sham tDCS is an effective treatment for MDD. However, there is still a need for further studies investigated tDCS efficacy in depression, as there was significant between-study heterogeneity in the reviewed trials.

Deep Brain Stimulation (DBS)

DBS consists on the implantation of an electrode in subcortical areas, with further application of an electrical current of 130–180 Hz. This preferred region is the subgenual cingulate area, since this area is hyperactive in depression, with partial normalization of its activity after antidepressant treatment [47]. The literature concerning DBS for depression is scarce, since there are few studies on the matter. One recent open label trial enrolled 17 patients with severe depression who were followed for 2 years, with significant improvement of mood symptoms [48]. Another study [49] enrolled six patients with treatment resistant depressive disorder to receive DBS. The authors found a sustained remission of depression among four out of six patients and hypothesized by neuroimaging assessment that disrupting focal activity in limbic-cortical circuits may be a key target of novel neuromodulation approaches.

Further follow-up data was obtained from an extended cohort of 20 patients with treatment resistant depression who underwent DBS for 3–6 years (mean 3.5 years) showing an average response rate of 64.3 % and an average remission rate of 42.9 % in depressive symptoms. Patients showed considerable improvement in social functioning and in the degree of involvement in work-related activity [50].

Cranial Nerve Stimulation

Vagus nerve stimulation (VNS) procedure stands for the disposal of a bipolar electrode around vagus nerve and further dissemination of low frequency electric pulse from the nerve towards central nervous system. The stimulation can be performed in several ways as with surgical implantation of electrodes around vagus nerve or transcutaneously. Electric stimulation of the nerve provides direct modulatory effect in subcortical sites. The specific network activated during the procedure varies according to certain parameters, suggesting that with more extensive knowledge, one could "direct" the VNS signal within groups of patients or even individually.

Recently, Mohr et al. found, in review of four clinical trials ($n = 355$) using VNS for resistant depression, a steadily increasing improvement of depressive symptoms after 6–12 months, which sustained up to 2 years follow-up. Bajbouj and colleagues [51], in an open label study analyzed 74 patients diagnosed with treatment-resistant depression, showing clinical response and benign adverse effects over a 2-year follow-up.

Safety-wise, Gerson et al. [52] described a case in which VNS treatment in a patient with epilepsy and unipolar depression was associated with the rapid development of manic symptoms. Another study described, in a sample of nine patients, transitional changes of time perception with vagus nerve stimulation (VNS), which was considered a minor, but relevant collateral effect [53]. When analyzing the cardiovascular risk, the same research group pointed VNS as a safe therapeutic strategy for treating depressive disorder [54]. Further collateral effects presented in literature include cough and vocal disturbances.

Another site of stimulation is the trigeminal nerve (TNS), which is performed in a 120 Hz frequency with pulse wave duration of 250 μs and cycle of 30 s. Electric stimuli determine an asymmetrical biphasic pulse wave adjustable from 0 to 100 mA. The trigeminal nerve conveys information to important structures in the brain including the nucleus solitarius, the locus coeruleus, the vagus nerve and the cerebral cortex. It also specifically sends signals to the anterior cingulate cortex, which is involved in mood, attention and decision-making. Shraeder et al. treated five patients (60 % female; man age: 49.6 years) with treatment-resistant depression who received TNS for 8 weeks. The authors verified depressive-symptoms remission rates up to 70 % among patients in a 2-month follow-up [55].

Table 14.5 Summary of rTMS studies with bipolar depression

Study	Sample	Age (years)	Stimulation site	Stimulation frequency	Design	MEP (%)	Control	Use of medication
Tamas 2007 [64]	4	44.5	Right DLPFC	1	Double blind, randomized	95	1 Sham, 3 active	Yes
Dell'Osso 2009 [65]	11	54.4	Right DLPFC	1	Open label	110	110	Yes
Nahas 2003 [63]	23	43	Left DLPFC	5	Blind, randomized	110	No	Yes
Huang 2008 [123]	46	44	Left DLPFC	5	Open label	100	No	Yes
Dolberg 2002 [62]	20	54	–	–	Double blind, randomized	–	10 Sham, 10 active	–

DLPFC dorsolateral prefrontal cortex, *MEP* motor evoked potential

Bipolar Disorder

Bipolar disorder (BD) is a recurrent, chronic and severe disease. It causes significant impact in the quality of life and also considerable distress in the relatives of the patients and in the society in general. The prevalence of the BD in the USA varies around 0.4–3.7 %. The functional incapacity of the disease is comparable to most of chronic diseases such as cardiac conditions, since its comorbid both physical and psychiatric are due to low adherence in the prescribed treatment.

Pharmacotherapy

The treatment of bipolar disorder is divided in the acute and maintenance phases. In the acute phase the objective is to treat manic/depression symptoms whereas the maintenance phase aims to decrease relapse with concomitant improvement of general psychological functions. Mainstream treatment is based on the use of mood stabilizers and antipsychotic agents [56]. These pharmacological groups have been clinically used as the first-line treatment for bipolar depression, largely because longer-term preventative therapies with these agents are useful. Depressive episodes that do not respond to lithium, divalproate, or another mood stabilizer, or episodes that "breakthrough" despite preventive treatment, often warrant treatment with further strategies such as antidepressant agents and ECT. Clinical trials suggest that lithium is superior to placebo in treating bipolar depression, but the efficacy of lithium in comparison to antidepressants remains uncertain [57–60].

