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SYSTEMATIC REVIEW

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Pharmacological interventions to diminish cognitive side effects of electroconvulsive therapy: A systematic review and meta-analysis

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Abstract

Objective: The authors conducted a systematic review and meta-analysis of pharmacological interventions to diminish cognitive side effects of ECT.

Methods: Electronic databases of Pubmed, PsycInfo, Embase and Scopus were searched from inception through 1 April, 2021, using terms for ECT (e.g. *electroconvulsive therapy*), cognitive outcome (e.g. *cogni**) and pharmacological intervention (e.g. *calcium channel blocker* and general terms, like *protein*). Original studies with humans receiving ECT were included, which applied pharmacological interventions in comparison with placebo or no additive intervention to diminish cognitive side effects. Data quality was assessed using Risk of Bias and GRADE. Random-effects models were used. PROSPERO registration number was CRD42021212773.

Results: Qualitative synthesis (systematic review) showed 52 studies reporting sixteen pharmacological intervention-types. Quantitative synthesis (meta-analysis) included 26 studies (1387 patients) describing twelve pharmacological intervention-types. Low-quality evidence of efficacy was established for memantine (large effect size) and liothyronine (medium effect size). Very low-quality evidence shows effect of acetylcholine inhibitors, piracetam and melatonin in some cognitive domains. Evidence of no efficacy was revealed for ketamine (very low-quality), herbal preparations with anti-inflammatory properties (very low to low-quality) and opioid receptor agonists (low-quality).

Conclusion: Memantine and liothyronine are promising for further research and future application. Quality of evidence was low because of differences in ECT techniques, study populations and cognitive measurements. These findings provide a guide for rational choices of potential pharmacological intervention research targets to decrease the burden of cognitive side effects of ECT. Future

Esmée Verwijk and Jeroen A. van Waarde contributed equally to this work

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research should be more uniform in design and attempt to clarify pathophysiological mechanisms of cognitive side effects of ECT.

KEYWORDS
cognitive outcome, electroconvulsive therapy, meta-analysis, pharmacological interventions, systematic review

1 | INTRODUCTION

Electroconvulsive therapy (ECT) is highly effective in treating major depressive disorder (MDD), with response-rates around 70% and remission-rates around 50% even in treatment-resistant patients.[1,2] Still, ECT is often regarded as a treatment of last resort, partly because of concerns about cognitive side effects. Memory loss after ECT has been reported in 22%–79% of patients.[3] Autobiographical retrograde amnesia may be detectable even six months after ECT.[4] Although, at a group level, global cognitive functioning at least will return to baseline after ECT, studies show considerable inter-individual variability.[5] Also, a discrepancy between subjective and objective cognitive side effects has been reported.[6] Cognitive side effects may contribute to the stigma of ECT and rejection of this effective treatment option.[7] Therefore, prevention or treatment of cognitive side effects will improve tolerability and may increase treatment motivation.

Cognitive side effects manifest in distinct cognitive functions, mainly in memory functions such as retrograde and anterograde amnesia. Global cognitive functioning, attention, executive and visuo-constructive functioning are less affected.[4,8] Multiple theories try to explain the pathophysiology of cognitive effects in ECT, including roles of changes in immunological, hormonal and neurotrophic factors, as well as alterations in electrical brain activity, permeability of the blood brain barrier, brain perfusion and neuroplasticity.[9] Based on these presumed pathophysiological mechanisms, several prevention and treatment options for ECT-induced cognitive side effects have been proposed. However, international clinical guidelines do not recommend any of such pharmacological interventions in ECT.[10–12] Earlier systematic reviews and meta-analyses only reviewed specific drug (groups) or global cognitive functioning, without comprehensively examining all pharmacological interventions or all cognitive outcomes.[13,14] Thus, an overview of the full range of studied interventions targeting cognitive side effects of ECT is lacking.

1.1 | Aim of the study

We present a systematic review and meta-analysis of published studies on pharmacological interventions aimed at diminishing cognitive side effects of ECT.

Summations

- This review provides a full overview of the range of pharmacological interventions tested for diminishing cognitive side effects of electroconvulsive therapy (ECT).
- Memantine and liothyronine show some efficacy in decreasing cognitive side effects of ECT and are suggested as high priorities for future research.
- In vulnerable patients suffering a high burden of cognitive side effects in ECT, memantine or liothyronine may be considered as potential additional treatment in clinical practice, because of the evidence that they may decrease these cognitive effects.

Limitations

- Overall quality of established evidence in our systematic review was low, mostly because of small sample sizes and several risks of bias.
- Conclusions are based on heterogeneous studies in terms of study population, type of cognitive outcome and ECT parameters hampering generalizability.

2 | MATERIAL AND METHODS

2.1 | Search strategy and selection criteria

Cochrane Guidelines for Systematic Review and Meta-analysis were used.[15] The review is reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (E-Table 1 in the Supplement)[16] and registered in PROSPERO (CRD42021212773).

