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BJPsych Advances (2023), vol. 29, 77–81 doi: 10.1192/bja.2022.88

ROUND THE CORNER

Treatment-resistant depression – is magnetic seizure therapy the novel treatment?[†]

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SUMMARY

Depression has a large socioeconomic burden, affecting an estimated 280 million people worldwide. Up to 55% remain symptomatic following pharmacological and psychological treatment and may be classified as having treatment-resistant depression. This commentary assesses two treatment options for this group – electroconvulsive therapy (ECT) and a novel approach, magnetic seizure therapy (MST) – with reference to a Cochrane Review comparing the two. The Cochrane analysis showed no clear benefit for MST, but the evidence is currently insufficient to draw firm conclusions.

KEYWORDS

Magnetic seizure therapy; treatment-resistant depression; electroconvulsive therapy; depression; depressive disorders.

Major depressive disorder has been defined as a period of at least 2 weeks 'during which a person experiences any combination of daily depressive symptoms'; these can include anhedonia, low mood and sleep disturbances among others (American Psychiatric Association 2013). In 2019, an estimated 280 million people were living with depression worldwide. It is a common condition with a large socioeconomic burden (Greenberg 2021). Although there are many therapeutic tools, both pharmacological and psychological, used by clinicians in primary and secondary care, up to 55% of patients remain symptomatic and thus may suffer from treatment-resistant depression (TRD) (Thomas 2013). TRD is ill-defined in both academic and clinical settings; however, is generally considered to be no response to one or two antidepressant medications within a single, current episode of depression (Sforzini 2022).

When pharmacological methods fail, what are the treatment options for TRD?

Electroconvulsive therapy (ECT) is the current most evidence-based, highly effective treatment for TRD, although its use in clinical practice tends to be reserved for more refractory types of depression (Leiknes 2012). Despite its high efficacy, ECT is associated with cognitive adverse effects such as processing speed impairment and anterograde and retrograde amnesia, and the amnesias can persist for up to 1 year (Porter 2020). Furthermore, ECT has been found to cause acute arrhythmia and acute heart failure, with incidences of 26 and 24 per 1000 individuals respectively (Duma 2019).

A novel alternative to ECT is magnetic seizure therapy (MST). MST involves inducing focal seizures using magnetic pulses under general anaesthesia. It is primarily targeted at the frontal cortex, delivered via a twin coil at 25–100 Hz (Daskalakis 2020).

ECT and MST – the proposed mechanism of action

ECT is shown to increase the volume and enhance connectivity of the temporal lobe cortices, anterior cingulate cortex and hippocampus, resulting in favourable clinical outcomes which are believed to be due to neuroplastic changes (Ota 2015; Joshi 2016; Cano 2017). However, the increase in hippocampal volume is associated with cognitive adverse effects, which evidence suggests improve as hippocampal volume decreases in the 6–12 months following completion of ECT (Bassa 2021). MST, in contrast, induces only superficial stimulation and passes through the skull unimpeded, resulting in a more targeted stimulation of focal structures (Weissman 2020). Thus MST, theoretically, could produce similar clinical results without the adverse effects experienced by those who receive ECT.

Glucose metabolism and its dysfunction within the anterior cingulate cortex, hippocampus and amygdala is also thought to play a role in the clinical manifestation of TRD (Paillère Martinot 2011). Positron emission tomography has been used to demonstrate a significantly higher glucose metabolism in responders compared with non-responders who received deep brain stimulation (Brown 2020). It is therefore theorised that a similar therapeutic effect could be observed in MST, with other

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First received 5 Oct 2022
Final revision 30 Nov 2022
Accepted 4 Dec 2022

[†]Commentary on… Magnetic seizure therapy for treatment-resistant depression (Cochrane Corner). See this issue.

https://doi.org/10.1192/bja.2022.88 Published online by Cambridge University Press

forms of magnetic treatment documented to achieve this (Paillère Martinot 2011).

This month's Cochrane Review (Jiang 2021) is the first systematic review of MST in the context of TRD and serves to consolidate past research, aiming to aid clinicians in their decision-making within the TRD demographic. The review has also been completed in the context of many forthcoming studies investigating the antidepressant effects of MST which are anticipated to build on the research discussed here.

