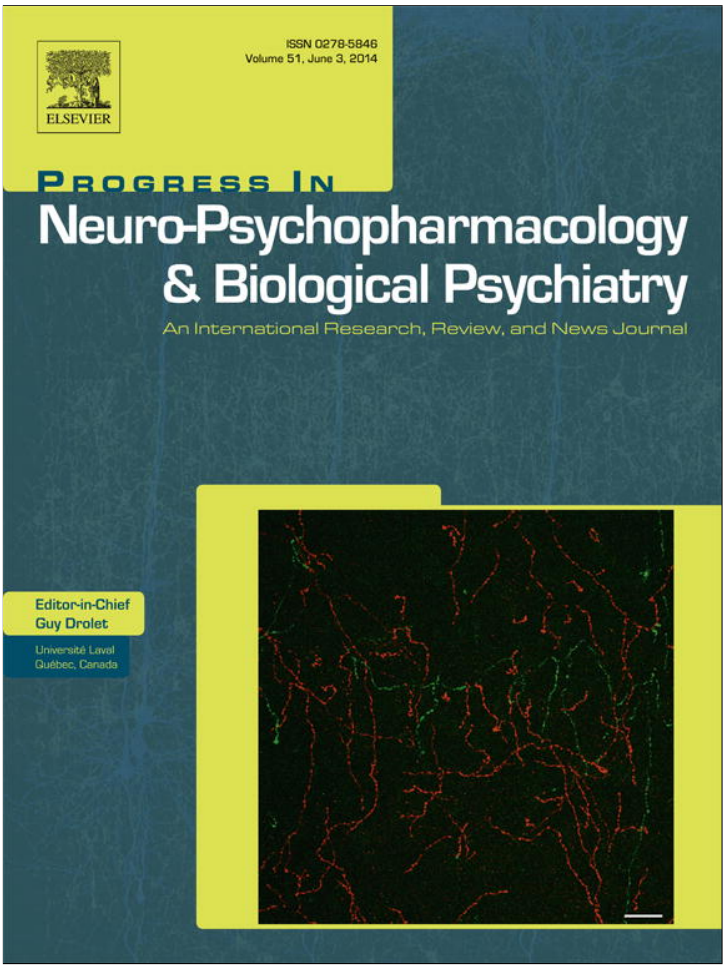

Progress in Neuro-Psychopharmacology & Biological Psychiatry 51 (2014) 181–189

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Review article

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

Juanjuan Ren [a], Hui Li [a,d], Lena Palaniyappan [b,c], Hongmei Liu [a], Jijun Wang [a,d,**], Chunbo Li [a,*], Paolo Maria Rossini [e]

[a] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China
[b] Centre for Translational Neuroimaging in Mental Health, Institute of Mental Health, Nottingham, UK
[c] Division of Psychiatry & Applied Psychology, University of Nottingham, UK
[d] Department of EEG Source Imaging, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China
[e] Department of Geriatrics, Neuroscience and Orthopedics, Catholic University of the Sacred Heart, Rome, Italy

ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 12 February 2014
Accepted 12 February 2014
Available online 18 February 2014

Keywords:
Electroconvulsive therapy (ECT)
Major depression
Meta-analysis
Randomized controlled trial (RCT)
Repetitive transcranial magnetic stimulation (rTMS)

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 HAMD 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.

Contents

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; HAMD, 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.

* Corresponding author at: Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Wan Ping Nan Road, Xuhui District, Shanghai 200030, China. Tel.: +86 21 3428 9888 73423; fax: +86 6438 7986.
** Corresponding author at: Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Wan Ping Nan Road, Xuhui District, Shanghai 200030, P.R. China. Tel.: +86 21 34773065 .
E-mail addresses: jijunwang27@163.com (J. Wang), chunbo_li@163.com (C. Li).

http://dx.doi.org/10.1016/j.pnpbp.2014.02.004
0278-5846/

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

given at any intensity and localization. ECT and rTMS may be administered in combination with other interventions such as pharmacotherapy or psychotherapy. We excluded single-pulse TMS and rTMS given for less than one week duration.

2.3. Data extraction

For each study, data were extracted independently by two authors (J.J.R. and H. L.), using a simple, structured form. We discussed any disagreement, document and report decisions and, if necessary contact authors of studies for clarification. The data extracted included (1) demographic, clinical and treatment characteristics (e.g. sample size, age, sex, interventions) (2) the study design; (3) the primary outcomes: a. Response: Clinically important response was defined as a 50% or more reduction in the baseline Hamilton Depression Rating Scale (HAMD) score at the end of treatment. b. Remission: Pre-defined HAMD based remission criteria from each individual trial. c. Acceptability: Assessed as number of patients leaving the study before the end-point (discontinuation rates) for any reasons d. mental state: continuous HAMD scores; (4) the secondary outcomes: a. Cognitive functioning: change of cognitive scores as defined by individual studies. b. Mental state: continuous Brief Psychiatric Rating Scale (BPRS) and Beck Depression Inventory (BDI) scores.

