



## Review article

## Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A systematic review and meta-analysis



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## ABSTRACT

Electroconvulsive therapy (ECT) is the most effective treatment of depression. During the last decades repetitive transcranial magnetic stimulation (rTMS), an alternative method using electric stimulation of the brain, has revealed possible alternative to ECT in the treatment of depression. There are some clinical trials comparing their efficacies and safeties but without clear conclusions, mainly due to their small sample sizes. In the present study, a meta-analysis had been carried out to gain statistical power. Outcomes were response, remission, acceptability and cognitive effects in depression. Following a comprehensive literature search that included both English and Chinese language databases, we identified all randomized controlled trials that directly compared rTMS and ECT for major depression. 10 articles (9 trials) with a total of 425 patients were identified. Methodological quality, heterogeneity, sensitivity and publication bias were systematically evaluated. ECT was superior to high frequency rTMS in terms of response (64.4% vs. 48.7%, RR = 1.41,  $p = 0.03$ ), remission (52.9% vs. 33.6%, RR = 1.38,  $p = 0.006$ ) while discontinuation was not significantly different between the two treatments (8.3% vs. 9.4%, RR = 1.11,  $p = 0.80$ ). According to the subgroup analysis, the superiority of ECT was more apparent in those with psychotic depression, while high frequency rTMS was as effective as ECT in those with non-psychotic depression. The same results were obtained in the comparison of ECT with low frequency rTMS. ECT had a non-significant advantage over high frequency rTMS on the overall improvement in HAM-D scores ( $p = 0.11$ ). There was insufficient data on medium or long term efficacy. Both rTMS and ECT were well tolerated with only minor side effects reported. Results based on 3 studies suggested that specific cognitive domains such as visual memory and verbal fluency were more impaired in patients receiving ECT. In conclusion, ECT seemed more effective than and at least as acceptable as rTMS in the short term, especially in the presence of psychotic depression. This review identified the lack of good quality trials comparing the long-term outcome and cognitive effects of rTMS and ECT, especially using approaches to optimize stimulus delivery and reduce clinical heterogeneity.

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**Abbreviations:** BDI, Beck Depression Inventory; BD, bipolar depression; BL, bilateral; BPRS, Brief Psychiatric Rating Scale; CNKI, Chinese National Knowledge Infrastructure; ECT, electroconvulsive therapy; Fre, frequency; HAM-D, Hamilton Depression Rating Scale; HF rTMS, high frequency rTMS; LF rTMS, low frequency rTMS; LDLPFC, left dorsolateral prefrontal cortex; MD, major depression; MD, weighted mean difference; MMSE, mini-Mental State Examination; MT, motor threshold; NA, not available; RCT, randomized controlled trial; RDLPFC, right dorsolateral prefrontal cortex; RR, risk ratio; rTMS, repetitive Transcranial magnetic stimulation; RUL, right unilateral; VIP, Chongqing VIP Database.

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## 1. Introduction

Electroconvulsive therapy (ECT), is a well-established and effective option for patients refractory or intolerant to pharmacotherapy (Janicak et al., 2002). It is the most effective short term treatment for severe major depression (MD) (Eranti et al., 2007) and has relatively high response and initial remission rates (Daly et al., 2001; Fink and Taylor, 2007; Husain et al., 2004; Lisanby, 2007; McClintock et al., 2011) especially in the presence of catatonia or psychosis (Bauer et al., 2002). Despite the high antidepressant efficacy of ECT (Eranti et al., 2007; Husain et al., 2004; Janicak et al., 1985, 1989), a substantial number of depressed patients cannot tolerate ECT (Janicak and Martis, 1999) and the prospect of achieving prolonged remission with ECT is uncertain (McClintock et al., 2011; Sackeim et al., 2001). In some individuals, ECT adversely affects cognitive function, disrupting both new learning and remote memory, limiting its overall acceptability (Eranti et al., 2007). Additionally, the use of ECT is often limited by other issues such as need for anesthesia and seizure induction (Lisanby, 2007; Rose et al., 2003).

