

## RESEARCH ARTICLE

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# Treatment-resistant depression: experience of the first repetitive transcranial magnetic stimulation clinic in the UK

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**ABSTRACT** **Aim:** To report the clinical outcomes of 62 treatment-resistant depressed patients treated with repetitive transcranial magnetic stimulation (rTMS) in the first rTMS clinic in the UK during 2013. **Materials & methods:** Sixty-two treatment-resistant depressed patients (12 of them bipolar) referred to an rTMS Clinic in London during 2013 completed self-report Beck Depression (BDI-II) and Anxiety Inventories (BAI) at baseline and at the end of their treatment course. **Results:** Sixty-six percent reached remission, as defined by a score of 12 or below in the BDI-II at the end of the treatment course. Length of illness did not affect the likelihood of recovery. The treatment was generally well tolerated. **Conclusions:** rTMS appears to be a safe and effective intervention for 'real world' treatment-resistant patients.

An episode of depression serious enough to require treatment occurs in about one in four women and one in ten men at some point in their lives, according to the National Institute for Health and Care Excellence [1]. It is estimated that about half of those diagnosed with this disorder will not reach remission with antidepressant medication [2]. Treatment-resistant depression is a major health problem in our society and the strategies available to clinicians to manage it are relatively limited [3].

Repetitive transcranial magnetic stimulation (rTMS) is gradually becoming recognized as a valuable therapeutic option in treatment-resistant depression. It is based on Faraday's law of electromagnetic induction, by which the electrical activity in the brain tissue can be influenced by a magnetic field. rTMS delivers a series of trains of magnetic pulses, separated by brief intervals, through a magnetic treatment coil, usually placed over the patient's left dorsolateral prefrontal cortex. The changes in magnetic field induce an electric current that excites the neurons in the area below the coil and produce measurable physiological changes in the brain tissue. rTMS has been shown to increase blood flow and glucose metabolism in the stimulated regions of the brain [4] and it also induces an increase in neurotransmitter activity, such as dopamine and glutamine [5].

The first reports on transcranial magnetic stimulation in connection with the treatment of major depressive disorders began to emerge in late 1995 [6]. A number of randomized placebo-controlled trials have compared real versus sham rTMS. These trials have consistently demonstrated the efficacy of this treatment against major depression. In fact, there have also been a number of meta-analyses of RCTs [7–9] and even metareviews of meta-analyses [10,11], all confirming the efficacy of rTMS in treatment-resistant major depression. A large multisite randomized placebo-controlled trial, using sham versus real rTMS with 301 medication-free patients, obtained positive results and led to FDA approval of this treatment in 2008 [12]. The value of rTMS in the management of treatment-resistant depression has, therefore, been systematically tested and is now widely accepted. rTMS is approved and licensed in North America and Europe for the treatment of depression in patients who have not improved to a satisfactory extent with antidepressant medication.

**KEYWORDS**

• depression • magnetic  
• rTMS • treatment  
resistance

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A typical rTMS treatment course consists of five sessions per week over a 3–6-week period. Each treatment session lasts approximately 30 min. During the treatment, the patient is fully awake and no sedation is necessary. Patients use the time of the treatment in different ways, such as reading, talking with the therapist, or simply relaxing. Their head is maintained in a fixed position throughout the treatment, with the help of a specially designed pillow.

Materials & methods

Every depressed patient referred to an rTMS clinic in London during 2013 (n = 62) completed self-report Beck Depression [13] and Anxiety Inventories [14] at baseline and at the end of their treatment course. Their average age was 38 years and just over half of them were females (Table 1). There was no significant difference in age between the genders. All were resistant to antidepressant treatment and remained on a variety of psychotropic medications throughout treatment, unchanged since the point of referral. They received rTMS for an average 4.3 weeks (SD: 2.4).

Sixty individuals were treated with a 10 Hz (pulses per second) protocol, with trains of pulses lasting 4 s and 26 s intertrain intervals. They received 75 trains of pulses (3000 pulses in total per treatment session) over their left dorsolateral prefrontal cortex (DLPFC), at a dose of 120% of their motor threshold.

The rTMS device used was a MagPro R30 manufactured by Magventure®. The treatment amplitude was calibrated on a weekly basis. The method used for determining the motor threshold was the minimum single pulse TMS energy needed to observe an abductor pollicis brevis (APB) contraction in the contralateral hand. The DLPFC was identified by using the ‘5 cm rule’: the positioning of the treatment coil over the DLPFC defined as 5 cm anterior to the APB site in the parasagittal plane.

Twelve out of these 60 patients were in a depressed phase of a bipolar affective disorder. These 12 depressed bipolar patients had also failed to improve with standard antidepressant interventions before they attended the clinic.

