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Comparative Efficacy of Augmenting Escitalopram with Modified Electroconvulsive Therapy or High-Frequency Repetitive Transcranial Magnetic Stimulation on Depressive Symptoms, Quality of Life, and Cognitive Function in Treatment-Resistant Depression

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Treatment-resistant depression (TRD) poses significant therapeutic challenges despite available interventions. Escitalopram (ESC) is a highly selective antidepressant. This study aimed to compare ESC alone and ESC combined with modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in TRD patients. Ninety participants were randomized into ESC alone, ESC + MECT, and ESC + HF-rTMS groups. Notable differences were observed in Hamilton Depression Rating Scale (HDRS-17) scores at 12 weeks among ESC (14.37), ESC + MECT (10.27), and ESC + HF-rTMS (10.77) groups (P = 0.006). In terms of overall quality of life (QoL) evaluated using the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF) at 12 weeks, the ESC, ESC + MECT, and ESC + HF-rTMS groups scored 2, 3, and 3.5, respectively. ESC + MECT/HF-rTMS groups showed reduced depressive symptoms compared to the ESC group, accompanied by higher overall QoL scores and increased satisfaction with health. Patients receiving ESC + MECT demonstrated no significant alterations in short-term memory and orientation, as measured by the Montreal Cognitive Assessment (MoCA), before and after treatment. Moreover, a decline in language was observed compared to baseline (12 weeks: median 2, IQR 2-3; baseline: median 1, IQR 1-3; P = 0.022). The positive impact of ESC with HF-rTMS on cognitive function was evidenced by improvements in all domines MoCA. Combining ESC with MECT or HF-rTMS exhibited enhanced effectiveness in alleviating depressive symptoms and enhancing QoL compared to ESC monotherapy. Specifically, the ESC + HF-rTMS combination displayed potential as a comprehensive treatment strategy for TRD, addressing both emotional and cognitive aspects.

Keywords: escitalopram; high-frequency repetitive transcranial magnetic stimulation; modified electroconvulsive therapy; treatment-resistant depression
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Introduction

Depression affects 3.8-5.0% of the global adult population, accounting for approximately 280 million cases annually, with major depressive disorder (MDD) ranking as the fourth leading cause of the global disease burden (Vida et al. 2023). Despite first-line antidepressant treatments, approximately one-third of MDD patients experience treatment-resistant depression (TRD), characterized by a failure to achieve remission or response (Alkahtani et al. 2021). TRD has significant socio-economic consequences, including reduced work productivity and increased healthcare resource utilization (HCRU) (Yildiz et al. 2023). TRD, with its socio-economic consequences, has become a significant focus of clinical and research attention, highlighting the need for innovative therapeutic approaches.

Escitalopram (ESC), the S-enantiomer of citalopram, is a highly selective antidepressant used off-label for various conditions, including social anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress

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disorder, premenstrual dysphoric disorder, and vasomotor symptoms of menopause (Landy et al. 2023). Despite its efficacy in selectively binding to the human serotonin transporter, inhibiting serotonin reuptake, and evaluating serotonin levels in synaptic clefts (Ali and Lam 2011), its monotherapy effectiveness may be limited in TRD patients, prompting exploration of combination therapies (Krause-Sorio et al. 2020; Mi et al. 2021; Li et al. 2023).

Non-pharmacological treatments, encompassing physical therapies, primarily include interventions such as repetitive transcranial magnetic stimulation (rTMS), modified electroconvulsive therapy (MECT), vagus nerve stimulation, and deep brain stimulation (Papp et al. 2022). However, the surgical implantation requirement restricts the usage of vagus nerve stimulation and deep brain stimulation (Carpenter et al. 2006). Presently, rTMS and MECT are recognized and recommended for their efficacy and ease of implementation in addressing TRD. MECT, inducing seizures through electrical stimulation, aligns with guidelines from various countries (Nygren et al. 2023), and it has demonstrated significant efficacy in treating TRD patients (Cano et al. 2023). High-frequency rTMS (HF-rTMS), a non-invasive technique, is particularly recommended for MDD patients, especially those unresponsive to pharmacotherapies (Weissman et al. 2023; Yamazaki et al. 2023).

However, existing treatments for TRD exhibit notable limitations, often resulting in incomplete symptom relief or poor tolerability. This inadequacy necessitates more effective and better-tolerated treatment strategies to comprehensively address the complexities of TRD. Our study aims to bridge this gap by investigating the comparative impact of ESC monotherapy against combined approaches involving ESC with either MECT or HF-rTMS on depressive symptoms, cognitive function, and quality of life in TRD patients.