Electroconvulsive Therapy

Different clinical trials have reported the efficacy of ECT in bipolar depression. Response rates are quite variable among studies with a general tendency of satisfactory clinical outcome. The possibility of shifting from depression to hypomania or mania in patients treated with ECT appears equivalent to that associated with conventional antidepressant treatment [61]. For the manic episode, ECT is an adjuvant treatment in manic/mixed acute states. It can also be used in treatment-resistant patients.

Repetitive Transcranial Magnetic Stimulation (rTMS)

The physiological rationale concerning the use of rTMS for treating BD is the same as for MDD: high-frequency stimulation on the left DLPFC and/or low-frequency stimulation on the right DLFPC. Dolberg et al. [62] randomized 20 patients to receive either active or sham rTMS, finding superiority for active rTMS [62]. Nahas and colleagues, in a study with similar design, did not demonstrate efficacy of the technique in 23 patients with BD [63]. Tamas and colleagues conducted a study with five patients diagnosed with bipolar depression in current use of mood stabilizers. Positive clinical outcomes were observed after 6 weeks of follow-up [64]. A recent open-label study with 11 subjects focused on treatment-resistant bipolar depression. The authors showed improvement in depressive symptoms with low frequency rTMS over the right DLPFC [65] (Table 14.5).

A few studies also investigated rTMS for the treatment of manic episodes. An initial study with 18 patients in mania demonstrated the clinical efficacy of high-frequency rTMS in improving manic symptoms [66]. Other two open-label studies showed significant improvement in manic symptoms [67] and/or mixed episodes [68] in BP patients. Both studies applied rTMS in the right DLPFC. In addition, a sham-controlled study also found significant improvement in manic symptoms also using high-frequency rTMS in the right DLPFC [69]. Another study used rTMS for over 2 weeks, finding improvement of manic symptoms [67].

Table 14.6 Diagnosis criteria for schizophrenia based on DSM-IV [122]

A. Characteristic Symptoms: delusions, hallucinations, disorganized Speech, grossly disorganized or catatonic behavior, negative symptoms of time during a 1-month period
B. Social/Occupational dysfunction
C. Duration: Continuous signs of the disturbance persist for at least 6 months
D. Schizoaffective and Mood Disorder exclusion
E. Substance/General Medical Condition exclusion
F. Relationship to a Pervasive Developmental Disorder exclusion

Transcranial Direct Current Stimulation

Currently, there are no trials that investigated tDCS as a treatment for the manic episode. For the depressive episode, Brunoni et al. [43] used anodal tDCS over the left DLPFC in 31 patients (14 with BD, 17 with MDD). Depressive symptoms in both study groups improved immediately after the fifth session. The beneficial effect persisted after 1 week and 1 month [43].

Schizophrenia

Schizophrenia is a common psychiatric disorder with an overall prevalence of 1–1.5 % and a chronic course through life. The disease onset is in early adulthood although preclinical symptoms might be present in childhood and adolescence [70, 71]. Its symptoms can be grouped into three relatively distinct phenomenological presentations: (a) positive symptoms, (b) impairment or "negative" symptoms, and (c) cognitive dysfunction. Positive symptoms are characterized by hallucinations and delusions; negative symptoms by impairments in sociability, expression of affect and motivation; and cognitive dysfunction by deficits in executive functioning (attention and/or memory) [72, 73].

Diagnostic criteria according to the DSM-IV are based on the presence of at least two of five symptoms (hallucinations, delirium, disorganized speech, disorganized or catatonic behavior and negative symptoms) (Table 14.6) [74]. Traditionally, positive symptoms occur within the first 10–15 years of the disease, while negative and cognitive symptoms exhibit a more chronic, persistent, and sometimes progressive presentation [75].

Patients with schizophrenia have, in general, low-functionality in performing daily life activities, lower quality of life and greater incidence of comorbidities such as depressive symptoms, substance related disorders, suicidal behavior, and cardiovascular risk [76, 77].

Pharmacological Treatment for Schizophrenia

Approximately 25 % of patients with schizophrenia do not respond to conventional drug treatment [78]. Several antipsychotics among "typical" (first generation, developed between 1950 and 1970) and "atypical" (second generation, developed since the 1990s) are available for the pharmacological treatment of schizophrenia. However, recent clinical studies using some of these drugs have failed to show efficacy of any particular medication. The CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness), sponsored by the National Institute of Mental Health (NIMH) recruited almost 1,500 patients with schizophrenia to receive olanzapine, quetiapine, risperidone, or ziprasidone in a double blind, randomized study. The authors observed high rates of dropouts (74 %), similar effectiveness among different drugs and relevant collateral effects such as metabolic and extrapyramidal symptoms [79]. Another study (the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study [CUtLASS]), sponsored by the National Health System (NHS), randomized 227 people with schizophrenia to receive either first or second generation antipsychotics, which found no differences in quality of life, symptom improvement, or financial costs in 1 year of follow-up [80].

One antipsychotic drug, however, needs to be analyzed separately: clozapine, which is two times more effective than other antipsychotics, according to a meta-analysis [81]. Clozapine also seems to be one of the few, if not the only, antipsychotic that may show some improvement over negative symptoms [82]. Although effective, clozapine use is limited by potentially severe collateral effects such as neutropenia and agranulocytosis. This requires constant monitoring for leukopenia for patients on clozapine [83]. Other side effects include sedation, drowsiness; drooling and weight gain [84]. Nonetheless, approximately 40 % of refractory patients do not respond adequately to clozapine—a condition known as super-refractory [82].

