Transcranial Magnetic Stimulation for the Treatment of Depression in Neurologic Disorders

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

Introduction

Transcranial magnetic stimulation (TMS) is a technique for noninvasive, painless brain stimulation. TMS generates a small electric current in the brain that induces, if applied repetitively, a modulation in brain cortical excitability—an increase or decrease, depending on the parameters of stimulation. Given these characteristics, repetitive TMS (rTMS) has being explored as a potential novel therapeutic tool for neuropsychiatric diseases. The first studies on clinical applications of rTMS were done in patients with Parkinson's disease (PD) [1] and patients with major depression [2–4,5••]. Since these first publications, this investigation has been extended to several other neurologic diseases such as stroke [6], writer's cramp [7], epilepsy [8–10], and migraine [11], and psychiatric diseases such as schizophrenia [12–14], mania [15,16], posttraumatic stress [17], and obsessive-compulsive disorder [18]. Although some of these studies show positive results, the evidence is not strong enough to make any definitive conclusion for most of these diseases about the role of rTMS in clinical practice. However, for depression treatment, several well-done, prospective, randomized controlled trials have been done and most of them show that rTMS has a significant antidepressant effect [19].

One of the main advantages of rTMS for the treatment of depression is that this technique is associated with few adverse events. Therefore, it seems intuitive to extend the use of this novel treatment of depression to patients with neurologic disorders. The relationship between depression and neurologic disorders is well established for disorders such as PD [20], epilepsy [21], stroke [22], multiple sclerosis (MS) [23], and Alzheimer's disease [24]. As the standard treatment, antidepressants may have a negative impact on patients with neurologic disorders because of the drug-drug interactions and adverse effects. Depression often is untreated (or poorly treated) in patients with neurologic diseases. Nevertheless, depression is a major determinant of quality of life and life expectancy in these patient populations. We argue that rTMS may be a good antidepressant treatment for these patients. Randomized clinical trials have shown that rTMS is effective for the treatment of depression in PD [25••] and stroke [26•] without significant side effects. Another advantage of rTMS compared with antidepressant medications is that rTMS can be used for the treatment of the underlying neurologic disease in addition to having an impact on depression. For example, several studies have shown that rTMS treatment is associated with a significant antiepileptic effect in patients with refractory epilepsy [8,9,27], and improvement of the motor function in patients with PD [28–30] and stroke [6]. Therefore, rTMS treatment for depression in patients with neurologic diseases may treat not only psychiatric symptoms, but also neurologic symptoms. rTMS treatment for depression in PD patients has been reported to improve

mood and motor function simultaneously [31]. Additionally, other techniques of brain stimulation have shown a simultaneous effect on neurologic and psychiatric symptoms, such as electroconvulsive therapy for PD patients with depression [32], and vagus nerve stimulation for patients with epilepsy and depression [33,34].

Perhaps the most challenging issue in using rTMS for the treatment of depression in patients with neurologic disorders is determining the best parameters of stimulation, such as the site, frequency, and intensity of stimulation, to optimize the therapeutic impact of rTMS on neurologic and psychiatric symptoms. Some difficulties may be anticipated, such as the site of stimulation in patients with stroke or MS because these patients may have multiple lesions. Safety in epilepsy also should be considered because rTMS can trigger seizures. It is critical to address these and related issues to increase the external validity of this novel approach. Therefore, the risks and benefits of rTMS for the treatment of depression in patients with neurologic disorders are discussed in this review. Furthermore, we propose a framework that includes the parameters of stimulation (intensity, frequency, number of pulses, and site of stimulation) for the treatment of depression in PD, epilepsy, stroke, MS, and Alzheimer's disease.

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression

Repetitive TMS has been extensively investigated for the treatment of depression. Although the results of these studies are mixed, with some trials showing a significant antidepressant effect of this technique compared to sham stimulation [5••,35,36] and other trials showing no significant difference between active and sham rTMS [37,38], most of the evidence supports a significant antidepressant efficacy of rTMS in patients with medication-resistant depression. Unfortunately, most of the rTMS trials generally are small, single-center trials, and are not adequately powered. Two meta-analyses of rTMS treatment for depression showed a pooled standardized mean difference in depression scores between active and sham rTMS ranging from 0.35 to 0.88 in favor of the active treatment [19,39]. However, a recent meta-analysis concluded that rTMS treatment for depression is not different from sham rTMS [40], but methodologic limitations, such as number of studies selected and quantitative analysis methodology, make the results from this study uncertain. The heterogeneity across rTMS studies, such as study sample and TMS parameters, may explain different results and therapeutic failures in some of them.