2.2 | Data sources and searches

Electronic databases of Pubmed, PsycInfo, Embase and Scopus were searched by the first two authors (JV, MvK)

from inception through 1 April, 2021, and included terms for electroconvulsive therapy (e.g. *electroconvulsi*, electroshock, ECT*), cognitive outcome (e.g. *cogni*, amnes*, neuropsychological*) and pharmacological intervention (i.e. a broad selection of previously examined types of drugs, like *calcium channel blocker*, and general terms, like *protein*). The full search strategy is available in EMethods in the Supplement.

2.3 | Study selection

Studies were included if they (i) were a primary original study; (i) used a human population receiving ECT; (iii) used pharmacological interventions administered during the ECT-course; (iv) applied placebo or no additive intervention as control condition and (v) measured the cognitive outcome on continuous cognitive scales. Publication year was not restricted. To gain a full overview of available evidence, all study designs and population diagnoses were allowed in the qualitative synthesis. Subsequently, only randomized, controlled, non-crossover trials (RCTs) using a square-wave pulse stimulus were included in the quantitative synthesis. To improve reproducibility, 55% of all identified titles, abstracts and full articles were independently examined by two reviewers (JV, MvK). Disagreements were settled by consensus.

2.4 | Data extraction

Data extraction was performed by three independent reviewers (JV, MvK and JvW), each performing 37% of total extraction, which created overlap to ensure homogenous methods and consistency. The Cochrane Risk of Bias Tool 2 was used,[17] and overall quality of outcomes was rated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).[18] Imprecision was rated 'large' if confidence intervals (CI) crossed the clinical decision threshold of effect size (SMD, Hedges' $g < 0.5$), or in case of less than 300 patients per outcome variable. 'Very large' imprecision was scored if less than 50 patients were included. In cases of missing data, we attempted to contact the first authors of studies for additional information.

2.4.1 | Extracted patient and ECT characteristics

From all eligible studies, we extracted first author, year of publication, country, setting, psychiatric diagnoses, method to determine diagnoses, symptoms severity scores (e.g. Hamilton Depression Rating Scale [HDRS] score), mean age, distribution of sex, dose and frequency of intervention, type of control condition and known ECT-parameters influencing cognitive side effects (e.g. ECT-device, electrode placement, pulse amplitude [current], pulse width, anaesthetic, muscle relaxant and seizure durations[19]).

2.4.2 | Extracted cognitive outcome variables

To meet the primary goal of this systematic review and meta-analysis, the cognitive tests used, the cognitive functions, timing of measurements and scores of cognitive outcomes were extracted (if available). Raw continuous values of cognitive scales at baseline and follow-up were noted (i.e. means, standard deviations, standard errors or F-scores). To synthesize the available evidence, outcome measurements were grouped according to timing. In line with previous ECT-research,[20] these time-intervals were 'immediate' (i.e. $\leqq$ 24 h after ECT-session), 'short-term' (i.e. $\geq$24 h and $\leqq$14 days after ECT-course) and 'medium-term' (i.e. between 24 days and two months after the ECT-course; we chose 24 days, because no studies reported outcomes between 14 and 24 days).

2.5 | Statistical analysis and data synthesis

This study comprised (i) qualitative synthesis of studies meeting the general inclusion criteria, (ii) quantitative synthesis of RCTs reporting sufficient data of comparable measures of cognitive outcome in one or two studies and (iii) meta-analysis of RCTs reporting sufficient data of comparable measures of cognitive outcome in three or more studies (see Figure 1).

Descriptive statistics were used to report on the included studies. Using random-effects models, effect estimates with 95%-CI were calculated using mean differences (MD) in outcomes with a single type of cognitive measure. Also, for all outcomes, we calculated the standardized mean difference (SMD, Hedges' *g*) to gain a measure of effect size. All SMDs were calculated by the difference between conditions at each of the different post-ECT timepoints. SMDs were considered small ($(0.2 \leqslant \text{SMD} < 0.5)$), medium ($0.5 \leqslant \text{SMD} < 0.8$) or large ($\text{SMD} \geqslant 0.8$).[21] Analyses were performed using Review Manager (version 5.4).[22]

To synthesize available evidence, pharmacological interventions were pooled in groups according to the