The treatment of schizophrenia usually starts with either a typical or atypical antipsychotic with expected clinical response within 4–6 weeks. Further adjustments may be required and whether symptoms persist, a second antipsychotic is associated. For these cases, lack of clinical response will characterize refractoriness and clozapine should be, therefore, recommended over the following 6 months. If still no response is observed, there are several strategies available, however, with discrete level of evidence such as ECT, rTMS, and tDCS.

Electroconvulsive Therapy

Electroconvulsive therapy alone is less effective than antipsychotics according to trials comparing directly these two therapeutic modalities [85]. It also has better clinical response for patients with positive symptoms or catatonic presentation [11, 86]. In a systematic review performed by Chanpattana et al. [87], the authors suggested that ECT might be effective in acute episodes of certain types of schizophrenia and for the reduction in relapse occurrence.

Repetitive Transcranial Magnetic Stimulation

Several trials evaluated the efficacy of rTMS for auditory hallucinations (AH) and negative symptoms in schizophrenia. For AH, low-frequency rTMS is applied on the left temporoparietal site. Studies addressing the use of rTMS for AH mostly target the temporoparietal cortex region [88], since this area is related to primary auditory processing. Hoffman et al. [89] conducted a double blind, cross-over trial with three schizophrenic patients with persistent AH. They used low frequency rTMS (1 Hz) on the left temporoparietal area (80 % of motor threshold, total of 2,880 pulses). All three patients showed improvement in the intensity of hallucinations, and two had nearly complete remission of hallucinations for 2 weeks. Similar results were found by d'Alfonso et al. [90]. Recently, Hoffman et al. [91] randomized 20 patients with schizophrenia or schizoaffective disorder who had refractory AH to receive either rTMS or sham intervention. The stimulation was performed at 1 Hz for 9 days with 90 % motor threshold. These authors found a response (reduction of at least 50 % in symptoms) in 9 of 12 patients treated with rTMS.

It seems that negative symptoms are related to decreased activity of the left prefrontal lobe. Cohen et al. [92] performed the first study showing improvement of negative symptoms with rTMS. The authors studied six patients with chronic schizophrenia on standard antipsychotic regimen. They received high-frequency rTMS for 2 weeks at 80 % of motor threshold. There was a statistically significant decline in negative symptoms of Positive and Negative Syndrome Scale (PANSS) [92]. Nahas et al. [63] conducted a crossover double-blind study with seven patients with schizophrenia with predominantly negative symptoms. Patients were randomized to receive either active vs. sham rTMS (20 Hz, 100 % motor threshold, 40 pulses at two second intervals over 20 min, total stimuli: 1,600) over the left DLPFC. Results showed that active rTMS improved negative symptoms. A recent meta-analysis was conducted to assess the efficacy of prefrontal rTMS for treating negative symptoms of schizophrenia. The authors evaluated nine trials ($n = 213$) and found that overall mean weighted effect size for rTMS vs. sham was statistically significant ($d = 0.43$; 95 % CI, 0.05–0.80). Studies with a longer duration of treatment (>3 weeks) had a larger mean effect size when compared to studies with shorter treatment duration [93].

Transcranial Direct Current Stimulation

Hitherto, only one trial investigated tDCS for the treatment of AH in schizophrenia. Thirty patients with persistent AH were randomized to receive either active or sham tDCS. The cathode was placed on the left temporoparietal region and the anode on the left DLPFC. The rationale was to simultaneously perform an inhibitory stimulation over the area related to positive symptoms (AH) and an excitatory stimulation over the area correlated with negative symptoms. TDCS was applied twice daily for 5 days. The authors showed an improvement of AH (primary endpoint) after the end of stimulation, with sustained clinical response after 1 and 3 months of treatment [94].

Eating Disorders

Eating disorders present two main diagnostic categories: anorexia nervosa (AN) and bulimia nervosa (BN). There are other categories of Eating Disorders (ED) that are not diagnosis "per se," but rather include partial characteristics of AN and BN, referred as Eating Disorders Not Otherwise Specified.

The DSM-IV criteria for anorexia nervosa consist of intense fear for gaining weight or becoming fat, distortion of one's body shape, intense food restriction, and amenorrhea. Bulimia nervosa is characterized by periods of binge eating when large amounts of food are consumed and a sense of control is absent. Both can be indulged with different types of purging behavior to prevent weight gain.

The physical complications of a long-term eating disorder are important issues, and because of that, anorexia nervosa and bulimia nervosa are illnesses that should involve a more

careful approach when considering the course of therapy applied. With limited resources endorsed by the medical community in terms of efficient treatment for eating disorders, neuromodulation techniques may play a role in unveiling the mechanisms behind cerebral functions and as a possible strategic therapeutic treatment tool. In this context, non-pharmacological brain stimulation might aid to overcome current challenges in treating eating disorders. The techniques further discussed aim to increase response and remission rates and also to decrease adverse effects, thereby increasing treatment adherence.