Despite the heterogeneous results across different TMS studies, some conclusions about site, frequency, and intensity of stimulation for rTMS treatment may be outlined. In the first double-blind, sham stimulation controlled trial of rTMS in depression, Pascual-Leone *et al*. [5••] explored different sites of rTMS application for depression treatment. In this study, the left and right dorsolateral prefrontal cortices and vertex were stimulated, and the results showed that high-frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC) resulted in a significant improvement of depression in comparison with stimulation of the other sites. After this study, several other authors confirmed that high-frequency rTMS of the left DLPFC results in depression improvement [35,36,41–43]. Furthermore, because of the asymmetric brain activity between the right and left prefrontal cortex in depression and the cortical network effects of rTMS, it was hypothesized and proven that low-frequency rTMS of the right dorsolateral prefrontal cortex also can be effective for depression alleviation [44–46].

Although several well-done clinical trials have been done to date investigating rTMS treatment for depression, there is uncertainty about the best parameters of stimulation. For example, should high-frequency rTMS treatment use 5, 10, 15, or 20 Hz? Past studies reported significant antidepressant effects of similar magnitude using these differently [5••,25••,41,43]. However, no study has systematically addressed this question comparing these parameters in only one study. The same question applies to the intensity of stimulation. Perhaps different frequencies (for high-frequency rTMS) and intensity of stimulation may yield similar antidepressant effect. However, past research suggested that higher frequency of stimulation may be associated with a larger antidepressant effect in animals [47], and may induce larger cerebral blood flow in the stimulated area in humans [48]. This leads to the question of whether the highest frequency and intensity of stimulation should be adopted. However, an increase in the parameters of stimulation has an important cost: it may increase the risk of seizure. Therefore, these parameters have to be carefully selected when planning a TMS treatment for depression, particularly, in patients with an increased risk for seizures. Ultimately, it is possible that the parameters of stimulation may need to be adjusted for each individual patient and if so, guiding the rTMS settings with the concurrently recorded and analyzed impact on brain activity (indexed, for example, by online electroencephalographic monitoring) may be desirable. Additional studies to understand the pathophysiology of depression and the mechanisms of action of rTMS are needed to explore such questions.

Safety of Repetitive Transcranial Magnetic Stimulation Treatment

Because high-frequency rTMS can increase brain cortical excitability and thereby cause seizures, safety is an important issue to consider. Safety of rTMS was reviewed and discussed at a National Institutes of Health consensus conference in June 1996 in Bethesda, MD [49••]. In summary, this consensus conclusion was that the risk of seizures depends on several parameters, such as TMS intensity, frequency, train duration, and intertrain interval. Specific guidelines were proposed. Following these guidelines, no additional seizures have been reported to date,

although rare, isolated seizures have occurred when stimulation has been applied outside of the safety guidelines. Overall, nine seizures induced by rTMS have been reported. This constitutes a risk of approximately one seizure in 10,000 rTMS applications (these numbers are a very crude approximation and the risk may be lower). Although the National Institutes of Health consensus conference suggestions constitute state-of-the-art recommendations, they do not address the risk of seizures associated with rTMS in patients with neurologic disorders, such as epilepsy and stroke. In addition, the guidelines do not fully cover the application of rTMS to nonmotor brain areas.

Although the risk of seizures in subjects with neurologic disorders being treated with rTMS has not been systematically assessed, some conclusions can be inferred from the few studies that have investigated the use of this technique in these patients. For instance, several rTMS studies on patients with PD have been done to date [25••,29,30,50–53]. These studies showed no adverse events associated with this therapy. However, less information is available on other neurologic disorders. For instance, low-frequency rTMS has been shown to be safe in patients with epilepsy [8,9] and stroke [6], and single-pulse TMS caused no adverse effects in patients with MS [54,55] or Alzheimer's disease [56,57].

