Pharmacotherapy to Improve Cognitive Functioning After Acquired Brain Injury: A Meta-Analysis and Meta-Regression

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Cognitive impairments, common sequelae of acquired brain injury (ABI), significantly affect rehabilitation and quality of life. Currently, there is no solid evidence-base for pharmacotherapy to improve cognitive functioning after ABI, nevertheless off-label use is widely applied in clinical practice. This meta-analysis and meta-regression aims to quantitatively aggregate the available evidence for the effects of pharmacological agents used in the treatment of cognitive impairments following ABI. We conducted a comprehensive search of Embase, Medline Ovid, and Cochrane Controlled Trials Register databases for randomized controlled and crossover trials. Meta-analytic effects were calculated for each pharmaceutical agent and targeted neuromodulator system. Cognitive outcome measures were aggregated across cognitive domains. Of 8,216 articles, 41 studies (4,434 patients) were included. The noradrenergic agent methylphenidate showed a small, significant positive effect on cognitive functioning in patients with traumatic brain injury (TBI; $k=14$, $d=0.34$, 95% confidence interval: 0.12–0.56, $P=0.003$). Specifically, methylphenidate was found to improve cognitive functions related to executive memory, baseline speed, inhibitory control, and variability in responding. The cholinergic drug donepezil demonstrated a large effect size, albeit based on a limited number of studies ($k=3$, $d=1.68$, $P=0.03$). No significant effects were observed for other agents. Additionally, meta-regression analysis did not identify significant sources of heterogeneity in treatment response. Our meta-analysis supports the use of methylphenidate for enhancing cognitive functioning in patients with TBI. Although donepezil shows potential, it warrants further research. These results could guide clinical decision making, inform practice guidelines, and direct future pharmacotherapeutic research in ABI.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ Cognitive functioning is a critical aspect of recovery after acquired brain injury (ABI), including traumatic brain injury (TBI) and stroke. However, the use of pharmacotherapy for cognitive deficits in this context is predominantly off-label, with existing evidence being fragmented and inconclusive.

WHAT QUESTION DOES THIS STUDY ADDRESS?

☑ The study addresses the effectiveness of various pharmacological agents in improving cognitive functioning post-ABI. It involves a comprehensive meta-analysis and meta-regression of available randomized controlled trials.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study provides robust evidence for the beneficial effect of methylphenidate in enhancing cognitive functioning in patients with TBI. It also suggests the potential of donepezil, warranting further research.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The findings support the use of methylphenidate for cognitive improvement in patients with TBI and guide clinical decision making. The study informs practice guidelines and directs future research in ABI pharmacotherapy, highlighting the need for precision medicine approaches in neurorehabilitation.

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Received September 26, 2023; accepted January 10, 2024. doi:10.1002/cpt.3186

Cerebrovascular accidents and traumatic brain injury (TBI) are the most common causes of acquired brain injury (ABI), affecting an estimated 85 million people annually around the world.[1,2] Patients with ABI are at risk of debilitating long-term impairments in a wide range of function domains, such as physical, neurocognitive and behavioral functioning.[3,4] Patients with ABI are typically referred for neurorehabilitation treatment in order to optimize recovery, limit the consequences of ABI, and maximize independency in daily living.[5] Cognitive impairments are particularly common after ABI and can have a profound impact on a patient's ability to engage in neurorehabilitation therapy.[6] Moreover, persisting cognitive impairments beyond the window of treatment severely threaten societal participation and quality of life.[7] Therefore, providing patients with effective interventions to improve cognitive functioning is a pivotal aspect of rehabilitation after ABI.

The treatment of cognitive impairments in patients with ABI is challenging due to the complex interplay between factors that determine the nature and severity of cognitive impairment after ABI, such as injury characteristics (e.g., type, severity, and location), demographic characteristics (e.g., age and educational level), and premorbid functioning (e.g., comorbid conditions).[8,9] Nevertheless, therapeutic options for cognitive impairments are available, including both non-pharmacological (e.g., cognitive rehabilitation)[10,11] and pharmacological approaches. Pharmacotherapy has shown to be an effective intervention for the improvement of cognitive functioning in a range of psychiatric and neurological disorders, including attention-deficit/hyperactivity disorder,[12] major depressive disorder,[13] schizophrenia,[14] and Alzheimer's disease.[15]