Pharmacotherapy

When analyzing separately the pharmacotherapy used for each type of eating disorder, the literature on medications is sparse and inconclusive [95]. For AN, few trials found positive results in weight outcome and relapse events, even though diverse classes of medications were evaluated. AN might be associated with serotonin dysregulation and often presents comorbid anxiety, depression, and obsessive-compulsive disorders. Thus, several studies have examined the efficacy of SSRIs. It should be noted that SSRIs are preferable over tricyclics given the more common adverse effects of the latter [96–98]. Further, there is limited evidence as to whether antidepressants improve the comorbid disorders as a secondary outcome or if they primarily induce to weight gain and improvement of dysfunctional cognition related to eating [99]. In fact, psychotherapy is the mainstream treatment for AN. Cognitive behavioral therapy (CBT) is the form of psychotherapy best supported by the available evidence [100]. There are limitations when considering psychotherapy, given the cognitive rigidity of patients with AN, this might reflect its limited progress with the cognitive component of treatment [101].

In BN, antidepressants show more positive results than AN [102]. Early studies have analyzed the use of tricyclic medication, which shows efficacy in decreasing binge episodes compared to placebo. However, currently the psychopharmacological research focuses on the SSRIs, since tricyclic have considerable side effects [103–105]. There are several studies showing that the use of fluoxetine at 60 mg/day is also successful in reducing binge/purge frequency as well as concerns with food, drive for thinness and it has been well tolerated by the patients. CBT is also used in BN. Currently, fluoxetine and CBT combined are considered the optimal treatment for BN, although the remission rates are still below the expected, which maintains the need for continued new approaches.

Neuromodulation Strategies

In order to summarize the current neuromodulation techniques, a systematic review of all available studies was carried through (Table 14.7).

In the reviewed studies, only 6.7 % of patients were males. Comorbidity with depression occurred in all studies, except for one, in which no scale was used for assessment. Anxiety was observed in one study concomitantly with depression. These data reinforce the general concept that eating disorders have a significant relationship with mood disorders.

Craving and purging were the primary outcomes assessed in studies with BN, and decrease in symptoms was observed for both. AN was contemplated only in case reports/pilot studies and outcome assessment varied considerably, but all articles observed improvement either in one of the criteria: "feeling full," concern with shape/body, increase of body mass index (BMI). Urge to restrict or urge to exercise was less clear.

The techniques applied appear to be safe and with minimal side effects. Brain modulation might possibly have an effect in the core symptoms of eating disorders. In the majority of the studies, samples were small and larger studies are needed to validate these techniques as adjuvant therapeutic tools. From these preliminary results, it can be speculated that neuromodulation techniques shed a promising filed of treatment in a psychiatric disorders that lacks still nowadays a current effective pharmacological treatment.

Obsessive Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) has a prevalence of approximately 2–3 % in the general population [106, 107]. This makes OCD the fourth most prevalent psychiatric disorder. Among adults the prevalence is equivalent in men and women, differing only in adolescents and children with higher rates for men. The mean age is 20 years. This syndrome is characterized by the presence of obsessions and compulsions sufficiently severe to cause disruption in the patient's life, resulting in considerable suffering. Symptoms are perceived by the patient as intrusive and often cause significant distress [108] Obsessions are described as thoughts, images and impulses undesired and repetitive. Compulsions are behaviors or mental attitudes that the patient feel compelled to execute. This pattern has the objective of reducing the anxiety caused by the obsessions (Table 14.8).

Table 14.7 Studies of noninvasive brain stimulation and eating disorders

Author	Sample	Female (%)	Study	Age real rTMS	Age sham	BMI real rTMS	BMI sham	Comorbid	Eating disorder	Primary outcome
Walpoth [124]	14	1	Between subjects	27.4 ± 4.8	22.6 ± 2.6	19.6 ± 2.4	19.7 ± 1.7	Depression	BN	No difference in both groups in purge behavior and in scales
Van den Eynde [125]	37	86	Between subjects	30.5 ± 11.2	29.5 ± 8.4	25.8 ± 11.5	25.0 ± 8.5	Depression	BN, EDNOS-BN	Reduced cue-induced food craving
Van den Eynde [126]	7	1	Between subjects	22.9 ± 2.9	–	22.2 ± 2.7	–	Depression and anxiety	BN, EDNOSBED	Comparison with right-handed trial group in Van den Eynde, 2010. Mood worsened in left-handed × improved in right handed. Improvement observed in craving with the FCSs measure but not with the VAS. Sham-rTMS with right-handed reduced craving
Claudino [127]	22	1	Between subjects	28.2 ± 9.2	28.9 ± 8.5	26.8 ± 13.2	22.2 ± 3.1	–	BN, EDNOS-BN	Real rTMS showed lower cortisol levels compared with sham, thus real rTMS reduces craving but not superior effect on tension, mood, hunger, urge to binge eat. Real rTMS showed less binge in the 24 h following

HS healthy subjects, *BN* bulimia nervosa, *EDNOS-BN* eating disorder not otherwise specified-bulimia nervosa, *BED* binge eating disorder

Table 14.8 Diagnosis criteria for OCD [122]

Either obsessions or compulsions.
At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive unreasonable.
The obsessions or compulsions cause marked distress, are time-consuming.
If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it.
The disturbance is not due to the direct physiological effects of a substance.

Pharmacotherapy

Common treatments include the antidepressant clomipramine, followed by the selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, sertraline, fluoxetine, citalopram, and fluvoxamine. The protocol used for medical intervention consists of starting with SSRIs, followed by the use of three different SSRIs and, after that, by a trial with clomipramine. The addition of an atypical antipsychotic such as risperidone can be used [109].