Ultimately, the risk associated with seizure will heavily depend on the frequency of stimulation (*ie*, low- vs high-frequency rTMS). Low-frequency rTMS has been shown to decrease cortical excitability [58••,59]; therefore, it generally may protect against seizures. Past research showed that low-frequency rTMS decreases seizures frequency [8,9,27] or does not increase it [10] in patients with refractory epilepsy. However, it is important to realize that some subjects may paradoxically show an increase in cortical excitability in response to low-frequency rTMS [60,61], and the situation in patients may be more variable depending on the underlying pathophysiology. However, high-frequency rTMS generally increases cortical excitability [60–62] and can induce seizure. Consequently, additional caution is necessary when using high-frequency rTMS in patients with epilepsy or stroke. However, this risk also may depend on the area that is being stimulated (*ie*, because the effect of rTMS is focal, this risk likely will depend on whether the epileptic focus is being stimulated directly). Therefore, stimulation of areas distant from the epileptic focus may be safe and perhaps cause an advantageous modulation of the epileptogenic focus. Additional studies evaluating the safety of high-frequency rTMS in these patients using dose-escalating techniques would provide valuable information.

Lastly, although it is widely accepted that rTMS can transiently disrupt function in the targeted area, no long-lasting effects on cognitive, motor, or sensory functions have been reported [49••,63]. Other adverse effects such as transient headache and neck pain have been reported in approximately 20% of the patients stimulated, but these side effects generally are mild and of short duration.

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression in Parkinson's Disease

Depression is the most common psychiatric problem in PD [64]. The prevalence of depression in patients with PD varies in different studies, but can affect up to 40% of patients [64–66]. Depression is an important factor for the quality of life of patients with PD [67], impacting daily functional activities [65,66], but it often is untreated [64,65], perhaps because it is frequently of only mild to moderate intensity, and suicide is rare [65]. Treatment options for depression in PD include antidepressants and electroconvulsive therapy [68]. However, there are concerns regarding the relative efficacy and tolerability of available antidepressants for patients with PD [69], and although electroconvulsive therapy is an excellent antidepressant [70] and can lead to motor improvement [70,71] in PD, it is associated with mental status changes including confusional states and transient intertreatment delirium [70], affecting up to 50% of patients in some series [70].

Motivated by these reasons, two studies have explored the question of whether rTMS treatment for depression in PD is effective. The first study was an open trial by Dragasevic *et al.* [31] done in 10 patients. This study showed that 10 days of slow-frequency rTMS of the left and right prefrontal cortices resulted in a significant improvement of depression [31]. In addition, this study showed a significant improvement in motor function. After this study, Fregni *et al.* [25••] did a randomized, double-blind, controlled study to evaluate the effects of high-frequency rTMS on mood in patients with PD. In this study, patients were randomized to receive active rTMS and placebo pill or sham rTMS and fluoxetine. The authors showed that 10 consecutive sessions of rTMS resulted in similar antidepressant effect as that induced by fluoxetine [25••]. Moreover, 2-week rTMS resulted in an antidepressant effect that lasted for at least 2 months. This study also showed a potential cognitive improvement that was further explored by Boggio *et al.* [72•]. In this subsequent investigation, a detailed neuropsychologic battery in patients with PD and depression who had 10-day treatment of high-frequency rTMS showed a cognitive improvement associated with this therapy that was mood independent and long lasting [72•].

Given the results of these studies, high-frequency rTMS of the left DLPFC for at least 10 sessions seems to be effective to alleviate mood symptoms in patients with PD and depression, and may result in cognitive improvement. A prolongation of this treatment (to 15 sessions) may be beneficial for patients who do not respond in the first 10 sessions. Low-frequency rTMS of the right hemisphere also may be a satisfactory option, and it may improve the motor function additionally (Table 1). In summary, additional studies comparing low- and high-frequency rTMS of the prefrontal cortex for patients with PD and depression seem warranted.

