Transcranial direct current stimulation and repetitive transcranial magnetic stimulation in consultation-liaison psychiatry

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Abstract

Patients with clinical diseases often present psychiatric conditions whose pharmacological treatment is hampered due to hazardous interactions with the clinical treatment and/or disease. This is particularly relevant for major depressive disorder, the most common psychiatric disorder in the general hospital. In this context, nonpharmacological interventions could be useful therapies; and, among those, noninvasive brain stimulation (NIBS) might be an interesting option. The main methods of NIBS are repetitive transcranial magnetic stimulation (rTMS), which was recently approved as a nonresearch treatment for some psychiatric conditions, and transcranial direct current stimulation (tDCS), a technique that is currently limited to research scenarios but has shown promising results. Therefore, our aim was to review the main medical conditions associated with high depression rates, the main obstacles for depression treatment, and whether these therapies could be a useful intervention for such conditions. We found that depression is an important and prevalent comorbidity in a variety of diseases such as epilepsy, stroke, Parkinson's disease, myocardial infarction, cancer, and in other conditions such as pregnancy and in patients without enteral access. We found that treatment of depression is often suboptimal within the above contexts and that rTMS and tDCS therapies have been insufficiently appraised. We discuss whether rTMS and tDCS could have a significant impact in treating depression that develops within a clinical context, considering its unique characteristics such as the absence of pharmacological interactions, the use of a nonenteral route, and as an augmentation therapy for antidepressants.

Key words: Neuromodulation; Liaison; Major depressive disorder; Transcranial stimulation

Introduction

Patients admitted to the general hospital ward often present psychological complaints regardless of the reason for their hospitalization (1). The causes for the association of medical with psychological symptoms range from acute psychological reactions (e.g., anxiety, denial, fear in a sickness context) to overt psychiatric symptoms (e.g., "lupus psychosis") caused by a medical condition. In many situations, however, the psychiatric condition develops after, and in parallel with the medical illness. In this scenario, not only the clinical but also the psychiatric condition should be treated. Considering the aging of the population and the development of treatments and interventions that have extended survival rates for many conditions (e.g., myocardial infarction, cancer, HIV/AIDS), this is the most common scenario for consultation-liaison psychiatry at the present time (2).

In this regard, "secondary depression" is the most prevalent psychiatric disorder due to a general medical condition that is diagnosed in patients with primary neurologic, oncologic, autoimmune, infectious, and painful diseases (2). In most cases, the treatment is similar to that of major depressive disorder (MDD), and in fact, antidepressant drugs can significantly improve the depressive symptoms of medical conditions (3). However, it is also true that, for such patients, the antidepressants interact with the medical treatment, increasing the rate of adverse effects (3). In addition, specific classes of antidepressants are forbidden in certain contexts because of the likelihood of hazardous interactions with the medical treatment (4). Finally, antidepressants per se can cause side effects that are similar to those of the illness (4). As a result, depression in medical illness is still an undertreated condition in which the efficacy of antidepressants is hindered for multiple reasons such as more overt side effects and restrictions for specific antidepressant classes and titration to increase the dose compared to primary depression.

In this context, nonpharmacological interventions might be useful and, in fact, different forms of psychotherapy, such as interpersonal, cognitive-behavior, or brief, are effective interventions for depression (5). On the other hand, psychotherapy requires trained healthcare providers and an active engagement by the patients, which are circumstances that are not always available. Moreover, psychotherapy is more effective in patients with mild or moderate depression (5). Another nonpharmacological intervention that has gained attention in recent years is noninvasive brain stimulation, which is represented by two main techniques, described below.

Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) depolarizes neurons through a potent, relatively focal, electromagnetic field that is generated beneath a coil positioned over the patient's scalp. The electric depolarization induced is strong enough to trigger action potentials (6). When applied repetitively, rTMS induces not only neuromodulatory changes, but also neuroplasticity in the targeted area. It is known that high-frequency stimulation ($>$10 Hz) can increase the excitability of the target cortex and low-frequency stimulation ($<$1 Hz) can decrease the excitability of that area (7). Over the past 20 years, more than 50 randomized, sham-controlled trials have investigated the antidepressant effects of rTMS (i.e., excitatory effects), showing that it is effective in the treatment of MDD (8). In fact, rTMS was recently approved by several international regulatory agencies as a clinical (not experimental) treatment for MDD. The most used target to treat depression with rTMS consists of high-frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) (8). Generally, the patient receives from 10 to 20 sessions of rTMS, with resulting long-term benefits (9).

Transcranial direct current stimulation (tDCS)

In contrast with TMS, tDCS is based on the application of weak (0.5-2 mA), direct electric current to the brain through relatively large electrodes placed on the scalp (10). One electrode is necessarily placed over the scalp, above the cortical area to be stimulated. The other electrode can also be positioned over the scalp, or, alternatively, over an extracephalic position (e.g., the deltoid muscle). One electrode is the anode and the other is the cathode. The first is responsible for stimulation of the chosen area and the latter for inhibition of the chosen area. A direct electric current flows from the anode to the cathode. During tDCS, the cortical areas close to the anode are hypopolarized, and those close to the cathode are hyperpolarized, leading to an increase or a decrease, respectively, in cortical excitability). One important difference of tDCS compared to rTMS is that the former does not trigger action potentials, but rather modulates spontaneous neuronal network activity (11). This occurs because the membrane potentials are changed by only a few millivolts during tDCS, which is much lower than the necessary threshold for eliciting action potentials (11). For MDD, the anode is placed over the area corresponding to the left DLPFC and the cathode, either over the right DLPFC or left supraorbital region (6). Generally, each patient receives from 10 to 20 sessions of about 20 min each (12). The current is usually 1-2 mA (12).

tDCS is still considered an investigational intervention, although encouraging results from prior trials (13) and data from our group (14) suggest that it might be incorporated in the therapeutic arsenal for MDD in the near future. Therefore, the aim of this comprehensive review is to address the main medical conditions in which MDD occurs, assessing the efficacy of noninvasive brain stimulation.

Methods

Our first step was choosing the medical conditions that would be assessed in this review. For this goal, we reviewed consultation-liaison psychiatry articles describing the medical specialties that present high depression rates (1,15). We also assessed recent textbooks on general psychiatry, consultation-liaison psychiatry, and psychosomatic medicine (2,16). After that, we summarized and described the main medical conditions for which depression treatment is challenging because of either its high rate of occurrence or specific contraindications.

The second step was assessing the main challenges for treating depression in each reviewed disease or group of diseases. After that, we determined whether there were studies on noninvasive brain stimulation for these disorders. Finally, considering the bulk of reviewed evidence, we discuss the potential advantages and disadvantages of using these nonpharmacological therapies for treating depression in a clinical context.

Results

Cardiology

Myocardial infarction (MI). Rates of depression post-MI are high, with 20-30% of patients presenting major depression (17). Post-MI depression is associated with a 4-fold increased risk of mortality, an effect that is observed for at least 18 months (18). Several mechanisms have been proposed to explain such increased mortality risk, e.g., increased catecholamine levels, decreased heart rate variability (19), and poor compliance with a healthy lifestyle and dietary habits (20).

Despite the high prevalence of post-MI depression, only 10% of cases are adequately diagnosed and treated (21). The use of antidepressants also has some limitations. Tricyclics and monoamine oxidase inhibitors have a variety of adverse effects that can hinder adequate treatment, e.g., anticholinergic effects, arrhythmias, orthostatic hypotension, and tachycardia. Conversely, novel antidepressants

such as the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion do not present these effects (22,23). However, SSRIs interact with cytochrome P450, an issue that can limit their use, since cardiac patients often use several drugs (24). Non-SSRI antidepressants, however, might also be limited. For example, mirtazapine might induce weight gain (25), and venlafaxine can increase blood pressure levels (26). We found only one rTMS case report evaluating post-MI depression, in which the left DLPFC was stimulated for the treatment of a 55-year-old man with depression and panic disorder 6 months after MI (27). Two sessions of rTMS were performed daily for 3 weeks, and the condition of the patient improved more than 50% on the Hamilton Depression Rating Scale.