Quality of included studies was evaluated based on criteria specified in the Cochrane handbook (5.2.0) (Higgins et al., 2012) and GRADE system (Schünemann et al., 2008). Two researchers (J.J.R. and H. L.) performed both the risk of bias and GRADE evaluation independently. The discrepancies were resolved by consensus with a consultation from the senior author (C.B.L.).

2.4. Statistical analysis

Meta-analysis was conducted using RevMan 5.2.0 developed by Cochrane Collaboration (Higgins et al., 2012). The effect size of continuous variables was summarized by weighted mean difference (MD). The effect size of dichotomous variables was summarized by risk ratio (RR). The results of pooled analyses are shown using forest plots.

We used chi-squared test and I^2 to assess the heterogeneity among studies. I^2 assesses the proportion of variance in the MD that is due to cross-study heterogeneity. If the chi-square test is not significant ($p > 0.05$) and $I^2 < 50\%$, the possibility that the studies are heterogeneous is small, so the fixed-effect model is used to assess pooled results. But when the significance of the chi-square test is <0.05 or $I^2 > 50\%$, the studies are considered heterogeneous so the random-effect model is used to assess pooled results (Higgins et al., 2003) and the sources of the heterogeneity need to be considered.

Sensitivity analysis was conducted to assess the stability of the results and funnel plots were used to assess the possibility of publication bias. To assess the potential effect of each study on the overall conclusion, each included study was sequentially removed and the MD from the remaining studies was compared with the MD from all studies. We compared subgroups on potential difference between the patient type (depression with or without psychosis).

3. Results

3.1. Results of literature search and characteristics of included studies

Of 658 articles obtained from the search, 10 articles (Dannon et al., 2002; 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) met the selection criteria and were thus included in further analysis. The study selection process is shown in Fig. 1. Two of the included articles (Dannon et al., 2002; Grunhaus et al., 2000) reported on the short-term and long-term results

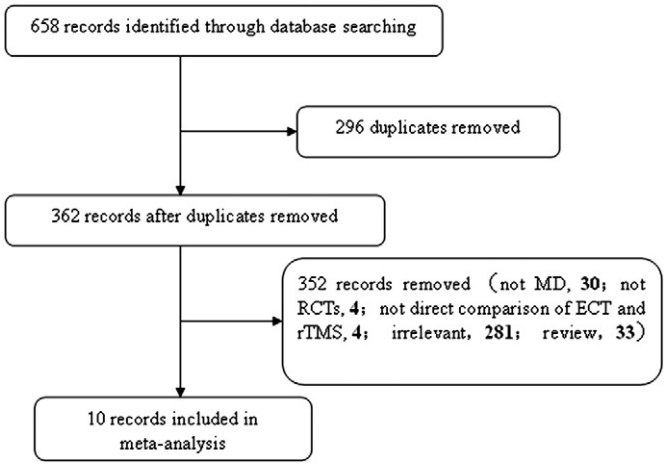

Fig. 1. Study flow diagram displaying the search process for trial selection. MD, major depression; RCTs, randomized controlled trials; repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT).

of the same sample; these results were considered as a single trial in the meta-analysis.

The demographic, clinical characteristics and treatment parameters of the included studies are summarized in Table 1. Pooling all the 10 articles from 9 studies, a total of 212 patients were randomized to ECT (mean age = 49.8 ± 12.6; 61.8% females). Among these, 201 (94.8%) patients were diagnosed with major depressive disorder and 11 (5.2%) with bipolar depression. A total of 217 patients were randomized to rTMS (mean age = 47.6 ± 12.4 years; 57.1% females). Of these, there were 202 (93.1%) patients had major depressive disorder and 15 (6.9%) had bipolar depression. There were 23 (15.2%) patients with psychotic depression in rTMS group and 33 (15.6%) in ECT group. Hansen et al. (2011) used low frequency right DLPFC rTMS. Keshtkar et al. (2011) provided no detail of the frequency of rTMS. All other studies employed high frequency left DLPFC rTMS. Also, rTMS and ECT were used as an augmentation strategy for depression in almost all studies (nine out of ten) except Rosa et al. (2006), in which patients were all drug-naïve and did not receive any antidepressants, antipsychotics and mood stabilizers during the treatment.

3.2. Quality of the studies

As shown in Supplementary Fig. 1, seven of them provided the descriptions of the random sequence generation (Dannon et al., 2002; Eranti et al., 2007; Grunhaus et al., 2000; Hansen et al., 2011; Keshtkar et al., 2011; Pridmore et al., 2000; Rosa et al., 2006). Four studies described allocation concealment (Eranti et al., 2007; Hansen et al., 2011; Keshtkar et al., 2011; Rosa et al., 2006). Four studies described single blinding (Eranti et al., 2007; Grunhaus et al., 2003; Pridmore et al., 2000; Rosa et al., 2006) and four studies were open labeled (Dannon et al., 2002; Grunhaus et al., 2000; Hansen et al., 2011; Keshtkar et al., 2011). Two studies (Janicak et al., 2002; Wang et al., 2004) did not report the details of blinding. Only one study (Hansen et al., 2011) had a double blind design. No selective reporting was found in the included studies. All studies except Pridmore et al. (2000) and Rosa et al. (2006) reported not being funded by the industry. The issues outlined above gave us reason to judge the risk of bias to be moderate (Supplementary Figs. 1–2). The overall quality of the evidence assessed by GRADE criteria was moderate (Supplementary Table 1).