The urgency to explore innovative and integrated treatment methods that might offer improved outcomes for TRD patients drives this investigation. By evaluating the effectiveness of these combined therapeutic approaches, our study seeks to provide valuable insights that could potentially enhance the clinical management of TRD and inform future research initiatives.

Methods

Ethical statement

This study adhered to the principles of the Helsinki Declaration, obtaining informed consent from all participants and approval from the ethics committee of Wenzhou Seventh People's Hospital.

Participant recruitment

Ninety TRD participants aged 18 or older and of both sexes between January 2022 and June 2023 were enrolled. Participants were randomly assigned to three groups (using sealed envelopes); ESC group, ESC + MECT group, and ESC + HF-rTMS group, each comprising 30 individuals. TRD was defined as depression unresponsive to at least one prior antidepressant treatment during their current episode of depression (Bretlau et al. 2008). The inclusion criteria for participants in the study mandated a Hamilton Depression Rating Scale (HDRS-17) score > 17, indicative of at least moderate depression severity (Vinberg et al. 2016). Additionally, individuals needed to demonstrate full mental capacity, literacy, the absence of physical or neurological diseases, and not be at a severe risk of suicide. On the other hand, exclusion criteria encompassed the coexistence of specific serious systemic diseases, such as epilepsy, severe brain diseases, recent stroke, severe heart diseases, significant hypertension, severe clotting disorders, marked anemia, advanced osteoporosis, aortic aneurysms, thrombophlebitis, or certain ophthalmological diseases. Women who were pregnant or breastfeeding were excluded, along with subjects possessing potential risk factors for ESC treatment, MECT or rTMS.

Treatments

For the ESC + MECT group, patients underwent MECT using the SOMATICS company's Wakeful Pulse Multifunctional Electric Convulsive Therapy apparatus. The procedure involved inducing anesthesia with atropine (1 mg), propofol (2.0-2.5 mg/kg), and succinylcholine (50-80 mg). Electrical stimulation was applied three times per week for 4 weeks. In the ESC + HF-rTMS group, transcranial magnetic stimulation was conducted over 20 consecutive working days for 4 weeks, targeting the left dorsolateral prefrontal cortex. The treatment utilized a NeuroMS/D device with an 8-shaped coil, applying parameters such as 110% motor threshold, 10 Hz, 40 pulses in each train, and a 20-second intertrain interval. In all three groups, ESC was administered at a dose of 10 mg daily in the first week, followed by a fixed dose of 20 mg daily throughout the 12-week treatment phase.

Outcome measurements

The present analysis focused on the HDRS-17; a clinician-rated measure of depressive symptoms that consists of 17 items rated using a semi-structured interview. A score ≤ 7 was required for obtaining clinical remission or at least a 50% reduction at HDRS, defined as positive treatment response (Ramasubbu et al. 2023). On this basis, we distinguished patients with recovered and non-recovered status at 12 weeks. The World Health Organization Quality of Life Questionnaire (WHOQOL-BREF) consists of 26 questions (Ilic et al. 2019). The first question inquiries about overall Quality of Life (QoL), and the second question assesses satisfaction with health. Responses for these two items are rated on a 1-5 Likert-type scale. The remaining 24 specific questions gauge four QoL domains: physical (7 items), psychological (6 items), social relationships (3 items), and environmental (8 items). Scores for each domain range from 4 to 20, where higher values indicate a superior QoL. The Montreal Cognitive Assessment (MoCA) comprehen-

sively evaluates cognitive function through specific tasks in various domains (O'Driscoll and Shaikh 2017). With a maximum score of 30 points, each domain assesses distinct cognitive aspects. These include visuospatial-executive abilities (score: 0-5), naming (score: 0-3), language (score: 0-3), short-term memory (score: 0-5), abstraction (score: 0-2), attention and calculation (score: 0-6), and orientation (score: 0-6). The cumulative score acts as a comprehensive indicator of cognitive health, with higher scores reflecting superior overall cognitive function.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA), with significance defined as $P < 0.05$. Categorical data are presented as n (%). Continuous data, when normally distributed, are presented as mean ± standard deviation (SD) or median (interquartile range, IQR). The normality assumption was assessed using the Shapiro-Wilk test. For normally distributed continuous data, within-group comparisons before and after treatment utilized the Paired t-test, while comparisons among the three groups employed ANOVA followed by Holm-Sidak's multiple comparisons test. Non-normally distributed data were analyzed using the Wilcoxon matched-pairs signed-rank test, with Kruskal-Wallis (K-W) test followed by Dunn's multiple comparisons test for comparisons among three groups.