They were treated with the same standard tTMS protocol as their unipolar counterparts.

While all 62 individuals in the cohort had treatment-resistant depression (12 of them in the context of a bipolar affective disorder), two female nonbipolar individuals also had a diagnosis of Fibromyalgia at the time of their referral to the clinic. Low-frequency rTMS to the right hemisphere has been found to be effective in the treatment of fibromyalgia [15], so these two individuals were treated with a 1 Hz frequency protocol over their right DLPFC, at a dose of 120% of their motor threshold. They received 1600 pulses per session.

Results

The mean initial Beck Depression Inventory (BDI-II) score of the entire cohort (n = 62) was 31.6 (SD: 8.8) (Table 2). The reductions in the depression inventory scores are illustrated in Figures 1 & 2. Overall, 66.1% of all depressed patients treated with rTMS reached remission, as defined by a score of 12 or below in the BDI-II at the end of the treatment course. Female gender was positively associated with remission, although this association did not reach statistical significance: 23 (74.2%) females and 18 males (58%) were in remission at the end of the treatment course (odds ratio: 1.3 [95% CI: 0.6–2.8]).

Length of illness prior to the referral for rTMS was classified categorically as either above or below 10 years. A longer length of illness did not affect the likelihood of recovery with rTMS (odds ratio: 1.3 [95% CI: 0.5–3.6]).

There were no significant differences in treatment length, initial depression and anxiety scores, or outcomes, between the unipolar and bipolar patients, although a higher proportion of bipolar patients reached remission at the end of the treatment, compared to the unipolar group. However, unipolar patients started treatment with a higher average depression score (Table 2).

Three patients, two of whom were known bipolar affective disorder sufferers, experienced mixed affective symptoms, such as psychomotor agitation, racing thoughts and subjective feelings of dysphoria, irritability and psychological

Table 1. Remission rate.	
Females – males	32–30
Age (average; SD)	38.2; 14.6
Length of illness (% >10 years)	50% (n = 31)
SD: Standard deviation.	

**Table 2. Average reduction in depression and anxiety scores and remission rates.**

	Treatment protocol	Average length of treatment (in weeks)	Average initial BDI-II score	Average reduction in BDI-II score	Average initial BAI score	Average reduction in BAI score	In remission at end of treatment
Complete cohort (n = 62)		4.3 (SD: 2.4)	31.6 (SD: 8.8)	17.9 (SD: 11.1)	19 (SD: 11)	11 (SD: 10.4)	41 (66.1%)
Depressed unipolar subset (n = 48)	10 Hz left DLPFC	4.4 (SD: 2.6)	32.2 (SD: 9.3)	17.6 (SD: 11.5)	19.2 (SD: 11.3)	10.5 (SD: 10.7)	28 (58.3%)
Depressed bipolar subset (n = 12)	10 Hz left DLPFC	4.9 (SD: 1.5)	29.6 (SD: 6.4)	20.3 (SD: 9.8)	16.8 (SD: 10.7)	11.4 (SD: 10.2)	9 (75%)
Fibrom. subset (n = 2)	1 Hz right DLPFC	4	21.5 (SD: 0.7)	9.5 (SD: 0.7)	20 (SD: 1.4)	17 (SD: 4.2)	1 (50%)

DLPFC: Dorsolateral prefrontal cortex; SD: Standard deviation.

tension. The three felt distressed and their rTMS treatment was discontinued. They were not being treated with antidepressant medication. After some adjustments were made to their mood-stabilizing medications, the mental state of the two bipolar individuals normalized. The nonbipolar patient improved spontaneously after the discontinuation of rTMS. She remained medication-free, but was given *a posteriori* a diagnosis of depression in the context of a bipolar affective disorder spectrum.

The two female patients with fibromyalgia, treated for 4 weeks with a 1-Hz protocol over their Right DLPFC, experienced comparatively larger reductions in their levels of anxiety than those without this diagnosis (Table 2).

Other than the already mentioned agitation suffered by three individuals, no other significant adverse or side effects were reported during the treatment.

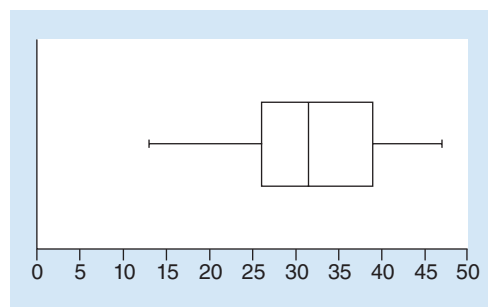
## Discussion

rTMS is a safe intervention in treatment-resistant depression, with a benign tolerability profile [16]. It is an effective alternative to the drug combinations used in treatment-resistant depression, which are often difficult to tolerate [17]. Because of its noninvasive nature and tolerability, rTMS is a very attractive treatment option in certain clinical circumstances.