3.3. Response, remission and acceptability of treatment

The meta-analysis for response, remission and acceptability was summarized in Fig. 2. For comparison of high frequency rTMS (HF rTMS) with ECT, 48.7% (56/115) subjects in HF rTMS group and 64.4%

Table 1
List of randomized controlled studies comparing rTMS and ECT for major depression: demographic, clinical characteristics and treatment parameters.

Authors year (Ref. #)	Design	Treatment groups	Diagnosis	N (M/F)	Mean age (SD)	Stimulus intensity	Fre (Hz)	Train duration (s)	No. of trains	Pulses per session	Total sessions	Drug free
Eranti et al. (2007)	Randomized controlled trial, single blind	LDLPFC rTMS	2 BD, 22 MD (4 psychotic)	24 (8/16)	63.6 (17.3)	110% MT	10	5	20	1500	13.7 ± 2.7 (range 5–15)	No
		RUL ECT and BL ECT	2 BD, 20 MD (3 psychotic)	22 (6/16)	68.3 (13.4)	1.5× seizure threshold for BL ECT and 2.5 × seizure threshold for RUL ECT					6.3 ± 2.5 (range 2–10)	No
Grunhaus et al. (2000)	Open and randomized	LDLPFC rTMS	MD (9 psychotic)	20 (8/12)	58.4 (15.7)	90% MT	10	2 (8 patients), 6 (12 patients)	20	400−1200	20	Clonazepam (1–2 mg/day)
		12 RUL ECT only; 8 RUL and BL ECT	MD (10 psychotic)	20 (6/14)	63.6 (15.0)	2.5× seizure threshold and increased progressively					9.6 (range 7–14)	No
Grunhaus et al. (2003)	Single-masked raters and randomized	LDLPFC rTMS	MD (non-psychotic)	20 (6/14)	57.6 (13.7)	90% MT	10	6	10	1200	20	Lorazepam (3 mg/day)
		13 RUL ECT only; 7 RUL and BL ECT	MD (non-psychotic)	20 (5/15)	61.4 (16.6)	2.5× seizure threshold and increased progressively					10.3 ± 3.1 (range 4–13)	Lorazepam (3 mg/day)
Hansen et al. (2011)	Open, randomized controlled trial	RDLPFC rTMS	4 BD, 26MD (5 psychotic)	30 (7/23)	46 (NA)	110%	1	NA	NA	NA	15	No
		RUL ECT	4 BD, 26MD (8 psychotic)	30 (11/19)	52 (NA)						9	No
Janicake et al. (2002)	Open and randomized	LDLPFC rTMS	4 BD (1 psychotic) 10 MD (2 psychotic)	15 (11/4)	42.9 (12.9)	110%	10	5	20	1000	10–20	Minimal rescue medications
		BL ECT	4 BD (3 psychotic) 7 MD (3 psychotic)	11 (6/5)	42.7 (14.0)						4–12	
Keshtkar et al. (2011)	Randomized controlled trial, open	LDLPFC rTMS	MD	33 (13/20)	34.0 (9.9)	90%		NA	10	408	10	No
		BL ECT	MD	40 (8/32)	35.6 (8.1)	MECT					10	No
Pridmore et al. (2000)	Single-masked raters and randomized	LDLPFC rTMS	11MD, 5 BD	16 (4/12)	44.0 (11.9)	100% MT	20	2	30–35	1200–1400	12.2 ± 3.4	No
		RUL ECT	15MD, 1 BD	16 (3/13)	41.5 (12.9)	504 mC				30	6.2 ± 1.6	No
Rosa et al. (2006)	Single-masked raters and randomized	LDLPFC rTMS	MD (non-psychotic)	20 (8/12)	41.8 (10.2)	100% MT	10		25	2500	20	Yes
		RUL ECT and BL ECT*	MD (non-psychotic)	15 (8/7)	46.0 (10.6)	1152 mC					4 weeks	Yes
Wang et al. (2004)	Single-masked raters and randomized	LDLPFC rTMS	MD	18 (7/11)	31.0 (5.0)	70% MT	20	5	35	500	7	NA
		BL ECT	MD	18 (8/10)	32.0 (6.0)						6–10	NA
Dannon et al. (2002)	Open and randomized	LDLPFC rTMS	MD (2 psychosis)	21 (7/14)	56.85 (15.27)	90% MT	10	2 (8 patients), 6 (12 patients)	20	1200	20	Clonazepam (3 mg/day)
		12 RUL ECT only; 8 RUL and BL ECT	MD (6 psychosis)	20 (6/14)	57.43 (16.66)	2.5× seizure threshold and increased progressively					9.6 (range 7–14)	No

Abbreviations: ECT, electroconvulsive therapy; rTMS, transcranial magnetic stimulation; BL, bilateral; RUL, right unilateral; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; BD, bipolar depression;MD, major depression; MT, motor threshold; Fre, frequency; NA, not available.