Results

Baseline characteristics

The sociodemographic characteristics of 90 patients enrolled in three treatment groups were examined (Table 1). No significant differences were observed in sex distribution, with 16 males in the ESC group, 15 in the ESC + MECT group, and 18 in the ESC + HF-rTMS group ($\chi^2 = 0.627$, $P = 0.731$). Analysis demonstrated no noteworthy variations in age, with ranges spanning from 38.83 to 41.27 years across all groups and no significant differences observed ($F = 0.319$, $P = 0.728$). Body mass index (BMI) variations were negligible, with mean values fluctuating from 20.58 to 20.91 kg/cm² among the groups, exhibiting no significant differences ($F = 0.330$, $P = 0.720$). Education levels, represented in years, displayed comparable median values of 11 to 12 years (range: 9-13) across groups, and no significant discrepancies were noted ($F = 0.842$, $P = 0.434$). Marital status exhibited comparable frequencies, with 20 married individuals in the ESC group, 19 in the ESC + MECT group, and 22 in the ESC + HF-rTMS group, along with 10, 11, and 8 unmarried individuals, respectively ($\chi^2 = 0.712$, $P = 0.700$). The mean duration of illness (years) was 4.55 ± 1.983 in the ESC group, 4.943 ± 2.229 in the ESC + MECT group, and 4.333 ± 2.594 in the ESC + HF-rTMS group ($F = 0.551$, $P = 0.579$). The number of previous depressive episodes also exhibited no significant differences among the groups ($F = 0.551$, $P = 0.328$).

Impact of ESC with either MECT or HF-rTMS on depression symptoms in TRD patients

As indicated in Fig. 1 and Table 2, initially, at baseline, the mean HDRS-17 scores for the ESC, ESC + MECT, and ESC + HF-rTMS groups were 24.10 ± 3.49, 24.53 ± 3.32, and 25.07 ± 3.74, respectively. ANOVA analysis revealed comparable mean HDRS-17 scores among the groups ($F = 0.568$, $P = 0.569$). Holm-Sidak's multiple comparisons test indicated no significant differences in baseline scores between the two groups (all $P > 0.05$). Over 12 weeks, all groups exhibited a reduction in HDRS-17 scores (all $P < 0.05$). At 3 weeks ($F = 6.058$, $P = 0.003$), the HDRS-17

Table 1. Baseline characteristics of 90 patients enrolled in three treatment groups.

Characteristics	ESC group (n = 30)	ESC + MECT group (n = 30)	ESC + HF-rTMS group (n = 30)	*P*
Sex				
Males	16 (53.3%)	15 (50.0%)	18 (60.0%)	
Females	14 (46.7%)	15 (50.0%)	12 (40.0%)	0.731
Age (years)	39.6 ± 11.47	41.27 ±12.67	38.83 ±12.01	0.728
BMI (kg/cm^2)	20.7 ± 1.664	20.91 ±1.661	20.58 ±1.498	0.72
Education level (years)	11 (9-13)	12 (9-13.25)	11 (9.75-13)	0.434
Marital status				
Married	20 (66.7%)	19 (63.3%)	22 (73.3%)	
Unmarried	10 (33.3%)	11(36.7%)	8 (26.7%)	0.7
Duration of illness (years)	4.55 ± 1.983	4.943 ±2.229	4.333 ± 2.594	0.579
Number of previous depressive episodes				
Patients with 1-5 episodes	16 (53.3%)	22 (73.3%)	21 (70.0%)	
Patients with 6 or more episodes	14 (46.7%)	8 (26.7%)	9 (30.0%)	0.218

Data are shown as n (%) or mean ± SD.

BMI, body mass index; ESC, Escitalopram; MECT, modified electroconvulsive therapy; HF-rTMS; high-frequency repetitive transcranial magnetic stimulation.

