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COMPARING THE ANTI-DEPRESSIVE EFFECT OF ELECTROCONVULSIVE THERAPY (ECT) VERSUS TRANSCRANIAL MAGNETIC STIMULATION (TMS) IN THE TREATMENT OF PATIENTS WITH DEPRESSION

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SUMMARY

Background: *Electroconvulsive therapy (ECT) is one of the most effective treatments for depressive disorders. However, ECT has a number of limitations, such as significant side effects in the neurocognitive domain and the requirement for general anesthesia. Transcranial magnetic stimulation (TMS) is an intervention that applies electric stimulation to the brain without causing convulsions, thus representing an attractive alternative to ECT. The aim of our study is to review systematic reports of the effectiveness of ECT and TMS in the treatment of depressive spectrum disorders.*

Subjects and methods: *We performed search queries in PubMed and eLibrary databases, which retrieved 391 articles, of which 14 met our inclusion criteria for the analysis. The articles comprised three comparisons: TMS vs SHAM, ECT vs sham ECT (SECT), and ECT vs PHARM. The protocol parameters analyzed for TMS were coil type, targeted brain area, amplitude of resting motor threshold, duration of session, number of sessions in total and per week, number and pulses per session and inter-train pause. For ECT, we evaluated the type of ECT device, targeted brain area, type of stimuli, and for ECT vs PHARM we recorded types of anesthesia and antidepressant medication.*

Results: *Three of 6 studies showed a therapeutic effect of TMS compared to placebo; efficacy was greater for TMS frequency exceeding 10 Hz, and with stimulation of two areas of cerebral cortex rather than a single area. There was insufficient data to identify a relationship between the success of TMS and intertrain pause (IP). Three of four studies showed a therapeutic effect of ECT compared to placebo. Three studies of bilateral ECT showed a significant reduction in depression scores compared to the SECT groups. ECT protocols with brief pulses were generally of lesser efficacy. Four of 5 ECT vs PHARM studies showed superior efficacy of ECT compared to PHARM. Among several antidepressants, only the ketamine study showed greater efficacy compared to ECT.*

Conclusions: *There of six TMS studies and 7 of 9 ECT studies showed efficacy in reducing depressive symptoms. A prospective study of crossover design might reveal the relative efficacies of ECT and TMS.*

Key words: *antidepressive effect - depressive disorder – electroconvulsive therapy - systematic review - transcranial magnetic stimulation*

Abbreviations: *DLPFC, VLPFC - dorsolateral or ventrolateral prefrontal cortex; TMS – transcranial magnetic stimulation; dTMS, rTMS - deep or repetitive transcranial magnetic stimulation; ECT – electroconvulsive therapy; SECT – sham electroconvulsive therapy; IP – intertrain pause; PPS - pulses per a session; PHARM – pharmacological treatment; RMT – resting motor threshold; NS – number of session*

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INTRODUCTION

Numerous clinical studies have demonstrated superiority of electroconvulsive therapy (ECT) over placebo for the treatment of depressive disorders, particularly in cases of severe drug-resistant depression (Abdel Latif et al. 2020). As such, ECT is one of the most effect treatments for depressive disorders. Furthermore, ECT may have a superior safety profile compared to antidepressant pharmacotherapy in patient groups such as pregnant women, adolescents, and the elderly. However, ECT calls for temporary anesthesia, and can produce transient impairments in cognition and memory (Ren et al. 2014), which together bring a significant stigmatization against its use in clinical practice (Buchholtz et al. 2020).

Transcranial magnetic stimulation (TMS) utilizes local electromagnetic stimulation of the cerebral cortex, without inducing a general seizure, and may thus be preferable to ECT in the treatment of depression. Numerous studies have demonstrated the superiority of TMS over placebo, and highlighted to relative lack of adverse side effects (Ren et al. 2014). While there have been several clinical trials aiming to compare the effectiveness and safety of ECT and TMS, the available data do not support strong conclusions due the generally small patient sample sizes. Therefore, we undertook a systematic review of the literature, aiming to establish better the relative efficacies of the procedures as compared to placebo or pharmacotherapy in patients with depression spectrum disorders.