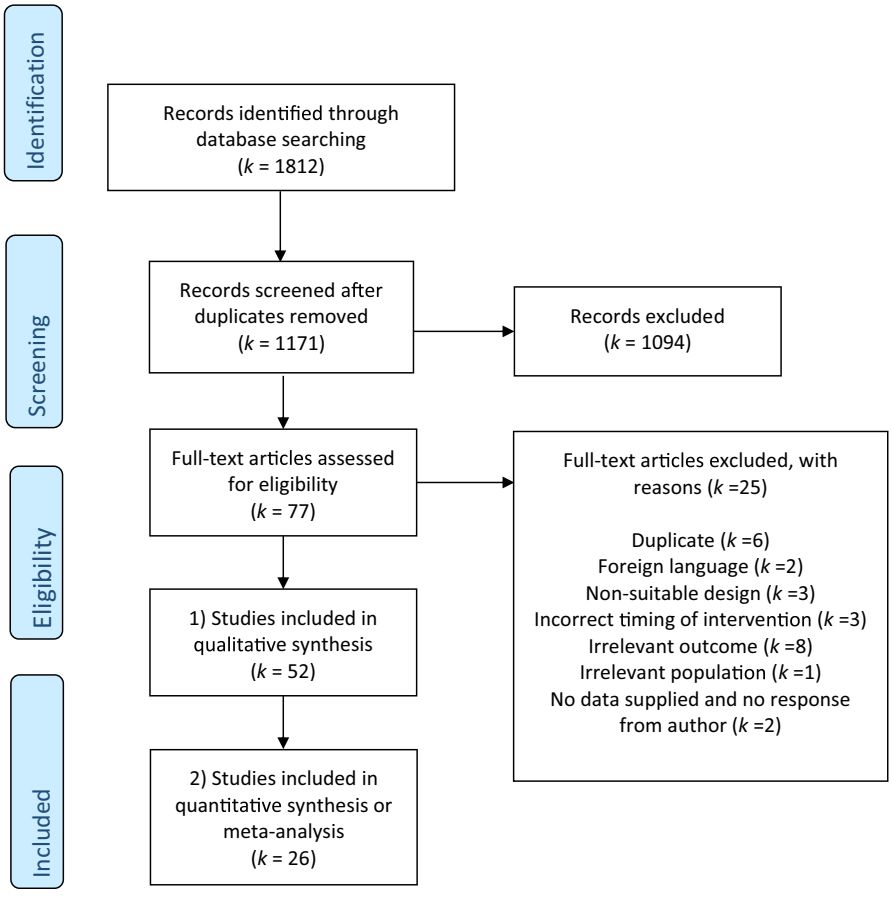


FIGURE 1 Flowchart of study selection

supposed mechanism of action. Because cognitive status would be influenced by specific psychiatric diagnoses,[23,24] we analysed studies with exclusively MDD, multiple diagnoses, mania and schizophrenia, separately. We combined unipolar depressive episode and studies reporting 'depression' without further specification. Level of evidence was characterized per intervention group as *evidence for effect, evidence for no effect* and *insufficient evidence*. Statistical heterogeneity was assessed by the I^2 statistic with 95%-CI, *Chi-squared* tests with p-values and by inspection of forest plots. If $p < 0.10$ and $I^2 > 50\%$, heterogeneity was considered to be substantial and, consequently, this outcome analysis was degraded in GRADE.

3 | RESULTS

In total, 1812 articles were identified of which 1171 were unique (see Figure 1). After screening, 77 articles appeared suitable for full text inspection. Of these, 52 studies met criteria for inclusion in the qualitative synthesis. Of these, 26 articles met criteria for inclusion in the quantitative synthesis.

Characteristics of studies included in the qualitative synthesis ($k = 52$) are summarized in Table 1, showing 23 different pharmacological interventions. These interventions were merged into sixteen treatment groups according to mechanisms of action. Further details of the qualitative synthesis are presented in E-Table 2 in the Supplement.

The following paragraphs concern the studies included in the quantitative synthesis ($k = 26$), together describing results on twelve pharmacological interventions.

3.1 | Study quality, risk of bias and GRADE

All included studies ($k = 26$) were scrutinized regarding bias because of randomization process, deviations from the intended interventions, missing outcome data, measurement of outcome and selection of reported results. Risk of bias for each included study is depicted in E-Figure 1 in the Supplement. Evidence for all outcomes started high because of the RCT design. Most studies ($k = 23$, 88%) compared the pharmacological intervention with placebo. However, all evidence had to be downgraded at least one level because of imprecision (risk of bias, publication/reporting bias, imprecision and/or inconsistency according to GRADE; E-Table 2). Checking trial registrations revealed a high risk of bias in selection of the reported results in three trials (11%). Funnel plots and statistical methods to assess the publication bias could not be applied, because there were insufficient studies for all

TABLE 1 Characteristics of studies included in the qualitative synthesis ($k = 52$) and meta-analysis ($k = 26$) on pharmacological interventions aimed at diminishing cognitive side effects of electroconvulsive therapy