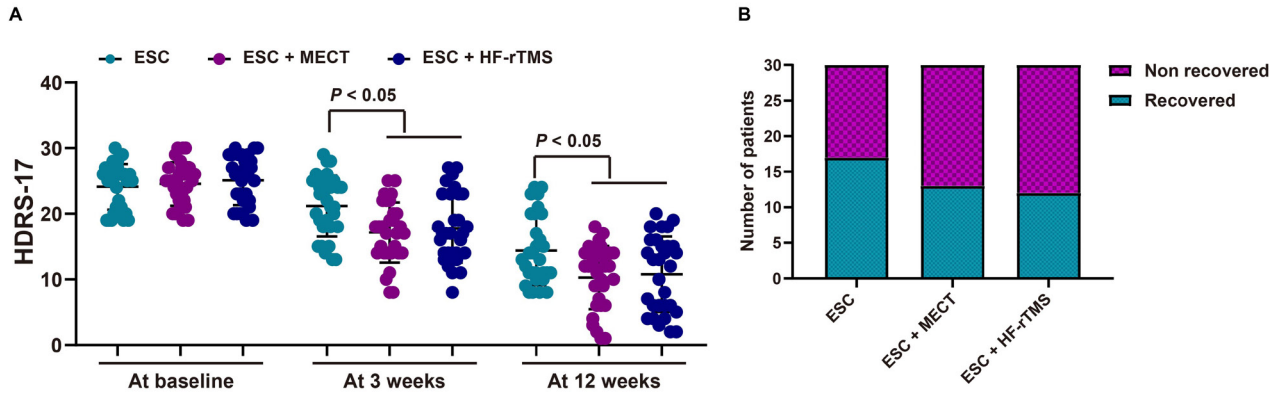

Fig. 1. Augmenting escitalopram (ESC) with either modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) enhances depression improvement in treatment-resistant depression (TRD) patients.
A. Comparison of the Hamilton Depression Rating Scale (HDRS-17) among three groups at baseline, 3 weeks, and 12 weeks. B. No significant differences in the number of recovered patients (a score ≤ 7 or at least a 50% reduction at HDRS-17 among the three groups at 12 weeks).

Table 2. Augmenting escitalopram (ESC) with either modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) enhanced depression improvement in treatment-resistant depression (TRD) patients.

Groups	Baseline	3 weeks	12 weeks
ESC	24.10 ± 3.49	21.17 ± 4.65$^{\#,\&}$	14.37 ± 5.22$^{\#,\&}$
ESC + MECT	24.53 ± 3.32	17.13 ± 4.60*$^{,\#,\&}$	10.27 ± 4.81*$^{,\#,\&}$
ESC + HF-rTMS	25.07 ± 3.74	17.77 ± 5.21*$^{,\#,\&}$	10.77 ± 5.75*$^{,\#,\&}$
F	0.568	6.058	5.396
P	0.569	0.003	0.006

*denotes a statistically significant difference in comparison to the escitalopram alone group at the corresponding time point.
$^{\#}$signifies a statistically significant difference compared to the Baseline data.
$^{\&}$indicates a statistically significant difference compared to the 3 weeks data.

scores showed significant differences among ESC (21.17 ± 4.65), ESC + MECT (17.13 ± 4.60), and ESC + HF-rTMS (17.77 ± 5.21) groups. By the 12-week mark (F = 5.396, P = 0.006), further notable distinctions were evident: ESC (14.37 ± 5.22), ESC + MECT (10.27 ± 4.81), and ESC + HF-rTMS (10.77 ± 5.75). Specifically, the ESC + MECT and ESC + HF-rTMS groups exhibited substantial decreases in depressive symptomatology compared to the ESC alone group, as indicated by significantly lower mean scores at both 3 weeks and 12 weeks (all $P < 0.05$). No significant difference was observed between the ESC + MECT and ESC + HF-rTMS groups (all $P > 0.05$). This trend suggests that augmenting ESC with either MECT or HF-rTMS contributes to a more pronounced and rapid improvement in depressive symptoms compared to ESC monotherapy. There was no significant difference in the number of patients who recovered, defined as achieving an HDRS-17 score ≤ 7 or at least a 50% reduction, among the ESC, ESC + MECT, and ESC + HF-rTMS groups (χ^2 = 1.875, P = 0.391), with 17, 13, and 12 patients recovering, respectively.