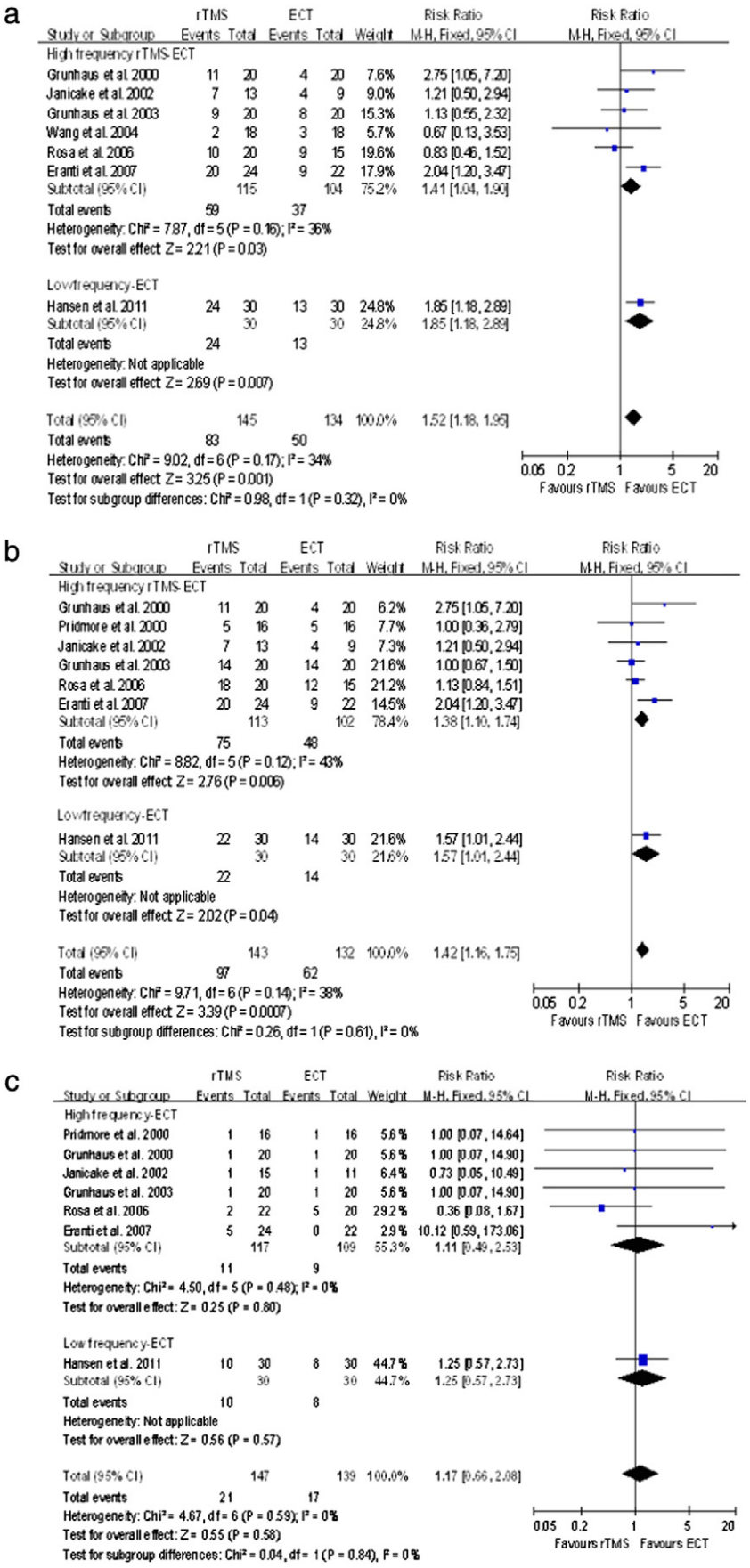

Fig. 2. Meta-analysis of repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT). (a) Response. (b) Remission. (c) Acceptability. Please note that events shown in this plot refer to lack of response, remission and all-cause discontinuation (numerically higher in rTMS group than in ECT group).

(67/104) in ECT group respectively were classified as responders to treatment. When compared low frequency rTMS (LF rTMS) with ECT, 20% (6/30) subjects in LF rTMS group and 56.7% (17/30) in ECT group were considered as responders. The pooled RR for clinical response of HF rTMS with ECT and LF rTMS with ECT was 1.41 [95% confidence interval (CI) = 1.04–1.90, Z = 2.21, N = 6, p = 0.03] and 1.85 [95% CI = 1.18–2.89, Z = 2.69, N = 1, p = 0.007] respectively, both comparisons indicating a significant difference in outcome favoring ECT therapy (Fig. 2a). We did not find significant heterogeneity between studies and subgroups (Chi^2 = 9.02, df = 6, I^2 = 34%, p = 0.17).

