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Review article

An update on the clinical use of repetitive transcranial magnetic stimulation in the treatment of depression

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is an increasingly used treatment for patients with depression. The use of rTMS in depression is supported by over 20 years of clinical trials. There has been a significant increase in knowledge around the use of rTMS in recent years.
Objective: The aim of this paper was to review the use of rTMS in depression to provide an update for rTMS practitioners and clinicians interested in the clinical use of this treatment.
Methods: A targeted review of the literature around the use of rTMS treatment of depression with a specific focus on studies published in the last 3 years.
Results: High-frequency rTMS applied to the left dorsolateral prefrontal cortex is an effective treatment for acute episodes of major depressive disorder. There are several additional methods of rTMS delivery that are supported by clinical trials and meta-analyses but no substantive evidence that any one approach is any more effective than any other. rTMS is effective in unipolar depression and most likely bipolar depression. rTMS courses may be repeated in the management of depressive relapse but there is less evidence for the use of rTMS in the maintenance phase.
Conclusions: The science around the use of rTMS is rapidly evolving and there is a considerable need for practitioners to remain abreast of the current state of this literature and its implications for clinical practice. rTMS is an effective antidepressant treatment but its optimal use should be continually informed by knowledge of the state of the art.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a treatment for depression that is now widely used in clinical practice with its use having evolved from a lengthy period of evaluation and research including an extensive series of clinical trials. However, there remains significant gaps in the knowledge of mental health professionals in regards to the evidence underpinning its use and how it should be clinically applied. There is a rapidly expanding knowledge base informing our current clinical application of rTMS and how we are likely to modify clinical practice in the foreseeable future. In fact, in recent years there has been a proliferation of studies informing the clinical application of rTMS. Therefore, the purpose of this paper is to review the current state of knowledge and emerging trends as they apply to the use of rTMS in the treatment of depression in clinical practice.

2. General overview

The process of rTMS treatment involves patients undertaking repeated sessions of therapy on a daily basis usually over a series of 4 to 6 weeks, often followed by a short taper period. During each of these sessions, they receive a large number of rTMS pulses applied to a specifically defined cortical region, usually the dorsolateral prefrontal cortex (DLPFC). Production of each of these rTMS pulses involves using a large coil placed on the scalp to induce a strong magnetic field (Barker, 1991). The magnetic field passes into the brain and induces electrical activity in cortical neurones producing depolarisation (Barker, 1991). During treatment, the repeated firing of neurons is used to induce changes in local and distal cortical activity. Although for many years the effects of rTMS have been proposed to occur through mediation of local cortical activity, rTMS produces substantive distal

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effects as well (Bohning et al., 1999) and the relative contribution of local effects to clinical benefits remains somewhat uncertain. However, research has demonstrated that specific forms of rTMS, especially applied at high frequencies, do produce increases in elements of local cortical excitability and low-frequency stimulation can have the opposite effect (Fitzgerald et al., 2006d).

3. Evidence for the antidepressant effects of rTMS in depression

3.1. Evidence base

The use of rTMS as a treatment for depression was first proposed in the mid-1990s and since that time its efficacy has been evaluated in an extensive series of clinical trials. This evidence base includes a large number of independently funded and conducted, small or moderate sized clinical trials, and several larger multisite investigations. The first substantive multisite trial, and the one that led to clinical approval of treatment in the US, was sponsored by a device manufacturer and published in 2007 (O'Reardon et al., 2007). This study found a significant benefit of active treatment over sham (on some but not all measures) although interpretation of the results of this study was somewhat confounded by issues with the choice of the rating scales applied for inclusion and outcome assessment. The positive results from this trial were subsequently confirmed in a NIMH sponsored independent multisite clinical trial published in 2010 (George et al., 2010). These two trials used very similar treatment methodology and the basic parameters applied in these two studies have widely been adopted as the standard methods for rTMS application in clinical practice (see Table 1) (see response and remission rates in Table 2). These two studies were conducted on patients withdrawn from antidepressant medication although many clinical trials have been conducted in patients who have continued with medication therapy (and in some trials patients have been commenced on medication simultaneously with beginning rTMS treatment).

The common protocol features that have been adopted from these trials involve the application of stimulation at 10 Hz to the left DLPFC in trains of four seconds duration. Typically 75 of these trains are applied on a daily basis with an inter-train interval of 26 s with

Table 1
Standard parameters for common treatment paradigms.

Approach	Frequency (Hz)	Coil	Train details
High frequency left DLPFC	10	Figure of 8	75 trains 4 s duration 15–26 s ITI 120% RMT
Low frequency right DLPFC	1	Figure of 8	1 single train 20 min duration 120% RMT
Sequential bilateral	10 on left 1 of right	Figure of 8	Left most commonly 50 trains of 4 s duration Right – one train of 20 min duration Both - 120% RMT
Deep TMS	18	H Coil	2 s trains 20 s ITI 55 trains 120% RMT
iTBS	50/5	Figure of 8	50 Hz triplets repeated at 5 Hz for 2 s in one train 20 trains 8 s inter-train interval 70–120% RMT

DLPFC = Dorsolateral prefrontal cortex, ITI = intertrain interval, RMT = resting motor threshold, iTBS – intermittent theta burst stimulation.

Table 2
Outcome measures across larger clinical studies.

Type of study	rTMS	Sample	Response rate (%)	Remission rate (%)	Comments
Randomised blind trial, medication free (O'Reardon et al., 2007)	75 trains per day of 10 Hz stimulation (3000 pulses)	301 patients with TRD	23.9 versus 15.1	17.4 versus 8.2	Rates at 6 weeks
Randomised blind trial, medication free (George et al., 2010)	75 trains per day of 10 Hz stimulation (3000 pulses)	190 patients with TRD	15 versus 5	14.1 versus 5.1	Rates at 3 weeks
Randomised blinded 3 arm study: rTMS, venlafaxine (up to 225 mg/day) or combination (Brunelin et al., 2014)	Six trains per day of 60 s of 1 Hz (360 pulses)	155 patients with TRD	rTMS: 59 venlafaxine: 60 combination: 54	rTMS: 40.7 venlafaxine: 43.1% combination: 28%	Up to 6 weeks of treatment, rTMS and medication response were equivalent
Randomised double blind trial, concomitant medication allowed (Yesavage et al., 2018)	100 trains per day of 10 Hz stimulation (4000 pulses)	164 Veterans with TRD, ~ 50% with PTSD, ~50% with substance use disorder		40.7 versus 37.4	Up to 6 weeks
Randomised blind trial, medication free (Levkovitz et al., 2015)	55 trains of 20 Hz stimulation daily (1980 pulses), deep TMS coil	212 patients TRD, 181 patients in per protocol (PP) analysis	38.4 versus 21.4	32.6 versus 14.5	Response and remission rates at 5 weeks for PP analysis
Pooled outcome data from 11 clinical trials (Fitzgerald et al., 2016a)	Multiple protocols, left, right and bilateral rTMS	1132 patients in multiple trials	46.8	31.4	Assessment based on end of acute treatment
Randomised 4 group trial (2 doses X 2 conditions – left and right) (Fitzgerald et al., 2020)	125 or 50 10 Hz Trains per day or 20 min or 60 min of 1 hz stimulation	300 patients with TRD	47.3–52.5	18.6–31.9	Rates at 4 weeks across 4 groups
Randomised controlled comparative trial, on medication (Blumberger et al., 2018)	rTMS: 75 trains per day of 10 Hz stimulation (3000 pulses) iTBS: 600 pulses over 189 s	385 patients with TRD	47 (rTMS) versus 49 (iTBS)	27 (rTMS) versus 32 (iTBS)	Rates at 4 weeks

rTMS = repetitive transcranial magnetic stimulation, TRD = treatment resistant depression, iTBS – intermittent theta burst stimulation.

stimulation applied at 120% of the resting motor threshold (RMT). The RMT is a measure of cortical excitability established by applying single rTMS pulses to the motor cortex on the site of treatment and assessing the minimum stimulation intensity required to produce a regular muscle twitch in the hand. This can be assessed electrophysiologically but it typically evaluated based on visual inspection (Badran et al., 2019).