Table 1. Repetitive transcranial magnetic stimulation treatment for depression in Parkinson's disease

Treatment	Possible advantages	Possible disadvantages
High-frequency rTMS of the left prefrontal dorsolateral cortex at 15 Hz, 120% MT, 3000 pulses/ session for 10 sessions*	Previously shown to be effective in treating depression† Possible cognitive improvement More data showing the antidepressant effects of high-frequency rTMS in healthy patients	No potential improvement of motor function
Low-frequency rTMS of the right prefrontal dorsolateral cortex at 1 Hz, 110% MT, 3000 pulses/ session for 10 sessions	Safer than high-frequency rTMS‡ Additional motor improvement	Lack of controlled studies evaluating this approach

*Intensity may need to be adjusted depending on the frontal atrophy
†Effects similar to fluoxetine
‡Patients with PD do not have an increased risk of seizure
MT—motor threshold; PD—Parkinson's disease; rTMS—repetitive transcranial magnetic stimulation

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression in Epilepsy

Patients with epilepsy have a high prevalence of psychiatric disorders, estimated at 20% to 50% [73]. The most frequent comorbid psychiatric disorder in epilepsy is depression [74,75], which not only affects these patients' quality of life, but also increases the risk of suicide [76]. Although the association between epilepsy and depression has been shown, the treatment of depression in epileptic patients often is neglected by neurologists [77]. One of the reasons is that physicians are concerned that antidepressants may worsen epilepsy is because they can lower the seizure threshold and negatively interact with antiepileptic drugs [78,79]. In a review, Rosenstein *et al*. [80] reported that the risk of seizure after introduction of tricyclic antidepressants is related to the rate of metabolism of these drugs (slow metabolizers having a higher risk), rapid dosage titration, the presence of central nervous system abnormalities, and personal history of seizure. In addition, most antidepressant and antiepileptic drugs (AEDs) are metabolized in the liver; therefore, comedication may lead to drug interactions and may interfere with antiepileptic drug metabolism. These concerns support the need for a new therapy for depression in epilepsy.

Because rTMS improves depression through different mechanisms than antidepressants, thereby not worsening epilepsy and not interacting with AEDs, this technique may be beneficial for patients with epilepsy and depression. Furthermore, rTMS can have an antiepileptic effect. A few animal [81] and human studies [8,27,82] have suggested that low-frequency rTMS may be clinically effective in patients with refractory epilepsy. Although a recent randomized controlled study failed to find beneficial effects of rTMS on seizure control [10], the negative findings from this study may be attributable to the TMS parameters and characteristics of the epilepsy. Some of these patients had deep, mesotemporal seizure onset, which occurs in a region less accessible to rTMS than neocortical foci.

Because rTMS has focal effects and the location of the epileptic focus usually is different from the stimulation site for depression treatment, it is unclear if rTMS treatment for depression modulates the epileptogenic foci. However, several experimental studies have shown that the effects of rTMS are not restricted to the stimulation site. For instance, it has been shown that the focal modulation in the cortical brain activity induced by TMS can spread trans-synaptically to other cortical areas [6,83–86]. According to this concept, the modulation of the DLPFC by rTMS also could modulate distant cortical or subcortical areas, including the epileptic focus. Therefore, rTMS treatment for depression in epilepsy also may yield an antiepileptic effect.

Given the potential antiepileptic effects of low-frequency rTMS, the natural choice of the parameters of rTMS for depression treatment in epilepsy would be low-frequency rTMS of the right DLPFC. However, neuroimaging studies of patients with depression and epilepsy show that these patients often have diffuse prefrontal hypoactivity, rather than an interhemispheric asymmetric prefrontal activity. In this context, high-frequency rTMS may be preferable to treat depression in these patients because high-frequency rTMS generally increases cortical excitability and thereby brain activity. However, to maximize safety, the use of high-frequency rTMS should depend on the location of the epileptogenic focus. To avoid a potential increase in the cortical excitability of the epileptogenic focus (see Table 2), patients with frontal epileptogenic lesions should not receive high-frequency rTMS, but low-frequency rTMS instead.