Chronic heart failure (CHF). The incidence of CHF is increasing worldwide and is associated with high mortality (28). The prevalence of depression associated with CHF ranges from 13 to 77% (29). Like MI, depression associated with CHF increases mortality (30). There are some mechanisms that account for the association between these two conditions. One is that depression can hyperactivate the hypothalamic-pituitary-adrenal axis, leading to an increase in blood cortisol levels and, worsening CHF with increased sympathetic activity (31).

Also, in cases of CHF, depression is often under-diagnosed, possibly due to the co-occurrence of similar symptoms in both conditions such as fatigue, loss of energy, cognitive complaints, weight alterations, and sleep disorders (32).

Antidepressant therapy in CHF has the same issues as that for MI, since CHF itself requires treatment with several drugs, many of which interact with cytochrome P450. At the present time, the treatment for depression associated with CHF is mainly limited to SSRIs, with a few controlled studies showing evidence for sertraline, paroxetine, and fluoxetine (32).

Respiratory diseases

Chronic obstructive pulmonary disease (COPD). The prevalence of depression in COPD is about 10-40% (33). The prevalence of depression increases with the severity of COPD, being 2.5 times higher in severe COPD patients (34). The association of both conditions leads to more COPD exacerbations, more hospital readmissions, and an increase in mortality (35). These factors can be explained by the poor adherence of depressed patients to medical recommendations (36). Another possible explanation is the significant association between smoking and mental disorders (37). One hypothesis to account for the high prevalence of depression in COPD is that chronic hypoxia could lead to a decrease in production of monoamines like dopamine and noradrenaline, and this predisposes to depression (38). One psychosocial reason would be the loss of independence and self-confidence in these patients (39).

As occurs with other chronic conditions, only 44% of COPD patients with depression are diagnosed correctly (40). One possible reason is the association of some symptoms in both conditions such as loss of energy, sleep disturbance, and weight loss. Treatment with antidepressants also has some concerns. Sedative psychotropic drugs (e.g., tricyclic antidepressants such as mirtazapine) can worsen COPD symptoms, as they might decrease activity in the respiratory center during sleep (41).

Oncology

Although almost all types of cancer have high rates of depression, two of them are particularly important: pancreatic (because of a high depression incidence) and breast (because of its high prevalence) (42,43).

In fact, depression also precedes pancreatic cancer more than four times more often than with other malignancies (44). According to a recent study, almost 80% of patients with pancreatic cancer present depression, which is more than other gastrointestinal malignancies such as liver (60%), esophageal (24%), gastric (36%), and colorectal (20%) cancer (45). The depressive symptoms are usually treated with tricyclic antidepressants that are also advantageous for controlling pain symptoms and with SSRIs (46); although side effects associated with these antidepressants might limit proper treatment.

Almost 1 of 4 women with breast cancer develops depression (47). Importantly, tamoxifen - an agent that has antiestrogenic properties in the breast - is used for treatment of women with estrogen receptor positive tumors to decrease the risk of recurrence or the development of a new primary tumor. This drug is metabolized by CYP2D6 to endoxifen, its active form. SSRI antidepressants, however, also act on CYP2D6, and therefore the use of this drug class in women taking tamoxifen is contraindicated. In fact, buproprion and other common antidepressants also act on CYP2D6, limiting the therapeutic arsenal of treatment of depression in these patients mainly to venlafaxine and desvenlafaxine (48).