METHODS

We conducted searches in PubMed and e-Library databases using the keywords "TMS AND depression," "ECT AND depression", "ECT versus TMS AND depression" and "ECT versus sham ECT (SECT) AND depression". The inclusion criteria for our analysis were as follows: the usage of TMS in the therapy of depressive disorders, evaluation of the reduction in depressive symptoms using scales such as HDRS or MADRS, sham-controlled study design for both ECT and TMS, and open-label studies only for ECT. The exclusion criteria were as follows: studies involving non-depressive disorders, studies with fewer than two psychiatric assessments, absence of data on TMS parameters and depression score changes after treatment, studies without reported results, trials or reviews predating 2013 (no such limitation for the ECT versus SECT protocol due to a lack of studies published over the past decade), studies with abstracts only, and studies focusing solely on neurocognitive effects. We identified a total of 391 articles, out of which 14 were included in our analysis. We categorized these 14 studies into three groups: TMS vs SHAM, ECT vs SECT, and ECT vs PHARM.

In our analysis, we considered the following parameters for TMS: coil type, targeted brain area, amplitude of resting motor threshold (RMT), duration of each session, number of session (NS) – total and per week, number of pulses per session (PPS) and inter-train pauses (IP). For ECT, we analyzed the following parameters: type of ECT device, targeted brain area, type of stimuli (brief or ultra-brief), and the type of antidepressant medication or acute anesthesia used in studies comparing ECT vs PHARM.

RESULTS

Most of the TMS studies targeted the left dorsolateral prefrontal cortex (dlPFC) as the stimulation point (except for Kaster et al. 2018, who chose both left ventrolateral prefrontal cortex (vlPFC) and dlPFC). The total number of sessions ranged from 20 to 30, with an applied TMS frequency of 10 Hz (except for Kaster et al. 2018, who used 18 Hz) and an amplitude set at 120% of the RMT. The parameters such as PPS and IP differed substantially between studies (Table 1).

The TMS protocol by Croarkin et al. (2021) included 3000 PPS and a 26-second IP for unilateral repetitive TMS (rTMS), but did not specify the type of coil. Furthermore, there was no significant difference between the reduction in Hospital Anxiety and Depression Scale (HADS) scores between active TMS (from 28.8 to 18.1) and sham TMS (from 29.5 to 19.2) groups, thus indicating a lack of efficacy. Similarly, Taylor et al. (2018) did not find a specific effect of rTMS in improving the Montgomery-Asberg Depression Rating Scale (MADRS) scores compared to placebo. Although their study protocol was similar to that in other reports, they did not provide specific information about IP.

Siddiqi et al. (2019) used a double 70 mm air-cooled coil for active TMS and a double 70 mm Alpha sham coil for placebo. They administered bilateral dlPFC stimulation with 4000 left-sided excitatory pulses and 1000 right-sided inhibitory pulses, providing 5-second trains and a 20-second IP. Their active treatment group showed greater improvement in MADRS scores compared to the sham group (Cohen's d = 1.43).

Yesavage et al. (2018) used Cool-B65-A/P coil for active rTMS in a protocol including 4000 PPS unilaterally. However, there were no clinically significant effects in either the active treatment group (40.7% of participants achieved remission) or the placebo group (37.4% achieved remission).

Kaster et al. (2018) applied a deep TMS protocol entailing H1 and H1L coils with a 2-second pulse train, and 167 trains with a 20-second IP, resulting in a total of 6012 PPS over 61 minutes. Their remission rate was significantly higher in the active dTMS group compared to the sham group (40.0% vs. 14.8%).

Tsukarzi et al. (2015) directly compared the efficacy of rTMS versus ECT. Their protocol included 12 NS of TMS provided on the F7 and F8 areas at the left dlPFC with a frequency of 15 Hz, an amplitude of 100% of the patient's RMT, 6-second trains, and a 60-second IP, with each session lasting 20 minutes (20 trains and PPS 1800 in total). They conducted an average of 6-8 ECT sessions per patient, with general anesthesia. Their study indicated as a significant improvement in CGI-I scores in 19 of 37 patients (51.5%) in the rTMS group and in 22 of 34 patients (64.7%) in the ECT group (Table 2).