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression in Stroke

According to a population-based study, 4 months after a stroke, the prevalence of depression is 29%. Therefore, it is greater than in an age-matched population [87]. Depression in these patients decreases the overall quality of life and can hinder or slow functional recovery. Furthermore,

Table 2. Repetitive transcranial magnetic stimulation for depression in epilepsy

Location of epileptogenic focus	Stimulation site	Parameters*
Single epileptogenic focus; distant from prefrontal cortex, such as in temporal epilepsy	Left DLPFC	5 Hz, 40 trains of 5 seconds with 60-second intervals between trains, per session for 20 sessions over 4 weeks†
Single epileptogenic focus; located in the frontal cortex	Right DLPFC	1 Hz, 1000 pulses/session, 100% MT, for 20 consecutive sessions over 4 weeks
Multiple foci or generalized epilepsy	Right DLPFC	1 Hz, 1000 pulses/session, 100% MT, for 20 consecutive sessions over 4 weeks

*Suggested parameters (additional trials are needed for validation)
†Continuous monitoring with electroencephalography would be recommended
DLPFC—dorsolateral prefrontal cortex; MT—motor threshold

stroke can reduce survival and increase vascular events in these patients. Given that most of the disability after stroke cannot be satisfactorily treated, the treatment of depression in this population of patients represents a good opportunity to improve the overall quality of their lives.

There are few trials that systematically evaluated the treatment of depression in patients with stroke. Most of these trials used pharmacologic treatment. The results of these trials, as synthesized by a recent meta-analysis, show that the treatment of depression with antidepressants is not significantly different than placebo treatment [22]. In addition, even if there is a significant "true" effect of antidepressants, the clinical impact may be irrelevant. Therefore, other antidepressant treatments, such as rTMS, are needed. Based on these considerations, Jorge *et al.* [26•] did a clinical trial in which patients with stroke and depression had rTMS for the treatment of depression. In this study, active rTMS (10Hz, 110% of the motor threshold, 1000 pulses, trains of 5 seconds separated by 60-second interval), compared with sham stimulation, significantly reduced depressive symptoms and was associated with a trend toward cognitive improvement. Based on continuous monitoring with electromyography, the authors concluded that this treatment is safe in patients with stroke.

TMS has an important advantage over most antidepressant medications: this treatment also may be useful for stroke recovery. Mansur *et al.* [6] showed that low-frequency rTMS of the unaffected hemisphere can enhance motor function after stroke. However, one caveat must be considered: the anatomic changes after stroke can perturb the electric current induced into the brain by TMS. Wagner *et al.* [88] have recently shown that when rTMS is applied in the immediate vicinity of the stroke area, the location and intensity of the induced electric current in the brain can be greatly disrupted. Therefore, caution is necessary when applying rTMS over brain areas near the stroke lesion, and careful modeling of the induced current in each individual patient's brain may be necessary.

Given these concerns, we recommend that patients with stroke receive rTMS for depression in brain areas distant from the stroke lesion. Because rTMS for depression generally is applied over the prefrontal cortex, patients with middle cerebral artery lesions that involve prefrontal areas would have to receive rTMS over the hemisphere contralateral to the lesion. Another consideration in patients with stroke is the increased risk of seizures. Although a previous study showed that high-frequency rTMS for patients with depression and stroke is safe if the stroke lesion is distant from the stimulation site [26•], the first option for depression treatment in these patients may be low-frequency rTMS of the right DLPFC. If the stroke lesion is located in the right prefrontal cortex or close to it, then high-frequency rTMS of the left DLPFC may be pursued. However, patients with multiple strokes (in the right and in the left hemispheres) with previous history of seizure should not receive rTMS treatment because of the increased risk of seizure until additional safety studies are completed. Also, rTMS parameters aiming at safety, such as long interinterval stimulus and low stimulation intensity, should be used. Furthermore, if possible, patients should be continuously monitored with electroencephalography to detect an early epileptic activity; therefore, TMS may be aborted if necessary (see Table 3).

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression in Multiple Sclerosis

Multiple sclerosis is another neurologic condition associated with high prevalence of depression. The lifetime prevalence of depression in MS may be as great as 50% [89]. Because MS is associated with progressing motor, sensory, and autonomic disability, the high prevalence of depression in these patients could be attributable to a psychologic reaction to disability. However, a previous study showed that the incidence of depression in MS is higher than in healthy control subjects and patients with other chronic diseases [90]. Therefore, independent of the degree of disability, MS seems to promote depression, presumably on the basis of functional disconnections of specific neural circuits in the brain. For example, lesions in the arcuate fasciculus may be crucial contributors to the incidence of depression in MS [91]. Although depression in MS often is undetected and untreated [23], it is an important factor in the quality of life for patients with MS [92].