In addition to these clinical trials, the efficacy of rTMS has also been evaluated in a relatively lengthy series of meta-analysis published over the last 10 years (for example Cao et al. (2018), Gaynes et al. (2014), Mutz et al. (2018) and Sehatzadeh et al. (2019)). These have consistently demonstrated significant benefits of rTMS versus sham stimulation. For example, Gaynes et al. found that patients with treatment resistant depression receiving rTMS were three times more likely to respond or five times more likely to achieve remission, than when receiving sham (Gaynes et al., 2014). Meta analyses have shown significant benefits of active treatment over sham when investigating unilateral high-frequency left-sided rTMS alone and also when including studies conducted with a variety of other stimulation paradigms. rTMS treatment has also been demonstrated to be effective when combined with antidepressant medication or when applied as a standalone therapy. Studies have shown significant benefits when analysing depression response as a continuous variable or when investigating differences in response and remission rates (Berlim et al., 2014).

There has been a relative paucity of studies comparing rTMS to other antidepressant strategies. The most substantive study randomising patients to receive rTMS or an antidepressant (in this case venlafaxine) found no difference in response between these two treatments (Brunelin et al., 2014). There have been a number of trials directly comparing response between rTMS and electroconvulsive therapy (ECT) although these are not necessarily competing treatments (Fitzgerald, 2004). Unfortunately, drawing conclusions from the studies is substantially problematic as they are mostly underpowered to show meaningful differences between the two treatments or significantly imbalanced in the way in which the treatments have been offered. For example, studies have compared an unlimited number of unilateral or bilateral ECT treatments to a fixed number of TMS treatment is of only one type (Grunhaus et al., 2000) and no studies have provided an rTMS approaching what is now considered standard (see details in Ren et al. (2014)). A meta-analysis of these studies suggested that ECT was more effective in patients with psychosis but that response rates were no different in the studies that did not include patients with psychosis (response rate: ECT: 51.4%, rTMS: 52.5%) (Ren et al., 2014).

Beyond direct comparisons, it is more challenging to draw inferences in regards to rTMS compared to other medication strategies for treatment resistant depression due to differences in the studies used to evaluate each form of treatment. A network meta-analysis reported in 2017 compared the effects of rTMS, ECT and pharmacological therapies for TRD. In regards to response rates, rTMS was the most effective treatment at 4 weeks post commencement of intervention and the only intervention statistically superior to placebo at 6 weeks (Papadimitropoulou et al., 2017). For remission rates, only rTMS and ECT were superior to placebo at 4 weeks and at 6 weeks rTMS had the highest remission rates/was ranked first. In regards to the actual rates of response and remission, those seen in rTMS studies are relatively similar to the rates recorded for medical treatment in the STAR*D trial. In one meta-analysis, a very average 'low dose' (mean 13 sessions) of rTMS in sham controlled trials resulted in response and remission rates of 29.3 and 18.6% (Berlim et al., 2014), similar to rates seen after 2 failed medications under open label STAR*D therapy (Sinyor et al., 2010).

Of note, not all the studies examining the use of rTMS therapy have been positive. A recent study explored the efficacy of rTMS in a substantive sample of veterans with depression (and a high rate of post-traumatic stress disorder comorbidity) (Yesavage et al., 2018). No difference was seen between active and sham treatment in a trial characterised by a very high remission rate in the active and sham group. There are numerous factors that may have contributed to a failure of this study to demonstrate the difference between the groups: this study had a much higher proportion of male patients than others and the patients had higher rates of comorbid PTSD and substance use disorders (around 50% of each).

3.2. Real world outcomes

A number of recent studies have described outcomes of rTMS treatment in samples of patients treated in real-world clinical practice or have pooled data across multiple clinical trials. An early study of this sort found a response rate of about 50% in 100 patients treated in standard clinical practice (Connolly et al., 2012). In a sample of over 1100 patients included in a variety of clinical trials, we found a response rate of slightly over 45% (Fitzgerald et al., 2016a). A recent English study found response rates of around 40% in a sample of 73 patients treated with rTMS as part of routine clinical care (Griffiths et al., 2019) and in a novel study Donse et al. found a 66% response rate in patients receiving rTMS combined with psychotherapy (Donse et al., 2018). Overall these studies suggest that response rates seen in clinical practice are likely to be at least comparable, and certainly not inferior, to those seen in clinical trials.

4. Differing forms of rTMS and the evidence for their clinical use

In addition to the use of high-frequency stimulation applied to the left DLPFC, there has been a progressive proliferation of different stimulation approaches, targets and paradigms investigated in clinical trials.

4.1. Low frequency right sided rTMS

The first alternative stimulation paradigms involved the application of low-frequency stimulation (1 Hz) to the right DLPFC (see Table 1). Multiple studies (for example Fitzgerald et al. (2003) and Klein et al. (1999)) have shown that this approach has antidepressant efficacy and that its efficacy is similar to, or not inferiori to, high-frequency stimulation applied to the left DLPFC. The efficacy (Mutz et al., 2018; Schutter, 2010), and non-inferiority (Chen et al., 2013), of this form of stimulation has now been confirmed in several meta-analysis. Although there are fewer studies demonstrating the efficacy of this form of stimulation compared to high-frequency left-sided rTMS, right-sided stimulation at low-frequency does have several potential advantages. Theoretically, low-frequency stimulation should pose less of a risk of seizure induction and it is usually better tolerated than high-frequency approaches (Kaur et al., 2019a). It appears to be a reasonable alternative in patients where there are concerns about seizure induction or significant tolerability issues with high-frequency stimulation.

4.2. Sequential bilateral rTMS

Sequential bilateral stimulation, involving the application of low-frequency right-sided rTMS followed by high-frequency left-sided rTMS within the same treatment session, was originally developed in an attempt to produce a form of stimulation that might have greater efficacy than unilateral stimulation approaches (Fitzgerald et al., 2006b). Although some studies have suggested superiority of efficacy (Blumberger et al., 2016), more have not (for example Fitzgerald et al. (2011, 2012, 2013b)) and overall bilateral stimulation demonstrates efficacy (Berlim et al., 2013) but at a level which appears to be similar to that seen with unilateral stimulation, confirmed by meta-analysis (Chen et al., 2014). In the absence of any consistent evidence of superiority of efficacy, there does not appear to be a clear case for the routine use of bilateral rather than unilateral stimulation as initial therapy in clinical practice.