Totally, more patients were classified as remitters at the end of study in ECT group than rTMS group [53.0% (70/132) versus 32.2% (46/143, of which, 38 subjects were treated with HF rTMS and 8 subjects were treated with LF rTMS), respectively]. The pooled RR for remission was 1.38 for HF rTMS compared with ECT (95% CI = 1.10–1.74; Z = 2.76; N = 6, p = 0.006) and 1.57 for LF rTMS compared with ECT (95% CI = 1.01–2.44; Z = 2.02; N = 1, p = 0.04) favoring ECT (Fig. 2b). Heterogeneity between subgroups did not exceed that expected by chance (Chi^2 = 9.71, df = 6, I^2 = 38%, p = 0.14).

As shown in Fig. 2c, no significant difference in acceptability of treatment was observed between rTMS and ECT [14.3% (21/147) versus 12.2% (17/139), respectively]. The pooled RR comparing HF rTMS with ECT from 6 studies was 1.11 (95% CI = 0.49–2.53, Z = 0.25, p = 0.80). When compared LF rTMS with ECT, the RR from 1 study was 1.25 (95% CI = 0.57–2.73, Z = 056, p = 0.57). No significant heterogeneity between studies (Chi^2 = 4.50, df = 5, I^2 = 0%, p = 0.48) and subgroups (Chi^2 = 4.67, df = 6, I^2 = 0%, p = 0.59) was found. Furthermore, the associated funnel plots were reasonably symmetrical suggesting a low risk of publication bias for all analysis.

3.4. Mental state

Data of mental state outcomes (continuous measures) of the endpoint scores on HAMD, BDI and BPRS were extracted and analyzed.

Seven studies (n = 251; 131 in the HF rTMS group and 120 in the ECT group) and one study contributed to the comparison of HF rTMS with ECT and LF rTMS with ECT respectively. Heterogeneity among subgroups within this analysis exceeded that expected by chance, implying that the variance among the effect sizes was greater than expected by sampling error (Chi^2 = 19.64, I^2 = 64%, p = 0.006). So random effects model was used to perform pooled analysis. The pooled MD between HF rTMS and ECT was 2.15 (95% CI = −0.50–4.81, p = 0.11), indicating that there was no significant difference in outcomes between HF rTMS and ECT. However, the LF rTMS was significant superior to ECT (p = 0.0002) (Fig. 3).

Two studies with an overall size of 78 patients (n = 38 for ECT group and n = 40 for HF rTMS) contributed to the analysis of average endpoint score for BDI. The pooled MD for HF rTMS versus ECT was 10.41 (95% CI = 5.02–15.79; p = 0.0002), indicating a significant difference in outcome favoring ECT (Supplementary Fig. 3). No studies contributed to the comparison of LF rTMS with ECT.

Four studies contributed to the average endpoint score analysis for BPRS with an overall size of 148 patients (n = 71 for ECT group, n = 77 for HF rTMS). The results showed a MD of 2.66 (95% CI = 0.08–5.24, p = 0.04), indicating a significant difference in favor of ECT (Supplementary Fig. 4).

4. Cognitive function

Five studies (Eranti et al., 2007; Grunhaus et al., 2000, 2003; Hansen et al., 2011; Rosa et al., 2006) reported on cognitive performance. Of these, three (Eranti et al., 2007; Grunhaus et al., 2000, 2003) reported on global cognitive performance as measured by Mini-Mental State Examination (MMSE). Pooled estimate from these studies revealed no difference in MMSE between rTMS and ECT (MD = 0.65; 95% CI = −0.51–1.82; p = 0.27, Supplementary Fig. 5). The heterogeneity of these studies was insignificant (Chi^2 = 2.03, p = 0.36, I^2 = 2.0%).

Rosa et al. (2006), Eranti et al. (2007) and Hansen et al. (2011) conducted the neuropsychological evaluation tests. We organized these outcomes into several variables that were independently meta-analyzed and presented according to several familiar cognitive domains (Semkovska and McLoughlin, 2010) (Supplementary Table 2). No significant difference was found in almost the entire cognitive spectrum except in the following variables: verbal fluency-animals (p = 0.001), Rey complex figure-copy (p = 0.02), Rey complex figure-delayed recall (p < 0.0001). These findings suggested that after treatment, the ECT group were significant more impaired on measure of visual memory and aspects of executive functioning (verbal fluency), in comparison to the rTMS group.

5. Side effects

Most of the studies reported the side effect profile of rTMS and ECT except Dannon et al. (2002) and Rosa et al. (2006). There were no significant adverse events (e.g., seizures) and generally only mild side effects were reported in the rTMS group. Four studies reported the numerical data about adverse events (Grunhaus et al., 2000, 2003; Hansen et al.,