Table 3. Repetitive transcranial magnetic stimulation for depression in stroke

Location of stroke lesion	Site of stimulation	TMS parameters*
Left MCA, subcortical, right MCA (posterior branches), posterior circulation, thalamic	Right DLPFC	1 Hz, 1000 pulses/session, 100% MT, for 20 consecutive sessions over 4 weeks
Right MCA (frontal involvement)	Left DLPFC	5 Hz, 40 trains of 5 seconds with 60-second intervals between trains, per session for 20 sessions over 4 weeks†
Multiple strokes and history of seizures	Insufficient data to support safety of rTMS in these patients	

*Suggested parameters (additional clinical trials are needed for validation)
†Continuous monitoring with electroencephalography would be recommended
DLPFC—dorsolateral prefrontal cortex; MCA—middle cerebral artery; rTMS—repetitive transcranial magnetic stimulation; TMS—transcranial magnetic stimulation

Table 4. Repetitive transcranial magnetic stimulation for depression in multiple sclerosis

Characteristics of MS lesions	Site of stimulation	parameters*
Frontal active MS plaques or previous seizure	Right DLPFC	1 Hz, 1000 pulses/session, 100% MT, for 20 consecutive sessions over 4 weeks; start with 100 pulses in the first session and increase to 1000 pulses/session by increments of 300 pulses
No active lesions, previous seizure, or use of epileptogenic drugs	Left DLPFC	5 Hz, 40 trains of 5 seconds with 60-second intervals between trains, per session for 20 sessions over 4 weeks

*Suggested parameters (additional clinical trials are needed for validation)
DLPFC—dorsolateral prefrontal cortex; MS—multiple sclerosis; MT—motor threshold

Few studies have evaluated the effect of antidepressants for depression treatment in MS. A randomized controlled trial showed that tricyclic antidepressants improve mood symptoms significantly when compared with placebo. However, anticholinergic effects of this class of medications limit its dosage in patients with MS [93]. Open studies show that selective serotonin reuptake inhibitors also are effective in treating depression in MS; however, these drugs are associated with an impairment of sexual function, a common problem in these patients [89]. That rTMS treatment is associated with few, benign adverse effects thereby lends support to the use of this technique for the treatment of depression in MS.

Because seizures are more frequent in patients with MS than in the general population, this potential risk should be incorporated into rTMS treatment planning. In a case-report, Haupts *et al*. [94] showed that single-pulse TMS, for diagnostic purpose, triggered a focal, secondarily generalized seizure in a patient with MS. In this case, the authors speculated that an active cortical plaque plus epileptogenic medication were responsible for this complication [94]. Nonetheless, low-frequency rTMS of the right prefrontal cortex would be recommended in patients with active plaques in the frontal lobe or using medications that decrease the seizure threshold, such as psychotropic medications. Furthermore, in these patients with active plaque, we would consider a dose-escalating rTMS treatment to minimize the potential risk of a prolonged seizure episode. However, for other patients (without active plaque and use of epileptogenic drugs), high-frequency rTMS of the left prefrontal cortex may be a better choice because this treatment is associated to an improvement of cognitive function [72•,95,96]. However, safety studies are clearly also needed (see Table 4).

Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurologic disease that tends to increase its prevalence with the growing age of the population. Currently, 2 to 3 million people in the United States have AD [97]. Psychiatric comorbities, such as depression, are common in AD and an important negative factor in the quality of life of patients with AD and their caregivers [98]. Epidemiologic studies have suggested that the prevalence of depression (major and minor) in AD is estimated to be 30% to 50% [99]. Despite these considerations, depression treatment in AD remains poorly managed. The results of trials that investigated the use of antidepressants in AD are mixed, with some showing a significant improvement after the use of these medications [100,101], and others showing no beneficial effect [102,103]. Electroconvulsive therapy also has been proposed for the treatment of depression in these patients, but the adverse cognitive effects of this therapy limit this approach. Therefore, because rTMS treatment for depression is not associated with cognitive impairment, and may induce a cognitive enhancement, this therapy could be advantageous for depression in AD.