	Qualitative synthesis	Meta-analysis
Number of studies (k)	52	26
Number of patients (n total)	2320	1387
Country (k, percent)		
United States	14; 27%	4; 15%
Iran	13; 25%	11; 42%
China	6; 12%	4; 15%
Israel	5; 10%	1; 4%
Sweden	3; 6%	1; 4%
India	2; 4%	1; 4%
Great Britain	2; 4%	1; 4%
Australia	1; 2%	1; 4%
Kuwait	1; 2%	1; 4%
The Netherlands	1; 2%	0
Japan	1; 2%	0
Greece	1; 2%	0
South Africa	1; 2%	0
Norway	1; 2%	0
Year of publication (median; range)	2002; 1968-2020	2013; 1978-2020
Mean age (in years; median; range)	Not available[a]	40.9; 29.5-65.7
Sex (percentage female; range)	Not available[a]	47%; 0-67%
Included psychiatric disorder		
Unipolar depressive episode	21; 40%	8; 30%
Various diagnoses	17; 33%	7; 27%
Depressive episode without further specification	11; 21%	9; 35%
Mania	1; 2%	1; 4%
Schizophrenia	2; 4%	1; 4%
Electrode placement (k, percent)		
Bifrontotemporal	33; 63%	15; 58%
Right unilateral according to d'Elia	8; 15%	6; 22%
Mix of unilateral and bifrontotemporal	3; 6%	2; 7%
Not specified	8; 15%	3; 11%

[a]Not reported because of missing demographic data in many studies.

comparisons. In sum, all evidence was appeared of moderate to very low-quality.

3.2 | Patient and ECT characteristics

Detailed patient characteristics of the quantitative synthesis and meta-analysis ($k = 26$) are presented in Table 1. Mean of sample sizes was 53 ± 33 patients (range: 18-137 patients). Most studies originated from Iran ($k = 11$; 41%). In 42% ($k = 11$), patients were recruited from in-patient settings, but mostly ($k = 12$, 46%) location of recruitment was not reported. Median of mean ages of included patients was 40.9 years (interquartile range [IQR]: 34-45 years), and median frequency of female sex was 46% (IQR: 41-62%). All studies showed heterogeneity in terms of diagnosis.

Several ECT-devices were used, mostly brief-pulse, square-wave systems of MECTA (31%, k = 8; MECTA Corporation, Portland, USA) and Thymatron (31%, k = 8; Somatics Inc, Lake Bluff, USA). One study[25], using sine-wave stimuli was excluded, because this method was regarded obsolete and would influence cognitive functioning differently compared with square-wave methods. Although fifteen studies did not specify the pulse width, ten studies (38%) used brief-pulse stimulation

(0.5–1.0 ms) and one study used ultra-brief stimulation (0.3 ms). Regarding anaesthesia, most studies (50%; k = 13) described the use of propofol and succinylcholine. Most studies (58%; k = 15) used bifrontotemporal electrode placement and 23% (k = 6) used right unilateral ECT, which might have impacted cognitive outcomes substantially. In sum, included studies varied substantially regarding use of independent determinants of cognitive side effects after ECT.

3.3 | Data synthesis

Studies examining the following pharmacological interventions were included in our quantitative synthesis and meta-analysis: acetylcholine inhibitors, ketamine, thyroid pathway, piracetam, memantine, opioid receptor agonists, herbal preparations with anti-inflammatory properties, melatonin, opioid receptor antagonists, calcium antagonists, L-tryptophan and vasopressin analogues. Quantitative synthesis of other (miscellaneous) interventions ($k = 23$) was not possible.

3.4 | Cognitive outcome measures

A variety of cognitive functions was reported as outcome measures, of which the global cognition outcome measures were used most frequently (54%, $k = 14$; i.e. Montreal Cognitive Assessment [MOCA][26] or Mini-Mental State Exam [MMSE][27]). More specific cognitive functions were immediate and delayed recall, general memory abilities, visuospatial memory, biographical memory, semantic memory, working memory, language, attention and executive functions. No study reported statistically significant differences at baseline. Studies appeared largely heterogeneous in timing of outcome measurements. Immediate cognitive outcome was measured in only one study.[28] Most other studies (65%, $k = 17$) examined short-term outcome and 27% ($k = 7$) reported medium-term outcome.

E-Table 2 summarizes the cognitive outcome measures, grouped by pharmacological intervention and time-intervals, of which the qualitative synthesis, quantitative synthesis and meta-analysis will now be described.

3.4.1 | Acetylcholine inhibitors (k = 9)

Qualitative synthesis

Four studies reported divergent effects on cognitive outcomes (see E-Table 2 in the Supplement).[25,29–31]

A total of five studies ($n = 209$) included in quantitative synthesis and meta-analysis reported on 12 cognitive outcomes.[28,32–35]

Quantitative synthesis

Eight outcomes were of low-quality evidence, and one outcome of very low-quality. One study ($n = 30$, galantamine) found a large effect on short-term delayed recall (MD = 19.67 (4.32, 35.02)).[32] One study ($n = 45$) found evidence of a large effect of donepezil on immediate recall (MD = 15.70 [8.39, 23.01]) and medium effect on autobiographical memory (MD = 9.00 [1.90, 16.10]) immediately after the ECT-course.[28] Regarding other cognitive outcomes reported by a single study, no significant effects were found.

