Psychiatria Danubina, 2023; Vol. 35, Suppl. 2, pp 26-35
Conference paper
Review

ELECTRICAL AND MAGNETIC STIMULATION OF THE BRAIN; ARE THESE METHODS USED APPROPRIATELY IN TREATING DEPRESSION? PART 1.

Where should Transcranial Magnetic Stimulation be placed in an Algorithm for the treatment of Resistant Depression?

Michaela Agius[1] & Mark Agius[2]
[1]University of Malta, Msida, Malta
[2]Centro Studi Psichiatrici Iseo, Provaglio d'Iseo, Italy

SUMMARY

Depression is a common condition which causes serious of morbidity among the population. While treatment is often provided with pharmacological antidepressants and psychotherapy, many patients do not respond to such treatment, and therefore algorithms have been proposed to develop treatments for resistant depression. Transcranial Magnetic Stimulation is a relatively new form of treatment for depression, which appear to have a good safety profile and appear to be acceptable to patients. Other forms of Brain Stimulation, such as Electro-Convulsive therapy, have a more complex safety profile, and require anaesthesia. Still other forms of electrical stimulation of the brain, such as Vagus nerve Stimulation are invasive in nature.

The position of a particular modality of treatment in the Algorithm for the treatment of Resistant Depression depends on a balance between effectiveness of treatment, side effect profile, acceptability to the patients, availability of treatment, invasiveness of treatment, and the possibility of combining it with other treatments.

Here we assess the position of Transcranial Magnetic Stimulation in such an Algorithm for the treatment of Resistant Depression. Given its effectiveness and its relatively good side effect profile, we suggest that it could be used early in the treatment of depression, however its use may be limited by lack of necessary equipment. On the other hand, Electro-convulsive therapy must be reserved for much more resistant cases, because of the need for anaesthesia and muscle relaxants, as well as its side effect profile, even though it might be somewhat more effective than the other modalities. Further study of Transcranial Magnetic Stimulation and are warranted.

Key words: *Resistant Depression - Transcranial Magnetic Stimulation - antidepressant medication*

* * * * *

INTRODUCTION

Major depressive disorder is a common disorder, which is widely distributed in the population, and is associated with substantial symptom severity and impairment of functioning (Kessler 2003, Reddy 2010, Agius 2023, McKeever 2017). While the recent increase in treatment is encouraging, inadequate treatment remains a serious concern (Kessler 2003). Emphasis on screening for depression and expansion of treatment needs to be accompanied by a parallel emphasis on the improvement of treatment quality and the development of more acceptable treatments (Kessler 2003).

Treatment-resistant depression (TRD) is a relatively common condition and it accounts for a large proportion of the overall burden caused by depression (Fekadu 2009). Treatment-resistant depression is associated with a poorer clinical outcome, especially in those patients who require multiple antidepressant medications (Fekadu 2009). In order to plan treatment for depression, including treatment-resistant depression, different National Health Authorities have issued guidance, in the form of Algorithms of treatment. Such guidance are the NICE Guidelines in the UK (Nice 2022) and the STAR*D report (Rush 2006) in the USA. Such Guidance typically will suggest treatment beginning with a single SSRI antidepressant for 6 months, together with lifestyle changes and the change or addition of further antidepressants or other modes of treatment, including Psychotherapy such as Cognitive behaviour therapy. In NICE, further steps would include changes in antidepressant medication, Lithium or Mirtazepine Augmentation, and Electroconvulsive therapy would only be considered under specialist supervision as a fourth level of treatment (Nice 2022). In the STAR*D trial, *in Level 1, participants received citalopram as their first treatment step. Level 2 provided seven possible treatments involving four switch treatments (citalopram was stopped and new treatment initiated with sustained-release bupropion, cognitive therapy, sertraline, or extended-release venlafaxine) and three augmentation options (citalopram plus bupropion, buspirone, or cognitive therapy)* (Rush 2006).Step 3 included two medication switch strategies to Mirtazapine or Nortriptyline or two medication augmentation strategies with Lithium or T3, while Step 4 was treatment with either Tranylcypromine or extended-release Venlafaxine plus Mirtazapine (Gaynes 2008).

Transcranial Magnetic Stimulation is a new form of treatment for depression, which appear to have a good safety profile and appear to be acceptable to patients (Martin, 2020). Other forms of Brain Stimulation, such as Electro-Convulsive therapy, have a more complex safety profile, and require anaesthesia. Still other forms of electrical stimulation of the brain, such as Vagus nerve Stimulation (MIND 2022) are invasive in nature.

The position of a particular modality of treatment in an Algorithm for the treatment of Resistant Depression depends on a balance between the effectiveness of the treatment, the side effect profile, its acceptability to the patients, the availability of the treatment, the invasiveness of treatment, and the possibility of combining it with other treatments.

In this paper we attempt to assess the position of Transcranial Magnetic Stimulation in an Algorithm for the treatment of Resistant Depression, such as the NICE or the Star-D guidance, and compare this position to that of Electro-Convulsive Therapy, which is known to have an important side effect profile.