Table 5. Repetitive transcranial magnetic treatment for depression in Alzheimer's disease

Treatment options	Site of stimulation	Parameters*
First option	Left DLPFC	5 Hz, 40 trains of 5 seconds with 20-second intervals between trains for 20 sessions over 4 weeks; may be extended to 6 weeks
Second option†	Bilateral DLPFC	5 Hz, 20 trains of 5 seconds with 20-second intervals between trains per session in each hemisphere for 20 sessions over 4 weeks; may be extended to 6 weeks

*Suggested parameters (additional clinical trials are needed for validation)
†This was speculated by the authors because the effects of high-frequency stimulation on the right DLPFC are unknown
DLPFC—dorsolateral prefrontal cortex

One important consideration is that brain atrophy associated with AD may alter the properties of the TMS-induced electric current in the brain. Mathematical modeling of the electric current induced by rTMS in the brain of patients with various degrees of cortical atrophy show that the degree of atrophy is negatively correlated to the magnitude of the induced current and may significantly distort the current paths, and thereby the geometry of the induced field, making precise targeting of specific brain structures difficult (Wagner, personal communication, 2005).

Nahas *et al.* [104] suggested that a low response of elderly patients to rTMS antidepressant therapy is associated to the degree of brain atrophy, and did a study in which they showed that rTMS treatment using an intensity adjusted for the frontal atrophy in elderly patients results in a significant antidepressant effect (*ie*, higher intensity in patients with higher atrophy). Furthermore, Jorge *et al.* [26•], investigating the effects of rTMS in patients with stroke showed that the depression improvement was negatively correlated to the degree of brain atrophy. Therefore, it may be concluded that rTMS treatment in patients with AD should use a higher intensity compared with the standard values. However, a simple increase of the applied rTMS intensity may not be sufficient to control for the distortion of the induced current discussed above. Generally, high-frequency rTMS may be a better strategy for these patients because AD is associated with a widespread reduction in the regional cerebral metabolic rate for glucose in most major neocortical sites, and high-frequency rTMS treatment increases brain activity of the stimulated areas [105]. Furthermore, left dorsolateral prefrontal high-frequency rTMS has been shown to improve cognition in PD [72•] and major depression [95,96,106]. Considering the cognitive effects of prefrontal rTMS and the diffuse brain hypometabolism in AD, bilateral high-frequency rTMS could be an advantageous treatment for these patients. However, the effects and safety of bilateral stimulation with high-frequency rTMS have been insufficiently studied to date (see Table 5).

Conclusions

Depression in neurologic diseases often is undertreated. Many reasons, such as drug-drug interactions (antidepressants vs drugs for neurologic diseases); adverse effects of antidepressants on neurologic symptoms; and lack of appreciation for the importance of depression in these patients' quality of life by health care providers, all contribute to this scenario. rTMS is a good approach for depression treatment because it is associated with few adverse effects, and may improve some neurologic symptoms.

Although depression alone and depression in neurologic disease may share common underlying pathophysiologic mechanisms, they have some differences that should be considered. For instance, the brain changes associated with stroke and AD can alter the electric current induced by TMS. For this reason, differential approaches of rTMS antidepressant treatment for each neurologic disorder should be pursued, and ultimately individualized stimulation parameters may be desirable. Another method, not discussed in this paper, that may optimize rTMS treatment is the concurrent use of neuroimaging (single photon emission computed tomography or functional magnetic resonance imaging) or neurophysiologic electroencephalography techniques to optimally define the target of stimulation and the stimulation parameters while monitoring the neurophysiologic impact.

Lastly, other types of brain electrical stimulation also may be helpful for depression treatment in patients with neurologic disorders. For instance, invasive brain stimulation, such as deep brain or epidural cortical stimulation, can be successfully used to treat neuropsychiatric disorders such as depression [107] and epilepsy [108]. Moreover, a less invasive technique of brain stimulation, vagus nerve stimulation, has been reported to have antidepressant effects in patients with epilepsy [33,34,109]. Another type of noninvasive brain stimulation, transcranial direct current stimulation, is being explored for epilepsy treatment and depression. Preliminary data have shown positive results on mood [110] and cognition.

In this paper, a framework for rTMS treatment for depression in neurologic diseases is proposed. However, these guidelines are based on theoretical considerations in most of the cases, and must be validated in clinical studies before application in clinical practice. Nevertheless, the recent data from rTMS clinical trials make us optimistic that this technique may be an important adjuvant treatment for depression in neurologic disorders.

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