Impact of ESC with either MECT or HF-rTMS on QoL in TRD patients

The overall QoL scores within the ESC, ESC + MECT, and ESC + HF-rTMS groups were 2 (IQR: 1-2), 2 (IQR: 1-3), and 2 (IQR: 1-2), respectively (K-W = 1.572, P = 0.456). Additionally, the assessment of satisfaction with health revealed scores of 2 (IQR: 1-3), 2 (IQR: 1-3), and 2 (IQR: 2-3) in the ESC, ESC + MECT, and ESC + HF-rTMS groups, respectively (K-W = 3.706, P = 0.157). These findings suggest that there were no statistically significant differences among the three groups regarding overall QoL or satisfaction with health prior to treatment (Fig. 2). After the 12-week treatment period, the overall QoL scores were 2 (IQR: 2-3), 3 (IQR: 2.75-4), and 3.5 (IQR: 2-4) for the ESC, ESC + MECT, and ESC + HF-rTMS groups, respectively. In terms of satisfaction with health, the scores were 3 (IQR: 2-3), 3 (IQR: 3-4), and 3 (IQR: 3-4) for the ESC, ESC + MECT, and ESC + HF-rTMS groups, respectively. Following the treatment, both the ESC + MECT and ESC + HF-rTMS groups exhibited significantly higher scores compared to the ESC group at the 12-week assessment (all $P <$ 0.05). Moreover, as indicated in Table 3, the scores for the

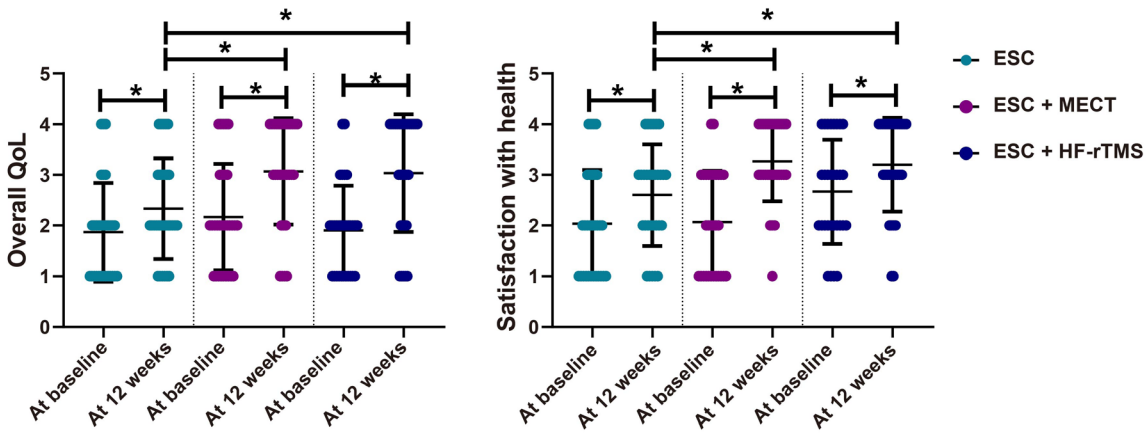

Fig. 2. Impact of escitalopram (ESC) with modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on overall quality of life (QoL) and satisfaction with health in treatment-resistant depression (TRD) patients as assessed by the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF).
*$P < 0.05$.

four QoL domains (physical health, psychological, social relationships, and environmental) showed no significant differences at baseline among the three groups (all $P > 0.05$). Nevertheless, significant enhancements were observed across various domains in the ESC alone group, showing improvements in physical health (from 10 to 12, $P = 0.035$), psychological well-being (from 7 to 10, $P < 0.001$), social relationships (from 10 to 11.5, $P = 0.041$), and environmental factors (from 10 to 11.5, $P = 0.040$). However, these improvements were notably more pronounced in the combined therapy groups for physical health (ESC + MECT: from 10.5 to 15, $P = 0.001$; ESC + HF-rTMS: from 9 to 14.5, $P < 0.001$), psychological well-being (ESC + MECT: from 7.5 to 14, $P < 0.001$; ESC + HF-rTMS: from 8 to 12.5, $P < 0.001$), social relationships (ESC + MECT: from 10 to 13.5, $P = 0.004$; ESC + HF-rTMS: from 8.5 to 13.5, $P < 0.001$), and environmental factors (ESC + MECT: from 11 to 15, $P < 0.001$; ESC + HF-rTMS: from 10 to 16, $P < 0.001$). Furthermore, at the 12-week assessment, both the ESC + MECT and ESC + HF-rTMS groups displayed higher scores in these domains compared to the ESC group (all $P < 0.05$).