Meta-analysis

Two outcomes were of low-quality evidence, and one of very low-quality. Four studies ($n = 184$) showed evidence that acetylcholine inhibitors (i.e. galantamine, rivastigmine and donepezil) are associated with a medium effect on short-term global cognitive outcome (SMD = 0.72 [0.11, 1.34]; forest plots of global cognitive outcomes in Figure 2).[32–35] However, no statistically significant effects were found when looking separately at studies enrolling patients with depressive episodes and various diagnoses.

3.4.2 | Ketamine (k = 8)

Qualitative synthesis

Two studies ($n = 112$) established absence of correlations with cognitive outcome after ECT.[36, 37]

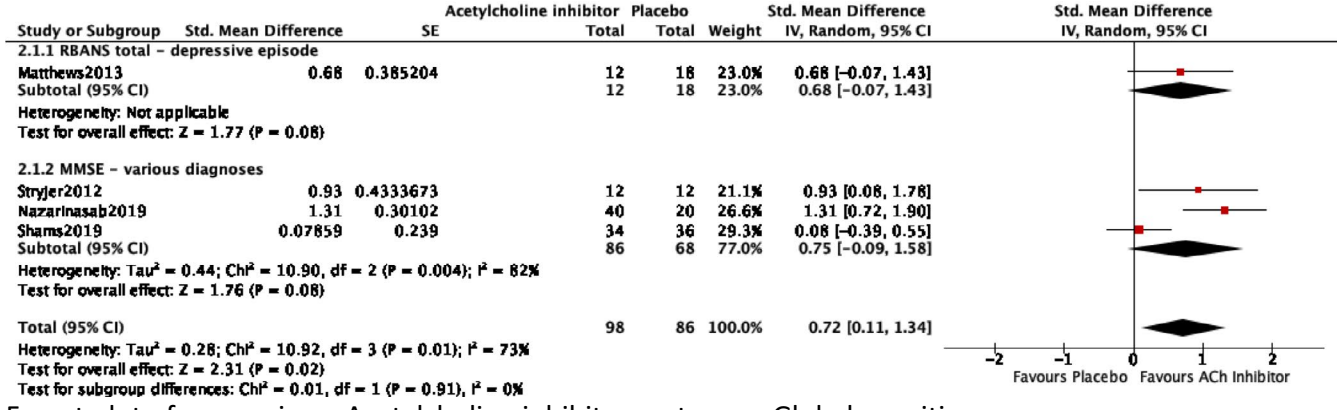
Quantitative synthesis and meta-analysis

Six studies ($n = 517$) reported 19 outcomes, ranging from very low- to medium-quality evidence (E-Table 2).[38–43] None of the outcomes showed statistically significant effects on cognitive outcome, except for three studies reporting very low-quality evidence for an association with small effect on short-term immediate recall (SMD = 0.33 [0.08, 0.58]).[40,42, 43]

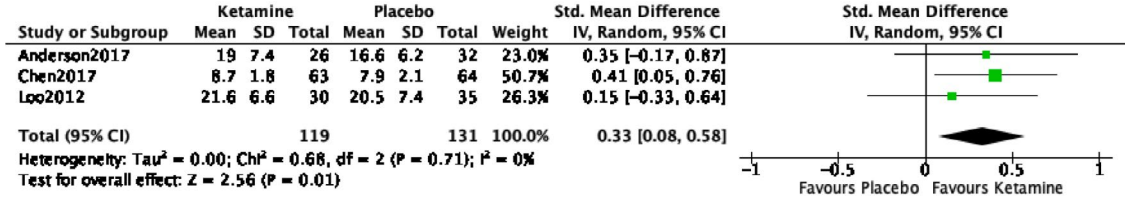
3.4.3 | Memantine (k = 2)

Quantitative synthesis

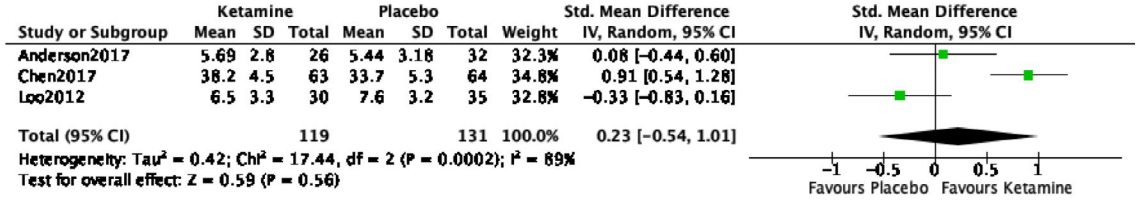
Two studies ($n = 78$) were included in the meta-analysis, reporting seven cognitive outcomes in patients with MDD[44] and in patients with various diagnoses.[45] Quality of the evidence ranged from very low to low. Memantine showed medium effect on short-term global cognitive outcome (MD = 0.73 [0.25, 1.20]; Figure 2). Also, evidence