We analyzed the ECT studies in two groups: ECT vs sham ECT (SECT) and ECT vs antidepressant pharmacotherapy (PHARM).

Table 1. Summary of the TMS protocols' parameters used across the original studies targeting the depressive disorders

Authors	Patients sample size (age, diagnosis)	Type of the coil used	Brain area of stimulation	Sessions' schedule	Assessments	Efficacy
Croarkin et al. (2021)	102 (12-21 y.o.), MDD	No data	left DLPFC	30 sessions (evaluating - baseline, four weeks, six weeks). Frequency 10 Hz. Amplitude 120% of the patient's RMT, PPS 3000. time of session (min) – 37.5 min (75 trains), IP 26 sec.	HDRS, MADRS, CDRS-R, CGI-S, QIDS-A17-SR	There were no statistically significant differences in clinical outcomes between the active TMS and sham TMS groups.
Yesavage et al. (2018)	164, (18-80 y.o.), MDD	Cool-B65-A/P	left DLPFC	20-30 sessions (baseline, 3 weeks). Frequency 10 Hz. Amplitude 120% of the patient's RMT. PPS 4000, time of session n/a, IP n/a, number of trains n/a.	HDRS, MADRS, BDI-II	There was no evidence of difference in remission rates between the active and sham treatments.
Siddiqi et al. (2019)	32, (18-65 y.o.), MDD induced by TBI	double 70-mm air-cooled coil and double 70-mm Alpha sham coil	bilateral DLPFC	20 sessions (baseline, 5 weeks). Frequency 10 Hz. Amplitude 120% of the patient's RMT. 5-sec trains and 20-sec IP, PPS 4000 left-sided excitatory pulses, 1000 right-sided inhibitory pulses.	MADRS	MADRS improvement was greater in the active treatment group than in the sham group (Cohen's d = 1.43).
Tsukarzi et al. (2015)	37 (16-85 y.o.), F32 (4), F33 (22), F31(11)	double ring butterfly coil	left DLPFC, F-7 and F-8	12 sessions. Frequency 15 Hz. Amplitude 100% of the patient's RMT. 6-sec trains and 60-sec IP. Time of one session - 20 min (20 trains), PPS 1800.	HDRS	The number of patients who achieved remission (≤ 7 points on the Hamilton scale) with TMS was 27.03%, and with ECT - 41.18% ($p < 0.05$).
Taylor et al. (2018)	32 (22-65 y.o.), MDD	No data	left DLPFC	20 sessions + №5 tapper sessions (5 days per week) Phase 1 MRI session, Phase 2 - rTMS. Frequency 10 Hz. Amplitude 120% of the patient's RMT. PPS 3000, time of session n/a, IP n/a number of trains n/a.	MADRS, HDRS17, QIDS-SR, WSAS	There was no significant effect of active rTMS over sham on the primary outcome measure (MADRS), with both groups improving over time, and no specific effect of rTMS (sham vs active) on connectivity.
Kaster et al. (2018)	52 (60-85 y.o.), MDD	H1 coil, H1 L-coil (the first six participants)	left DLPFC, left VLPFC	20 sessions (five times per week, four weeks and two extra weeks – twice per week - for early remitters). Frequency 18 Hz. Amplitude 120% of the patient's RMT, 2 s pulse train, 20 s IP, 167 trains, for a total of 6012 PPS over 61 min.	HDRS-24, SSI, HRQOL	Remission rate was significantly higher with active than sham rTMS (40.0% vs 14.8%)

Note: DLPFC – dorsolateral prefrontal cortex area; F31 - depression in bipolar disorder; F32 - single depressive episode; F33 - unipolar (recurrent) depression; IP – intertrain pause; MDD – major depressive disorder; MRI - Magnetic resonance imaging; TBI – Traumatic brain injury; PPS – pulses per a session; RMT – resting motor threshold; TMS – transcranial magnetic stimulation; VLPFC - ventrolateral prefrontal cortex area; Scales used and mentioned here in the order of presenting in the Table: Hamilton rating scale for depression (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Children's Depression Rating Scale, Revised (CDRS-R), Clinical Global Impression Scale (CGI), The Quick Inventory of Depressive Symptomatology, Adolescent Version (QIDS-A17-SR), Weinberg Screen Affective Scale (WSAS), Scale for Suicide Ideations (SSI), Health related quality of life (HRQOL)