Impact of ESC with either MECT or HF-rTMS on cognitive function in TRD patients

Table 4 presented an analysis of MoCA scores for TRD patients across three distinct treatment groups at baseline and the 12-week mark. Significant enhancements were observed across several cognitive domains at the 12-week mark across all treatment groups (all $P < 0.05$), particularly in naming and attention and calculation abilities. Notably, both ESC + MECT and ESC + HF-rTMS groups showed significant improvements in visuospatial-executive abilities (ESC + MECT: $P = 0.043$; ESC + HF-rTMS: $P = 0.002$) and abstraction. Interestingly, the ESC + HF-rTMS group demonstrated significant language improvement [baseline: 2 (IQR: 1.75-3); 12 weeks: 3 (IQR: 2.75-3), $P < 0.001$], while the ESC + MECT group displayed a decline [baseline: 2 (IQR: 2-3); 12 weeks: 1 (IQR: 1-3), $P = 0.022$]. Conversely, ESC + MECT did not exhibit significant improvement in orientation ($P = 0.210$) or short-term memory ($P = 0.968$). Notably, the ESC alone group showed no substantial improvements in visuospatial-executive abilities ($P = 0.491$), language ($P = 0.965$), or abstraction ($P = 0.539$). Furthermore, at the 12-week mark, the ESC + HF-rTMS group displayed superior visuospatial-executive abilities compared to the ESC group ($P < 0.05$) and outperformed both groups in naming (all $P < 0.05$) and language scores ($P < 0.001$) as illustrated in Fig. 3A. Additionally, at baseline, the median MoCA scores were 22 (IQR: 20-23) for ESC, 22.5 (IQR: 20-25) for ESC + MECT, and 22 (IQR: 20-23.25) for ESC + HF-rTMS. After 12 weeks, these scores changed to a median of 24 (IQR: 24-26.25) for ESC, 23.5 (IQR: 21-25) for ESC + MECT, and 26 (IQR: 25.75-27) for ESC + HF-rTMS (all $P < 0.01$). Comparatively, the ESC + HF-rTMS group displayed significantly higher median MoCA scores than both the ESC and ESC + MECT groups at the 12-week assessment (Fig. 3B).

Discussion

The findings of this study underscore the effectiveness of ESC alone and its combinations with MECT or HF-rTMS in alleviating depressive symptoms, as evidenced by a notable reduction in HDRS-17 scores across all groups over the 12-week period. The observed more pronounced and rapid improvement in the combined therapy groups, sustained through the 12-week assessment, suggests a synergistic effect of augmenting ESC with either MECT or HF-rTMS. This aligns with previous research emphasizing the clinical significance of HF-rTMS as an add-on strategy in combination with ESC for patients with major depression resistant to non-tricyclic antidepressants (Bretlau et al.

Table 3. Impact of escitalopram (ESC) with modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on quality of life in treatment-resistant depression (TRD) patients.

WHOQOL-BREF score	ESC group			ESC + MECT group			ESC + HF-rTMS group		
	Baseline	12 weeks	*P*	Baseline	12 weeks	*P*	Baseline	12 weeks	*P*
Physical health	10 (7.5-12)	12 (8-14)	0.035	10.5 (8-14)	15 (10.75-17.25)*	0.001	9 (6-10)	14.5 (11-17)*	< 0.001
Psychological	7 (5-9)	10 (7.75-13)	< 0.001	7.5 (6-9.25)	14 (10-15)*	< 0.001	8 (5-10)	12.5 (11-16)*	< 0.001
Social relationships	10 (6.75-13)	11.5 (9-14)	0.041	10 (6.75-15)	13.5 (11.75-16.25)*	0.004	8.5 (6-13)	13.5 (11.75-16.25)*	< 0.001
Environmental	10 (8-11)	11.5 (8-16)	0.040	11 (9-13)	15 (14-17.25)*	< 0.001	10 (9.75-11.25)	16 (13.75-18)*	< 0.001

WHOQOL-BREF, World Health Organization Quality of Life Questionnaire.
*denotes a statistically significant difference in comparison to the escitalopram alone group at 12 weeks.

Table 4. Impact of escitalopram (ESC) with modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on cognitive function in treatment-resistant depression (TRD) patients.