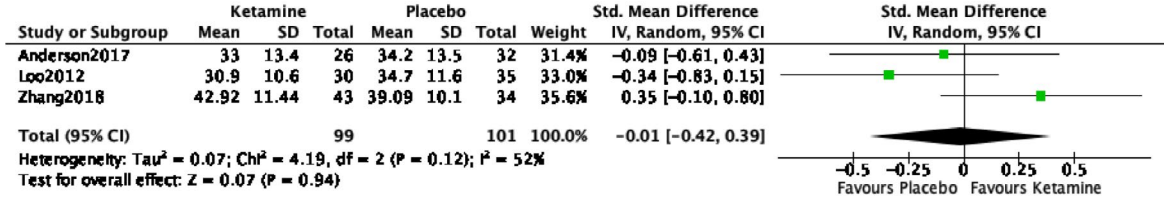
Forest plot of comparison: Acetylcholine inhibitor, outcome: Global cognitive measure - short-term.



Forest plot of comparison: 4 Ketamine, outcome: 4.5 Immediate recall (MCGCFT, MCGCFT, WMS immediate - short-term - depressive episode.



Forest plot of comparison: 4 Ketamine, outcome: 4.7 Delayed recall (HVLT-R delayed, WMS-long term, HVLT- delayed) - short-term - depressive episode.



Forest plot of comparison: 4 Ketamine, outcome: 4.11 Executive functions (letter fluency COWAT, RPS-NAB) - short-term - depressive episode.

FIGURE 2 Forest plots of meta-analyses

Forest plot of comparison: Acetylcholine inhibitor, outcome: Global cognitive measure - short-term. Forest plot of comparison: 4 Ketamine, outcome: 4.5 Immediate recall (MCGCFT, MCGCFT, WMS immediate) - short-term - depressive episode. Forest plot of comparison: 4 Ketamine, outcome: 4.7 Delayed recall (HVLT-R delayed, WMS-long term, HVLT- delayed) - short-term - depressive episode. Forest plot of comparison: 4 Ketamine, outcome: 4.11 Executive functions (letter fluency COWAT, RPS-NAB) - short-term - depressive episode.

was found of a statistically significant association with large effect on working memory (MD = 0.53 [0.12, 0.94]), as well as on immediate recall (MD = 1.10 [0.78, 1.42]). However, no effect on immediate recall was established when these MDs were combined. Data on medium-term cognitive outcome were absent.

3.4.4 | Thyroid pathway (k = 5)

Qualitative synthesis

Three studies did not meet criteria for inclusion in our quantitative synthesis; however, two of these were small crossover trials, which reported a statistically significant

effect on cognitive outcome.[46,47] One trial supplied insufficient data for quantitative synthesis, but described a significantly positive effect on global cognitive outcome (see E-Table 2 in the Supplement).[48]

Quantitative synthesis

Two RCTs (n = 50) with one cognitive outcome measure showed low-quality evidence that liothyronine was associated with a medium effect on short-term general memory abilities in patients with MDD after ECT (SMD = 0.73 [0.15, 1.30]).[49,50]

3.4.5 | Piracetam (k = 4)

Qualitative synthesis

Two trials did not meet criteria for inclusion in the quantitative synthesis; one study because of insufficient data[51] and the other because it used a crossover design.[52] Neither studies established an effect of piracetam on cognitive outcome.

Quantitative synthesis

All evidence was of very low-quality. Two RCTs (n = 68), both including patients with multiple diagnoses, tested piracetam for its efficacy in improving short-term cognitive outcome measured with five outcomes.[53, 54] One RCT (n = 30) found a statistically significant association with a large effect on short-term general memory abilities (MD = 20.20 [6.89, 33.51]).[53] However, the other RCT (n = 38) showed no effect on four other short-term cognitive measures.[54]

3.4.6 | Melatonin (k = 2)

Quantitative synthesis

One study (n = 40), reporting very low-quality evidence on two cognitive outcomes, tested melatonin in patients with MDD. The trial reported a statistically significant large effect on global cognitive outcome (MD = 2.95 [1.95, 3.95]; E-Table 2) and short-term immediate recall after ECT (MD = 0.55 [0.17, 0.93]).[55]