Table 2. Summary of the ECT vs SECT protocols' parameters used across the original studies targeting the depressive disorders

Authors	Patients' sample size (age, diagnosis)	Type of the ECT device	Brain area of stimulation	Sessions schedule	Assessments	Efficacy
Brandon et al. (1984)	95 (mid age 53-44), Depression with delusions, Depression with retardation, Neurotic depression	Ectron Mark IV	bilateral temporal ECT	8 sessions (2 times a week), sine wave	HDRS, MADRS	On the HDRS the improvement in the group given real treatment was significantly greater than that in the group given simulated treatment both at two weeks (p=0.014) and four weeks (p=0.0001). At follow up at 12 and 28 weeks there was no difference between the treatment groups.
Gregory et al. (1985)	69, MDD	Ectron Duopulse Mark IV	1) bilateral temporal ECT; 2) unilateral temporo-parietal	6 sessions (2 times a week)	HDRS, MADRS, PIRS	Bilateral and unilateral ECT were both highly significantly better than simulated with ECT (SECT vs UNI p=0.013, SECT vs BI p<0.001, UNI vs BI p=0.05)
Lambourn & Gill (1978)	32 (36-68 y.o.), depressive psychosis	Ectron Duopulse Mark IV	unilateral ECT	6 sessions (3 times a week), brief	HDRS	Active ECT did not produce a significantly superior therapeutic effect when compared with a SECT
Freeman et al. (1978)	40 (20-70 y.o.), depressive illness	Ectron Mark IV	bilateral ECT	6~7 sessions (2 times a week), sine wave	HDRS, BDI, WSRQ, VAS	After two treatments all four measures indicate that the patients in group R and in group S after active ECT were significantly less depressed (P<0.005 for HDRS, WSRQ, VAS and BDI). No significant difference at the end of the study (see details here: ECT vs SECT group after one week (2 ECTs) - invalidating end of treatment data 4/20 in the ECT group, 0/20 the SECT group – have been withdrawn without improvement, and not included into the calculating means).

Note: ECT – electroconvulsive therapy; MDD – major depressive disorder; SECT – sham electroconvulsive therapy; Scales used as mentioned here in the order of presenting in the Table: Hamilton rating scale for depression (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Psychiatric Illness Rating Scale (PIRS), Beck's depression inventory (BDI), Wakefield Self-Report Questionnaire (WSRQ), Visual Analog Scale (VAS)

Read et al. (2019) reviewed 11 articles comparing the effectiveness of ECT with SECT, of which only 4 articles met our inclusion criteria. The authors of those studies used the Ectron Duopulse Mark IV as the ECT device. Three of the four studies conducted bilateral ECT (Brandon et al. 1984, Freeman et al. 1978, Gregory et al. 1985), whereas Lambourn and Gill (1978) employed unilateral electrode placement. All four groups of authors assessed depression scores using the HDRS, and two groups also utilized the MADRS (Brandon et al. 1984, Gregory et al. 1985). Additionally, Gregory et al. (1985) used the PIRS, while Freeman et al. (1978) employed the Beck Scale, Wakefield Scale, and VAS.

On average, the authors conducted 6-8 sessions of ECT in both the active treatment and the SECT groups. According to Brandon et al. (1984), the improvement in HDRS scores was significantly greater in the active ECT group compared to the SECT group at two weeks ($p=0.014$) and four weeks ($p=0.00001$) after the last session. Gregory et al. (1985) achieved much better results in the verum ECT group compared to the placebo treatment group. Notably, the use of unilateral or bilateral ECT did not show significant differences in effectiveness (SECT vs. UNI $p=0.013$, SECT vs. BI $p<0.001$, UNI vs. BI $p=0.05$). Lambourn and Gill (1978) failed to find a clinically significant difference between ECT and SECT.