MoCA score	ESC group			ESC + MECT group			ESC + HF-rTMS group		
	Baseline	12 weeks	*P*	Baseline	12 weeks	*P*	Baseline	12 weeks	*P*
Visuospatial-executive abilities	4 (3-4.25)	4 (3-5)	0.491	4 (2.75-5)	4 (4-5)	0.043	4 (3-4.25)	5 (4-5)	0.002
Naming	2.5 (2-3)	3 (2.75-3)	0.037	2 (2-3)	3 (2-3)	0.035	2 (2-3)	3 (2.75-3)	0.006
Language	2 (1-3)	2 (1-3)	0.965	2 (2-3)	1 (1-3)	0.022	2 (1.75-3)	3 (2.75-3)	< 0.001
Short-term memory	3 (2-5)	4 (3-4)	0.024	3.5 (2-4)	3 (2-4)	0.968	4 (2-4.25)	4 (3-5)	0.023
Abstraction	1 (0-2)	1 (0-2)	0.539	1 (0-2)	1.5 (1-2)	0.002	1 (0-1.25)	2 (1-2)	0.001
Attention and calculation	4 (3-5)	5 (5-6)	0.001	4 (3-5.25)	5 (5-6)	0.002	4 (3-5)	5 (4-6)	0.008
Orientation	5 (5-6)	6 (5-6)	0.018	5.5 (5-6)	6 (5-6)	0.210	5 (4-6)	6 (5-6)	0.007
Total score	22 (20-23)	24 (24-26.25)	< 0.001	22.5 (20-25)	23.5 (21-25)	0.006	22 (20-23.25)	26 (25.75-27)	< 0.001

MoCA, Montreal Cognitive Assessment.

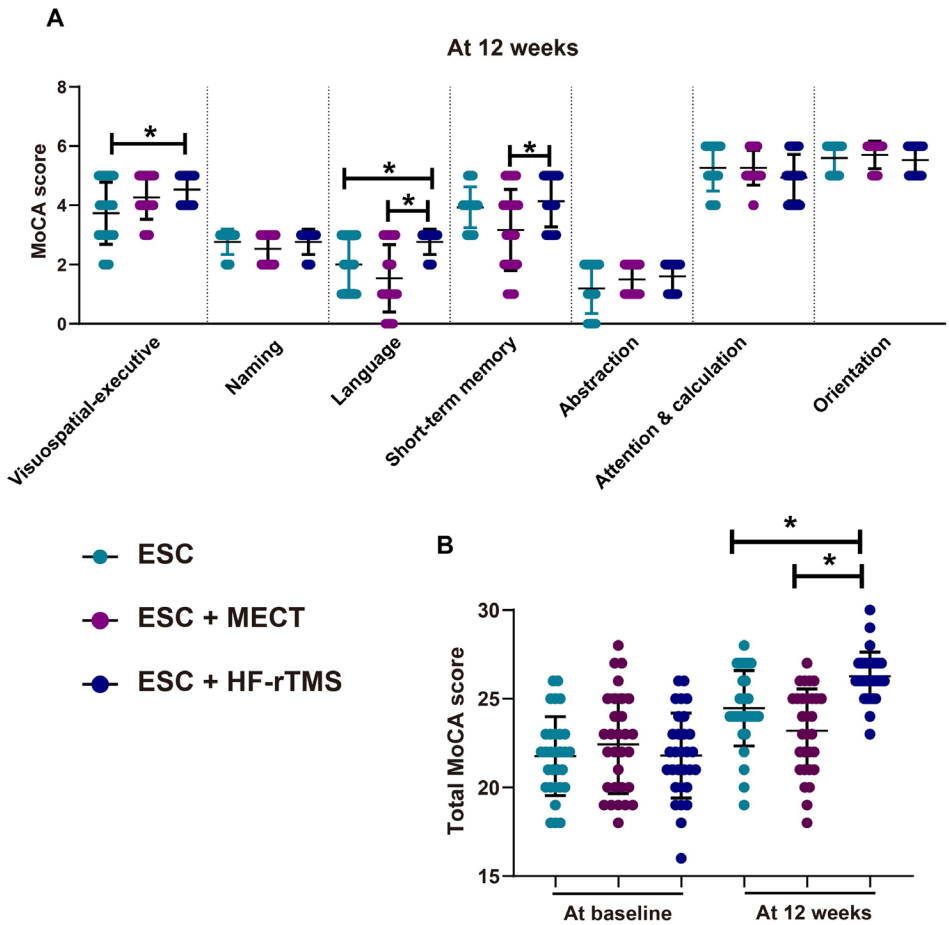

Fig. 3. Impact of escitalopram (ESC) with modified electroconvulsive therapy (MECT) or high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on cognitive function in treatment-resistant depression (TRD) patients. A. Comparative analysis of visuospatial-executive abilities, naming, language, short-term memory, abstraction, attention and calculation, and orientation among the three groups at the 12-week mark. B. Comparative evaluation of Montreal Cognitive Assessment (MoCA) total scores among the three groups at baseline and 12 weeks. *$P < 0.05$.