3.4.7 | Additional interventions

Qualitative synthesis

One study (n = 319) reported a significant association of using nortriptyline during ECT with a better short-term cognitive outcome.[56] One non-blinded trial (n = 20) found an association of pemoline (a stimulant drug) with better short-term outcome on global memory.[57] Two studies, one crossover trial[58] and one non-randomized trial,[59] found no evidence of effect of anticholinergic agents on immediate cognitive outcome. Three crossover trials[60–62] and one trial supplying insufficient data for quantitative synthesis[62] found no effect of pharmacological interventions targeting the cortisol pathway. One crossover trial (n = 15) did not detect an effect of myo-inositol.[63] Adrenergic antagonists had no effect on cognitive outcome in one crossover trial (n = 10).[64] One crossover study (n = 8) studying the effect of calcium antagonists found no statistically significant association with immediate cognitive outcome.[65] One crossover trial (n = 9) found no effect of vasopressin analogues, but one case-series (n = 2) found positive effect on immediate delayed recall.[66,67]

Quantitative synthesis

All evidence was of very low- to low-quality. One trial (n = 37) reported no effect of opioid receptor antagonists.[68] Calcium antagonists showed statistically significant effects, as tested in one single small trial (n = 26) with five cognitive outcomes.[69] One study (n = 44) found no effect of L-tryptophan on two measures of cognitive outcome.[70] One trial (n = 32) showed no effect of vasopressin analogues.[71] Two RCTs (n = 149) found no effect of opioid receptor agonists on short-term cognitive outcome after ECT.[72,73] Two RCTs (n = 137) tested herbal preparations with anti-inflammatory properties and found no effect on four cognitive outcomes at short-term.[74,75]

4 | DISCUSSION

This is the first systematic literature review and meta-analysis of the full range of pharmacological interventions used to attempt to diminish cognitive side effects of ECT. Quantitative synthesis reveals low-quality evidence for a large effect of memantine and a medium effect of liothyronine. Furthermore, very low-quality evidence—regarding short-term cognitive outcomes—suggests possible effects of acetylcholine inhibitors, piracetam and melatonin. Otherwise, quantitative synthesis and meta-analysis reveals evidence of no cognitive improvement with ketamine (very low-quality), herbal preparations with anti-inflammatory properties (very low-quality) and opioid receptor agonists (low-quality) after ECT.

Given the high burden of cognitive side effects in some patients,[5,76] this review and meta-analysis strongly encourages further research on memantine and liothyronine in their efficacy to diminish short-term cognitive side effects for ECT-patients. Overall, effect sizes of these interventions appear medium to large, and thus, potentially may have important implications for daily clinical practice. However, international clinical ECT guidelines

do not include any recommendations to use these scientifically substantiated interventions.[10–12,77,78] Moreover, guidelines do not advise against the use of agents that may have proven, although in (very) low-quality studies, ineffective. Therefore, these results also may provide a guide for clinicians in the use of potentially beneficial pharmacological interventions, in case ECT-patients show substantial cognitive side effects during treatment or in attempting to prevent such effects in particularly vulnerable patients (see Table 2).

Our systematic literature search finds several patterns throughout history regarding the study of pharmacological interventions in ECT. First, the majority of studies are published in the last ten years, especially in non-Western countries. Second, only a handful of research groups seems to have investigated this subject, strengthening our observation that generalization of the findings across the globe is very limited to date. An influential systematic review of ECT-efficacy included 73 RCTs,[79] while our study yields noticeably fewer studies ($k = 26$). Also, evidence from 40% of the included outcomes is rated as low and 54% as very low. These arguments may reflect low priority in studying cognitive side effects of ECT. Moreover, limited knowledge is available regarding underlying ECT-specific mechanisms of cognitive side effects. Hypotheses on the effects of melatonin, memantine, piracetam and acetylcholine inhibitors derive primarily from research of Alzheimer's disease.[80–82] Furthermore, potential interventions influencing the cortisol pathway have only been studied in the 1970's, which is understandable because evidence regarding cortisol dysregulation and MDD emerged in these years.[83] However, no further studies have been published since.

Worthwhile potential agents for further study may derive from our review and meta-analysis. Insufficient evidence is available regarding the use of opioid receptor antagonists, calcium antagonists, L-tryptophan, vasopressin analogues, anticholinergic agents, interventions targeting the cortisol pathway, myo-inositol, pemoline, nortriptyline and adrenergic antagonists, partly because most studies included very small samples (e.g. <10 participants, see E-Table 3 in the Supplement). Therefore, many studies were underpowered. Moreover, no replications or follow-up RCTs have been reported yet, and conclusions are not possible. Potential treatment or preventive modalities of cognitive side effects in ECT, still worth further study, are prioritized based upon our systematic review and summarized in Table 2.