Neurology

Stroke. Stroke is associated with depression in 5-72% of patients (49). Post-stroke depression is associated with increased morbidity and mortality (49). In addition, post-stroke depression treatment leads to an increase in the probability of 6-year survival (50). Some studies showed positive results of treatment with citalopram (51), but there were very frequent adverse effects. The stroke randomized trials by Kim et al. (52) and Jorge et al. (53) enrolled 18 and 20 patients, respectively, using rTMS over the left DLPFC. Both observed improvement of depression symptoms. Bueno et al. (54) described a patient with post-stroke depression with marked improvement of depressive symptoms after a 10-day course of tDCS.

Epilepsy. Depression is the most frequent psychiatric condition associated with epilepsy (55). Almost half of the patients with epilepsy present depression (56). Rates of suicide in patients with epilepsy and depression are four to five times higher than those in the general population (57). Poor control of seizures, complex partial seizures, and temporal lobe epilepsy are risk factors for depression (58).

Despite its high prevalence, MDD is underdiagnosed and undertreated in patients with epilepsy (56). An issue regarding pharmacological treatment of these patients is the important interaction between anticonvulsants and antidepressants. Some antidepressant drugs (bupropion, clomipramine) can decrease the seizure threshold and increase the risk of seizures (59). The most used antidepressants in this group of patients are the SSRIs.

Parkinson's disease (PD). The prevalence of depression in PD is about 50% (60). Difficulty in diagnosing depression in PD is probably due to overlapping symptoms between the two conditions such as psychomotor retardation, cognitive deficits, fatigue, decreased energy, appetite changes, and physical complaints (2). Pharmacological treatment in this group of patients involves dopaminergic medication and antidepressants. Regarding the former, pramipexole is the most studied, with a meta-analysis showing positive results (61). Other medications used for PD include catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase B inhibitors (62). Antidepressants include tricyclics, trazodone, SSRIs, SNRIs, and mirtazapine (2).

Side effects should be taken into consideration, due to the probability of interactions with other drugs, particularly those that are metabolized by cytochrome P450. The evidence for antidepressants is insufficient, with two systematic reviews being inconclusive (63). Tricyclics can improve sleep and ameliorate some PD symptoms by their anticholinergic actions (2). However, elderly PD patients are at a greater risk for the following adverse effects of tricyclics: delirium, hypotension, and urinary retention (60).

We found five studies using rTMS for the treatment of depression in PD. Two were randomized clinical trials (RCTs) and three were open trials (64-66). Fregni et al. (67) evaluated 42 patients using high-frequency rTMS over the DLPFC. They found an improvement of 38% in the rTMS group and 41% in the fluoxetine group. On the other hand, Pal et al. (68) studied 22 patients, also using high-frequency rTMS, and found a 26% improvement in the group using rTMS *vs* <1% in the sham group. The open trials used rTMS, and all showed improvement of depression (64-66). Two (64,66) of them used high-frequency rTMS on the left DLPFC, and Dragasevic et al. (65) used low-frequency rTMS on prefrontal cortex bilaterally. While the first two studies had a high percentage of improvement of depression, the last one

had only a moderate effect.

Infectious diseases

HIV. The prevalence of depression in patients with HIV is around 36% (69). There is an association between depression and alterations in the immune system (70). Also, there is a direct correlation between viral load and depression in women and an inverse correlation between the number of natural killer (NK) cells and depression (71). As discussed, most antidepressants are metabolized by cytochrome P450, and several anti-HIV drugs (e.g., ritonavir, indinavir, protease inhibitors) inhibit its metabolism (72). Because of these issues, treatment of depression in HIV patients is often a challenge since even small doses of antidepressants can lead to important adverse effects (2).