4.3. Dorsomedial rTMS and other targets

A more recently proposed and more novel treatment target for the application of rTMS therapy in depression is the dorsomedial area of the prefrontal cortex (DMPFC). Both a standard 10 Hz stimulation approach and an intermittent theta burst stimulation (iTBS) approach produced substantive antidepressant responses in a large comparative trial of stimulation at this site (Bakker et al., 2015). Stimulation of the DMPFC does not produce significant cognitive side-effects when stimulated alone or in combination with activation of the DLPFC (Kavanaugh et al., 2018; Schulze et al., 2016). However, no sham -controlled data of stimulation at this site has yet been published.

There is also preliminary evidence for a second prefrontal stimulation site, in this case the right lateral orbitofrontal cortex (OFC). Stimulation of this site in 42 patients (a mixture of medication and DMPFC rTMS non-responsive patients) demonstrated that 1 Hz stimulation was safe and produced a response rate of 37% (Feffer et al., 2018).

The DMPFC and OFC are both interesting prospective treatment targets that are well justified by what we understand about the neuroscience of MDD (Downar and Daskalakis, 2013). However, how they fit into standard therapeutic practice with rTMS treatment remains unclear and awaits the conduct of comparative effectiveness studies and studies exploring whether we can predict whether subgroups of patients will respond to treatment at one or other specific stimulation site. It is also worthy of note that stimulation at these normal sites can be differently perceived than when applied to the DLPFC. DMPFC stimulation has previously been applied using an angled coil which can be more uncomfortable and stimulation of the OFC can be painful due to the stimulation of nerves and muscles around the eye.

4.4. Deep rTMS

The most substantially different form of rTMS that is clinically available currently is deep rTMS (dTMS). This involves the use of a novel coil to produce a deeper penetrating stimulation field motivated by a desire to reach more deeply lying therapeutic areas. Although not exclusively so (Carpenter et al., 2017), the vast majority of the development of dTMS has occurred using several coils produced by Brainsway which have considerably more complex windings than those seen in a traditional figure-of-eight coil. The primary evidence for the efficacy of dTMS comes from a single large randomised controlled trial that was used to achieve device registration in the US and elsewhere (Levkovitz et al., 2015). In this study, 212 patients with MDD received active or sham stimulation over 4 weeks on a daily basis and then bi-weekly for 12 weeks. Efficacy data from the per-protocol (but not the intention to treat) analysis showed significant differences between active and sham stimulation with clinical benefits persistent across the maintenance phase. There was one seizure reported in this study and a seizure in the first patient enroled in a trial in adolescent depression (Cullen et al., 2016).

In addition to the initial registration trial, dTMS has been assessed in several other studies. Tavares et al. showed initial evidence of efficacy (at the end of treatment but not follow up) in a group of 50 patients with depression in the context of bipolar affective disorder (Tavares et al., 2017). A second recent study has showed evidence of efficacy in late-life depression (Kaster et al., 2018). A first attempt to compare dTMS to standard rTMS of the DLPFC has recently been published (Filipcic et al., 2019). In this study, 228 patients were randomised to 20 sessions of one of these two forms of rTMS or medication treatment alone. The authors hypothesised that dTMS would produce greater remission rates than standard treatment in part based upon an observation that dTMS produced greater remission rates in the initial dTMS registration trial (Levkovitz et al., 2015) than that seen in the initial standard rTMS registration trial (O'Reardon et al., 2007). This observation should be interpreted with caution, however. Response and remission rates reported by Levkovitz et al. for dTMS were reported for the per protocol, but not intention to treat sample, potentially significantly inflating these figures (Levkovitz et al., 2015). In the direct comparative study (Filipcic et al., 2019), the proposed hypothesis of superiority of dTMS was not confirmed as there was no difference in remission rates between the two rTMS groups (although both rTMS groups were superior to medication alone). However, some benefits on mean reduction in depressive symptoms and response rates were seen with dTMS at a cost of what appears to have been a somewhat higher rate of reported side effects. A recent meta-analysis attempted to compare dTMS and standard rTMS presenting dTMS as potentially producing better outcomes (Gellersen and Kedzior, 2019). However, this study only included studies using 20 Hz stimulation (most standard rTMS studies use 10 Hz), only analysed outcomes after 10 treatments (which is an inadequate duration) and the only randomised trial of dTMS included was the pivotal trial described above (Levkovitz et al., 2015) – in this study, even with the per protocol analysis, there was no separation at all between active and sham stimulation after 10 treatment sessions.

At this stage, the relative place of dTMS alongside standard rTMS remains unclear and one form has not been shown to have efficacy advantages over the other. Both have demonstrated efficacy but there is no clear evidence on which to base a decision to use one or the other. Trial data is especially required to evaluate whether one can be used successfully in patients who have failed to respond to a trial of the other intervention.

4.5. Theta burst stimulation

One of the most prominent recent developments in the clinical and research use of rTMS is the potential application of TBS protocols in clinical practice. TBS involves the patterned application of stimulation in 50 Hz (sometimes 30 Hz) triplets repeated at theta frequency (Huang et al., 2005). There are two standard TBS paradigms: intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) (Huang et al., 2005). ITBS has been shown in physiological studies to produce increases in cortical excitability in a similar fashion to high frequency rTMS. In contrast, cTBS can produce a reduction in cortical excitability like low-frequency rTMS. The substantial potential advantage of TBS paradigms over standard forms of TBS is that their effects can be achieved in a significantly compressed period of time: a standard application of cTBS takes 40 s and iTBS about three minutes.

Studies are increasingly investigating the use of both forms of TBS in the treatment of depression with iTBS typically applied to the left DLPFC, cTBS applied to the right DLPFC or these two paradigms combined together in a bilateral protocol. An initial meta-analysis including data from the first five randomised sham controlled trials (using a mixture of paradigms) found a significant and large effect size difference between active TBS and sham (Berlim et al., 2017). Bilateral and left iTBS approaches were found to have the greatest therapeutic promise. A substantive randomised non-inferiority trial was recently conducted comparing standard 10 Hz left DLPFC stimulation with a single daily application of iTBS to the same stimulation site (Blumberger et al., 2018). A total of 414 participants were randomised to the two groups and received treatment over four – six weeks. iTBS was found to be non-inferior to standard treatment. Self-rated intensity of the pain of stimulation was found to be greater in the iTBS group but dropouts did not differ.

At this stage, do we have sufficient evidence to potentially replace the use of standard rTMS with TBS in clinical practice? The study by Blumberger et al. (2018) is a substantial and meaningful demonstration of clinical efficacy. How this should be weighed against the much larger body of evidence supporting standard rTMS, and the clinical experience demonstrating its robust and long term safety, is hard to judge. The use of TBS at this stage would appear to be most clearly advantageous and

justified in situations where a rapidity of treatment administration is required for clinical or resource related reasons.

4.6. Priming stimulation (pTMS)

Based on physiological evidence that the response to low frequency stimulation can be enhanced by 'priming' the cortex with high frequency stimulation immediately prior to low frequency trains (Iyer et al., 2003), several studies have explored the use of a priming paradigm that involves the application of twenty subthreshold 6 Hz trains followed by fifteen minutes of 1 Hz stimulation with both applied to the right DLPFC. In the first study, priming stimulation produced a significantly greater antidepressant response compared to a single train of 1 Hz stimulation in a randomised controlled trial of 60 patients (Fitzgerald et al., 2008). In a subsequent study, 179 patients received either the same priming protocol or a standard sequential bilateral stimulation protocol (Fitzgerald et al., 2013b). Overall patients experienced a substantive 40% remission rate but there were no differences seen in response between the two groups.