The review's methods

During paper selection, randomised controlled trials (RCTs) including specifically cross-over and cluster RCTs were included but quasi-RCTs (Box 1) were excluded. Participants had to be over 18 years old and suffer from TRD. Comorbid non-psychotic mental disorders and somatic illnesses were included as long as the study did not solely focus on these. As mentioned above, TRD is ill-defined (Sforzini 2022); however, the definition used in this review was a 'major depressive episode' according to a diagnostic manual, for example DSM-5 (American Psychiatric Association 2013), ICD-10 (World Health Organization 1992) or the Chinese Classification of Mental Disorders (CCMD-3; Chinese Society of Psychiatry 2001). For TRD to be classified, participants had to have no response or only partial response to a minimum of 4 weeks of one or more antidepressant at recommended doses.

Jiang et al's (2021) review compared MST with sham MST, ECT, any antidepressant and other forms of electric/magnetic treatment. There were no limitations chosen for strength or duration of MST. Studies that met these criteria were included regardless of their outcomes. The authors reviewed symptom severity and cognitive function as their primary outcomes. Secondary outcomes were: suicide attempts, self-harm and suicide, quality of life, social functioning, drop-out for any reason, serious adverse events and adverse events that led to discontinuation of treatment. When assessing symptom severity the primary assessment tool was the Hamilton Rating Scale for Depression (Sharp 2015).

BOX 1 What is a quasi-RCT?

A quasi-randomised controlled trial is a study that employs a method for randomisation that is not truly random. For example, group selection could be decided by the order that participants are included in the study or the day of the week (Bandolier 2007). The main issue with quasi-RCTs is that confounding factors cannot be accounted for, and this raises concerns regarding the interval validity of the research owing to selection bias (Harris 2006).

How were the papers selected?

A Cochrane information specialist (Box 2) conducted a search in March 2020 of MEDLINE, Embase and grey literature and complementary searches on numerous Chinese biomedical databases. For each selected article, the references were reviewed for any further unidentified papers, and conference proceedings were hand-searched to identify unpublished work.

Two authors independently assessed the suitability of papers, extracted the data and assessed methodological bias. Any disputes were reviewed by a third arbitrator. Methodological bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Researchers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence. This is a framework to enable clinical recommendations by assessing the risk of bias, imprecision, inconsistency, indirectness and publication bias (Langendam 2013).

Continuous data outcomes were measured using mean differences (m.d.) with 95% confidence intervals (95% CI). Dichotomous outcomes were calculated as risk ratios (RR) with 95% confidence intervals using a random-effects model. Heterogeneity was assessed using the chi-squared statistic (χ^2). Results were deemed to be substantially heterogenous if I^2 was over 50% or P equalled less than 0.1 for χ^2.

Paper selection and results

A total of 382 papers were initially identified, of which 376 were excluded for reasons such as not analysing TRD and not being randomised. The remaining six papers covered three studies. Along with the three included trials, one ongoing trial was identified (NCT03191058), the recruitment phase of which is due to end in 2024. All three trials were single-site open-label parallel RCTs, and all were conducted by one research team at University Hospital Bonn, Germany. A total of 60 participants were recruited, with the mean age of 45.8 and 54.2 years for MST and ECT respectively; 48% of the participants were female.

All three studies classified TRD as a failure in response to two treatments. They excluded patients with a diagnosis of other psychiatric, neurological or cognitive disorders and those at high risk of harm from anaesthesia. The follow-up period for these studies was short – up to 6 weeks – and all took place during or before 2012.

All three studies delivered MST using twin coils at a pulse frequency of 100 Hz over 8–12 sessions. ECT was delivered unilaterally to all but one participant. All studies continued concomitant

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antidepressants and/or psychotherapy. The risk of bias was either unclear or high in all the trials, and high risk was seen in all three trials in relation to masking ('blinding') of participants and personal and outcome assessment; selective reporting was also noted.

Does MST work?

All studies compared MST with ECT; analysis showed no clear difference in reported symptom severity (40 participants: m.d. = 0.71, 95% CI −2.23 to 3.62, $P = 0.64$). In relation to cognitive function, two studies investigated multiple domains of cognitive function, but they did not report the methods they used, except the Wechsler Memory Scale. Analysis of both immediate and delayed memory outcomes showed no clear differences (20 participants: m.d. = 0.4, 95% CI −4.16 to 4.96, $P = 0.86$ and m.d. = 2.57, 95% CI −2.39 to 7.53, $P = 0.31$ respectively). Kayser et al (2011) reported skewed follow-up data for symptom severity and cognitive function and baseline data that were unbalanced. Polster et al's (2015) study suffered the same problem in relation to delayed memory.

