# PAST, PRESENT AND FUTURE OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN THE TREATMENT OF PSYCHIATRIC DISORDERS

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**Abstract**
Transcranial magnetic stimulation (TMS) is a brain stimulation technique used for the treatment of major depression and other psychiatric disorders. Initially used as a research tool in neurophysiology, TMS has been subsequently extended to the therapeutic area of depressive disorders and approved in many countries for this purpose. TMS uses magnetic fields to deliver electricity into specific areas of the cerebral cortex, mainly the dorso-lateral prefrontal cortex. Several randomized clinical trials (RCTs) conducted with TMS over the last decade have allowed its approval by the FDA for the treatment of major depressive episodes with poor response to standard antidepressants. In addition, meta-analyses and international treatment guidelines have more recently defined stimulation parameters and safety standards. Future directions in the field should further explore the clinical efficacy and safety of specific forms of TMS like deep TMS and theta burst stimulation, which allow to reach deeper anatomic targets and to shorten the overall duration of stimulation. The utility of maintenance session and the interaction with specific psychotropic compounds represent areas that need to be further investigated as well.
To date, TMS is likely the non-invasive brain stimulation intervention with the strongest evidence in terms of efficacy in psychiatric disorders, as documented by RCTs and meta-analyses. Nonetheless, the efficacy of TMS needs to be further investigated in other psychiatric disorders with preliminary, encouraging results in different fields. The tolerability and safety profile of TMS are advantageous, the technique being non-invasive, generally well-accepted and devoid of systemic side-effects.

**Key-words:** transcranial magnetic stimulation (TMS), major depression, guidelines, randomized controlled trials (RCTs), meta-analyses, future perspectives

## Introduction

Transcranial magnetic stimulation (TMS) is a brain stimulation technique that has been used in the psychiatric field, over the last two decades, with therapeutic purposes, mostly in patients with mood disorders and partial response to standard antidepressants.
TMS uses magnetic fields to penetrate the skull and the brain and deliver electrical current to the cerebral cortex, typically at 2-3 cm of depth, through a stimulator generating brief pulses with variable frequency and intensity, and a stimulating coil connected to the stimulator. The TMS coil is usually round or figure-eight (butterfly) in shape, the latter producing a stronger and more focal field than the circular one. Different and novel coil have been developed over the last years indeed [1].
Differently from the direct application of electrical current, as for the electroconvulsant therapy, magnetic fields can easily cross the skull and penetrate the brain, then converting into electrical current that can inter-

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fere with and modulate cortical excitability, through mechanisms of long-term potentiation and long-term depression [1]. In particular, these changes occur when TMS is delivered in form of repeated trains of stimuli, as happens with its use in clinical practice as repetitive TMS (rTMS).

In terms of mechanism of action and rational for the use of TMS in depressive disorders, it should be kept into account that current pathophysiological models converge to indicate that two major groups of brain regions – a "dorsal" and a "ventral" network – seem to account for the formation of the different symptoms of affective disorders [2-4]. Within this theoretical framework, depression is hypothesized to involve concurrent hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere [2-4]. Symptom remission, therefore, is supposed to require facilitation of hypoactive dorsal brain regions and inhibition of hyperactive ventral areas. Ultimately, transcranial neuromodulatory, brain stimulation techniques, like TMS, are supposed to restore the functional balance between the two hemispheres [2-4].

Different parameters characterize the clinical use of TMS as therapeutic intervention in neuropsychiatric disorders. One is represented by the frequency of stimulation, that identifies two main types of stimulation: low frequency (1Hz) and high frequency stimulation (10 Hz). The two types of stimulation are thought to exert opposite effects over the target area (inhibition for low frequency and enhancement for high frequency) [5]. Other important parameters are represented by the intensity of stimulation, which ranges from the 80% to 120% of patient's motor threshold – the minimal intensity required to produce contraction of the thumb (abductor pollicis brevis) –, the number of stimuli per single session of TMS, the total number of sessions (i.e., the duration of the trial), and the potential implementation of maintenance sessions.

TMS is currently considered a safe and well-tolerated intervention. Adverse reactions can include post-treatment mild and self-limited headache, scalp pain at the stimulation site, and potential transient hearing alterations due to the clicking sound of the machine. The most serious, although rare, potential adverse effect of TMS is the induction of seizure.