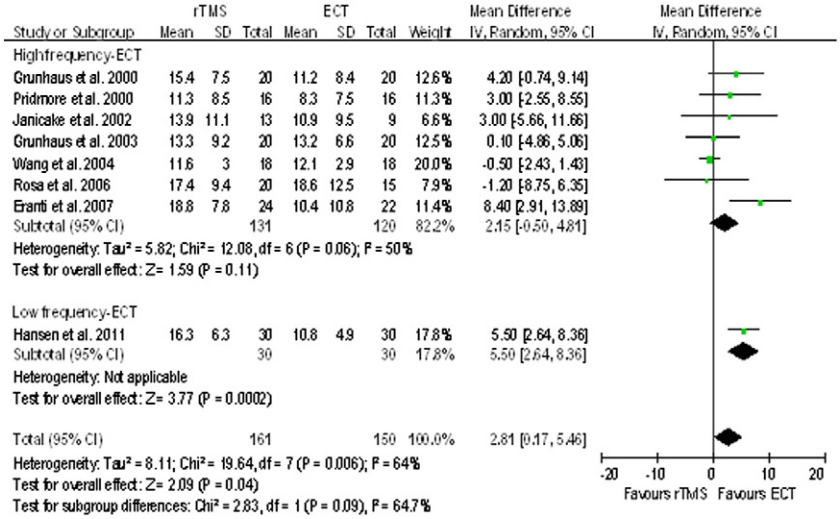

Fig. 3. Forest plot of continuous HAMD score differences between repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT). SD: Standard deviation. 2 studies contributing to significant heterogeneity were dropped from this analysis (please see the text for more information).

2011; Janicak et al., 2002) of rTMS. Altogether, in rTMS froup, 17.0% (9/53, data from Grunhaus et al., 2000, 2003 and Janicak et al., 2002) of subjects experienced mild headache, 10% (2/20, data from Grunhaus et al., 2003) of patients suffered from sleep disturbance; 46.2% (6/13, data from Janicak et al., 2002) patients experienced facial twitching and erythema, 30.8% (4/13, data from Janicak et al., 2002) patients felt nervousness or anxiety. 27.9% (12/43, data from Hansen et al., 2011 and Janicak et al., 2002) patients suffered from pain or discomfort. No special numerical recording of side effects were reported in ECT group.

Pridmore et al. (2000) performed side effect rating a self-developed shortened version of the Columbia ECT subjective side effects schedule. Eranti et al. (2007) modified this scale to included potential rTMS side effects. The pooled results on this measure from these two studies resulted in MD = 0.19 (95% CI = −1.84–2.22, p = 0.85), suggesting no significant difference between rTMS and ECT. Significant heterogeneity was found in this analysis ($Chi^2 = 4.16$, p = 0.04, $I^2 = 76\%$).

6. Psychotic symptoms

We also examined whether the RR for response and remission differed in trials that included patients with psychotic depression (Supplementary Figs. 6 and 7). Of the ten studies included in this meta-analysis, six included mixed samples of subjects with psychotic depression (Dannon et al., 2002; Eranti et al., 2007; Grunhaus et al., 2000; Hansen et al., 2011; Janicak et al., 2002; Pridmore et al., 2000), and two with only non-psychotic depression (Grunhaus et al., 2003; Rosa et al., 2006). Two studies had no details on the psychotic status. Meta-analysis was conducted to compare studies including mixed samples and non-psychotic samples. Results for remission and response suggested that ECT was more effective than HF rTMS in studies including mixed samples of subjects i.e. in the presence of psychosis (response rate: 66.7% and 33.3% respectively); while HF rTMS was as effective as ECT in non-psychotic samples (response rate: 51.4% for ECT and 52.5% for HF rTMS).

7. Discussion

In this systematic review and meta-analysis, 10 reports of 9 trials involving 425 participants were pooled. Our quantitative analysis found that ECT was more effective than rTMS for major depression, especially in short-term, particularly for patients with psychotic depression. There was less randomized evidence that the benefits are maintained in the long term. Furthermore, we found no significant between-group difference in all-cause discontinuation rates between the two treatments, suggesting comparable levels of acceptability. We found both rTMS and ECT were well tolerated with only minor side effects and no serious adverse events. The differences between rTMS and ECT for main outcome were summarized in Supplementary Table 3.

Unlike the categorical outcome of response and remission, the use of HAMD as a continuous measure provided equivocal results that did not favor HF rTMS over ECT. While the rTMS frequency used by Keshtkar et al. is unclear, Hansen et al. used a LF rTMS protocol. This raises the possibility that LF rTMS protocols may be less effective than ECT. The current evidence from Hansen et al. (2011) supports this notion. However, this finding should be interpreted with caution owing to the limited number of RCTs included in this comparison, especially given the observation placebo-controlled trials suggest that LF rTMS of right DLPFC (pooled effect size = 0.82) is at least as effective as HF rTMS applied to left DLPFC (pooled effect size = 0.53) (Slotema et al., 2010). In addition, given the shorter duration of stimulation, LF rTMS may have higher acceptability, though this needs to be investigated in clinical practice (Eche et al., 2012). Some evidence suggests that increasing stimulus intensities may improve the efficacy of rTMS while others refute this notion (Herrmann and Ebmeier, 2006; Hovington et al., 2013; Loo et al., 1999). In a recent meta-analysis, Jing Xie et al. (2013) included the same studies as ours, to investigate the effects of stimulus parameter on rTMS versus ECT. They concluded that rTMS of 20 Hz, ≥1200 pulses per day, ≥100% MT, four-week treatment period may be as efficacious as ECT. We suggest that future research comparing rTMS versus ECT take these observations into consideration (Xie et al., 2013).