4.7. Are any forms of rTMS superior to any others?

Clearly the clinical trial and meta-analytic evidence discussed above indicates that there is no evidence of significant differences in response between low-frequency right-sided rTMS and high-frequency left-sided rTMS or between unilateral and bilateral stimulation approaches (Chen et al., 2013, 2014). In addition, we lack sufficient data to infer whether dTMS or forms of TBS may have any efficacy advantages. The data at this stage indicates that all established forms of rTMS appear to have relatively equivalent efficacy.

Choice of stimulation approach

1st line treatment: the greatest evidence exists for the use of high frequency left sided rTMS (accumulative body of randomised control trials and meta-analysis) and this should be the defacto form of stimulation provided to the majority of patients.

Alternative 1st line options:

(a) There is a considerable body of evidence supporting the use of low frequency right sided stimulation but notably, this does not include the conduct of multi-site sham controlled trials. This is a reasonable first line choice in patients where there are issues of tolerability or safety with high frequency stimulation as low-frequency stimulation is more tolerable and less likely to induce seizure activity.
(b) There is accumulating evidence that iTBS applied to the left DLPFC has antidepressant effects that may be equivalent to high-frequency left-sided stimulation. The use of iTBS is likely to be a sensible approach in resource constrained environments.

2nd line approaches:

(a) Low-frequency right-sided stimulation or deep TMS are reasonable options in patients who have failed to respond to high frequency left sided rTMS.
(b) Sequential bilateral rTMS should be considered in patients who have experienced a partial response to high frequency left sided rTMS allowing continuation of the partially effective stimulation paradigm but also the introduction of right-sided treatment.

3rd line approaches: novel stimulation targets such as DMPFC and OFC should be reserved for patients who have failed to respond to other standard treatment options.

At this stage it remains unclear what accounts for the equivalent efficacy across multiple forms of rTMS. It may well be that there is a common mechanism of action, for example they all reset frontal – subcortical connectivity, for example through effects on the oscillatory binding of distal regions. It is also possible that different subgroups of patients are responding to different forms of rTMS but no studies have really be conducted to date to tease this out.

4.8. Are all rTMS devices equal?

Outside of the fairly profound differences between standard and dTMS devices, there is a an additional question as to whether clinical responses and tolerability significantly differ between rTMS devices that have been otherwise considered relatively equivalent. In recent years the FDA in the US has approved rTMS devices produced by several manufacturers after determining "substantial equivalency" to the Neurostar rTMS therapy device from Neuronetics that originally achieved approval. However, there are differences between devices in both the shape and configuration of the rTMS coil and in subtle differences in stimulation parameters such as the pulse width of individual pulses. To date only very limited research has explored whether there are meaningful differences in clinical response between standard rTMS devices. The first of these studies compared clinical responses in a retrospective open label fashion between 113 patients treated with a Magstim device and 41 patients treated with the NeuroStar system (Oliveira-Maia et al., 2016). No difference in response was seen between the two groups. A second open label non-randomised study compared response between treatment responses produced with a Magventure and NeuroStar device in 247 patients treated in routine clinical care (Davila et al., 2019). A proportionally greater degree of response was seen in patients treated with the MagVenture device compared to the NeuroStar system, even when accounting for a variety of potential confounding variables. This is by no means definitive evidence that differing responses are likely to emerge with different treatment systems but certainly suggests that this should be the focus of more systematic research. At this stage there is no clear basis in regards to evidence of efficacy on which to base a choice of stimulation equipment.

5. Patient selection and indications

5.1. Treatment resistance and illness chronicity

rTMS therapeutic trials have almost exclusively been conducted in patients with some degree of treatment resistance varying from one to many failed medication trials. rTMS has been shown to be effective in populations with both limited (O'Reardon et al., 2007) and substantive degrees of treatment resistance (Fitzgerald et al., 2016a). Some data has suggested that a greater degree of response is likely to be apparent in patients with a lesser degree of treatment resistance. For example, analysis of data from the pivotal trial that first resulted in FDA approval of rTMS found that a lesser degree of treatment resistance was associated with a greater likelihood of response (Lisanby et al., 2009). However, a large study of over 1100 patients failed to replicate this relationship (Fitzgerald et al., 2016a) and efficacy was seen in this analysis in a group of substantially treatment resistant patients. Even if the relationship seen in Lisanby et al. reflects the likely pattern of clinical outcome, the relationship was not strong (seen in the blind but not open label phase of the study) and could not be considered 'predictive' in a way that should influence decision making. In fact, especially in light of the conflicting finding (Fitzgerald et al., 2016a) there is no real evidence to exclude patients with higher degrees of treatment from access to rTMS. Of note, some reports have described benefits in patients who have failed to respond to ECT (Fitzgerald et al., 2013b).

In regards to patients with limited or no treatment resistance, a

recent meta-analysis synthesised the results of six studies including the outcomes of patients who had failed one or fewer medication trials concluding that rTMS was effective in this population. However, few of these studies were in patients with no failed trials and although there is increasing interest in the application of rTMS in completely non treatment resistant populations, there remains limited evidence supporting its use in these circumstances (Kiebs et al., 2019).

Somewhat separate from the issue of treatment resistance, is the question of whether duration of illness relates to the likelihood of rTMS response. Patients were excluded from the initial FDA registration trial who had an episode duration of more than three years but within the included patients there was a relationship between shorter illness duration and better outcome (O'Reardon et al., 2007). When data was analysed from a much larger sample of 1132 subjects from 11 trials, none of which placed a restriction on the duration of premorbid illness, duration of illness was also related to response (Fitzgerald et al., 2016a).

5.2. Bipolar depression

What we know about the potential use of rTMS treatment for depression in patients with bipolar affective disorder can be inferred from trials conducted exclusively in this population but also from trials conducted in mixed groups of patients with unipolar and bipolar depression. Following early pilot studies (Dell'osso and Altamura, 2009; Nahas et al., 2003), there has been a slow increase in trials exclusively in bipolar depression. One study found no benefit of sequential bilateral stimulation (Fitzgerald et al., 2016b) and a second no benefit of high or low frequency stimulation provided with quetiapine (Hu et al., 2016) but these studies were both underpowered. A third randomised trial in a similar sample used dTMS in bipolar depression with greater antidepressant effects of active stimulation seen compared to sham (Tavares et al., 2017).

There is clearer evidence supporting the use of rTMS in bipolar depression from studies in mixed samples. Studies have reported no difference in response rates (e.g. Carnell et al. (2017)) or a trend favouring response in bipolar subjects (e.g. Fitzgerald et al. (2006e)). A meta-analysis including data from all accessible bipolar depression trials found a significant benefit of active over sham stimulation (McGirr et al., 2016). There is no evidence that concurrent mood stabilising treatment interacts adversely with rTMS or lessens outcomes (Fitzgerald et al., 2016a) and the risk of switch to mania with rTMS appears low (Xia et al., 2008). The use of rTMS does seem a reasonable treatment option in bipolar depression.