Cognitive-Behavioral Therapy

It is generally agreed that cognitive-behavioral therapy (CBT) such as exposure and response prevention, should be the first approach to treatment, along with family counseling for children and adolescents [110, 111]. For adults, CBT can be initially combined in association with pharmacotherapy [111].

Transcranial Magnetic Stimulation

Recent studies have reported mixed findings regarding the efficacy of rTMS for OCD treatment. For instance, Sachdev et al. [112] found negative results using high-frequency rTMS over the DLPFC. Conversely, Nauczyciel et al. [113] found positive findings when stimulating the orbitofrontal cortex, in a sham-controlled study. Recently, Volpato et al. [114] investigated the effects of rTMS and tDCS in a case report. They suggested tDCS to be more effective than rTMS in reducing depression and anxiety, although both therapies had no effect on obsessive-compulsive symptoms.

To conclude, given the heterogeneity of the protocols used, it is difficult to directly compare the results. This could indicate that disparate protocols lead to different outcomes (given that the higher frequency used could increase the potential of excitability) and, therefore, more rTMS studies to address the efficacy of the technique are necessary.

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a syndrome defined by a persistent pattern of lack of attention and/or hyperactive behavior and impulsiveness, which tends to be more severe than what should be expected in children of the same age and in the same level of cognitive development [115]. Attention Deficit Hyperactivity Disorder (ADHD) is one of the most frequently diagnosis made in neuropsychiatric childhood disorders. A core symptom is a motor hyperactivity. It accounts for approximately 3–8 % of the diagnosis made in childhood. Over the past decade the use of medication for treating ADHD increased considerably.

Pharmacotherapy

The treatment of ADHD involves a multidimensional approach combining psychosocial and psychopharmacological interventions. When considering the psychosocial treatment, efforts should be directed towards information regarding the clinical aspects of the disorder to family members. A special training program for parents in order to learn how to manage their children's symptoms can be endorsed. The school environment also has to be specialized for these children, and teachers should have a special training so that external stimuli can be minimal. Physical activities are an important therapeutic tool in terms of enhancing concentration in other school activities. Also, it can be necessary in some cases psychomotor reeducation for motor control. In terms of psychosocial interventions, clinical psychotherapy can be introduced to cope with comorbidities such as depressive and anxiety symptoms, self-esteem issues, lack of control of hyperactivity, and impulse symptoms [116].

The psychostimulants are the first line of pharmacological treatment for ADHD. Effectiveness is similar for adolescents and children. Methylphenidate is used between 20 and 60 mg/day (0.3 to 1 mg/kg/day); it acts through increasing dopaminergic and noradrenergic synaptic efflux throughout the brain and presents a rapid onset of action [117].

Neuromodulation Strategies

In a preliminary study, 13 adults, who had ADHD diagnosed on DSM IV criteria, participated in a double blind randomized crossover study that compared sham and active rTMS [118]. There was a specific beneficial effect on attention 10 min after a real rTMS course with no effect evident in

the sham rTMS. Another study applied rTMS over the right DLPFC at 10 Hz, with 100 % of the observed motor threshold, for 2,000 pulses per session, in a 10-session course over 2 weeks in a sham-controlled crossover design. The patients showed no significant difference in symptoms comparing sham and active stimulation [119]. Niederhofer et al. [120] applied low frequency at 1 Hz, 1,200 pulses per session for 5 days of rTMS and it was observed improvement in attention and hyperactivity symptoms that lasted for 4 weeks. Finally, Bloch et al. [121] found substantial improvement on attention 10 min after active rTMS. This study applied a single session of high-frequency of rTMS in the right DLPFC in a double-blind randomized, sham controlled design. The sham stimulation had no effect in the analyzed patients [121].

Conclusion

Mental disorders are estimated to be the leading cause of disability worldwide. Presently there are still important challenges to optimize psychiatric treatment, which faces high refractoriness and recurrence rates with well-known burden for patients, their families, and society. Neuromodulation strategies have been systematically addressed as valuable tolls to face these challenges as shown by clinical and basic scientific investigations. The development of research in neuromodulation techniques can impact outcome of different neuropsychiatric disorders as major depression. Lower costs, a decreased rate of adverse effects and satisfactory clinical outcomes have been reassuring tDCS as a relevant issue in current neuroscience. Further translational research is also crucial to guide a more practical use of neuromodulation research findings in clinical psychiatric with a broad understanding of advantages and limitations inherent to each treatment strategy. Further research in neuromodulation is a current challenge in psychiatric scenario.