Current hypotheses of the pathophysiology of cognitive side effects in ECT span multiple candidate mechanisms. Recent studies have found potential roles of oxidative stress, inflammation, neurotrophic factors, immunological factors, hormones, alterations in electrical brain activity, permeability of the blood brain barrier, brain perfusion, changes in functional networks with a lag of integration of new neurons and volume changes

TABLE 2 Recommendation for priority of further research of potential agents to diminish or prevent cognitive side effects in electroconvulsive therapy, based on qualitative synthesis and meta-analysis of the systematic literature review

Recommendation for further study	Intervention	Effect size	Quality of evidence (GRADE)
High priority	Memantine	Large	Low
	Liothyronine	Medium	Low
Medium priority	Acetylcholine inhibitors	None to large	Very low
	Melatonin	Medium to large	Very low
	Piracetam	None to large	Very low
	Interventions targeting cortisol Pathway[a]		
	Myo-inositol[a]		
	Adrenergic antagonists[a]		
	Calcium antagonists[a]		
	Vasopressin analogues[a]		
	Opioid receptor antagonists[a]		
Low priority	Ketamine	None	Very low
	Anti-inflammatory herbal preparations	None	Very low
	Opioid receptor agonists	None	Low

[a]No effect size or GRADE was calculated since studies did not meet criteria for inclusion in meta-analysis.

of the hippocampus.[9,84,85] Further study of the worthwhile pharmacological interventions in this review may help elucidate the mechanisms of cognitive side effects in ECT. In addition, the study of novel candidates may contribute to further understanding of these mechanisms. Erythropoietin, currently under investigation,[86] is hypothesized to reduce cognitive side effects of ECT by reducing inflammation and oxidative stress, and inducing greater hippocampal activation and reinforcement of dorsolateral prefrontal activity networks. Also, preventing postictal vasoconstriction accompanied with cerebral hypoperfusion by using blood vessel dilating agents (e.g. calcium antagonists, cyclooxygenase-2 [COX-2] inhibitors) is suggested to reduce postictal phenomena, such as postictal cognitive dysfunction.[87]

In this systematic review and meta-analysis, modern and robust techniques are applied.[15,17] Another strength is the wide inclusion strategy, avoiding exclusion in advance of potential pharmacological interventions. However, our results must be considered in light of some limitations. First, we searched for data regarding ECT variables, which would have determined cognitive side effects inevitably (i.e. electrode placement, pulse width, anaesthesia).[19] Unfortunately, such data were lacking to correct for in our analyses. We expect considerable differences in ECT techniques between studies because of broad inclusion of study year and country. Moreover, 71% ($k = 19$) of the included studies in the quantitative synthesis appeared from only three countries, which probably may reduce worldwide generalizability of our findings. Second, substantial clinical heterogeneity existed in our included studies (e.g. regarding studied populations, sample sizes, investigated cognitive functions, types of cognitive tests and time-intervals). Third, included studies applied ketamine as induction for anaesthesia, in contrast to the other interventions which were dosed in between ECT sessions which may hamper the comparability. Fourth, the majority of studies (54%) used the MMSE or MOCA to measure cognitive outcome. These cognitive screens may be unable to capture subtle changes because of ceiling effects, especially in younger patients.[88] Lastly, diagnostic types of depressive episodes were not always available, which decreased comparability between studies and increased statistical heterogeneity.

More uniformity in future research is advised to limit clinical heterogeneity, as is shown in our review. First of all, ECT variables such as electrode placement, pulse width and anaesthetic regime should be reported, and—ideally—only homogeneous patient groups should be included. Regarding the outcome measures, we advise adherence to standardized time-intervals (i.e. immediate [within 24 h after the ECT-session], short-term [within two weeks after the ECT-course], medium-term [two weeks to three months after the ECT-course], long-term [3–6 months after the ECT-course] and very long-term (> 6 months after the ECT-course]). Moreover, we suggest defining standard instruments for each specific cognitive function. We advise to minimally include the following cognitive functions in test batteries: global cognitive functioning (e.g. MOCA[89]), immediate and delayed recall (e.g. Rey Auditory Verbal Learning Test) and executive functioning (e.g. Category and Letter fluency). Additionally, we suggest functions of attention (e.g. Trail Making Test A), cognitive flexibility (e.g. Trail Making Test B), working memory (e.g. WAIS-IV backward numbers), autobiographical memory (e.g. Columbia Autobiographical Memory Interview, given an improved new scoring system[90–92]), processing speed (e.g. STROOP) and subjective memory (e.g. Subjective Assessment of Memory, SAMI). Though, because of high attrition rates in these often severely ill populations, future research may focus on short tools with documented sensitivity to cognitive side effects.[6]

In conclusion, this systematic review and meta-analysis shows urgency to further study the efficacy of memantine and liothyronine in improving short-term cognitive outcome after ECT. Acetylcholine inhibitors, piracetam and melatonin may also show potency to diminish cognitive side effects of ECT in some cognitive domains, although they are less promising. Studies appear clinically heterogeneous. Because of the sometimes very high patient burden of cognitive side effects, and some evidence for the efficacy and safety of these interventions during ECT, memantine and liothyronine may be considered for use in clinical practice in vulnerable patients.

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CONFLICT OF INTERESTS

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The full data sheet is available upon request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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