TRANSCRANIAL MAGNETIC STIMULATION

TMS is a non-invasive method for stimulating the human brain (Agius 2023). TMS operates using the principles of electromagnetic induction. When an electric current flows through a primary coil, according to the EM induction principle, a magnetic field is produced. The neural tissue (secondary coil) is stimulated when the magnetic flux flows towards it, creating a secondary electrical field in the process (Brunoni 2019). The neural tissue undergoes electrical effects because it behaves as secondary coils. Therefore, it is possible to create quickly alternating magnetic fields at high frequencies by altering the direction of current flow, which in turn stimulates the deeper neurons and their respective fibres (Chail 2018). A small area of the brain underneath the coil can be stimulated or inhibited by the field. All superficial regions of the brain located just below the skull may be affected, but the motor cortex where a localized muscle twitch, called the motor-evoked potential (MEP) may be produced, has been the subject of the majority of investigations. Even a single stimulus can cause detectable effects by depolarizing neurons (Agius 2023). The cerebral cortex's excitability can be altered by trains of stimuli (rTMS), both at the stimulation site and in distant regions along relevant anatomical relationships. This approach may be applied to map brain activity and investigate the excitability of various regions (Haraldsson 2004, Agius 2023). Additionally, TMS may develop into clinically effective diagnostic and prognostic tests, offer new insights into neural pathophysiology, and have therapeutic applications in a number of diseases. The studies that are currently available support this promise, but further research is necessary to determine TMS's place in clinical neurology (Ustohal 2018, Agius 2023).

MAGNETIC VERSUS ELECTRICAL BRAIN STIMULATION

It is worthwhile for our purposes to compare Transcranial Magnetic Stimulation to Electrical Brain Stimulation, which is another new treatment which needs to be fitted into the Algorithm for the treatment of depression.

DIFFERENCES BETWEEN MAGNETIC AND ELECTRICAL BRAIN STIMULATION IN PHYSIOLOGICAL OUTCOMES

The outcomes of TMS applied to the primary motor cortex resemble those of tES. However, one distinction with tES is a marginally shorter latency of response (Pearce et al. 2003, Agius 2023). By addressing this distinction, the excitation mechanisms of the two forms of stimulation could be better comprehended. However, since it is solely the stimulation across the primary motor cortex that provides measurements in such a detailed manner, it can only be assumed that the stimulation mechanism is similar in the other regions of the brain (Agius 2023). The characteristics of the corticospinal tract with respect to the descending volley generated by both kinds of stimulation appears to be connected to the variation in delay (Perez & Cohen 2009, Agius 2023). The D wave (direct wave) in tES is earlier than that in TMS, which suggests direct stimulation of descending axons (Agius 2023). Both types of stimulation result in an array of subsequent I waves (indirect waves), which represent the corticospinal neurons' synaptic activation. I waves occur at intervals of 1.5 ms and are either produced by recurrent synaptic networks or increasingly lengthy polysynaptic networks (Agius 2023). The largest MEPs in the brain are generated when the direction of current is in the posterior to anterior orientation at an ideal perpendicular angle to the central sulcus (Agius 2023). The initial wave produced is generally the I1 wave, about 1.5 ms after the D wave according to comparisons of the results obtained from turning the magnetic coil at various angles. A D wave may be generated first if the path of current is in the lateral to medial orientation. Finally, the I3 wave may be induced first when the direction of brain current is in the anterior-posterior orientation, following the D wave approximately 4.5 ms after (Hallett 2007, Agius 2023). When the muscle is at rest as opposed to when it is contracting at baseline, MEPs are also less pronounced and occur later. This is mainly because it is simpler to cause an increase in activation since the motor neurons are more active (Rosenkranz & Rothwell 2003, Agius 2023).

MODE OF ACTION OF TRANSCRANIAL MAGNETIC STIMULATION

Changes in synaptic strength or anatomical modifications, such as sprouting or changes to dendritic spines, are necessary for long-term effects on the brain. The primary goal of TMS treatment is to alter synaptic strength. Morphological alterations may likely be a subsequent effect of sustained changes in synaptic strength. Numerous disorders have been treated using this approach (Klein et al. 2015, Agius 2023).

TMS therapy is predominantly used for psychiatric disorders, particularly depression. Since electroconvulsive therapy has been shown to effectively treat depression, but has important side effects, in particular, the induction of convulsions and impairment of memory, researchers have explored the potential of TMS to deliver equally efficacious focal therapy with fewer adverse effects (Agius 2023).

There are numerous ways to apply TMS therapy, and the most effective location, stimulus frequency, intensity, and duration of treatment are still uncertain (Agius 2023). As patients with depression have been shown to have reduced activity in the left dorsolateral prefrontal cortex, therapy is typically focused on stimulating that region using an excitatory approach (Grimm 2008).

EVALUATION OF TMS. FOR TREATMENT OF DEPRESSION

Numerous clinical trials have been carried out to evaluate the effectiveness of Transcranial Magnetic stimulation. To evaluate the effectiveness of active stimulation and placebo effects, studies use sham stimulation. The sham stimulation must imitate the properties of active stimulation to maintain the integrity of blinding (Agius 2023).

An early meta-analysis of 33 studies considered In total, 475 patients were subjected to active transcranial magnetic stimulation, while 402 patients were subjected to sham stimulation across all the studies. This showed that active TMS treatment was effective, however there was considerable variability among the studies,which was likely due to differences in technique (Herrmann & Ebmeier 2006).

Schutter carried out a metanalysis of thirty double-blind sham-controlled parallel studies with 1164 patients in order to establish the efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex (Schutter 2009). He measured the percentage change in depression scores from baseline to endpoint of active versus sham treatment (Schutter 2009). The overall weighted mean effect size, d=0.39 [95% confidence interval (CI) 0.25-0.54], for active treatment was observed (z=6.52, p<0.0001) and was significant (Schutter 2009). This finding shows that high-frequency rTMS over the left DLPFC is superior to sham in the treatment of depression (Schutter 2009). It was considered that the effect size was robust and was comparable to a subset of commercially available antidepressant drug agents. Some studies have used a slow (inhibitory) TMS approach to the right dorsolateral prefrontal cortex as an alternative.