Freeman et al. (1975) evaluated depression scores after 2, 4, and 6 sessions of ECT/SECT. Importantly, their "R" group (active ECT) received ECT throughout the study, while the "S" (sham) group received SECT only for the first two sessions and then switched to real ECT. After the second assessment, there was a significant group difference in the improvement of depressive symptoms ($P<0.005$ for Hamilton, Wakefield, VAS, and Beck scales), which exceeded the difference at the fourth assessment (Group “S” $p<0.001$ for HDRS and Wakefield, $p<0.05$ for VAS and Beck). By the sixth assessment, there was no statistically significant difference in psychometric scores between the two groups, likely due to the introduction of verum ECT “S”, and to the premature withdrawal of some participants from the "R" group.

We next consider some relatively new studies comparing ECT with pharmacological treatment. Weeks et al. (2013) conducted a study comparing ECT with isoflurane, while Basso et al. (2020) compared ECT with ketamine, and Schoeyen et al. (2015) compared ECT with Algorithm-Based Pharmacological Treatment (ABPT). In the case of ECT versus isoflurane, ECT demonstrated a slightly superior therapeutic effect. Relative to the pre-treatment assessment, the decline in depression scores on the HDRS-24 scale showed a significant difference ($p<0.0001$) for ECT and a smaller difference ($p<0.005$) for isoflurane.

Basso et al. (2020) found an antidepressant effect of ECT comparable to that seen in the ketamine treatment group. The response was much faster with ketamine, as there were no significant statistical differences in MADRS values at 2 weeks after ketamine, as compared to 4 weeks with ECT. McCall et al. (2018) divided their protocol into two parts: non-randomized ECT plus venlafaxine and randomized groups with ECT alone or ECT plus venlafaxine (VEN) and lithium (Li). The group that received ECT in addition to the pharmacotherapy showed better relief from depressive symptoms compared to the group without ECT (all $p<0.02$).

Schoeyen et al. (2015) compared the efficacy of ECT against ABPT. They applied right unilateral brief ECT with a Thymatron System IV device or MECTA 5000 device, NS 18. In their PHARM protocol, patients received one of the following medications: alimemazine, chlorpromazine, chlorprothixene, mianserin, oxazepam, zolpidem or zopiclone. Relative to baseline assessment, depression scores on the MADRS, IDS-C-30, and CGI scales at 3 and 6 weeks post-treatment points indicated a significant improvement in depression scores in 73.9% versus 35.0% among all participants (Table 3).

DISCUSSION

Three of 6 studies comparing the efficacy of TMS compared to placebo showed superiority of TMS. However, these studies suffered from small sample size, and instances of missing data regarding the type of coil used (Croarkin et al. 2021, Taylor et al. 2018). The protocols of Croarkin et al. (2021), Taylor et al. (2018) and Yesavage et al. (2018) used the same NS, frequency, RMT amplitude, and stimulation area, but differed with respect to coil types. While Croarkin et al. (2021) and Taylor et al. (2018) did not identify the coil type; Yesavage et al. (2018) used the Cool-B65-A/P coil. Additionally, there were differing numbers of PPs, with 3000 in Croarkin et al. (2021) and Taylor et al. (2018), and 4000 in Yesavage et al. (2018), as well as differences in the duration of treatment (6, 4, and 3 weeks, respectively). These studies did not indicate significant improvements in depression scores in the TMS group compared to the placebo group.

In contrast, Siddiqi et al. (2019), Tsukarzi et al. (2015), and Kaster et al. (2018) identified significant superiority of TMS compared to placebo. The TMS frequencies used in these studies (10 Hz - Siddiqi et al. 2019, 15 Hz - Tsukarzi et al, 2015, 18 Hz - Kaster et al. 2018) were generally higher than those in the previous protocols, which may support the use of frequencies exceeding 10 Hz for effective TMS responses. Siddiqi et al. (2019) and Kaster et al. (2018) used a common RMT and NS (120% and 20, respectively),

Table 3. Summary of the ECT vs PHARM protocols parameters used across the original studies targeting the depressive disorders