In the past decade, rTMS has emerged as an effective, non-invasive physical intervention applied to the left or right dorsolateral prefrontal cortex (DLPFC) for MD (Berlim et al., 2012; Fitzgerald et al., 2003; George et al., 2010; Lingeswaran, 2011; O'Reardon et al., 2007; Pallanti and Bernardi, 2009; Rosa and Lisanby, 2012). rTMS appears to target distributed brain networks that are central to the pathophysiology of depression (George and Post, 2011; Schutter, 2009) and is not followed by epileptic seizure activity. Low frequency rTMS (stimulation frequency usually equal to or less than 1 Hz) is thought to inhibit the targeted brain region, while high-frequency rTMS (usually 5–20 Hz) is considered to increase excitability (Pal et al., 2005; Rodriguez-Martin José et al., 2009; Rossi et al., 2009). Depending on the parameters employed, cortical inhibition or excitation resulting from rTMS can last for up to several hours after stimulation (Di Lazzaro et al., 2005; Pal et al., 2005). Compared to ECT, rTMS does not require general anesthesia, and does not give rise to memorizing difficulties or other serious side effects.

To date, several RCTs have compared the antidepressant efficacy and safety of rTMS and ECT (Eranti et al., 2007; Grunhaus et al., 2000, 2003; Hansen et al., 2011; Janicak et al., 2002; Keshtkar et al., 2011; Pridmore et al., 2000; Rosa et al., 2006; Wang et al., 2004). While the antidepressant effects of rTMS are well established, its advantage over ECT continues to be controversial. Secondly, while it is generally accepted that rTMS protocols used for depression do not produce enduring cognitive disruption, it is unclear if this is a specific advantage when compared

to ECT in severe depression. Further, sustaining short-term efficacy to achieve long-term remission is a crucial therapeutic goal in MD that is closely linked to social, occupational and economic outcomes (Kelsey, 2004). Given the enduring nature and severity of depression in patients who are referred to receive somatic interventions such as rTMS and ECT, comparing the utility of these interventions with regard to long-term clinical efficacy will potentially aid in complex treatment decisions. To this end we undertook a systematic review and meta-analysis of RCTs that compare rTMS and ECT for depression, with or without psychotic symptoms. We specifically focused on clinically meaningful outcomes namely response, remission and acceptability. We also investigated the differences in self-rated mood improvement, general mental state, cognitive function and adverse effects between the two interventions.

## 2. Methods

### 2.1. Search strategy

Relevant randomized controlled trials of rTMS and ECT in patients with depression that were published or made available electronically before November 26, 2013, were identified via Pubmed, Embase, Ovid (all database including Medline, the Cochrane library, PsycInfo and so on) EBSCO host, and major Chinese databases – Chongqing VIP Database (VIP), Wan Fang Database and Chinese National Knowledge Infrastructure (CNKI). The search strategies combined free-text searching with key words probing. Our key search terms included English and Chinese versions of depression, depressive disorder, resistant depression, electroconvulsive therapy, electric shock therapy, electric convulsive therapy, electroshock therapy, ECT, TMS, rTMS, and transcranial magnetic stimulation. The detailed search procedures are listed in Supplementary search strategy.

### 2.2. Study selection

All relevant randomized controlled trials with a head to head comparison of rTMS and ECT were included. We excluded quasi-randomized studies, such as those allocating by using alternate days of the week, and where allocation is undertaken on surname. We included subjects with a diagnosis of primary major depressive episode (unipolar or bipolar) with or without psychotic symptoms by DSM-IV or ICD-10 or CCMD.

The interventions met the following criteria: 1) rTMS of high (stimulus rates of more than 1 Hz) or low frequency (stimulus rates of 1 Hz or less) with stimulating coil placed over the right or left DLPFC. 2) ECT

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