Of the review's six secondary outcomes, only three were reported in these studies. There were no clear differences between treatment groups in relation to quality of life and drop-out for any reason. One study reported two participants experiencing adverse events that led to discontinuation of treatment, both in the ECT arm of the trial. All analyses had a 'very low' quality of evidence.

Are there any limitations?

It is important to note that these three studies each lasted a maximum of 6 weeks. They gave a maximum treatment of 12 sessions of both ECT and MST, the frequency of which was not reported. As per the National Institute for Health and Care Excellence (NICE), ECT is usually conducted at a rate of two sessions a week (NICE 2003). Importantly, if ECT sessions occurred at an increased frequency in these studies then this might produce different results than are replicable in the community. Furthermore, the lack of follow-up beyond this means that we cannot assess medium- or long-term outcomes or adverse effects. This makes it hard to extrapolate the data safely to everyday use.

Removing selection bias is essential to ensure that the outcomes of the study are true and not due to participant differences (Catalogue of Bias Collaboration 2017). In Polster et al's (2015) trial, the inclusion criterion for undergoing MST was the 'absence of former ECT treatments'. This is significant as these patients were excluded from the MST treatment group but not the ECT group. Therefore, it could be proposed that if a participant was placed in the ECT group who had previously had a successful outcome from ECT, then this could increase the chance of ECT working and negate the true effect of MST. This is further confounded by the lack of background information regarding participants' previous treatments. For example, there are no data on previous interventions, which antidepressants had been used and whether ECT had been trialled, emphasising the difficulty assessing the effectiveness of MST when we are unable to allow for these confounding factors.

It is worth noting that the review did not mention esketamine as a potential novel treatment for TRD (Swainson 2019), especially with growing evidence that, as an adjunct, it might improve remission rates and treatment response (Papakostas 2020). This is important, as esketamine may prove to have greater efficacy than MST.

One of the advantages of the three studies is their definition of TRD as a 'failure of two different antidepressants'. This is important as the review's initial inclusion criterion of 'no response to at least 4 weeks of one or more antidepressants' might have generated results not in keeping with the consensus on the definition of TRD. This is that 'at least 2 antidepressants in adequate dose, duration and compliance' should 'fail to produce a clinical improvement' (Berlim 2007). Furthermore, one could argue (despite no documented evidence) that ECT is not usually offered in the UK after the failure of just one treatment for 4 weeks.

Moreover, these three studies were funded in part by MagVenture A/S, a manufacturer of the MST device, leading to potential sponsorship bias (Box 3), and were conducted by one research team at the University Hospital Bonn, thus limiting the generalisability of the results. One could suggest that changing the inclusion criteria for the review to include quasi-RCTs might have mitigated this risk despite the abovementioned increased risk of selection bias. This is because relevant data might have been missed by ruling out this type of study

BOX 2 Cochrane information specialists

The role of Cochrane information specialists (CIS) varies depending on the Cochrane department; however, their job usually consists of performing a literature search to identify studies for inclusion in a Cochrane review (Cochrane Information Specialist Support Team 2022). They can also conduct a grey literature search, obtain trial reports and hand-search papers and journals for missed sources. CIS can also be involved in maintaining specialist databases for a specific condition (Metzendorf 2018), such as 'common mental disorders' (Cochrane Common Mental Disorders Group 2022).

BOX 3 What is sponsorship bias?

Sponsorship bias, also known as funding bias, has been described as the 'distortion of design and reporting of clinical experiments to favour the sponsor's aims' (Jefferson 2020). It has been reported that industry-funded sponsorship might discourage the publication of unfavourable results. Furthermore, evidence has shown that papers funded by independent organisations have generated fewer positive findings than those conducted by industry-funded sponsors (Bekelman 2003).

when only three studies, all with a high/unclear risk of bias, were included.

Conclusions and implications

Jiang et al's (2021) review suggests that MST is not more effective than ECT in TRD. However, there was a very small and biased sample and therefore there are insufficient data to recommend the use of MST in routine treatment for TRD. However, with further research and the publication of the currently ongoing study, this might provide further information regarding whether it is beneficial and its potential adverse effects.

Author contributions

Both authors contributed equally to this paper.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

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