References

1. Wittchen HU, Knauper B, Kessler RC. Lifetime risk of depression. Br J Psychiatry Suppl. 1994:16–22.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet. 1997;349:1498–504.
3. Eaton WW, Anthony JC, Gallo J, et al. Natural history of diagnostic interview schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. Arch Gen Psychiatry. 1997;54:993–9.
4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905–17.
5. Cipriani A, La Ferla T, Furukawa TA, et al. Sertraline versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2010;4, CD006117.
6. Mendlewicz J, Massat I, Linotte S, et al. Identification of clinical factors associated with resistance to antidepressants in bipolar depression: results from an European Multicentre Study. Int Clin Psychopharmacol. 2010;25:297–301.
7. Steffens D, Krishnan K, Helms M. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. Depress Anxiety. 1997;6:10–8.
8. Anderson I. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety. 1998;7:11–7.
9. Demyttenaere K. Compliance during treatment with antidepressants. J Affect Disord. 1997;43:27–39.
10. Passione R. Italian psychiatry in an international context: Ugo Cerletti and the case of electroshock. Hist Psychiatry. 2004;15:83–104.
11. Mankad M, Beyer J, Krystal A. Clinical manual of electroconvulsive therapy. Washington, DC: American Psychiatric Publishing; 2010.
12. National Institute for Health and Clinical Excellence (NICE) (2003). The clinical effectiveness and cost effectiveness of electroconvulsive Therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. London: National Institute for Health and Clinical Excellence (NICE). Available online: http://www.nice.org.uk/TA059.
13. Fleck MP, Berlim MT, Lafer B, et al. [Review of the guidelines of the Brazilian Medical Association for the treatment of depression (Complete version)]. Rev Bras Psiquiatr. 2009;31 Suppl 1:S7–17.
14. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology. 2007;32:244–54.
15. Loo CK, Sainsbury K, Sheehan P, Lyndon B. A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. Int J Neuropsychopharmacol. 2008;11:883–90.
16. Loo CK, Schweitzer I, Pratt C. Recent advances in optimizing electroconvulsive therapy. Aust N Z J Psychiatry. 2006;40:632–8.
17. Prudic J. Strategies to minimize cognitive side effects with ECT: aspects of ECT technique. J ECT. 2008;24:46–51.
18. Brunoni AR, Teng CT, Correa C, et al. Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting. Arq Neuropsiquiatr. 2010;68:433–51.
19. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. J ECT. 2004;20:13–20.
20. Kennedy SH, Milev R, Giacobbe P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord. 2009;117 Suppl 1:S44–53.
21. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1:1106–7.
22. Barrett J, Della-Maggiore V, Chouinard P, Paus T. Mechanisms of action underlying the effect of repetitive transcranial magnetic stimulation on mood: behavioral and brain imaging studies. Neuropsychopharmacology. 2004;29:1172–9.
23. Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta Psychiatr Scand. 2000;101:11–20.
24. O'Reardon JP, Cristancho P, Pilania P, Bapatla KB, Chuai S, Peshek AD. Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. Depress Anxiety. 2007;24:537–44.
25. George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial

direct current stimulation (tDCS). Neuropsychopharmacology. 2010;35:301–16.
26. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med. 2009;39:65–75.
27. Schutter DJ. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Psychol Med. 2010;40:1789–95.
28. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71:873–84.
29. Cohen RB, Boggio PS, Fregni F. Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. Depress Anxiety. 2009;26:682–8.
30. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. J Clin Psychiatry. 2008;69:930–4.
31. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J. Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. Aust N Z J Psychiatry. 2006;40:764–8.
32. O'Reardon J, Peshek A, Romero R. Neuromodulation and transcranial magnetic stimulation (TMS): a 21st century paradigm for therapeutics in psychiatry. Psychiatry. 2005;3:30–40.
33. Rossi S. The safety of TMS consensus group. Clin Neurophysiol. 2009;120:2008–39.
34. Xia G, Gajwani P, Muzina DJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol. 2008;11:119–30.
35. Simpson KN, Welch MJ, Kozel FA, Demitrack MA, Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv Ther. 2009;26:737.
36. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95.
37. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006;8:203–4.
38. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006;23:482–4.
39. Rigonatti SP, Boggio PS, Myczkowski ML, et al. Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur Psychiatry. 2008;23:74–6.
40. Boggio PS, Rigonatti SP, Ribeiro RB, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008;11:249–54.
41. Loo CK, Sachdev P, Martin D, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol. 2010;13:61–9.
42. Ferrucci R, Bortolomasi M, Brunoni AR, et al. Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. Clin Neuropsychiatry. 2009;6:246–51.
43. Brunoni AR, Ferrucci R, Bortolomasi M, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:96–101.
44. Dell'osso B, Zanoni S, Ferrucci R, et al. Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. Eur Psychiatry. 2011;27(7):513–7.
45. Martin D, Alonzo A, Mitchell P, Sachdev P, Galvez V, Loo C. Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. J Affect Disord. 2011;134:459–63.
46. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42:1791–800.
47. Mohr P, Rodriguez M, Slavickova A, Hanka J. The application of vagus nerve stimulation and deep brain stimulation in depression. Neuropsychobiology. 2011;64:170–81.
48. Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry. 2012;69:150–8.
49. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651–60.
50. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. Am J Psychiatry. 2011;168:502–10.
51. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. J Clin Psychopharmacol. 2010;30:273–81.
52. Gerson R, Murray E, Price B, Frankel M, Douglass L, Cunningham M. Mania following vagus nerve stimulation: a case report and review of the literature. Epilepsy Behav. 2011;20:138–40.
53. Biermann T, Kreil S, Groemer T, et al. Time perception in patients with major depressive disorder during vagus nerve stimulation. Pharmacopsychiatry. 2011;44:179–82.
54. Sperling W, Biermann T, Spannenberger R, et al. Changes in gustatory perceptions of patients with major depression treated with vagus nerve stimulation (VNS). Pharmacopsychiatry. 2011;44:67–71.
55. Schrader L, Cook I, Miller P, Maremont E, DeGiorgi OC. Trigeminal nerve stimulation in major depressive disorder: first proof of concept in an open pilot trial. Epilepsy Behav. 2011;22:475–8.
56. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11:225–55.
57. Mendels J, Frazer A. Intracellular lithium concentration and clinical response: towards a membrane theory of depression. J Psychiatr Res. 1973;10:9–18.
58. Goodwin FK, Murphy DL, Bunney WE. Lithium-carbonate treatment in depression and mania—a longitudinal double-blind study. Arch Gen Psychiatry. 1969;21:486–96.
59. Greenspan K, Schildkraut J, Gordon E, Baer L, Aronoff M, Durell J. Catecholamine metabolism in affective disorder—III: MHPG and other catecholamine metabolites in patients treated with lithium carbonate. J Psychiatr Res. 1970;7:171–83.
60. Baron M, Gershon E, Rudy V, Jonas W, Buchsbaum M. Lithium carbonate response in depression. Arch Gen Psychiatry. 1975;32:1107–11.
61. Srisurapanont M, Yatham L, Zis A. Treatment of acute bipolar depression: a review of the literature. Can J Psychiatry. 1995;40:533–44.

62. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. Bipolar Disord. 2002;4 Suppl 1:94–5.
63. Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. Bipolar Disord. 2003;5:40–7.
64. Tamas RL, Menkes D, El-Mallakh RS. Stimulating research: a prospective, randomized, double-blind, sham-controlled study of slow transcranial magnetic stimulation in depressed bipolar patients. J Neuropsychiatry Clin Neurosci. 2007;19:198–9.
65. Dell'Osso B, Mundo E, D'Urso N, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. Bipolar Disord. 2009;11:76–81.
66. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: a controlled study. Am J Psychiatry. 1998;155:1608–10.
67. Michael N, Erfurth A. Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. J Affect Disord. 2004;78:253–7.
68. Saba G, Rocamora JF, Kalalou K, et al. Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients. Psychiatry Res. 2004;128:199–202.
69. Praharaj S, Ram D, Arora M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a randomized sham controlled study. J Affect Disord. 2009;117:146–50.
70. Loranger A. Sex difference in age at onset of schizophrenia. Arch Gen Psychiatry. 1984;41:157–61.
71. McGlashan T, Johannessen J. Early detection and intervention with schizophrenia: rationale. Schizophr Bull. 1996;22:201–22.
72. Andreasen N. Symptoms, signs, and diagnosis of schizophrenia. Lancet. 1995;346:477–81.
73. Wong A, Van Tol H. Schizophrenia: from phenomenology to neurobiology. Neurosci Biobehav Rev. 2003;27:269–306.
74. APA. Diagnostic and statistic manual of mental disorders, IV-TR ed. Washington, DC: American Psychiatric Association; 2000.
75. Weickert T, Goldberg T, Gold J, Bigelow L, Egan M. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry. 2000;57:907–13.
76. Conley R. The burden of depressive symptoms in people with schizophrenia. Psychiatr Clin North Am. 2009;32:853–61.
77. Bensenor I, Brunoni A, Pilan L, Goulart A, Busatto G. Cardiovascular risk factors in patients with first-episode psychosis in Sao Paulo, Brazil. Gen Hosp Psychiatry. 2012;34:268–75.
78. Bressan R, Chaves A, Pilowsky L, Shirakawa I, Mari J. Depressive episodes in stable schizophrenia: critical evaluation of the DSM-IV and ICD-10 diagnostic criteria. Psychiatry Res. 2003;117:47–56.
79. Lieberman J, Stroup T, McEvoy J, Swartz M, Rosenheck R. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–23.
80. Jones P, Barnes T, Davies L, Dunn G, Lloyd H. Randomized controlled trial of the effect on quality of life of second- vs. first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63:1079–87.
81. Davis J, Chen N, Glick I. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553–64.
82. Elkis H, Louza M. Psiquiatria Básica. 2nd ed. São Paulo: Atheneu; 2007.
83. Chong S, Remington G. Clozapine augmentation: safety and efficacy. Schizophr Bull. 2000;26:421–40.
84. Taylor D, Paton C, Kapur S. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust: prescribing guidelines. 10th ed. London: Informa Healthcare; 2009.
85. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD000076. Review.
86. Kho K, Blansjaar B, de Vries S, Babuskova D, Zwinderman AH, et al. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia—an open label study. Eur Arch Psychiatry Clin Neurosci. 2004;254:372–9.
87. Chanpattana W. (2007). A questionnaire survey of ECT practice in Australia. *Journal of ECT 23*(2):89-92.
88. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002;5:73–103.
89. Hoffman RE, Boutros NN, Berman RM, et al. Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated "voices". Biol Psychiatry. 1999;46:130–2.
90. d'Alfonso AA, Aleman A, Kessels RP, et al. Transcranial magnetic stimulation of left auditory cortex in patients with schizophrenia: effects on hallucinations and neurocognition. J Neuropsychiatry Clin Neurosci. 2002;14:77–9.
91. Hoffman RE, Hawkins KA, Gueorguieva R, et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. Arch Gen Psychiatry. 2003;60:49–56.
92. Cohen E, Bernardo M, Masana J, et al. Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study. J Neurol Neurosurg Psychiatry. 1999;67:129–30.
93. Dlabac-de-Lange J, Knegtering R, Aleman A. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. J Clin Psychiatry. 2010;71:411–8.
94. Brunelin J, Mondino M, Gassab L, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry. 2012;169(7):719–24.
95. Berkman N, Bulik C, Brownley K. Management of eating disorders. Evid Rep Technol Assess. 2006;135:1–166.
96. Attia E, Haiman C, Walsh B, Flater S. Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry. 1998;155:548–51.
97. Kaye W, Nagata T, Weltzin T. Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. Biol Psychiatry. 2001;49:644–52.
98. Fassino S, Leombruni P, Daga G. Efficacy of citalopram in anorexia nervosa: a pilot study. Eur Neuropsychopharm. 2002;12:453–9.
99. Brown T, Keel P. Current and emerging directions in the treatment of eating disorders. Subst Abuse. 2012;6:33–61.
100. Herpertz S, Hagenah U, Vocks S, von Wietersheim J, Cuntz U, Zeeck A. The diagnosis and treatment of eating disorders. Dtsch Arztebl Int. 2011;108:678–85.
101. Treasure J, Tchanturia K, Schmidt U. Developing a model of the treatment for eating disorder: using neuroscience research to examine the how rather than the what of change. Couns Psychother Res. 2005;5:191–202.
102. Hudson J, Pope HJ, Jonas J, Yurgelun-Todd D. Family history study of anorexia nervosa and bulimia. Br J Psychiatry. 1983;142:428–9.
103. Milano W, Siano C, Putrella C, Capasso A. Treatment of bulimia nervosa with fluvoxamine: a randomized controlled trial. Adv Ther. 2005;22:278–83.
104. Fichter M, Kruger R, Rief W, Holland R, Dohne J. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacol. 1996;16:9–18.
105. Milano W, Petrella C, Sabatino C, Capasso A. Treatment of bulimia nervosa with sertraline: a randomized controlled trial. Adv Ther. 2004;21:232–7.