Pharmacotherapy is a promising treatment option for cognitive impairments following ABI, with multiple agents available that target neuromodulating systems implicated in cognitive functioning.[16,17] Cholinesterase inhibitors, such as donepezil and rivastigmine, are examples of agents that primarily modulate the cholinergic system. Similarly, the dopaminergic system can be targeted with agents such as Levodopa-carbidopa and amantadine, whereas methylphenidate and atomoxetine can be used to modulate the adrenergic system. Selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, are examples of pharmacotherapeutic options that can affect the serotonergic system. Nevertheless, the state of the literature regarding the efficacy of pharmacotherapy for the treatment of cognitive impairment after ABI is inconclusive. Existing systematic (Cochrane) reviews from 2015 and 2016 concluded that there was insufficient evidence to determine whether pharmacotherapy is effective for chronic cognitive impairment in patients with TBI or stroke,[18,19] primarily due to a lack of randomized controlled trials (RCTs) with adequate sample size. Despite the absence of a solid evidence-base and guideline recommendations, pharmacotherapy is widely used as an off-label therapeutic option in clinical practice to improve cognitive functioning in patients with ABI.

This meta-analysis and meta-regression of RCTs aims to quantitatively aggregate the available evidence for the effects of pharmacological agents used in the treatment of cognitive impairments following ABI. Cognitive functioning encompasses a wide range of domains, each with its unique sensitivity to ABI and responsiveness to treatment. In this meta-analysis, we chose to aggregate different cognitive domains to provide an overarching perspective on cognitive functioning. Although this approach might overlook specific effects on specific domains, it offers a broader understanding relevant for clinical decision making. In addition, in-depth analysis at the level of cognitive domains was performed when data availability were sufficient. The results will contribute to a more comprehensive and reliable view on the fragmented evidence available, which can aid in clinical decision making for patients with ABI and cognitive impairments, contribute to the development of practice guidelines, and inform future research into promising pharmacological agents and involved neuromodulating systems.

METHODS

Protocol and registration

This systematic review was registered in the international prospective register of systematic reviews PROSPERO (#CRD42022150220), performed according to the Cochrane Library Handbook for Systematic Reviews of Interventions[20] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Identification and selection of studies

Eligibility criteria. Studies were considered eligible if the study design was an RCT or crossover trial (XOT) that compared a pharmacological intervention to a control condition consisting of either (i) no pharmacological treatment or (ii) placebo treatment. Studies had to enroll pediatric or adult participants with ABI (e.g., TBI or stroke). Studies with an onset of treatment during acute phase (< 24 hours) were excluded. The intervention had to consist of pharmacological agents that are (i) registered with the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA), (ii) are supposed to act on the central nervous system through modulation of one or more neurotransmitter systems, and (iii) were aimed at improvement of cognitive functioning. Studies had to use cognitive performance outcome measures that have been standardized in a healthy or brain injured population. Studies that were primarily focused on the treatment of a single symptom or condition were excluded (e.g., post-stroke depression, aphasia, and neglect).

The search strategy was designed together with a biomedical information specialist and involved a combination of search terms and their equivalents for "brain injury," "drug therapy," and "postacute." The search was performed on October 13, 2022, in the electronic bibliographical databases Embase, Medline Ovid, and Cochrane Controlled Trials Register (CENTRAL) using both simple search terms and hierarchical family forms (e.g., Mesh, Thesaurus, and Emtree). Specific search queries per database are documented in **Table S1**. The search was extended to the reference lists of included studies and relevant review articles were also screened for additional eligible studies.

In order to identify relevant studies, all titles and abstracts were independently screened by two reviewers (authors R.vdV. and S.B.). Subsequently, the full text versions of the remaining studies were examined independently by the reviewers to reach a final decision on study eligibility. In case of disagreement between reviewers, consensus was reached through discussion.

Data extraction

The variables used in the meta-regression analysis were chosen based on their potential to explain heterogeneity in the treatment effects across the included studies and included sample demographics, clinical characteristics, and treatment characteristics. The following data were extracted: (i) publication year and country; (ii) sample demographics

(mean age and percentage of female subjects), clinical characteristics, (type of ABI, ABI severity, and time since ABI); (iii) pharmacological agent(s) used; (iv) comparison condition type (no intervention, placebo); (v) timing, dosing, and duration of the intervention; (vi) and outcome measures.