After having obtained the first FDA approval in 2008 for the therapeutic use (i.e., Neurostar device) in major depressive episode with poor response to at least one antidepressant trial, TMS obtained two further approvals for such indication (i.e., Magstim and Brainsway devices) and it has been extensively investigated as therapeutic tool also in a series of different psychiatric disorders, including bipolar disorder, schizophrenia, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), addictions, and other conditions [6 7]. The increasing number of studies, randomized controlled trials (RCTs) in particular, allowed the development of the first meta-analyses and subsequent treatment guidelines – updated in 2014 – by the major international associations of psychopharmacologists, neurophysiologists and psychiatrists, defining the standard parameters for the use of TMS in psychiatric clinical practice and opening the way for a field in continuous evolution. In the last two years, further reviews and meta-analyses providing the most recent updates have been published, confirming the growing interest of the scientific community on the topic [8-10].

The aim of the present review was to provide a critical perspective of most recent acquisitions, current directions and future perspectives in the field of therapeutic use of TMS for psychiatric disorders, taking into particular account guidelines indications and recent publications, after a Pub-Med/Scopus detailed search.

## Treatment guidelines indications

In the last two decades, evidence-based guidelines elaborated by different international associations of experts in the field of clinical psychiatry, stemming from a consistent body of evidence in terms of RCTs, recognized the emerging role of TMS as therapeutic tool in a variety of neuropsychiatric conditions, in light of its non-invasiveness and favorable tolerability profile [11 12] (Figure 1). Although not being considered as the standard of care, guidelines recommendations may provide guidance for researchers and clinicians in order to offer TMS within a more individualized treatment plan.

For instance, the Canadian Network for Mood and Anxiety Treatments (CANMAT) [13] and the World Federation of Societies of Biological Psychiatry (WFSBP) [14] have been the first major associations providing updated evidence on the neurostimulation application in psychiatry, including a specific section on TMS. Even though the therapeutic utility of this stimulation technique has been claimed for depression, TMS also found application in acute mania, bipolar disorders, panic disorder, schizophrenia, OCD, PTSD, and drug craving.

In 2009, moreover, a group of international experts updated the previous safety guidelines for the appli-