Previous studies have shown that while ECT can adversely affect cognition, rTMS either has no adverse effects or some positive effects on cognition (Eranti et al., 2007). In the present meta-analysis, data on cognitive functioning were far from comprehensive. Findings on MMSE suggested that the ECT-treated patients' cognition performance did not differ with the rTMS-treated patients, However, MMSE is not particular sensitive to frontal-executive dysfunction in depressed patients and not specific to cognitive domains that are most affected by neuromodulation approaches (Dunne and McLoughlin, 2012). We combined data from more detailed neuropsychological tests when available, especially to evaluate memory deficits, which are often seen with ECT. While there was no significant difference between the two interventions for most of the cognitive domains, patients receiving ECT were significantly more impaired on visual memory and aspects of executive functioning (verbal fluency). Only visual memory performance improved specifically in response to rTMS treatment (Hansen et al., 2011). Although Hansen et al. (2011) found both groups improved on tests of psychomotor speed and attention, this improvement was significant neither between groups nor within groups when compared with their own performance before treatment. Contrarily, Eranti et al. (2007) reported there was a modest but significant improvement in attention and orientation in ECT group, but no differences were detected on the subscale for anterograde or retrograde memory. However, caution is warranted in interpreting these cognitive findings in light of small group size (Eranti et al., 2007). Taken together, these studies highlight the potential problem of different types of memory disturbance after ECT and the need for further rigorous research (Eranti et al., 2007). The current evidence does not provide a quantitative estimate of the degree of long-term cognitive impairment associated with ECT precluding any inferences on their persistence. Measuring changes in cognitive functions, especially in executive functions and visual memory, would be required in future trials to conclusively establish the cognitive gains on rTMS compared to ECT.

The evolution of ECT as a safe and effective intervention took several decades; still a number of unanswered questions exist regarding side effects and stimulus delivery. While the progress with rTMS has also been slow (Eranti et al., 2007) the optimal parameters for rTMS treatment are being actively sought. At present, both neuromodulation approaches are primarily employed as adjuncts for patients who are already medicated. Systematic investigations will be required in the future to select suitable pharmacological agents for combining with ECT/rTMS. The results of the current meta-analysis cannot be generalized to drug-naïve population or patients with less resistant or less severe forms of depression.

Unlike previous meta-analyses on this topic (Berlim et al., 2013; Burt et al., 2002), our review (1) searched a larger database that included studies reported in Chinese language (2) included nearly 46% more subjects (n = 294 in Berlim et al., compared to n = 429 in our study) (3) had broader inclusion criteria, studying the effects of both high and low frequency rTMS (4) considered the effect of variables that could influence patient selection in clinical practice such as side effects, cognitive effects, presence of psychosis and the effect on long-term outcomes. In addition, we also followed GRADE recommendations to assess the quality of individual trials.

7.1. Limitations

There are a number of shortcomings that should be considered when interpreting the results of this meta-analysis. First, the included studies enrolled a relatively small number of patients with depression. Overall, only ten studies were included for meta-analysis. Second, owing to the relatively small number of trials, we were unable to assess the differential effectiveness of rTMS and ECT in unipolar and bipolar depression or

when they are used as an augmentation strategy with medication or as a monotherapy for depression. Third, recent works suggest a number of methods that can be employed to optimize outcomes from rTMS treatment, e.g. neuro-navigation (Fitzgerald et al., 2009), connectivity based targeting (Fox et al., 2012). None of the studies considered here employed these procedures to improve the effect of rTMS. Fourth, loss of rater blinding is a potential source of bias. Finally, the differential effects of rTMS and ECT on a number of other patient-relevant outcomes such as quality of life, relapse prevention etc. and economic outcomes have not been considered in the RCTs included in this meta-analysis.

7.2. Implications

7.2.1. Clinical practice

The information in this review suggests that ECT is more effective than rTMS, especially for patients with psychotic depression, particularly when aiming for response or remission in the short term. However, the current data is unable to support the superiority of one treatment over the other when outcomes beyond one month are considered.

7.2.2. Future research

All included trials are generally small, and a large and high quality randomized trial is required to quantify both the benefits and risks. We call for future trials to (1) provide a clear description of randomization, allocation concealment and blinding (2) include clinically meaningful outcomes such as relapse, admission to hospital, quality of life, satisfaction with care (3) investigate the medium and long term effects (4) investigate the effectiveness of low frequency right DLPFC rTMS in comparison with ECT (5) report individual data for psychotic and non-psychotic subjects (6) consider rTMS protocols optimized for target selection as well as stimulus parameters.

This systematic review and meta-analysis is registered at the International prospective register of systematic reviews (CRD42012002701).

Acknowledgments

We would like to thank Stephanie Sampson for her helpful comments on a previous version of the manuscript.

This research was supported partly by grants from Research Leadership Development Plan of the City of Shanghai (XBR2011005) and Shanghai Key Laboratory of Psychotic Disorders (13dz2260500) for Chunbo Li, Wellcome Research Fellowship (WT096002/11/Z) for Lena Palaniyappan and Shanghai Health Bureau Youth Project (20124Y053, 2013SY003) for Juanjuan Ren and Jijun Wang.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2014.02.004.