5.3. Depression in the elderly

Relatively early in the development of rTMS treatment it was observed that increasing age may be a negative predictor of response to therapy based upon relative differences in scalp to cortical distance in prefrontal brain regions associated with ageing (Kozel et al., 2000). However, more recent analyses have failed to establish this relationship and the largest exploration of demographic predictors of response to treatment found the opposite (that older age was a positive predictor of outcome) (Fitzgerald et al., 2016a). A greater response rate in elderly subjects than young was found in a recent study of twice-daily rTMS (Desbeaumes Jodoin et al., 2019) and a second recent study showed a significant difference over sham stimulation of dTMS in an elderly group (Kaster et al., 2018). Finally, analysis of data from a group of 231 patients found no effect of older age (Conelea et al., 2017). This literature clearly indicates that older age should not be a barrier to accessing rTMS treatment for depression although the comorbid presence of cognitive and physical disorders needs to be taken into account (Sabesan et al., 2015).

5.4. Depression in the young

There is also a slowly accumulating evidence base exploring the use of rTMS in the treatment of young patients with depression. rTMS has been used fairly extensively in children for applications other than depression treatment and clinical and research experience in this group has slowly increased over time (Donaldson et al., 2014). A recent study provided open label treatment over three weeks to a group of 32 patients aged 13–21 years found a 56% response rate with no serious adverse events (MacMaster et al., 2019). A 40% response rate was seen in a sample of 15 patients (Rosenich et al., 2018) but a third open label study reported only 2 responders in 16 patients (Kaur et al., 2019b). rTMS treatment was associated with a reduction in suicidal ideation in adolescent patients but this relationship was explained by reduced depressive symptoms (Croarkin et al., 2018). Finally, a recent study compared outcomes of rTMS in 42 adolescents compared to 75 adult patients (Zhang et al., 2019). The authors found a significantly greater response rate in the younger group on both depressive and anxiety symptoms. Although this literature is by no means definitive, it certainly suggests a promising role for rTMS in young patients and justifies the conduct of larger scale randomised trials to validate this.

5.5. Depression in pregnancy and post-partum depression

Although its use has been quite limited to date, rTMS would appear to have considerable potential as a therapy for depression that occurs during pregnancy or breastfeeding as there are no systemic effects, as occurs as the result of medication treatment or risks as associated with ECT. There is also little likelihood that the magnetic field would reach the foetus in sufficient strength to produce any deleterious effects (Yanamadala et al., 2017). Case series and reports are gradually describing its use in pregnancy, in particular (Kim et al., 2011; Klirova et al., 2008; Nahas et al., 1999; Zhang et al., 2010). A recent follow-up study of children born from mothers who were treated during pregnancy found some language developmental delays but these were no different to those found in children of mothers with depression untreated with rTMS (Eryilmaz et al., 2015). Kim et al. recently published the results of a small randomised study of 1 Hz right sided rTMS in pregnant women in the second or third term of pregnancy (Kim et al., 2019). A greater degree of reduction in depression was seen with active compared to sham treatment. There were three late preterm berths in the active treatment group (two of these mothers had other risk factors for preterm delivery) but no other adverse maternal and delivery related outcomes. Theoretically, rTMS would appear to be a sensible option to consider in pregnant patients and to date research data supports this idea (see recent summary in Cole et al. (2019b)) but clearly larger samples of patient data should be systematically collected before this can be widely recommended.

In regards to the use of rTMS in postpartum depression, this has only been explored in a single case series, one small randomised trial and one open label trial all using high-frequency stimulation applied to the left DLPFC. In the case series, eight of nine patients achieved remission with symptoms and infant bonding improving within the first two weeks (Garcia et al., 2010). The only randomised trial included only 14 patients but still found significant benefits of active over sham stimulation (Myczkowski et al., 2012). A open label study included 25 patients of whom 14 achieved remission but of note 6 patients dropped out because of scheduling/access (Brock et al., 2016). Clearly more substantial trials in this population are necessary but this data suggests the promise of this treatment in patients who are likely to want to avoid pharmacotherapy.

5.6. Comorbid anxiety

There is a literature on the use of rTMS in the treatment of primary anxiety disorders that although limited, suggests potential efficacy (for

example Diefenbach et al. (2016)), and also an increasing interest in the effects of rTMS treatment on anxiety when patients are treated for MDD. The largest study (over 1100 patients) exploring the effect of a concurrent anxiety disorder comorbidity on antidepressant responses found that patients with a comorbid anxiety disorder had a lower rate of response than those without, although patients with an anxiety disorder still had a substantial response rate (Fitzgerald et al., 2016a). This varied between 35% for patients with panic disorder to 47% for generalised anxiety disorder and 48% for PTSD. A second study in 248 patients found no differences in outcomes for patients with comorbid anxiety disorder (Clarke et al., 2019). In a different approach, Chen et al. pooled data from 697 patients to investigate the pattern of change in anxiety symptoms in patients receiving rTMS treatment for depression (Chen et al., 2019). This study found a significant reduction in Beck Anxiety Inventory scores alongside a reduction in depressive symptoms regardless of whether patients were receiving high-frequency left-sided rTMS, low-frequency right-sided rTMS or sequential bilateral approaches. Improvement in depression was positively correlated with improvement in anxiety. In sum, when rTMS is used in the treatment of patients with depression, there is a reasonable expectation that patients are likely to experience a reduction in anxiety symptoms at the same time, whether or not the patient meets criteria for an anxiety disorder. The present of an anxiety disorder should not be considered a reason for not undertaking rTMS treatment of depression. Further research is required exploring the use of rTMS in primary anxiety disorders.

5.7. Depression with psychotic symptoms

Unfortunately, at this stage we know little about the likely benefits of rTMS treatment in patients with psychotic depression as they have been excluded from almost all clinical trials. The first head-to-head trial that compared antidepressant response of rTMS to ECT included a group of 19 patients with psychotic depression (Grunhaus et al., 2000). The nine patients who received TMS responded more poorly than the 10 who received ECT. However, only 400 TMS pulses were provided per day, for only 20 treatments and at only 90% of the resting motor threshold. This was compared to the provision of an unlimited number of unilateral and / or bilateral ECT. Several other ECT-rTMS trials have included some psychotic patients but very small numbers. In a small meta-analysis, ECT appeared to be more effective than rTMS in the studies with mixed samples (although not more effective in non-psychotic samples) but the total data was less than 60 subjects and not a single one of these trials used TMS at 120% of the RMT or for more than 20 sessions (Ren et al., 2014). At this stage we really have no meaningful data on whether rTMS is effective in patients with psychotic depression.

5.8. Concurrent medication use

In the largest study of concurrent medication use and antidepressant response to rTMS, no difference in response was seen in patients taking antipsychotic medications but higher rates of response were seen in patients taking antidepressants (47.8 versus 36.6%) or mood stabilisers (52.7 versus 43.8%) compared to those that were not (Fitzgerald et al., 2016a). A recent meta-analysis also suggested that whilst rTMS was an effective treatment regardless, it was more effective in patients taking antidepressant medications compared to when not (Sehatzadeh et al., 2019). These studies clearly indicate no deleterious effect of concurrent medication use although a slightly different picture might be the case with benzodiazepines.