106. Karno M, Golding J, Sorenson S, Burnam M. The epidemiology of obsessive compulsive disorder in five US communities. Arch Gen Psychiatry. 1988;45:1094–9.
107. Weissman M, Bland R, Canino G, Greenwald S, Hwu H, Lee C. The cross national epidemiology of obsessive compulsive disorder. J Clin Psychiatry. 1994;55:5–10.
108. Iancu I, Dannon P, Zohar J. Obsessive–compulsive disorder. Oxford: Oxford University Press; 2003.
109. Shin M, Choi H, Kim H, Hwang J, Kim B, Cho S. A study of neuropsychological deficit in children with obsessive-compulsive disorder. Eur Psychiatry. 2008;23:512–20.
110. March J, Mulle K. OCD in children and adolescents: a Cognitive behavioral treatment manual. New York: The Guilford Press; 1998.
111. Watson H, Rees C. Meta-analysis of randomized, controlled treatment trials for pediatric obsessive-compulsive disorder. J Child Psychol Psychiatry. 2008;49:489–98.
112. Sachdev P, Loo C, Mitchell P, McFarquhar T, Malhi G. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double blind controlled investigation. Psychol Med. 2007;37:1645–9.
113. Nauczyciel C, Drapier D. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder. Rev Neurol (Paris). 2012;168:655–61.
114. Volpato C, Piccione F, Cavinato M, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. Neurocase. 2013;19(4):360–70.
115. Barkley R. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997;121:65–94.
116. Swanson M, Kraemer C, Hinshaw P, Arnold E, Conners K, Abikoff B. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Psychiatry. 2001;40:168–79.
117. Kujirai T, Caramia M, Rothwell J, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993;471:501–19.
118. Moll G, Heinrich H, Rothenberger A. Transcranial magnetic stimulation in child and adolescent psychiatry: excitability of the motor system in tic disorders and/or attention deficit hyperactivity disorders. Z Kinder Jugendpsychiatr Psychother. 2001;29:312–23.
119. Weaver L, Rostain A, Mace W, Akhtar U, Moss E, O'Reardon J. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. J ECT. 2012;28:98–103.
120. Niederhofer H. Effectiveness of the repetitive transcranical magnetic stimulation (rTMS) of 1 Hz for attention- deficit hyperactivity disorder (ADHD). Psychiatr Danub. 2008;20:91–2.
121. Bloch Y, Harel E, Aviram S. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD subjects: a randomized controlled pilot study. World J Biol Psychiatry. 2010;11:755–8.
122. APA. Diagnostic and statistical manual of mental disorders DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Publishing; 2000.
123. Huang C, Wei I, Chou Y, Su T. Effect of age, gender, menopausal status, and ovarian hormonal level on rTMS in treatment-resistant depression. Psychoneuroendocrinology. 2008;33:821–31.
124. Walpoth M, Hoertnagl C, Mangweth-Matzek B, et al. Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. Psychother Psychosom. 2008;77:57–60.
125. Van den Eynde F, Claudino A, Mogg A, et al. Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. Biol Psychiatry. 2010;67:793–5.
126. Van den Eynde F, Claudino A, Campbell I, Schmidt U. Immediate cognitive effects of repetitive transcranial magnetic stimulation in eating disorders: a pilot study. Eat Weight Disord. 2011;16:45–8.
127. Claudino AM, Van den Eynde F, Stahl D, et al. Repetitive transcranial magnetic stimulation reduces cortisol concentrations in bulimic disorders. Psychol Med. 2011;41:1329–36.