2008). Rossini et al. (2005) and Guan et al. (2021) further support the efficacy of HF-rTMS in hastening the response to ESC, emphasizing its positive impact on early therapeutic effects and pre-attentive processing in depressed patients. Masdrakis et al. (2008) reported on the well-tolerated concurrent use of ESC (20 mg/day) during ECT in three female inpatients with major depressive episodes with only minimal side effects. The lack of significant differences among recovered patients in the three groups after 12 weeks implies that both combination therapies are equally effective in achieving clinical remission or a substantial reduction in depressive symptoms. This finding is consistent with comparable treatment responses in major depression reported in ECT and rTMS groups, where rTMS demonstrated cognitive stability or improvement while ECT led to memory recall deficits and persistent complaints (Schulze-Rauschenbach et al. 2005). Structural neuroplasticity and neuroinflammation can arise from right unilateral ECT (6 × seizure threshold), while in contrast, rTMS to the left dorsolateral prefrontal cortex does not induce meso- or macroscopic structural changes; nevertheless, both modalities demonstrate comparable clinical antidepressant properties (Cano et al. 2023). These findings support the notion that augmenting ESC with MECT or HF-rTMS offers enhanced therapeutic outcomes for TRD patients compared to ESC monotherapy alone. The post-treatment comparison indicates that both the ESC + MECT and ESC + HF-rTMS groups demonstrated higher Quality of Life (QoL) scores than the ESC-alone group at the 12-week mark, emphasizing the potential of augmentation therapies to yield superior outcomes not only in depressive symptoms but also in overall QoL. These enhancements extend across specific aspects such as physical health, psychological well-being, social relationships, and environmental satisfaction.

ECT stands out as the most effective acute antidepressant treatment for depression, despite its common limitation of cognitive side-effects (Ryan et al. 2022). In our study, patients receiving ESC + MECT showed no statistically significant changes in short-term memory and orientation before and after 12 weeks of treatment, coupled with a

decrease in language compared to baseline. These echoes observations of short-term memory difficulties frequently occurring immediately after ECT (Coetzer 2019). ECT has demonstrated a reduction in language capacities while enhancing visuo-executive and abstraction performances, as measured by MoCA, in depressed patients (Moirand et al. 2018). The initiation of ECT might transiently affect memory and executive function in patients with major depression, yet cognition appears largely unaffected during and after ECT (Vasavada et al. 2017). Following rTMS application, there were significant reductions in depression severity and explicit improvements in cognitive domains, including delayed memory, visual-spatial/executive abilities, and language points, in TRD patients (Aydin et al. 2018). Our results showed that HF-rTMS treatment significantly improved cognitive function in TRD patients. At the 12-week mark, the ESC + HF-rTMS group exhibited higher scores in visuospatial-executive abilities compared to the ESC group. Additionally, the ESC + HF-rTMS group displayed higher scores in naming than the other two groups and higher language scores compared to the ESC + MECT group. Moreover, the total MoCA score for the ESC + HF-rTMS group surpassed that of the other two groups. ECT treatment resulted in a significant decrease in the total MoCA score at the end of the 4-week post-intervention period, with a more pronounced decline in MoCA scores, delayed recall, and language performances from baseline to post-treatment in ECT compared to HF-rTMS (Chen et al. 2022). These findings suggested that combining ESC with HF-rTMS yields significant improvements in cognitive function compared to ECT, consistent with prior studies highlighting the cognitive side-effects of ECT.

However, it is crucial to address certain limitations within this study. The sample size, although suitable for preliminary analyses, could potentially restrict the wider applicability of the findings due to constraints in funding and time. Furthermore, exploring longer-term follow-ups could yield valuable insights into the durability of treatment effects and potential relapse rates, aspects that received limited exploration in this research. To overcome these limitations, future studies could consider larger, more diverse participant groups, extended follow-up periods, and assessments that focus on mechanistic studies to understand the underlying physiological changes. Additionally, comparative evaluations involving other treatment modalities or the optimization of different treatment methods could offer deeper insights into the best approaches for managing TRD.

In conclusion, this study provides valuable insights into the efficacy of combining ESC with MECT or HF-rTMS for TRD patients. The findings demonstrate enhanced therapeutic outcomes in terms of alleviating depressive symptoms and improving QoL compared to ESC monotherapy. Notably, the study highlights the cognitive benefits associated with the ESC + HF-rTMS combination, suggesting that this augmentation strategy not only effectively addresses depressive symptoms but also contributes positively to cognitive function in TRD patients. These observations underscore the potential of ESC with HF-rTMS as a comprehensive and promising treatment approach for TRD, emphasizing both emotional and cognitive well-being.

Conflict of Interest

The authors declare no conflict of interest.

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