Berlim et al. carried out a a meta-analysis of randomized, double-blind and sham-controlled trials to establish the efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) for treating primary major depression (Berlim 2013). They obtained data from eight RCTs, totaling 263 subjects with Major D depression (MD). They distinguished between patients who responded to treatment and those in which remission was achieved (Berlim 2013). They found that, after an average of 12.6±3.9 rTMS sessions, 38.2% (50/131) of subjects receiving active LF-rTMS and 15.1% (20/132) of subjects receiving sham rTMS were classified as responders (OR=3.35; 95% CI=1.4-8.02; p=0.007) (Berlim 2013). Furthermore, 34.6% (35/101) of subjects receiving active LF-rTMS and 9.7% (10/103) of subjects receiving sham rTMS were classified as remitters (OR=4.76; 95% CI=2.13-10.64; p<0.0001) (Berlim 2013). They calculated that the Number Needed to Treat for both response and remission rates was 5 (Berlim 2013). They concluded that, LF-rTMS is an effective treatment for Major Depression, because it provided clinically useful benefits which are comparable to those of standard antidepressants and high-frequency rTMS (Berlim 2013). They also observed that LF-rTMS appeared to be acceptable intervention to the depressed patients (Berlim 2013).

A further review of TMS was carried out in 2013 (Berlim 2013) seven RCTs, totaling 279 subjects who suffered from Major Depression. After an average of 12.9 (s.d. = 2.7) sessions, 24.7% (40/162) and 6.8% (8/117) of subjects who received active bilateral rTMS and sham rTMS respectively were classified as responders [OR 4.3, 95% confidence interval (CI) 1.95-9.52, p<0.0001] (Berlim 2013). Also, 19% (23/121) while 2.6% (2/77) of subjects were remitters following active bilateral rTMS and sham rTMS, respectively (OR 6.0, 95% CI 1.65-21.8, p=0.006) (Berlim 2013). It was concluded that bilateral TMS gave similar benefits as antidepressant medication and unilateral TMS (Berlim 2013).

Berlim et al. (2014) carried out a further systematic review and meta-analysis of randomized, double-blind and sham-controlled trials of the response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression. In this study they assessed data from 29 RCTs including 1371 subjects with Major Depression (Berlim 2014). Following approximately 13 sessions, 29.3% and 18.6% of subjects receiving HF-rTMS

were classified as responders and remitters, respectively (compared with 10.4% responders and 5% remitters of those receiving sham rTMS). The pooled OR was 3.3 ($p<0.0001$) for both response and remission rates (with associated NNTs of 6 for responders and 8 for remitters) (Berlim 2014). They assessed that HF-rTMS was equally effective as an augmentation strategy or as a monotherapy for Major Depression (Berlim 2014), and that this was so whether HF-rTMS was used in a group of patients with primary unipolar MD or in a group of patients some of which had unipolar and some of which had bipolar Major Depressive Disorder (Berlim 2014). They concluded that HF-rTMS appeared to be associated with clinically effective antidepressant effects and had a benign tolerability profile (Berlim 2014).

On the other hand, Lepping et al. (2014) , carried out a systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. They studied 63 studies. For depression, the mean percentage change in HAMD scores in all sham-controlled rTMS treatment arms was 35.63 (SD 16.35) and for sham-rTMS 23.33 (SD 16.51). For Treatment Resistant Depression, active rTMS in sham-controlled studies showed a mean Hamilton Depression Rating Scale (HAMD) percentage reduction of 45.21 (SD 10.94) versus 25.04 (SD 17.55) for sham-rTMS (Lepping 2014). This data was then translated into Clinical Global Impression-Improvement scale (CGI-I) scores. Thus the notional CGI-I score difference between rTMS and sham-rTMS was 0.5 in favour of rTMS, while for Treatment Resistant Depression, it was 0.75 in favour of rTMS (Lepping 2014). It was concluded that rTMS appears to be efficacious for both non-refractory and treatment-resistant depression (Lepping 2014).

Chen et al. carried out a meta-analysis of randomized controlled trials in order to determine the efficacy of bilateral vs. unilateral repetitive transcranial magnetic stimulation (rTMS) in treating major depressive disorder (MDD) (Chen et al. 2014). Data on 509 subjects was obtained from seven randomized controlled trials (RCTs) (Chen et al. 2014). Bilateral and unilateral rTMS showed comparable efficacy in treating MDD with a pooled odds ratios of 1.06 (95% confidence interval (CI)=0.58-1.91) for response rates and 1.05 (95% CI=0.52-2.11) for remission rates (Chen et al. 2014). Also, bilateral rTMS was equally effective as both left and right unilateral rTMS (Chen et al. 2014).

Levkovitz et.al. carried out a prospective multicenter randomized controlled trial to study the efficacy and safety of deep transcranial magnetic stimulation for major depression (Levkovitz 2015). They recruited 212 Major Depressive Disorder outpatients, who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments during the current episode and randomly assigned them to monotherapy with active or sham dTMS (Levkovitz 2015). Twenty sessions of dTMS (18 Hz over the prefrontal cortex) were applied during 4 weeks and then biweekly for 12 weeks (Levkovitz 2015). dTMS induced a 6.39 point improvement in Hamilton Depression Rating Scale (HDRS-21) score, while a 3.28 point improvement was observed in the sham group ($p=0.008$), resulting in a 0.76 effect size (Levkovitz 2015). The response and remission rates were higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, $p=0.013$; remission: 32.6 vs. 14.6%, $p=0.005$) (Levkovitz 2015). Therefore it appears that dTMS is an effective intervention in Major Depressive Disorder, which is efficacious and safe in patients not responding to antidepressant medications, and whose effect remains stable over 3 months of maintenance treatment (Levkovitz 2015).