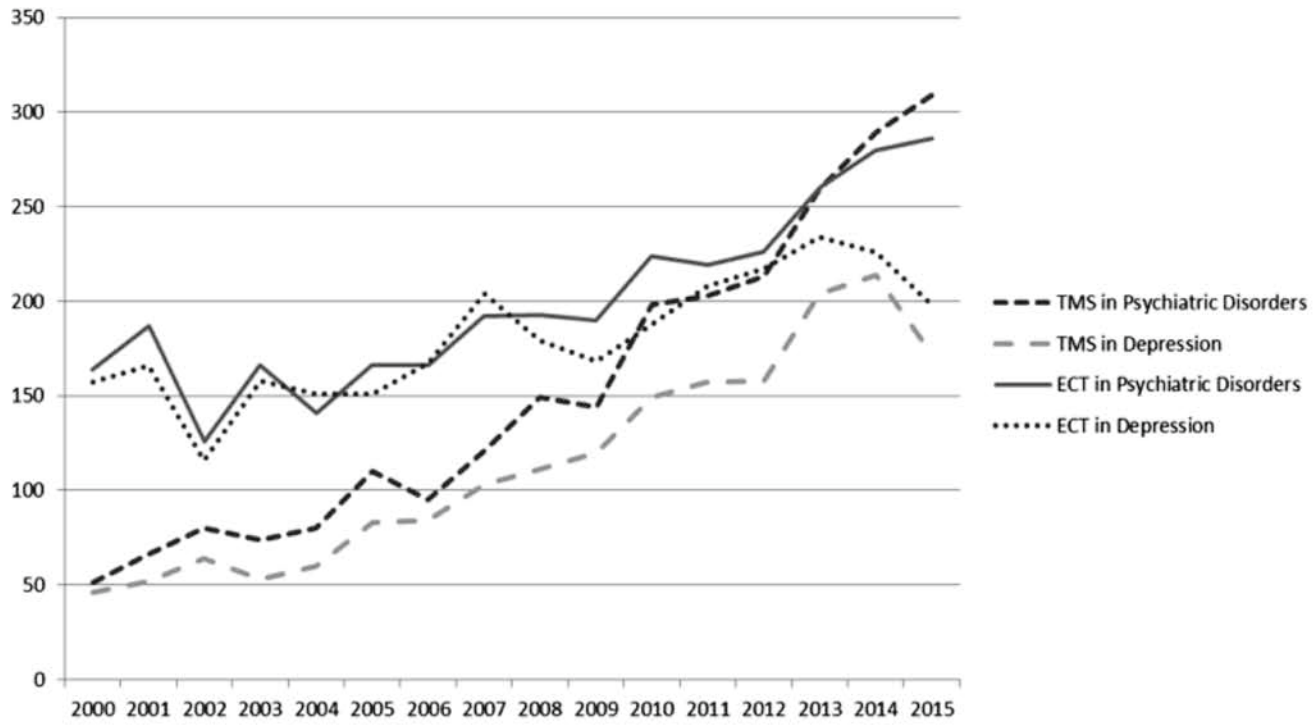


FIGURE 1.
TMS and ECT publications (PUBMED) from 2000 onward in psychiatric disorders and major depression.

cation of TMS in research and clinical settings [15].
Furthermore, in 2014, Lefaucheur and colleagues published the first evidence-based guidelines specifically focused on the clinical application of TMS in the treatment of different neuropsychiatric disorders: to date these guidelines represent the most complete and updated report on the topic [16].
According to CANMAT guidelines, rTMS has been recommended as a second-line therapeutic intervention in adult patients with major depression, who failed to respond to at least one antidepressant, with a good level of evidence in terms of acute efficacy and safety/tolerability (level 1), and a minimal evidence for maintenance and relapse prevention (level 3). It should be performed at high frequency on the left dorso-lateral prefrontal cortex (DLPFC), with a better outcome for 20 *vs* 10 sessions. Even though available data did not allow to clearly define predictors of positive outcome to TMS, or the optimal eligibility criteria for candidate patients, some clinical variables, such as a lower duration of current depressive episode and the absence of comorbid anxiety disorders, were indicated to positively affect treatment response. Moreover, the augmentative use of rTMS with antidepressant medication was found to accelerate response under sham-controlled conditions [13].
With respect to WFSBP guidelines, TMS has been recommended with a good level of evidence for the acute management of patients with moderate treatment-resistant depression (TRD) – preferably without psychotic symptoms during the index episode – either alone or in augmentation with medications. Typically, the eligible candidates should have shown an inadequate response to at least one trial with antidepressants, although some class I evidence supported the acute TMS efficacy also in drug-free unipolar depressed individuals. Insufficient evidence was available on its application as a maintenance/preventive strategy for depression, after acute response. In all these circumstances, a specifically trained equipe should provide TMS within a medical setting, under the supervision of a licensed medical doctor, able to properly manage potential adverse-events and related consequences during and after stimulation sessions [14].
Evidence-based guidelines elaborated by Lefaucheur and colleagues in 2014 considered the application of TMS in a large number of neuropsychiatric disorders including major depression, schizophrenia, and anxiety disorders [16]. Summary of level of evidence for the efficacy of TMS in these conditions is presented in Table I.
Indeed, major depression represents the main clinical indication for the use of rTMS. The efficacy of

**Table I.** Use of rTMS in psychiatric disorders other than major depression as formulated by Lefaucheur et al. (2014).

| Psychiatric disorder | Evidence level |
|---|---|
| Schizophrenia | Potential efficacy (auditory hallucinations)<br>Potential efficacy (negative symptoms) |
| Bipolar Disorder | Insufficient |
| Panic Disorder | Insufficient |
| Generalized Anxiety Disorder | Insufficient |
| Post-Traumatic Stress Disorder | Potential efficacy |
| Obsessive-Compulsive Disorder | Variable (different targets) |
| Craving and cigarette smoking | Potential efficacy |

high frequency (HF) rTMS of the left DLPFC and low frequency (LF) rTMS of the right DLPFC in acute depression is definite, with a Level A of recommendation. Furthermore, rTMS is likely to have higher success rates when applied to individuals not older than 65 years, with partial treatment response or limited treatment resistance (one/two unsuccessful medical interventions, with or without the combination of focused psychotherapy).