Authors	Patients sample size (age, diagnosis)	Type of the ECT device	Brain area of stimulation	Sessions' schedule	Assessments	Efficacy
Weeks et al. (2013)	28 (18-65 y.o.), 21 MDD+7 BPD	The MECTA spECTrum 5000	bifrontal ECT	8-12 sessions ECT vs 10 sessions of ISO anesthesia treatments over a 2.5–3.5 weeks period. 1) pretreatment, 2) 24–48 hours after the last treatment session (Post-treatment), and 3) 4 weeks after the last treatment session (Follow-up point). ECT is provided in 60–120 sec. Average ECT procedure time lasted 20 min, with 30–45 min required for post-procedure recovery. Average ISO procedure time lasted 40–45 min.	HDRS-24, QIDS-SR16	ECT demonstrated modestly better anti-depressive effect at follow-up in the severity-matched patients.
McCall et al. (2018)	120 (>60 y.o.), MDD	Somatics Thymatron System IV (0.25 ms), MECTA spECTrum device (0.3 ms)	right unilateral ECT	ECT: ultrabrief, six times the seizure threshold; Phase 1: acute ECT three times per week and oral VEN; Phase 2: remitted patients were randomized into two groups - VEN+Li or VEN+Li+ECT (4 times a week) and an additional ECT session was provided as needed	HDRS-24, HRQOL	Patients randomized to ECT and PHARM had significantly higher quality of life scores at the 24-week visit point compared to patients in the PHARM group.
Basso et al. (2020)	50 (31 y.o.), depressed (unnknown type)	MECTA 5000Q, ultra-brief pulse stimuli (0.3 ms)	right unilateral ECT	9-16 sessions ECT (~12, three times a week) vs 6-9 sessions using KET	MADRS	ECT and KET administration were equally effective, however, the anti-depressive effects of ketamine occurred faster.
Tsukarzi et al. (2015)	34 (19-64 y.o.) - F32 (5), F33 (20), F31(9)	«Elikon-O1M »	bilateral ECT	6-8 sessions (in 1-2 days) and general anesthesia	HDRS	The number of patients who achieved remission (≤ 7 points on the Hamilton scale) with TMS was 27.03%, and with ECT - 41.18% ($p<0.05$).
Schoeyen et al. (2015)	73 (26-79 y.o.), BD	Thymatron System IV device or MECTA 5000 device	right unilateral ECT	18 sessions brief ECT (three times a week) or ABPT (alimemazine 10–30 mg/day, chlorpromazine 25–50 mg/day, chlorprothixene 20–40 mg/day, mianserin 10 mg/day, oxazepam 15–45 mg/day, zolpidem 10 mg/day or zopiclone 7.5 mg/day). Assessments - baseline, 3 weeks point, 6 weeks point.	MADRS, IDS-C-30, CGI	The response rate was significantly higher in the ECT group than in the group that received ABPT (73.9% vs 35.0%).

Note: ABPT - algorithm-based pharmacological treatment; BD, BPD – bipolar disorder; ECT – electroconvulsive therapy; F31 - depression in bipolar disorder; F32 - single depressive episode; F33 - unipolar (recurrent) depression; KET – ketamine; Li – lithium; MDD – major depressive disorder; PHARM – pharmacological therapy; TMS – transcranial magnetic stimulation; VEN – venlafaxine; Scales used here mentioned in the order of presenting in the Table: Hamilton depression rating scale (HDRS), The Quick Inventory of Depressive Symptomatology, Adolescent Version (QIDS-A16-SR), Montgomery-Asberg Depression Rating Scale (MADRS), Health related quality of life (HRQOL); Inventory of Depressive Symptomatology (IDS-C), Clinical Global Impression Scale (CGI)

while Tsukarzi et al. (2015) used 100% RMT and 12 sessions. Protocols used dual coils, except for Kaster et al. (2018), who used H1 and H1L coils for deep TMS. It is also worth noting that these studies showing efficacy targeted two cortical regions: bilateral dlPFC in Siddiqi et al. (2019), left dlPFC F-7 and F-8 in Tsukarzi et al. (2015), and left dlPFC and left vlPFC in Kaster et al. (2018). Considering the small sample sizes, these results generally suggest superior efficacy TMS with two cortical targets.