During 2016, Health Quality Ontario carried out a meta-analysis to determine the effectiveness of rTMS . Twenty-three RCTs compared rTMS with sham. There was a statistically significant improvement in depression scores with rTMS when trialed against sham therapy. (weighted mean difference [WMD] 2.31, 95% CI 1.19-3.43; $p<0.001$) (Health Quality Ontario 2016). A 10% absolute difference was reported between rTMS and sham in the rates of remission or response (Health Quality Ontario 2016). Therefore the number needed to treat was 10 (Health Quality Ontario 2016). Risk ratios for remission and response were 2.20 (95% CI 1.44-3.38, $p=0.001$ and 1.72 [95% CI], 1.13-2.62, $p=0.01$), respectively, favouring rTMS (Health Quality Ontario 2016).

There are several types of Transcranial Magnetic Stimulation. Brunoni et al. compared the efficacy of these different types (Brunoni 2017). Eighty-one studies (4233 patients, 59.1% women, mean age of 46 years) were included. The interventions which were more effective than sham were priming low-frequency (OR, 4.66; 95% CI, 1.70-12.77), bilateral (OR, 3.96; 95% CI, 2.37-6.60), high-frequency (OR, 3.07; 95% CI, 2.24-4.21), θ-burst stimulation (OR, 2.54; 95% CI, 1.07-6.05), and low-frequency (OR, 2.37; 95% CI, 1.52-3.68) rTMS. On the other hand, the novel rTMS interventions (accelerated, synchronized, and deep rTMS) were not more effective than sham (Brunoni 2017). Few differences were found in clinical efficacy and acceptability between the different rTMS modalities (Brunoni 2017). It was suggested that priming low-frequency and bilateral rTMS might be the most efficacious and acceptable interventions among all rTMS strategies, but further evidence is necessary to substantiate this (Brunoni 2017).

Bipolar depression (BD) that is, the depressive phase of bipolar II disorder, is a highly prevalent condition with limited therapeutic options. Therefore, Tavares et al. investigated the Treatment of Bipolar Depression with Deep TMS, by carrying out a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical

Trial (Tavares et al. 2017). Out of 50 patients, 43 completed the trial (Tavares et al. 2017). It was found that active dTMS was superior to sham at end point (difference favoring dTMS=4.88; 95% CI 0.43 to 9.32, p=0.03) but not at follow-up (Tavares et al. 2017). There was a trend for greater response rates in the active (48%) vs sham (24%) groups (OR=2.92; 95% CI=0.87 to 9.78, p=0.08), however remission rates were not statistically different (Tavares et al. 2017). It was therefore concluded that Deep TMS is a potentially effective and well-tolerated add-on therapy in resistant bipolar depressed patients receiving adequate pharmacotherapy (Tavares et al. 2017).

Mutz et al. (2018) carried out a systematic review and meta-analysis of randomised sham-controlled trials to assess the efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression (Mutz 2018). They analysed effects on response, remission, all-cause discontinuation rates and continuous depression severity measures. Response rates demonstrated efficacy of high-frequency rTMS over the left DLPFC (OR = 3.75, 95% CI [2.44; 5.75]), right-sided low-frequency rTMS (OR = 7.44, 95%CI [2.06; 26.83]) bilateral rTMS (OR = 3.68, 95% CI [1.66; 8.13]), deep TMS (OR = 1.69, 95% CI [1.003; 2.85]), intermittent TBS (OR = 4.70, 95% CI [1.14; 19.38]), but not for continuous TBS, bilateral TBS or synchronised TMS (Mutz 2018). There were no differences in all-cause discontinuation rates (Mutz 2018). The strongest evidence for efficacy was for high-frequency rTMS over the left DLPFC (Mutz 2018).

A further meta-analysis study by Mutz et al. was carried out to demonstrate the Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults (Mutz 2019). It randomly allocated to electroconvulsive therapy (ECT), transcranial magnetic stimulation (repetitive (rTMS), accelerated, priming, deep, and synchronised), theta burst stimulation, magnetic seizure therapy, transcranial direct current stimulation (tDCS), or sham therapy (Mutz 2019). It showed that ,In network meta-analysis, priming transcranial magnetic stimulation (6.02, 2.21 to 16.38), magnetic seizure therapy (5.55, 1.06 to 28.99), bilateral rTMS (4.92, 2.93 to 8.25), bilateral theta burst stimulation (4.44, 1.47 to 13.41), low frequency right rTMS (3.65, 2.13 to 6.24), intermittent theta burst stimulation (3.20, 1.45 to 7.08), high frequency left rTMS (3.17, 2.29 to 4.37) were all associated with higher response compared with sham therapy (Mutz 2019).

The Mutz 2019 study also showed that: bitemporal ECT (summary odds ratio 8.91, 95% confidence interval 2.57 to 30.91), high dose right unilateral ECT (7.27, 1.90 to 27.78) were also associated with higher response compared with sham therapy (Mutz 2019). Network meta-analysis indicated that bitemporal ECT and high dose right unilateral ECT were associated with increased response compared with all the other therapies studied thus suggesting that ECT was rather more effective than the TMS interventions of all modalities (Mutz 2019). This confirms a previous meta-analysis by Chen et al. (2017) which studied the comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression (Chen 2017). In this study, 1288 individuals with Major Depressive Disorder were studied from 25 studies (Chen 2017). ECT was non-significantly more efficacious than B-rTMS, R-rTMS, and L-rTMS. Left prefrontal rTMS was non -significantly less efficacious than all other treatment modalities (Chen 2017). R-rTMS was found to be non-significantly better tolerated than ECT, B-rTMS, and L-rTMS (Chen 2017). ECT was found to be the most efficacious treatment with the cumulative probabilities of being the most efficacious treatment being: ECT (65%), B-rTMS (25%), R-rTMS (8%), and L-rTMS (2%) (Chen 2017). R-rTMS was found to be the best-tolerated treatment with the cumulative probabilities of being the best-tolerated treatment being: R-rTMS (52%), B-rTMS (17%), L-rTMS (16%), and ECT (14%) (Chen 2017).