As regards schizophrenia, preliminary but encouraging evidence supports the role of rTMS in reducing negative symptomatology (level B), probably related to the beneficial effect on the depressive component resulting from HF rTMS of the left DLPFC. In a previous comprehensive review, moreover, Fitzgerald and Daskalakis provided preliminary but limited data supporting the role of TMS in reducing negative symptoms and improving cognitive function in schizophrenia [17]. However, insufficient data recommended the use of TMS in the treatment of psychotic symptoms in schizophrenia. However, some studies suggest that TMS, in particular at the level of the temporoparietal area, may improve positive symptoms (i.e., auditory hallucinations) compared with sham TMS [18]. Moreover, according to a recent meta-analysis, low frequency TMS was found to be effective in treating resistant auditory hallucinations in schizophrenic subjects, although showing no effect on other positive symptoms or cognitive deficits [19].

In relation to anxiety disorders, rTMS should be considered a potential second-line treatment in PTSD, for individuals who failed to respond to conventional therapies. Up to date, results from the few studies investigating this issue in PTSD are heterogeneous, with the only recommendation (level C) for a potential effect of HF rTMS on right DLPFC [20].

LF rTMS specifically targeting the orbitofrontal cortex or the supplementary motor area seems to be the most promising use of TMS in OCD [21], given that rTMS of the DLPFC has shown poor evidence of superiority over sham therapy [22]. Nonetheless, a recent sham-controlled trial of rTMS of DLPFC reported a significant improvement in obsessions but not in compulsions, with Y-BOCS scores reduction, as well as relief in depressive and anxiety symptoms [23]. Ultimately, the guidelines level of evidence for the use of TMS in OCD is of possible efficacy, requiring further investigation.

Considering cigarette craving, a level C of recommendation has been reported for the possible efficacy of HF rTMS to the left DLPFC in reducing consumption.

Finally, Lefaucheur and colleagues stressed the need of further investigation, in order to better clarify specific issues including TMS efficacy in bipolar depression, non-response *vs* treatment-resistance level in candidate patients, potential concomitant pharmacotherapy, and the usefulness of maintenance protocols.

## Potential limitations and new perspectives in the therapeutic use of rTMS in psychiatric practice

TMS is, at current time, one of the most promising novel and innovative treatments in clinical psychiatry, particularly for major depression. In the U.S., for instance, three different devices for TMS have received FDA approval for use in major depression, such indication being reimbursed by most insurance companies. Nonetheless, if, on one hand, previous and more recent treatment guidelines provide converging evidence on the efficacy and safety of rTMS in patients with major depression, some aspects beyond those already considered by the guidelines (e.g., interference of concomitant pharmacological therapy, usefulness of maintenance session, need for further studies in other psychiatric disorders) need to be taken into account in order to overcome current

limitations and barriers to the use of TMS in clinical practice.

To authors' opinion, two main issues may limit the use and diffusion of TMS in some psychiatric conditions and in specific populations: the limited depth of penetration and the duration of session and overall trial with traditional TMS. In fact, a first potential limitation for the use and extension of TMS in other psychiatric disorders is represented by its limited power of penetration (2-3 cm on average), allowing to mostly target the grey cortical matter up to the junction with white matter. Such characteristic is considered a potential limitation for the treatment of resistant patients and elderly patients, who may have different degrees of cortical atrophy, and patients with psychiatric disorders with pathophysiological mechanisms implying the prominent involvement of subcortical circuits. The availability of deep TMS seems to be of particular relevance for these and other cases.

With respect to the duration of a single session and entire course of TMS, these parameters are quantified around 30-45 minutes per session, 5 days per week, for not less than 3 to 4 weeks. Such features contribute to the overall costs of the intervention and limit its access to candidate patients for different reasons. In such perspective, the recent development of patterned TMS protocols, including Theta Burst Stimulation, might be of particular interest in order to reduce the overall duration of stimulation.

### *Deep TMS*

A relatively new alternative to classic TMS is Deep Transcranial Magnetic Stimulation (DTMS), a form of rTMS operated with a particular coil, the so called H-Coil [24], that can lead to a non invasive stimulation of a deeper area of the brain, up to 6 cm of depth, compared with the classic figure-of-eight coils. This stimulation can affect extensive neuronal pathways, including deeper cortical regions and fibers targeting subcortical regions, reducing the stimulation of the superficial cortical areas [25-27]. In particular, main targets are the dorsolateral and ventrolateral frontal areas that projects to other centers of the brain reward system [28]. DTMS is considered a secure and safe treatment: scalp discomfort, transient headache and dizziness, insomnia, numbness in the right temporal and right cervical zone, and, very rarely, generalized seizures have been reported as possible side effects and adverse events [9]. In the recent years, DTMS has been thoroughly investigated [29-33] and in 2013, the Food and Drug Administration issued a specific approval for a DTMS device (Brainsway), indicated for the treatment of adult patients suffering from TRD.