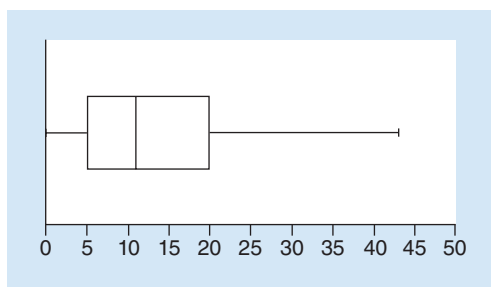
The efficacy of high frequency rTMS in the management of treatment-resistant depression has already been established by a substantial body of empirical evidence, underpinned by a number of meta-analyses of randomized controlled trials [10,11]. However, its effectiveness with 'real world' treatment-resistant patients, who tend to present with complex comorbidities

in every diagnostic domain, is less well established, although some naturalistic studies on rTMS in clinical settings have been published. These studies found that between half and two-thirds of treatment resistant depressed patients responded to high frequency rTMS [18,19]. Our results confirm that rTMS is an effective and well tolerated therapeutic tool in these 'real world' clinical situations. It is to be expected that the clinical outcomes of these studies will differ to a significant extent, given that patients who seek treatment in a clinical setting are inevitably heterogeneous. It is also important to bear in mind that the therapeutic relationship between patient and rTMS practitioner is an integral part of the rTMS treatment package, which will vary in each particular clinical instance. Their differing pharmacological treatments will also affect the clinical outcomes.

This report used remission as the outcome measure. Remission as the outcome measure has been used in other depression treatment studies, such as the landmark Star\*D sequential treatment study on the effectiveness of different antidepressant treatments, funded by



**Figure 1. BDI-II scores at beginning of treatment.**



**Figure 2.** BDI-II final scores.

the National Institute of Mental Health [17]. Remission is arguably more clinically significant than response (usually defined a drop of 50% or more in the depression scale), as the former has been shown to be associated with a much better prognosis. This study describes the treatment outcomes in a 'real world' clinical setting, in which the aim is to continue to treat patients up to the point of remission, when they report that they have recovered and are practically free of depressive symptoms. In this type of setting, a certain and predetermined drop in the depression inventory score is less meaningful clinically than a virtual cessation of symptoms.

There is some evidence in the literature supporting the efficacy of rTMS in bipolar depression [20–22], but in common with any other antidepressant intervention in bipolar depression, there is a potential risk of treatment-emergent mania. However, a review of randomized controlled trials found this risk to be equivalent to that associated with sham treatment [23].

Our results suggest that rTMS is an effective intervention in the management of bipolar depression, a condition that presents particularly difficult challenges to the clinician. It is possible that the patients in our sample who developed mixed affective symptoms while receiving rTMS perhaps suffered a spontaneous change in their mood, which could potentially be attributable to

the natural course of their illness. However, this remains speculative.

The fact that the length of illness, which should correlate with level of resistance to treatment, did not affect the likelihood of recovery seems counterintuitive. It is also inconsistent with the generally accepted principle that a higher level of resistance to previous treatments affects negatively the chances of achieving remission with a new therapeutic intervention. Further research should help elucidate this point.

### Limitations

This is a report of treatment outcomes in a 'real world' clinical setting. These outcomes should not be interpreted empirically, as the treatment sample was very heterogeneous and other variables undoubtedly contributed to the results reported here, such as the careful preparation of patients before they were referred for rTMS, or the nature of the therapeutic relationship between staff and patients during treatment.

Being an observational, naturalistic report, there was no comparison group.

Remission was identified with the use of a single main outcome measure (BDI-II).

### Conclusion

We believe that rTMS offers a valuable and effective treatment alternative to the very large number of patients we see in our clinical practice who do not respond to standard antidepressant interventions and who continue to experience distressing symptoms associated with their low mood. Further research will help establish the optimum rTMS parameters for treatment-resistant unipolar and bipolar depression.

### Financial & competing interests disclosure

*R Euba is a Consultant Psychiatrist who carries out paid clinical work at The London Psychiatry Centre, the source*

## EXECUTIVE SUMMARY

- The efficacy of rTMS in treatment-resistant depression has already been established by a substantial body of empirical evidence, but its effectiveness in 'real world' clinical settings is less well established.
- This report confirms that rTMS appears to be a safe and effective intervention for 'real world' treatment-resistant patients.
- Length of illness did not affect the likelihood of recovery.
- A majority of patients with bipolar depression benefited from this treatment and tolerated it well.
- Further research will help establish the optimum rTMS parameters for treatment-resistant unipolar and bipolar depression.

of the clinical outcomes described in this report. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter

or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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