Another variant of TMS is deep transcranial magnetic stimulation. Hung et al carried out a meta-analysis to assess the efficacy and tolerability of deep transcranial magnetic stimulation (dTMS) for treatment-resistant depression (TRD) (Hung 2020). They included Fifteen studies including three randomized controlled trials (RCTs) (n=417) and twelve uncontrolled clinical trials (n=284,) were included (Hung 2020). Deep transcranial magnetic stimulation significantly improved the symptoms of depression (Hedges' g = -1.323, 95% CI = -1.651 to -0.995, p<0.001) and anxiety s (Hedges' g = -1.282, 95% CI = -1.514 to -1.051, p<0.001) in patients with treatment-resistant depression(TRD) (Hung 2020).

In 2022, Valiengo et al carried out a meta-analysis to elucidate the efficacy of rTMS in older patients (Valiengo 2022). Out of Fourteen RCTs, 26 studies, including 10 RCTs and 16 open-label studies were included in the meta-regression (Valiengo 2022). Active rTMS was found to be significantly superior to sham treatment for reduction of symptom severity (SMD = 0.36; 95% CI = 0.13-0.60), and also for response (OR = 3.26; 95% CI = 2.11-5.04) and remission (OR = 4.63; 95% CI = 2.24-9.55) (Valiengo 2022).The results showed that rTMS is an effective, safe, and well-tolerated treatment for Major Depressive Disorder in older adults and that therefore it should be considered in the treatment of this vulnerable population (Valiengo 2022).

Because the issue being discussed in the present study is whether TMS is superior or similar in efficacy to Antidepressant Medication, and hence where it should be placed in an algorithm for the treatment of

depression, we wished to find some studies which directly compared TMS to Antidepressant Medication. In many of the studies listed above, it is stated that the efficacy of TMS appeared to be comparable theoretically to Antidepressant Medication, however we wanted some direct comparisons. In fact we were able to find one, in a special group of patients; those suffering from Parkinson's disease. In this study, 42 patients were enrolled into two groups: group 1, active rTMS (15 Hz rTMS for 10 days) and placebo drug treatment; group 2, sham rTMS and fluoxetine 20 mg/day. Hamilton rating scale for depression (HRSD) and Beck depression inventory (BDI) were improved to the same extent in both groups after two weeks of treatment (38% and 32% for group 1, 41% and 33% for group 2, respectively). Thus, rTMS has the same antidepressant efficacy as fluoxetine and may have the additional advantage of some motor improvement and earlier cognitive improvement, with fewer adverse effects (Fregni 2004) Hence, in this study, at least, TMS appears to be directly comparable in efficacy to fluoxetine 20 mg/day.

We were also able to find some studies which demonstrate the effect of Adding TMS to antidepressant medication. Rossini et al. (2005) assessed the effectiveness of rTMS started concomitantly with antidepressant medications in non-drug-resistant major depressive disorder patients (Rossini 2005). This was a 5-week, double-blind, randomized, sham-controlled study of 99 inpatients suffering from a major depressive episode (Rossini 2005). The patients were randomly assigned to receive venlafaxine, sertraline, or escitalopram in combination with a 2-week period of sham or active 15-Hz rTMS on the left dorso-lateral prefrontal cortex (Rossini 2005). The active rTMS group showed a significantly faster reduction in Hamilton Rating Scale for Depression (HAM-D) scores compared with the sham group (p=0.0029) (Rossini 2005). These findings demonstrated the efficacy of rTMS in hastening the response to antidepressant drugs in patients with major depressive disorder (Rossini 2005). The effect of rTMS appeared to be unaffected by the specific concomitantly administered drug (Rossini 2005).

In another study (Huang 2012), designed as a 2-week double-blind study with a 2-week extended antidepressant phase, 60 first-episode young major depressive patients were randomly assigned to citalopram in combination with 2 weeks of either active or sham rTMS treatment (Huang 2012). There was a significantly greater number of early improvers (a reduction of HAMD-17 score $\geq$20% within the first 2 weeks) observed in the active rTMS group compared to the sham group (57% vs. 29%, χ^2=4.667, p=0.031) (Huang 2012). There was no significant difference observed in responder rates (46% vs. 36%, χ^2=0.295, p=0.586) or in remission rates (39% vs. 29%, χ^2=0.319, p=0.572) between the two groups at 4 weeks (Huang 2012). There was a significant difference seen in both HAMD-17 and MADRS scores between the two groups at 2 and 4 weeks (Huang 2012). The active rTMS group showed a significantly faster score reduction compared to the sham group at 2 weeks (HAM-D-17, t=13.444, p=0.001; MADRS, t=30.123, p=0.000), which was maintained at 4 weeks on both scales (HAMD-17, t=46.915, p=0.000; MADRS, t=39.996, p=0.000) (Huang 2012). Thus, RTMS accelerated the rapidity of the antidepressant response in first-episode young depressive patients (Huang 2012).

Another Study, (Bretlau 2008) studied 45 patients with with medication-resistant major depression. The patients had experienced two failed antidepressant treatment attempts with non-tricyclic antidepressants before being included in the study. They were randomised so that 23 patients received sham TMS and 22 patients received active, high-frequency rTMS over the left cortex, while all patients in both groups were also prescribed 20 mg escitalopram daily (Bretlau 2008). Over the 3 weeks, the active rTMS treatment was superior to sham TMS with effect sizes on the HAM-D(6) rating scale above 0.70, which indicated both a statistically and a clinically significant effect (Bretlau 2008). Both the rTMS and escitalopram were well-tolerated (Bretlau 2008).