The only large multisite RCT involving 212 patients with TRD suggested that DTMS monotherapy was significantly more effective than sham DTMS in reducing depression scores at the Hamilton Depression Rating Scale, with a 0.76 effect size, and in improving response (38.4% *vs* 21.4%) and remission rates (32.6% *vs* 14.6%) [34]. This study underlined also the safety of the procedure and a stable therapeutic effect for up to 12 weeks of maintenance phase.

Two recent reviews specifically assessed the efficacy of DTMS. The first one stated that a 20 session-HF-DTMS course was an efficacious and acceptable treatment in unipolar depressed, multi-resistant patients, with overall weighted response and remission rates of 60% and 29%, respectively [35]. The second literature review [36] showed also an anxiolytic effect for the procedure in unipolar depressed patients, even though such effect seems to be more heterogeneous among studies compared to the antidepressant action of DTMS.

HF-DTMS seems to be effective also on cognitive functioning in depressed unipolar patients, including visuospatial and working memory, executive functions, information processing speed, orientation, as recently highlighted [37] with a higher degree of improvement compared to ECT and rTMS [38].

If, currently, DTMS may be considered an effective intervention in the therapy of TRD, the technique has also shown some positive result in the treatment of other psychiatric disorders, such as bipolar depression [39 40], obsessive compulsive disorder [41], PTSD [42], cognitive and negative symptoms in schizophrenia [43] and neurologic disorders, like Parkinson's disease [44]. More in detail, different specific coils have been developed for some of the abovementioned conditions. In addition, it needs to be stressed that DTMS allows an overall shorter duration of session, approximately 20 minutes.

### *Theta Burst Stimulation*

Theta-burst stimulation (TBS) is a form of rTMS in which short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz, 500 ms), as a continuous (cTBS), or intermittent (iTBS) trains [45]. The effects of this technique on synaptic plasticity occur faster than with traditional rTMS protocols, and TBS can produce long-lasting results on corticospinal excitability, involving long-term potentiation or depression-like effects on cortical synapses, depending on the pattern applied [1]. In particular, studies on

the human motor cortex showed that iTBS, giving short TBS trains intermittently, produced a prevalent excitatory effect yielding long-term potentiation-like effects; cTBS, on the other hand, led to an inhibitory effect, inducing a long-term depression-like reduction of cortical excitability [46 47].

Over the recent years, TBS has been applied in patients with various types of neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy; rehabilitation of aphasia or hand function after stroke; pain syndromes, such as neuropathic pain, visceral pain or migraine [47 48]. As regards psychiatric disorders, TBS has been utilised in TRD patients, with the underlying hypothesis that such individuals manifest a hypoactivity of the left DLPFC and a hyperactivity of the right DLPFC [49].

In 2010, Chistyakov and colleagues applied TBS to subjects with TRD in an open-label study, reporting clinical improvement after 2 weeks of treatment with left prefrontal iTBS (1200 pulses) and right prefrontal cTBS (1200, 1800 and 3600 pulses). Authors also showed a dose dependent effect, since 3600 pulses cTBS were significantly more effective than 1200 pulses cTBS in reducing depressive symptoms severity [50]. Moreover, a recent RCT of daily prefrontal TBS in patients with TRD by Li and colleagues showed that left prefrontal iTBS was more effective than right prefrontal cTBS and sham TBS; in addition, treatment refractoriness at baseline was an important and independent variable in predicting TBS antidepressant response [48].

***Other stimulation parameters***

From the first experiments of the technique in neurophysiology, TMS has obtained different approvals for the therapeutic use in neuropsychiatric disorders and is currently considered a safe and efficacious treatment for MDD and other psychiatric disorders [5]. Nonetheless, there are several ongoing directions to further refine the application of TMS in order to achieve superior therapeutic utility. First of all, the vast majority of TMS investigation has focused on the acute efficacy of the treatment with scattered and inconsistent data on the long term effect and the risk of relapse after treatment suspension [7 51]. Literature reports a high variable relapse risk, between 20% [52] to less than 80% [53] at six months. These findings suggest the need of a maintenance phase after the acute phase effect of TMS. In particular, maintenance phase is indicated for patients that showed a positive response after the acute phase without reaching remission or for individuals that relapsed after the acute phase treatment [5].