Knotkova et al. (73) studied the use of tDCS in patients with HIV and depression. They administered 10 sessions of tDCS for 20 min at 2 mA at each visit. The electrodes were placed over the DLPFC in the F3 position for anodal stimulation and the contralateral supraorbital region for cathodal stimulation. The authors found a substantial improvement of depression. In the same study, a nonrandomized trial was performed with 10 patients with HIV and depression, also after a 10-day course of tDCS, and there was improvement of depressive symptoms.

Antenatal and postnatal depression

Perinatal depression is a common condition, with a prevalence of 15-22% (74). Some depressive symptoms such as lack of appetite, pessimistic thoughts, and insufficient self-care can be especially hazardous during pregnancy, affecting both the mother and the fetus. The treatment of antenatal depression is challenging since some antidepressant drugs have been associated with birth defects, e.g., paroxetine (75), sertraline (75), citalopram (76), and fluoxetine (76). In addition, several antidepressant drugs are not recommended for postnatal depression - some examples include SSRIs, venlafaxine, and lithium (77).

Four studies (78-81) with rTMS and tDCS in antenatal depression were found, all of them using rTMS. The study by Kim et al. (78) was an open trial in which 10 women were treated with low frequency over the right DLPFC and showed a 70% response rate. The remaining three studies were case reports, all with antidepressant effects of high-frequency rTMS over the left DLPFC (79-81). We found that only one study by Garcia et al. (82) using 10 Hz rTMS over the left DLPFC to treat postpartum depression in 9 women showed a significant reduction in depressive symptoms by the end of the second week of treatment.

Patients without enteral access

Inpatients might present conditions that temporarily or

permanently prevent them from taking oral medicines. Such conditions include upper gastrointestinal, pharyngeal, and head and neck tumors, sequelae of traumatic accidents, and neurologic conditions. In such cases the prevalence of depression might be even higher than in the general population, and proper treatment is hindered due to the lack of an oral route for antidepressants.

rTMS and tDCS trials

We identified some studies using rTMS and tDCS to treat depression associated with medical conditions (Table 1). Most of them were nonrandomized trials and case reports, although we found 4 RCTs - 2 in stroke patients and 2 in PD. We described them earlier under the respective associated medical condition.

We did not find studies using neuromodulation to treat depression in other disorders such as cancer, epilepsy, COPD, arrhythmias, and CHF, and in patients without enteral access.

Only two studies used tDCS to treat secondary depression: Bueno et al. (54) and Knotkova et al. (73), both described earlier.

Discussion

We reviewed the medical conditions that are particularly associated with depression. In almost all scenarios, the use of antidepressants for the treatment of depression has important restrictions. This occurs due to two main aspects of antidepressant drugs: a) as reviewed, most of them are metabolized by cytochrome P450 enzymes, thus leading to interaction with drugs used for the treatment of medical conditions; and b) the adverse effects can exacerbate symptoms of physical illness, increasing discontinuation rates.

All studies described improvement of depression, with few adverse effects reported. The most used technique of neuromodulation used was rTMS (13 of 15). Except for one study (65), all used the DLPFC as a target for neuromodulation, with all studies over the left DLPFC,

Table 1. Clinical studies of noninvasive brain stimulation in secondary depression.