Another study (Bares 2012) compared the efficacy of 1 Hz rTMS over the right prefrontal dorsolateral cortex with venlafaxine ER in the treatment of resistant depression. Venlafaxine is an SNRI, which is a rather more potent antidepressant than SSRI antidepressants. Sixty inpatients with depressive disorder who previously did not respond to at least one antidepressant treatment, were randomly assigned to 1 Hz rTMS with placebo or venlafaxine ER with sham rTMS for 4 weeks (Bares 2012). This design enabled the comparison of the two treatment modalities while the patients remained blinded to the treatment given. The main outcome measure was the score change in the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) and Beck Depressive. Inventory-Short Form (BDI-SF) scales were also used (Bares 2012). There were no significant differences between the treatment groups in MADRS (p=0.38), BDI-SF (p=0.56) and CGI (p=0.17) scores from baseline to endpoint (Bares 2012). Response rates for rTMS (33%) and venlafaxine (39%) as well as remission (MADRS score < or=10 points) rates (19% vs. 23%) and drop-out rates did not differ between treatment groups (Bares 2012). There were significant reductions of MADRS, CGI and BDI-SF scores in both groups (Bares 2012). The findings of this study show that, right sided rTMS produces a clinically effective reduction of depressive symptomatology in patients with resistant depression which is comparable to the effect of venlafaxine ER (Bares 2012).

Furthermore, a meta-analysis study was carried out to observe weather High-frequency repetitive transcranial magnetic stimulation might accelerate and enhance the clinical response to antidepressants in major depression (Berlim 2013). Six such randomized controlled trials (RCTs), totaling 392 subjects with major depression were identified. In all combined rTMS and antidepressant treatment was given. There was significantly higher response rates for active HF-rTMS (43.3%; 84/194) compared to sham rTMS (26.8%; 53/198) (OR = 2.5; 95% CI, 1.12-5.56; p=0.025); however, remission rates did not differ between groups (p=0.33). It was found that HF-rTMS was a promising strategy for accelerating clinical response to antidepressants in major depression (Berlim 2013).

Bipolar Depression is a condition which is difficult to treat. A systematic review and meta-analysis has recently addressed the issue of whether Repetitive Transcranial Magnetic Stimulation is effective for treating Bipolar Depression (Tee 2020). Eleven randomized sham-controlled studies were included, with a total of 345 patients with Bipolar Disorder (bipolar depression = 257, mania = 86, mixed affective states = 2) (Tee 2020). Trials of rTMS in bipolar depression (N = 8) showed a small but significant improvement in depression scores [standardized mean difference = 0.302, p<0.05], when compared to the control group (Tee 2020). It was also found that the use of rTMS brought about a higher remission rate than sham-controls [RD = 0.104±0.044, p<0.05, NNT = 10; as well as a trend of greater response rate [RD = 0.074±0.039, p=0.06] (Tee 2020). However, the results were inconclusive for the effect of rTMS in mania (Tee 2020). No serious adverse events were reported In either the depressive or the manic groups. (Tee 2020) It was reported that the risk of treatment-emergent mania appeared to be low (Tee 2020). It was concluded that rTMS appeared to be safe and effective in treating bipolar depression, while further studies are required to assess the effect of rTMS in Mania (Tee 2020).

Hence, all the above studies suggest that the reduction in symptoms of depression brought about by the use of Transcranial Magnetic stimulation is comparable to the reduction caused by SSRI and SNRI antidepressants, while TMS is better tolerated because of its low side effect profile compared with antidepressant medication.

SAFETY CONSIDERATIONS AND SIDE EFFECTS TRANSCRANIAL MAGNETIC STIMULATION

It is generally safe to deliver a single pulse of TMS to the brain. Advances in technology now allow for rTMS to produce strong effects lasting beyond the stimulation period. At lower frequencies, rTMS can inhibit while at higher frequencies it can excite neural activity. However, rTMS has the potential to cause seizures even in healthy individuals (Rossi 2009). Safety guidelines have been established to prevent most problems by regulating the combinations of frequency, intensity, and train length used in rTMS (Wassermann 1998, Agius 2023).

BRIEF COMPILATION OF STUDIES COMPARING TRANSCRANIAL MAGNETIC STIMULATION ELECTROCONVULSIVE THERAPY

Slotema et al. (2010) conducted a direct comparison of repetitive transcranial magnetic stimulation (rTMS) with electroconvulsive therapy (ECT) and found that ECT was more effective in treating depression (mean weighted effect size based on pretreatment-posttreatment comparisons. -0.47, p=0.004). However, rTMS was found to have a more favourable acceptability and side effect profile.

In 2013, Berlim et al. carried out a meta-analysis to examine the efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (HF-rTMS) and electroconvulsive therapy (ECT) for treating major depression. They obtained data from 7 randomized trials, totalling 294 subjects with Major Depression. After an average of 15.2 HF-rTMS and 8.2 ECT sessions, 33.6% (38/113) of rTMS patients and 52% (53/102) of ECT patients were classified as remitters (OR = 0.46; p=0.04) (Berlim 2013). The associated NNT for remission was 6 in favour of ECT (Berlim 2013). Furthermore, reduction of depressive symptomatology was significantly more pronounced in the ECT group (Hedges' g = -0.93; p=0.007) (Berlim 2013). They concluded that ECT seems to be more effective than HF-rTMS for treating MD (Berlim 2013).

In 2016,Health Quality Ontario carried out a Meta-Analysis of rTMS against ECT to assess the efficacy of rTMS. Six RCTs compared rTMS with electroconvulsive therapy (ECT) (Health Quality Ontario 2016). Trials of rTMS versus ECT showed a statistically and clinically significant difference between rTMS and ECT in favour of ECT (WMD 5.97, 95% CI 0.94-11.0, p=0.02). Risk ratios for remission and response were 1.44 (95% CI 0.64-3.23, p=0.38) and 1.72 (95% CI 0.95-3.11, p=0.07), respectively,showing ECT to be more Efficacious (Health Quality Ontario 2016).