Four of the 6 reports on TMS mentioned the duration of the IP. While Kaster et al. (2018), Croarkin et al. (2021), and Siddiqi et al. (2019) used an IP duration of 20-26 seconds; Tsukarzi et al. (2015) used 60 seconds. Due to the limited sample sizes, we cannot ascertain any relationship between the success of TMS and IP duration.

Three of the 4 TMS studies extracted from Read et al. (2019) reported efficacy of ECT compared to placebo. All 4 studies were conducted using the Ectron Mark IV device; two studies used sine wave stimulation, whereas Lambourn & Gill (1978) used a brief wave, and Gregory et al. (1985) did not specify the waveform. On average, these studies consisted of 6-8 TMS sessions. Brandon et al. (1984) and Freeman et al. (1978) used bilateral ECT, Lambourn & Gill (1978) used unilateral ECT, and Gregory et al. (1985) used both unilateral and bilateral ECT. Importantly, all studies with bilateral ECT reported a significant reduction in depression scores compared to the corresponding SECT groups. Gregory et al. (1985) reported efficacy of both unilateral and bilateral ECT compared to placebo, while Lambourn & Gill (1978) did not find significant efficacy. In summary, despite the typically small sample sizes, we conclude that bilateral ECT is significantly more effective than SECT, and seemingly superior to unilateral ECT. Furthermore, the use of brief pulses by Lambourn & Gill (1978) may have contributed to the lower efficiency of their approach. It is remarkable that, as noted by Read et al. (2019), there are no new studies comparing ECT and placebo since 1985. This highlights the need for sufficiently powered double-blind placebo-controlled studies.

Four of the 5 open label ECT vs PHARM studies showed comparable therapeutic responses to ECT. McCall et al. (2018) and Basso et al. (2020) applied ECT using ultra-brief pulses and Schoeyen et al. (2015) used brief pulses, while the other studies did not specify the type of pulses. Among the various types of antidepressants investigated, only ketamine proved superior to ECT with respect to depression scores (Basso et al. 2020). As with the other contrasts, the ECT vs PHARM studies suffered from small sample sizes, the heterogeneity of the antidepressant treatments and, most notably, the absence of blinding.

CONCLUSIONS

We undertook a literature search for articles reporting on the efficacy of TMS and ECT for treating various depression spectrum disorders. We found that the most effective TMS protocols involved the stimulation of two brain areas, specifically the bilateral dlPFC, left dlPFC F-7 and F-8, and left dlPFC and left vlPFC. These protocols also utilized a stimulation frequency above 10 Hz. Thus, cannot attribute the efficacy in those TMS studies to the one or the other factor, i.e. multiple targeting and high frequency. On the other hand, our analysis of studies comparing ECT with SECT suggests that protocols involving bilateral stimulation are more effective than those utilizing unilateral stimulation. Additionally, the study by Lambourn & Gill (1978) demonstrated insignificant effects of brief ECT pulses on depressive symptoms in comparison to SECT. Most studies comparing ECT with PHARM showed significantly higher efficacy compared to antidepressant therapy, with the exception that ketamine produced a greater response (Basso et al. 2020).

Overall, we find that 3 of 6 TMS studies (50%) and 7 of 9 ECT studies (78%) showed efficacy in reducing depressive symptoms compared to placebo treatment. As such, present data suggest a probable superiority of ECT compared to TMS, while calling for further prospective research (such as a placebo-controlled crossover study) aiming to establish more firmly the responses to TMS and ECT.

Limitations

Due to the heterogeneous designs of the analyzed studies and the generally low sample sizes, we see an obvious need for further clarification of the optimal parameters for TMS and ECT use in the treatment of depression.

Conflict of interest: *None to declare.*

Contribution of individual authors:

Oxana Chigareva, Daria Smirnova & Anna Gradinar have composed the primary idea and specified the hypothesis.

Oxana Chigareva & Arseny J. Gayduk: have been responsible for the literature data collection, its systematization and analysis, and wrote the first draft of the manuscript.

Daria Smirnova, Darya Astafeva, Olga Izmailova, Mikhail Sheyfer, Paul Cumming, & Alexander Sack managed the research documents formalization, detailed manuscript editing and revision, and gave their final approval of the manuscript for submission.

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