Hunter et al. studied the outcomes of 181 patients who had received a 6 week course of rTMS (Hunter et al., 2019). Benzodiazepine use was associated with less overall improvement and less improvement at week 2 of treatment. In a second study analysing patterns of response in patients from a large trial of 10 Hz stimulation compared to iTBS, low dose benzodiazepine use was associated with a lower likelihood of being in the 'rapid response' group and came close to being associated with non-response (odds ratio = 2.25, CI = 0.99 and 5.11) (Kaster et al., 2019). These findings ameliorate any concerns about concurrent antidepressant use, which appears to be a favourable predictor of response, but raise a considerable concern about concurrent use of benzodiazepines. It is of note that many successful rTMS trials have not excluded patients on benzodiazepines and these are retrospective analyses but prudent practice would probably be to avoid these during a course of rTMS if it is possible to do so.

Patient selection considerations and recommendations

- rTMS may be effective in patients across the spectrum of treatment resistance and should not be withheld because of a concern that patients have too great a degree of treatment resistance.
- rTMS may be provided to patients with unipolar or bipolar depression. In patients with bipolar affective disorder, especially type I, concurrent mood stabilisation should be usually utilised to prevent manic switching.
- rTMS treatment of depression should be considered effective in both adult and elderly patients.
- rTMS treatment of depression remains experimental in children and adolescents.
- There is emerging evidence for the safety of rTMS treatment in pregnancy and the postpartum period although rTMS has been used to very limited degrees in these patient groups.
- There is a reasonable likelihood that patients with comorbid anxiety will experience a reduction in anxiety symptoms during treatment of MDD regardless of the choice of rTMS stimulation approach.
- Clinical trials have not adequately explored whether rTMS can be used in the treatment of patients with depression with psychotic symptoms.
- rTMS is effective in the treatment of depression whether patients are receiving antidepressants, antipsychotic or mood stabiliser medication or whether they are medication free.

There is some limited emerging evidence that the concurrent use of benzodiazepines may reduce the effectiveness of rTMS therapy of depression but there is no evidence that it ameliorates the effectiveness of rTMS in the majority of patients. It is prudent to minimise benzodiazepine use but caution should be used in reducing or stopping benzodiazepine use as this may increase the likelihood of seizure induction.

6. Scheduling options and issues

Until very recently, few studies have explored some of the practical elements of rTMS delivery, including the scheduling of treatment sessions. One study showed that administering treatment three times per week could produce equivalent antidepressant effects as the traditional five times a week although antidepressant effects took longer to develop (Galletly et al., 2012). In the opposite direction, two different approaches to produce antidepressant responses over a shorter duration of treatment have been tested: applying treatment twice daily and the use of intensive treatment schedules, usually with many treatment sessions applied over a limited number of days.

6.1. Twice daily rTMS

Although twice daily approaches have been used for other applications of rTMS, there have only been a few studies exploring this approach in depression. Only marginal benefits over sham were seen in one study of limited sample size (Loo et al., 2007) but a substantially greater effect was seen in a more recent study (Theleritis et al., 2017). In this report, greater effects were seen with twice rather once daily rTMS and much greater than sham. However, the twice versus once

daily comparison is challenging to interpret as the twice daily patients received a much higher overall dose of treatment. Two retrospective studies compared once to twice daily responses and described faster but not greater therapeutic response with twice daily treatment (Modirrousta et al., 2018; Schulze et al., 2018). A recent open label analysis found greater responses to a twice daily protocol in elderly versus younger patients without safety issues arising in the older group (Desbeaumes Jodoin et al., 2019). The evidence base to date does not support the routine use of twice daily treatment in the absence of substantive sham controlled or non-inferiority trials.

6.2. Intensive 'Accelerated' rTMS

A small number of studies have utilised very intensive rTMS paradigms to try to achieve clinical response in a markedly shorter period of time than is typically found with 4–6 week treatment courses. In the first of these studies, 15 relatively low dose rTMS sessions were applied across a two-day period in patients admitted to an inpatient program explicitly to undergo this treatment (Holtzheimer et al., 2010). 14 patients were treated showing a response rate of 43% at the end of treatment and 36% at six week follow-up. Two crossover studies, one using standard rTMS and one using iTBS have also provided supportive evidence that accelerated treatment is feasible, safe and may provide clinical benefit (Baeken et al., 2013; Desmyter et al., 2016). One larger trial has directly compared the clinical outcomes achieved with accelerated treatment to standard once daily rTMS (Fitzgerald et al., 2018b). A sample of 115 patients were randomised to receive four weeks of daily rTMS or 250 trains (10 Hz) provided across three stimulation sessions on three days in the first week, two days in the second and one day in the third with no significant differences in outcomes seen between the two groups. A recent open label study provided 20 iTBS sessions over 40 days and reported a very high remission rate of over 90% with all patients having a remission from suicidal ideation (Cole et al., 2019a). In all, these studies suggest that accelerated forms of rTMS show considerable promise but the variation in study protocols at this stage limits the conclusions that can be drawn from this literature.

7. Treatment of relapse

Data on the duration of persistence of benefit and response rates on re-treatment are presented in Table 3. rTMS is now widely used in clinical practice to treat depressive relapses in patients who have responded to an index course of therapy. This is clinically sensible and also supported by the limited literature that has explored the reintroduction of rTMS in patients experiencing a relapse. This literature suggests that in the majority of cases, patients will respond to rTMS treatment when applied in subsequent episodes (Demirtas-Tatlidede et al., 2008; Fitzgerald et al., 2006c; Janicak et al., 2010; Philip et al., 2016). For example in the study of Janicak et al., 38 patients were retreated during the 24 weeks of follow up and 32 (84.2%) subsequently improved (Janicak et al., 2010). In several studies the duration of treatment at reintroduction has been shorter than the duration of treatment in the index episode (Dunner et al., 2014; Philip et al., 2016).

8. Maintenance treatment

Studies have evaluated two methods of using rTMS as a maintenance strategy (Rachid, 2018). The first approach involves the application of single rTMS treatment sessions, at a frequency of between one per week and one per month, usually after titrating down from the index treatment course. In a randomised trial including 49 patients, a single treatment once per month was not statistically significantly better than no maintenance rTMS treatment (Philip et al., 2016). In a second sham -controlled study, there seem to be benefit of active treatment over sham whilst sessions were being applied on a weekly basis but not when the treatment schedule became less intense (Benadhira et al., 2017). A similar relapse rate was seen across three groups receiving either rTMS, venlafaxine or a combination of these two treatments in a study where maintenance was gradually reduced from 2 per week to 1 every 2 weeks (Haesebaert et al., 2018). Deep rTMS was found to have useful maintenance properties when applied twice weekly for 12 weeks following acute stabilisation in a sham controlled sample (Levkovitz et al., 2015).

The alternative approach has been the application of around 5 treatments in a 'cluster' (usually 2 per day), about every 4 weeks (Fitzgerald et al., 2013a). This has shown benefit in several small uncontrolled studies (for example Fitzgerald et al. (2013a)) but also in a very large study (281 patients) where rTMS with or without medication resulted in lower relapse rate than medication alone but this was in a group of patients who had responded to medication initially, not rTMS (Wang et al., 2017).

This literature provides some indication that maintenance rTMS may be of value but does not provide definitive evidence of efficacy. The frequency of sessions does seem of particular importance, especially when individual sessions only are being used with sessions less frequent than one every 2 weeks seemingly unlikely to have meaningful efficacy.