Chen et al. (2017) conducted a similar comparison in the context of treatment-resistant depression (TRD) and included 25 studies with 1288 patients with major depressive disorder (MDD). They found that ECT was more effective than bilateral prefrontal cortex rTMS, but the difference was not statistically significant (Agius 2023). Razza et al. (2018) reported that while there may

be a placebo response to rTMS in depression trials, current protocols achieve response rates ranging from 29% to 49% and remission rates ranging from 19% to 34% in TRD, indicating intermediate efficacy between medication and ECT. The study by Mutz et al. also shows an greater effectiveness for ECT as compared to TMS (Mutz 2019).

Finally, a study by Dannon et al. (2016) was conducted to determine the effectiveness and patient preference between ECT and TMS for treatment-resistant depression patients, taking into account cost-benefit analysis. The study found that ECT was more effective than TMS, although the difference was not statistically significant in the group effect. However, ECT patients reported more side effects, while TMS treatment was more preferred by patients. Despite this, the cost-benefit of ECT was higher than TMS. The study suggests that patient preference for treatment could be more favourable towards TMS if it was to be incorporated in the Health Maintenance Organization's service list (Agius 2023).

CONCLUSION

Transcranial magnetic stimulation (TMS) is a valuable tool for investigating human brain physiology and supplements other non-invasive methods. While motor and sensory function have been extensively studied, future research will focus on more complex aspects of human cognition and behaviour. In terms of therapy, TMS has mild and transient effects, and further development is needed to make them more robust and long-lasting. In the other hand, tDCS and tACS offer unique neuromodulatory options, allowing for functionally or spatially specific targets. These techniques possess the ability to modulate or stimulate task-related neural networks, potentially normalizing dysregulated neural activity associated with specific psychiatric disorders.

Ultimately, in treatment-resistant depression, ECT has been found to be slightly more effective than TMS. Nonetheless, patients seem to generally prefer TMS over ECT since it is associated with fewer side effects, and is a more overall positive experience. However, this difference was not found to be statistically significant. Therefore, it is evident that more research is required, especially in areas targeting disorders other than treatment-resistant depression, in order to promote holistic patient-centred care.

How, therefore, should we place TMS within the Algorithm of treatment for depression. It is clear from all the above that TMS is effective in treating depression, and compares well with antidepressant medications, while it has a better side effect profile. It has a better side effect profile than ECT, although ECT appears to be rather more effective. The most important drawback is that the equipment to deliver TMS is only available in special centres. Medication is available where ever a doctor can write a prescription. Therefore, it is our view that TMS could be seen as a first or second choice after a first trial of antidepressant medication, always assuming that , in order that patients are able to deal with their negative thoughts, all patients with negative thoughts are also offered appropriate Cognitive behavioural psychotherapy.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Both Authors contributed to the literature search and the drafting of the text.

References

1. *Agius M: Transcranial Magnetic and Electrical Stimulation of the Brain. Unpublished Dissertation University of Malta, 2023*
2. *Bares M, Kopecek M, Novak T, Stopkova P, Sos P, Kozeny J, Brunovsky M, Höschl C: Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: a double-blind, single-centre, randomized study. J Affect Disord 2009; 118:94-100*
3. *Berlim MT, Van den Eynde F, Daskalakis ZJ: Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013; 38:543-51*
4. *Berlim MT, Van den Eynde F, Daskalakis ZJ: High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. J Clin Psychiatry 2013; 74:e122-9*
5. *Berlim MT, Van den Eynde F, Daskalakis ZJ: A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med 2013; 43:2245-54*
6. *Berlim MT, van den Eynde F, Daskalakis ZJ: Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety. 2013; 30:614-23*
7. *Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ: Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014; 44:225-39*