Disease/Reference	Technique	Design	Sample	Duration (days)	Position	Results
Parkinson's						
Pal et al. (68)	TMS	RCT	22	10	left DLPFC	Active was superior to sham
Fregni et al. (67)	TMS	RCT	42	10	left DLPFC	TMS had the same antidepressant efficacy as fluoxetine
Epstein et al. (64)	TMS	OT	14	10	left DLPFC	High improvement in depression symptoms
Kormos (66)	TMS	OT	7	10	left DLPFC	6 of 7 patients were responders at 2 weeks
Dragasevic et al. (65)	TMS	OT	10	10	PFC	Moderate but significant decrease in scores of depression
Stroke						
Bueno et al. (54)	tDCS	Report	1	10	left DLPFC	Marked improvement of depressive symptoms
Kim et al. (52)	TMS	RCT	18	10	left DLPFC	Significant decrease in scores of depression
Jorge et al. (53)	TMS	RCT	20	10	left DLPFC	Significant improvement of depressive symptoms
HIV						
Knotkova et al. (73)	tDCS	OT	10	10	left DLPFC	Depression scores significantly decreased
Postpartum						
Garcia et al. (82)	TMS	OT	9	20	left DLPFC	Moderate effect-sizes at 2 weeks
Kim et al. (78)	TMS	OT	10	20	right DLPFC	Improvement of 70% on depressive symptoms
Pregnancy						
Zhang et al. (79)	TMS	Report	1	14	left DLPFC	Euthymic at the end of treatment but with relapse 2 months later
Tan et al. (80)	TMS	Report	1	-	left DLPFC	Remission of symptoms
Nahas et al. (81)	TMS	Report	1	5	left DLPFC	Remission of symptoms
MI						
Sakkas et al. (27)	TMS	Report	1	21	left DLPFC	Remission of symptoms

TMS: transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; RCT: randomized clinical trial; OT: open trial; DLPFC: dorsolateral prefrontal cortex; PFC: prefrontal cortex; MI: myocardial infarction.

except for one, which stimulated the right DLPFC (78).

The greatest advantages of methods of noninvasive stimulation for the treatment of depression associated with physical illness are that they overcome the difficulties resulting from pharmacokinetic interactions, the possibility of being given in association with SSRIs for augmentation of treatment, and the possibility of treatment of patients without enteral access.

The adverse effects associated with both rTMS and tDCS are minimal and short lived. Side effects of rTMS consist of transient headache, hearing changes and, rarely, seizures. Neurological patients with chronic headache could therefore be a concern, but studies have shown no increase in pain in such patients, because the headache is usually self-limiting. Also, one review article showed that rTMS is safe for migraine patients (83). Another possible concern is using rTMS in epilepsy. Studies have shown the safety of this technique in epilepsy using low-frequency rTMS. In addition, even the use of high-frequency rTMS as a noninvasive procedure did not activate epileptogenic foci, with the exception of a minority of patients with progressive myoclonic epilepsy (84). Therefore, with few and self-limited adverse effects, TMS and tDCS can be alternatives for use in medical conditions associated with depression. Importantly, the efficacy of rTMS in depression has been confirmed in randomized clinical trials and supported by meta-analysis, with moderately greater effectiveness in favor of active TMS (85,86). For tDCS, one meta-analysis and one large clinical trial showed positive results (13,14) for it as a promising therapeutic intervention in the future. One of these studies used a factorial design, randomizing 120 patients with depression into four groups: active tDCS with sertraline, sham tDCS with sertraline, active tDCS with oral placebo, and sham tDCS with oral placebo (14). Groups using active tDCS in monotherapy or combined with sertraline presented greater improvement of depression, with the combined treatment group showing the highest rates of improvement. This can be useful in clinical patients, because in some cases the dose of antidepressants might not be titrated upward due to adverse effects or interactions with other drugs. In such cases, tDCS augmentation could be an interesting option.

Another advantage of the use of tDCS in these groups of patients could be the relative low cost compared with rTMS (87) and the possibility of its use in primary health care. Because the device is portable, affordable, and easy-to-use, it could be easily adapted for application in primary care units.

To conclude, rTMS and tDCS have some unique characteristics that position them as interesting alternatives for the treatment of mental illnesses associated with organic diseases. Examples of these characteristics are less adverse effects and antidepressant effects of similar magnitude to antidepressant drugs. Another observation is that some conditions can benefit from TMS or tDCS. Noninvasive brain stimulation interventions can be a suitable option for patients having difficulties adhering to therapy, particularly those who present comorbidities, the elderly, and those on multiple medications. Future RCTs are necessary to evaluate the role of rTMS and tDCS in the treatment of depression associated with medical conditions.

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