The efficacy of maintenance treatment has been supported by different reports from literature studies for both rTMS [54-57] and DTMS [34 58] in MDD and bipolar depression [59], even though, in mentioned studies, maintenance treatment was performed under different protocols in terms of duration and frequencies. Consequently, a univocal protocol is urgently needed. A recent study focusing on depressed patients who were medication free for one year maintenance period showed that maintenance TMS was not superior to "watch and wait" approach, although it was associated with a non-significantly longer time to relapse [60]. This study underlines how a better understanding of the interactions between pharmacologic treatments and TMS is needed for future investigation in order to implement optimal maintenance TMS plans.

In fact, patients undergoing TMS frequently receive other forms of therapy, such as psychotherapy, neurorehabilitation, and psychotropic medications, being the latter the primary safety concern for a possible interaction with TMS [15]. Actually, TMS produces limited side effects, and the most serious is the occurrence of seizures [61]. In particular, several antidepressants and neuroleptics may increase seizure risk, while anticonvulsants lower it [62]. Therefore, before starting a TMS protocol, clinicians should assess patients' seizure risk, taking also into account factors like medications dosages, speed of dose changes, and combination with other psychotropic drugs. In particular, the intake of one or a combination of the following psychotropic drugs poses a higher potential hazard for the application of TMS, due to their significant seizure threshold lowering potential: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine. In these cases, TMS should be performed, when required, with particular caution [15 63]. Certainly, the chapter of the interactions between TMS and specific classes of pharmacological treatments needs to be further investigated.

## Conclusions

Among brain stimulation interventions used as therapeutic tools for psychiatric disorders with poor response to standard treatments, TMS certainly represents the technique with the largest body of evidence in terms of RCTs and meta-analyses, with multiple indications and specific approvals by major regulatory agencies, such as the American FDA, and recently updated international treatment guidelines.

Certainly the favorable profile of tolerability with no associated systemic side-effects and the very low potential to induce adverse events played a crucial role in the widespread diffusion of TMS.

While the efficacy of TMS, particularly in major depression with poor response to antidepressants, is supported by the available literature, its effects in other mental disorders are still under investigation with preliminary evidence in some contexts (i.e., auditory hallucinations and negative symptoms in schizophrenia, nicotine craving and consumption, PTSD) and encouraging findings in some anxiety disorders and OCD. Other clinical areas and aspects to be further investigated are represented by the efficacy of the technique in bipolar depression and by the usefulness of maintenance sessions in patients beyond the acute treatment.

Notwithstanding the significant growth of TMS as therapeutic tool in major depression and other psychiatric disorders, there are still some open and debated issues about its real placement within the treatment algorithm of major depression, given that the mean duration of a TMS course should not last less than 3-4 weeks, 5 days per week for an average duration of 30 to 45 minutes per session. Such characteristics make it necessary to perform specific analyses of cost-utility for the clinical use of TMS in order to place the technique in the most appropriate position within the therapeutic algorithms of public and private psychiatric services. This is why, over the future years, further investigation in the field of TBS and DTMS might provide new advantages in terms of time reduction of the overall trial and single sessions of stimulation as well as in terms of possibility to treat more resistant patients.

Undoubtedly, the last decade represented a major step forward in the investigation and clinical application of TMS in the treatment of psychiatric disorders, which, ultimately, allowed the technique to be considered among current international guidelines as a valid therapeutic option in the treatment of major depression. It is, therefore, more than likely that the future decade of research and clinical acquisitions in the field of TMS will allow to definitely complete the transition for the technique from an investigational to a practical level of use within the therapeutic interventions for major depression and other psychiatric disorders.

## Take home messages for psychiatric care

- TMS is likely the non-invasive brain stimulation intervention with the strongest evidence in terms of efficacy in psychiatric disorders, in light of its non-invasiveness and favorable tolerability profile, as documented by RCTs and meta-analyses
- It has been approved by the FDA for the treatment of major depressive episodes with poor response to at least one antidepressant trial and then extensively investigated as therapeutic tool also in other psychiatric disorders
- We provided a critical perspective of most recent acquisitions on the use of TMS in psychiatric field, taking into account guidelines indications and more recent publications
- Future investigation should address the clinical efficacy and safety of specific forms of TMS (e.g., deep TMS, theta burst stimulation), which allow to reach deeper anatomic targets and to shorten the overall duration of stimulation.

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