9. Safety and tolerability

The safety and tolerability of rTMS in the treatment of depression has been well established in its use over 20 years (Rossi et al., 2009). As recently summarised, the discontinuation rates in placebo trials in patients receiving active rTMS are extremely low (2.5%). This rate was actually numerically lower than the rate seen in sham treated patients (2.7%) (Zis et al., 2019). The rates were slightly higher in patients just in depression trials (3.2% versus 2.2% with sham – this difference was not significant). The overall side effect rate was 35.2% (12.2% on sham). The only side effect reported in more than 5% of patients was discomfort at stimulation site or headache (~20% of patients).

The major known risk with rTMS therapy is the induction of a seizure (Loo et al., 2008; Wassermann, 1998). Since the development and use of safety guidelines defining safe stimulation parameters (Wassermann, 1998) these have only been reported very uncommonly and the risk appears very low: a recent study estimated the risk in patients without risk factors and treated within safety guidelines as being below 0.02 seizures per 1000 treatment sessions (Lerner et al., 2019).

There are a number of other possible safety issues. With hearing protection there does not appear to be a substantive risk of a change in auditory thresholds (Janicak et al., 2008; O'Reardon et al., 2007). Manic switching in bipolar patients is possible but the overall risk seems fairly modest (Xia et al., 2008). Overall rTMS appears cognitively safe, with no negative impact on memory or other elements of cognitive function (Galletly et al., 2016; Hoy et al., 2012). There have been reports of the successful treatment of patients with what has traditionally been considered contraindications to rTMS, such as epilepsy (Fitzgerald, 2014), but use of rTMS in these populations should only occur in limited circumstances and in tertiary settings. rTMS should only be used with considerable caution if there is the presence of metal in the head, especially of a ferromagnetic type, or where patients have magnetically controlled implantable devices (Rossi et al., 2009).

10. Challenging clinical questions

10.1. Is stronger better, are more pulses better?

The intensity of rTMS treatment provided is usually relative to the measurement of an individual patient's RMT. The intensity of

Table 3
Studies describing the patterns of relapse and likelihood to response to retreatment following an index course of rTMS.

Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments
16 patients (14 followed up), no medication, retreatment when evidence of relapse including HAMD > 17 (Demirtas-Tatlidede et al., 2008)	4 years	64 total courses	5 months between courses on average	Mostly of short duration (9 treatments only initially) low dose (pulse number and intensity)	Antidepressant response consistently achieved with each course	3 (of 14) achieved a stable response not requiring further treatment for up to 31 months
19 patients (16 initial responders, 6 initial partial responders), mixed other treatments (4 medication free) (Fitzgerald et al., 2006a)	3 years	30 total courses	Average 10 months between episodes	Usually no more than 20 treatments, low dose (pulse number and intensity)	Antidepressant response consistently achieved with each course	
99 partial responders (to a 6 week course of rTMS plus taper period), on antidepressant medication, 70 followed for full 2 years (Janicak et al., 2010)	2 years	38 worsened sufficiently to justify retreatment	Time to reintroduction was 109 +/− 5 days	Reintroduction averaged 14.3 sessions	84.2% of re-treatment episodes resulted in benefit	Partial responders more likely to require retreatment than full responders
257 patients (responders and non responders), 205 followed full 12 months (Dunner et al., 2014)	1 year	93 received repeat treatment Average 16.2 days therapy, much more likely to need further treatment if less initial response	Remitters who relapsed did so spread across the year, highest likelihood between months 3 and 9		There was an overall persistence of long term benefit in initial treatment responders and remitters.	78 initial remitters – 70.5% remained well throughout the 12 months
49 medication free patients randomised to have one TMS session per month or no treatment, responders most in remission, only 16 followed for full 12 months (Philip et al., 2016)	1 year	35–39% of the patients did not require repeat treatment	Mean (± SD) duration from end of the acute treatment to reintroduction: 91.2 ± 65.8 days for the once per month group, 77.1 ± 51.7 days for the non treatment group	14.3 ± 17.8 rTMS sessions in the one treatment per month group and 16.9 ± 18.9 in the no treatment group.	14/18 (78%) for the once per month group responded and 17/27 (63%) for the no treatment group (response = return to the HAMD17 score they reached at the end of acute treatment, or better)	
120 patients received an initial course and 30 Patients a second course of treatment (Pridmore et al., 2019)			27.5 +/- 16.7 weeks		Same degree of response seen for first and second course of treatment	
16 patients had a second course out of 225 studied (Kelly et al., 2017)					Average percent change in BDI across induction was similar to that after reintroduction (57.967.7% and 56.569.4%, respectively; paired-samples *t*-test, $p = 0.9$). Ten of 16 (62.5%) patients were responders to the initial rTMS treatment course, and 11 of 16 (68.8%) patients were responders to reintroduction.	

stimulation used in clinical trials of rTMS has increased over time from the 80–90% level to the standard 120% of the RMT adopted widely since this was used in the main rTMS pivotal trials. Although this has evolved as the standard of care, it is notable that this increase has not been supported over time by systematic dose finding research. In a similar manner, the number of pulses provided per day in each treatment session has markedly increased over time but this variable has not been subject to any substantive dose finding studies published to date. A meta-analysis comparing studies conducted using different doses did suggest that fewer pulses were associated with greater antidepressant responses rather than more (Kedzior et al., 2014) and in a recent study exploring dose/pulse number for both right and left sided forms of rTMS, a clear advantage of higher dose stimulation was not apparent (Fitzgerald et al., 2020).

10.2. How long is long enough?

There is more a data available to inform our understanding of how long an rTMS treatment course should progress for. In particular, if we look at the pattern of clinical responses across many randomised studies these tend to show a progression of clinical improvement that continues right up until the end of treatment, whether the trials are of four or six week duration. Typically, clinical response has not plateaued at the end of treatment in many of these randomised studies. For example, in one of the first studies providing 6 weeks of rTMS treatment, depression ratings fell throughout the entire 6 weeks in the active group but had not plateaued at study end (Fitzgerald et al., 2006b). In a follow on study of the George et al. large multi-site trial published in 2010 (George et al., 2010), further periods of treatment were directly associated with higher remission rates (McDonald et al., 2011). A similar effect has been shown with dTMS with longer treatment associated with a growing response rate (Yip et al., 2017).

At this stage it seems reasonable to conclude that better responses accumulate with longer durations of treatment but we really don't have a clear answer to what is a sufficiently long trial. Of note, subjects in the study of McDonald et al. (2011) continued in treatment if they were showing improvement but had not remitted: this would seem a sensible standard for practice – to have a standard length of treatment to establish if there is response, but to be flexible to extend this time if patients are partially responding. What the more appropriate minimal trial length is, however, it not completely clear but likely to be 4–6 weeks in most circumstances.