8. *Bretlau LG, Lunde M, Lindberg L, Undén M, Dissing S, Bech P: Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. Pharmacopsychiatry 2008; 41:41-7*
9. *Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I, Rios RM, Razza LB, Loo C, Padberg F: Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry 2019; 41:70–81*
10. *Brunoni AR, Chaimani A, Moffa AH, et al.: Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis. JAMA Psychiatry 2017; 74:143-52*
11. *Chail A, Saini R, Bhat P, Srivastava K, Chauhan V: Transcranial magnetic stimulation: A review of its evolution and current applications. Ind Psychiatry J 2018; 27:172*
12. *Chen S-T, Shaw-Ji C, Chun-Hung C, Hsin-Chi T, Lin CCH: Superior antidepressant effect occurring 1 month after rTMS: add-on rTMS for subjects with medication-resistant depression. Neuropsychiatr Dis Treat 2013; 9:397-401*
13. *Chen JJ, Liu Z, Zhu D, et al.: Bilateral vs. unilateral repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomized controlled trials. Psychiatry Res 2014; 219:51-7*
14. *Chen JJ, Zhao LB, Liu YY, Fan SH, Xie P: Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: A systematic review and multiple-treatments meta-analysis. Behav Brain Res 2017; 320:30-6*
15. *Dannon P, Magnezi R, Aminov E, Shmuel D, Dreifuss M: Comparison between neurostimulation techniques rapid transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness. PPA 2016; 10:1481–1487. https://doi.org/10.2147/ppa.s105654*
16. *Fekadu A, Wooderson SC, Markopoulo K, Donaldson C, Papadopoulos A, Cleare AJ: What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. J Affect Disord 2009; 116:4-11*
17. *Fregni F, Santos CM, Myczkowsk ML, Rigolino R, Gallucci-Neto J, Barbosa ER, Valente KD, Pascual-Leone A, Marcolin MA: Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75:1171–1174*
18. *Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M: The STAR*D study: treating depression in the real world. Cleve Clin J Med 2008; 75:57-66*
19. *Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Niehaus L, Boeker H, Northoff G: Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. Biological Psychiatry 2008; 63:369–376*
20. *Hallett M: Transcranial Magnetic Stimulation: A Primer. Neuron 2007; 55:187–199*
21. *Haraldsson H, Ferarelli F, Kalin N, Tononi G: Transcranial Magnetic Stimulation in the investigation and treatment of schizophrenia: a review. Schizophrenia Research 2004; 71:1–16*
22. *Health Quality Ontario: Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Ont Health Technol Assess Ser 2016; 16:1-66*
23. *Herrmann LL, Ebmeier KP: Factors Modifying the Efficacy of Transcranial Magnetic Stimulation in the Treatment of Depression. J Clin Psychiatry 2006; 67:1870–1876*
24. *Huang M, Luo B, Hu J, Wang S, Zhou W, Wei N, Hu S, Xu Y: Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: a double-blind, randomized, sham-controlled trial. Aust NZJ Psychiatry 2012; 46:257-64*
25. *Hung Y, Yang L, Stubbs B, Li D, Tseng P, Yeh T, Chen T, C Liang, Chu C: Efficacy and tolerability of deep transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2020; 99:109850*
26. *Ionescu DF, Rosenbaum JF, Alpert JE: Pharmacological approaches to the challenge of treatment-resistant depression. Dialogues in Clinical Neuroscience 2015; 17:111–126. https://doi.org/10.31887/DCNS.2015.17.2/dionescu*
27. *Kessler RC, Berglund P, Demler O, et al.: National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289:3095-105*
28. *Klein MM, Treister R, Raij T, Pascual-Leone A, Park L, Nurmikko T, Lenz F, Lefaucheur J-P, Lang M, Hallett M: Transcranial magnetic stimulation of the brain. Pain 2015; 156:1601–1614. https://doi.org/10.1097/j.pain.0000000000000210*
29. *Levkovitz Y, Isserles M, Padberg F, et al.: Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 2015; 14:64-73*
30. *Lepping P, Schönfeldt-Lecuona C, Sambhi RS, et al.: A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand 2014; 130:326-41*
31. *McKeever A, Agius M, Mohr PA: Review of the Epidemiology of Major Depressive Disorder and of its consequences for Society and the individual Psychiatr Danub 2017; 29(Suppl 3):222-231*
32. *Martin CR: Linking amyloid and depression in the development of Alzheimer's disease: Effects of neuromodulatory interventions by brain stimulation, in: Diagnosis and Management in Dementia: The Neuroscience of Dementia. Academic Press, 2020, pp. 761–775*
33. *Mind: Vagus Nerve Stimulation. 2022. https://www.mind.org.uk/media/13095/vagus-nerve-stimulation-vns-2022.pdf*
34. *Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY: Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. Neuroscience & Biobehavioral Reviews 2018; 92:291–303. https://doi.org/10.1016/j.neubiorev.2018.05.015*

35. *Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH: Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis BMJ 2019; 364:l1079*
36. *NICE guideline [NG222]: Depression in adults: treatment and management. 2022*
37. *Pearce SL, Miles TS, Thompson PD, Nordstrom MA: Responses of Single Motor Units in Human Masseter to Transcranial Magnetic Stimulation of Either Hemisphere. The Journal of Physiology 2003; 549:583–596*
38. *Perez MA, Cohen LG: The Corticospinal System and Transcranial Magnetic Stimulation in Stroke. Topics in Stroke Rehabilitation 2009; 16:254–269*
39. *Razza LB, Moffa AH, Moreno ML, Carvalho AF, Padberg F, Fregni F, Brunoni AR: A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2018; 81:105–113*
40. *Reddy MS: Depression: The Disorder and the Burden. Indian Journal of Psychological Medicine 2010; 32:1–2*
41. *Rosenkranz K, Rothwell JC: Differential effect of muscle vibration on intracortical inhibitory circuits in humans. The Journal of Physiology 2003; 551:649–660*
42. *Rossi S, Hallett M, Rossini PM, Pascual-Leone A: Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology 2009; 120:2008–2039*
43. *Rossini D, Magri L, Lucca A, Giordani S, Smeraldi E, Zanardi R: Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. J Clin Psychiatry 2005; 66:1569-75*
44. *Rush AJ, Trivedi MH, Wisniewski SR, et al: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905-17*
45. *Schutter DJ: Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009; 39:65-75*
46. *Slotema CW, Blom JD, Hoek HW, Sommer IEC: Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)? J Clin Psychiatry 2010; 71:873–884*
47. *Tavares DF, Myczkowski ML, Alberto RL, et al: Treatment of Bipolar Depression with Deep TMS: Results from a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial. Neuropsychopharmacology 2017; 42:2593-601*
48. *Tee MMK, Au CH: A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder. Psychiatr Q 2020; 91:1225-1247*
49. *Ustohal L: Introductory Chapter: Introduction to Transcranial Magnetic Stimulation in Neuropsychiatry. 2018*
50. *Valiengo L, Maia A, Cotovio G, Gordon PC, Brunoni AR, Forlenza OV, Oliveira-Maia AJ: Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder in Older Adults: Systematic Review and Meta-analysis. J Gerontol A Biol Sci Med Sci 2022; 77:851-860*
51. *Wassermann EM: Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section 1998; 108:1–16. https://doi.org/10.1016/s0168-5597(97)00096-8*

Correspondence:
Michaela Agius, Medical Student
Medical School Tal-Qroqq, University of Malta
Msida, Malta
E-mail: michaelaagius86@gmail.com