References

Bauer MWP, Angst J, Versiani M, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 2002;3:5–43.

Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med 2012:1–10.

Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety 2013;30:614–23.

Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol 2002;5:73–103.

Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. ECT in bipolar and unipolar depression: differences in speed of response. Bipolar Disord 2001;3:95–104.

Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals — preliminary report. Biol Psychiatry 2002;51:687–90.

Di Lazzaro V, Pilato F, Saturno E, Oliviero A, Dileone M, Mazzone P, et al. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. J Physiol 2005;565:945–50.

Dunne RA, McLoughlin DM. Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. World J Biol Psychiatry 2012;13:248–58.

Eche J, Mondino M, Haesebaert F, Saoud M, Poulet E, Brunelin J. Low- vs high-frequency repetitive transcranial magnetic stimulation as an add-on treatment for refractory depression. Front Psychiatry 2012;3:13.

Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry 2007;164:73–81.

Fink M, Taylor MA. Electroconvulsive therapy: evidence and challenges. JAMA 2007;298:330–2.

Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003;60:1002–8.

Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology 2009;34:1255–62.

Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012;72:595–603.

George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. Am J Psychiatry 2011;168:356–64.

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67:507–16.

Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry 2000;47:314–24.

Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry 2003;53:324–31.

Hansen PE, Ravnkilde B, Videbech P, Clemmensen K, Sturlason R, Reiner M, et al. Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. J ECT 2011;27:26–32.

Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. J Clin Psychiatry 2006;67:1870–6.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

Higgins JPT, Green S, The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions version 5.2. www.cochrane-handbook.org, 2012. [Available from].

Hovington CL, McGirr A, Lepage M, Berlim MT. Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med 2013;45:308–21.

Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. J Clin Psychiatry 2004;65:485–91.

Janicak PG, Martis B. Strategies for treatment-resistant depression. Clin Cornerstone 1999;1:58–71.

Janicak PG, Davis JM, Gibbons RD, Ericksen S, Chang S, Gallagher P. Efficacy of ECT: a meta-analysis. Am J Psychiatry 1985;142:297–302.

Janicak PG, Easton MS, Comaty JE, Dowd S, Davis JM. Efficacy of ECT in psychotic and non-psychotic depression. Convuls Ther 1989;5:314–20.

Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry 2002;51:659–67.

Kelsey JE. Achieving remission in major depressive disorder: the first step to long-term recovery. J Am Osteopath Assoc 2004;104:S6–S10.

Keshtkar M, Ghanizadeh A, Firoozabadi A. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. J ECT 2011;27:310–4.

Lingeswaran A. Repetitive transcranial magnetic stimulation in the treatment of depression: a randomized, double-blind, placebo-controlled trial. Indian J Psychol Med 2011;33:35–44.

Lisanby SH. Electroconvulsive therapy for depression. N Engl J Med 2007;357:1939–45.

Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry 1999;156:946–8.

McClintock SM, Brandon AR, Husain MM, Jarrett RB. A systematic review of the combined use of electroconvulsive therapy and psychotherapy for depression. J ECT 2011;27:236–43.

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62:1208–16.

Pal PK, Hanajima R, Gunraj CA, Li JY, Wagle-Shukla A, Morgante F, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on interhemispheric inhibition. J Neurophysiol 2005;94:1668–75.

Pallanti S, Bernardi S. Neurobiology of repeated transcranial magnetic stimulation in the treatment of anxiety: a critical review. Int Clin Psychopharmacol 2009;24:163–73.

Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. Int J Neuropsychopharmacol 2000;3:129–34.

Rodriguez-Martin José L, Barbanoj José M, Schlaepfer TE, Clos Susana SC, Pérez V, Kulisevsky J, et al. Transcranial magnetic stimulation for treating depression. Cochrane Database Syst Rev 2009;4(No.: CD003493). http://dx.doi.org/10.1002/14651858.CD003493.

Rosa MA, Lisanby SH. Somatic treatments for mood disorders. Neuropsychopharmacology 2012;37:102–16.

Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. Int J Neuropsychopharmacol 2006;9:667–76.

Rose D, Fleischmann P, Wykes T, Leese M, Bindman J. Patients' perspectives on electroconvulsive therapy: systematic review. BMJ 2003;326:1363.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001;285:1299–307.

Schünemann HJ, OA, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: interpreting results and drawing conclusions. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions; 2008. p. 359–83.

Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009;39:65–75.

Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry 2010;68:568–77.

Slotema CW, Blom JD, Hoek HW, Sommer IEC. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71:873–84.

Wang XM, Yang DB, Yu YF, Huang H, Zhao XQ. A controlled study of the treatment of repetitive transcranial magnetic stimulation in patients with major depression. Zhongguo Linchuang Kangfu 2004;8:770–1.

Xie J, Chen J, Wei Q. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a meta-analysis of stimulus parameter effects. Neurol Res 2013;10:1084–91.