10.3. Are there viable options when there is non-response to an initial course of rTMS

Is a single trial of one type of rTMS sufficient or are there rTMS options if patients fail to respond to an initial trial of therapy? Clearly with a number of forms of rTMS having been shown to be effective, it is pertinent to question whether there is value in potentially trying a second form of rTMS should patients fail to respond to an initial course of therapy. Unfortunately, only a few studies have addressed this to date. The first study to do this gave a small number of patients who failed either high-frequency left-sided rTMS or low-frequency right-sided rTMS the alternative treatment (Fitzgerald et al., 2003). Three patients crossing from right-sided to left-sided treatment (out of 10) achieved treatment response and 0/7 patients who switched in the opposite direction, but treatment was applied for only two weeks. In a second study that addressed this question, patients who had failed low-frequency right-sided stimulation received treatment with 5 or 10 Hz applied to the left DLPFC (Fitzgerald et al., 2009c). A significant antidepressant effect was seen with no difference between five and 10 Hz stimulation but the response rate was relatively low. An open label study reported outcomes for 17 patients who switched from 10 Hz left rTMS to sequential bilateral treatment (Cristancho et al., 2019) – 4 patients responded to this new protocol. McDonald et al. provided four weeks of low-frequency right-sided rTMS to patients who had failed to respond to a substantive course of high frequency left sided rTMS. 21 of 81 patients (26%) responded to this course of right-sided stimulation (McDonald et al., 2011). In a more recent study, non-responders to 3 weeks of high-frequency left-sided rTMS were randomised to continue with the same treatment for another three weeks or to switch and have three weeks of either low-frequency right or sequential bilateral rTMS (Fitzgerald et al., 2018a). Modest antidepressant effects were seen in all three groups. Finally, Feffer et al. found a 36% response rate when providing 1 Hz stimulation to the right orbitofrontal cortex in non-responders to dorsomedial stimulation (Feffer et al., 2018).

In total these studies provide a suggestion, but not definitive evidence, that a trial of a second form of rTMS may have value in initially non-responsive patients to a first rTMS trial. However, these effects may arise from just continuing with rTMS in general, especially as the initial trials of therapy and most of the studies have been relatively short. A decision to switch to a different form of rTMS should be made balanced with other therapeutic options.

11. Localisation and targeting of treatment

There has been considerable recent interest in developing improved methods of the targeting of the rTMS stimulus. It has been repeatedly established that the traditional '5 cm rule' results in localisation of stimulation in posterior frontal regions not considered DLPFC in a sizeable proportion of patients (for example Fitzgerald et al. (2009b) and Herwig et al. (2001)). The first clinical trial to directly test whether outcomes could be improved with MRI based targeting compared outcomes achieved with neuronavigationally determined treatment to stimulation provided using the 5 cm method showing improved outcomes with the former approach (Fitzgerald et al., 2009a). This study used neuronavigation to localise treatment to a predetermined target defined by a standardised coordinate (chosen from analyses of multiple neuroimaging studies). It is possible to use neuronavigation based on specific functional neuroimaging data at a group level (averaged scan data applied to an individual subject's scan converted into a normalised coordinate space) or to use an individual functional image although the later approach has been more problematic due to scan resolution. Recently, attention has been particularly focussed on whether mapping subgenual anterior cingulate (sACC) – DLPFC connectivity on resting state functional MRI scanning can be used to identify an improved method of treatment targeting. The potential value of this approach was initially suggested by an analysis reporting an association between the strength of DLPFC – sACC anticorrelation on resting state MRI in healthy controls and the DLPFC sites associated with greatest antidepressant effects in patient studies (Fox et al., 2012). There has been a prospective validation of this (Weigand et al., 2018) and a second validation by an independent group (Cash et al., 2019). However, the complexities inherent in this method and concerns as to whether accurate targeting will be possible on individual patient scans mean that further research and development is required before these approaches can be considered appropriate for clinical use. In the absence of an accurate and reliable neuroimaging based approach, using EEG based localisation such as the F3 EEG point seems a good alternative to basic measurement from the motor cortex as it will take variation of head size into account. A simple guide for the measurement of these sites has been published (Beam et al., 2009) and produces replicable results although at a slightly anterior site to localisation based on a manually placed EEG cap (Nikolin et al., 2019).

Recommendations around scheduling, dosing and treatment provision

- The standard evidence supported rTMS treatment approach involves the provision of daily treatment sessions five days per week for a minimum of four weeks. Approaches that substantially differ from this should still be considered experimental.
- rTMS is effective in the treatment of an index episode of MDD and is highly likely to be effective in treating a subsequent episode of depressive relapse.
- There is limited evidence currently supporting the use of maintenance rTMS approaches although these are being used relatively widely in clinical practice to address substantial clinical need.
- As provided in the largest multisite clinical trials, rTMS should typically be provided at 120% of the RMT if tolerated. There is a reasonable likelihood that rTMS may still be effective at lower stimulation intensities but if patients cannot tolerate treatment at 100% of the RMT or above, switching to low-frequency right-sided treatment should be considered.
- Four weeks is a reasonable choice for the minimum duration of an adequate trial of rTMS treatment in patients who are demonstrating no response. Continuing for another two weeks or switching to another form of stimulation are options that should be considered if patients have failed to respond after four weeks of standard therapy.
- Neuro-navigational approaches to localising stimulation have the potential to significantly improve clinical outcomes but have not been sufficiently evaluated at this time.
- We currently do not have any clinical or laboratory-based tests that can be used in a meaningful way to predict clinical response.

12. Prediction of response

Although there have been extensive efforts to establish clinical predictors of response to rTMS treatment, in large samples of patients the relationships that do exist between clinical or demographic variables (for example degree of treatment resistance, length of episode) and treatment outcome are weak and of no predictive value (for example Fitzgerald et al. (2016a) and Lisanby et al. (2009)). This has motivated efforts to explore the development of electrophysiological and neuroimaging based measures that might have greater clinical value. Some of the most promising of these approaches have obtained quite substantial predictive metrics, mostly when using machine learning algorithms to develop approaches using functional imaging and EEG based connectivity data (Bailey et al., 2018, 2019; Corlier et al., 2019; Ge et al., 2019). However, there remains an absence of prospective validation of any of these models and it is notable that at least one previous EEG response marker has failed to replicate independently (Krepl et al., 2018). It does now seem realistic, however, that one of these markers may be able to be developed sufficiently to be of clinical use.

13. Conclusions

Research has clearly established the antidepressant efficacy of rTMS treatment in patients with depression. Studies have established the efficacy of high-frequency stimulation applied to the left DLPFC, low-frequency stimulation applied to the right DLPFC, sequential bilateral stimulation and dTMS. rTMS appears to be a useful and effective treatment across a significant spectrum of treatment resistance and in patients with both unipolar and bipolar depression. It appears to be effective treatment in the elderly with depression and has promise in the treatment of adolescent patients and patients in the perinatal period. Although dropout rates and side-effect rates in TMS studies are low, some patients do find the treatment uncomfortable or even painful and there is an established risk of seizure induction. Accessing treatment on a daily basis over a prolonged period of time is also inconvenient and often challenging for patients. Intensive accelerated forms of rTMS have the potential to offer a more rapid and easily applied form of stimulation but require further evaluation. TBS offers a method of achieving similar rTMS benefits in a rapidly applied stimulus. Further research is required to optimise methods for stimulation targeting and to develop ways of usefully clinically predicting response. For now, rTMS seems to have a relatively clear role in clinical practice supported now in multiple clinical practice guidelines. Where available it should be considered in patients with non-psychotic major depression who have failed initial courses of antidepressant medication or in whom antidepressant medication is intolerable.

Declaration of Competing Interest

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Supplementary materials

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