Data for meta-analysis were extracted from the articles by the first author (R.vdV.) and this procedure was carefully checked by a second author (S.B.). The sample size, means, and accompanying SDs of all outcome measures for each group at all timepoints were extracted. If this information was not available, we extracted statistics describing the effect of the intervention on the outcome measure(s) (e.g., *F* or *t*-statistic, *P* value, odds ratio, and/or sample size of the experimental and control groups). If only the median and interquartile ranges were reported, methods described by Shi *et al*.[22] were used to determine whether the data were skewed away from normality before estimating the sample mean and standard deviation in accordance with Luo *et al*.[23] and Wan *et al*.[24] In instances where studies reported both intention-to-treat (ITT) and per-protocol approaches, the ITT data were chosen for analysis to better reflect real-world clinical outcomes.

Risk of bias analysis

Risk of bias was assessed by the 2 reviewers using the RoB 2,[25] a revised version of the Cochrane Collaboration Risk-of-Bias Tool.[26] The RoB 2 assesses bias arising from (i) the randomization process, (ii) deviations from the intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported results. Assessment led to judgments of "low risk of bias," "some concerns," or "high risk of bias." The judgments within each domain led to an overall risk-of-bias judgment for the result being assessed. In case of disagreement, consensus was reached through discussion.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis software (CMA) version 3. Meta-analysis was performed at the level of the targeted neuromodulator system and at the level of pharmacological agent, if two or more studies were available. When we were unable to retrieve the correlations between pre-post scores from the included studies, we followed Rosenthal's recommendation and assumed a conservative estimate of $r = 0.7$.[27] XOTs were handled as paired groups. If carry-over was deemed problematic (e.g., an insufficient wash-out[28]) or a crossover design was deemed undesirable for other reasons (e.g., a possible period effect[29]), only data from the first crossover period were included, essentially treating the first period of the crossover study as an RCT. Our primary effect size measure was the standardized mean difference (Cohen's *d*), interpreted as small ($0.2 \geq d < 0.5$), moderate ($0.5 \geq d < 0.8$), or large if ($d \geq 0.8$), according to Cohen.[30] Random-effects models were used to account for clinical and methodological differences between studies.[31] Cohen's *d* was computed from pretreatment to post-treatment (or timepoint closest to post-treatment). If a study used multiple relevant outcome measures and/or assessments at more than one timepoint, these data were combined into one effect-size per study by calculating the average standardized effect across outcome measures and timepoints using the built-in option in CMA. This approach will expose the effects of treatment on cognitive functioning in general, acknowledges that most cognitive functioning measures rarely rely on a single aspect of cognitive function, and utilizes all available evidence for estimation of the intervention effect. The resulting study effect size reflects the overall intervention effect across cognitive outcome measures and/or timepoints. Estimates and 95% confidence intervals (CIs) were graphically presented using forest plots, constructed in Microsoft Excel using the templates developed by Neyeloff *et al*.[32] We implemented a comprehensive, stepwise analytical approach. To specifically address the potentially distinct effects of pharmacotherapy in different typers of ABI, we conducted subgroup analyses for stroke and TBI populations. Furthermore, if the available number of studies ($k > 10$) and diversity of cognitive measures used in studies was sufficient, an in-depth analysis of the intervention effect was executed at the level of cognitive domains. We categorized cognitive outcome measures onto specific cognitive domains following the framework by Vertessen *et al*.[33] In cases of uncertainty regarding the mapping of cognitive outcome measures to cognitive domains, consensus was reached through discussion among authors (R.vdV., M.K., and J.O.). The resulting categorization is presented in **Table S2**.

Between-study heterogeneity was assessed using I^2 statistics. Heterogeneity of 25% was interpreted as minimal, 50% as moderate, and 75% as large.[34] Publication bias was assessed if more than six studies were available, by visually inspecting funnel plots for asymmetry and performing Egger's liberal one-tailed test of the intercept.[35]

Moderator variables with >10 observations that could explain the heterogeneity in meta-analytic effect-sized were investigated using meta-regression with restricted maximum likelihood using the Hartung-Knapp method. Additional sensitivity analysis utilizing the one-study-removed method assessed the impact of each individual study on the overall effect. *P* values < 0.05 were considered statistically significant.

RESULTS

Selection of studies

A PRISMA flow diagram of the study search and selection is provided in **Figure 1**. The search retrieved 11,797 records relating to 8,205 unique studies after removal of duplicates, whereas 11 records were identified through other sources. Screening of titles and abstracts led to exclusion of 7,905 studies. A total of 311 articles was assessed for eligibility based on full-text review, of which 41 articles were included for meta-analysis. There were 26 studies (63.4%) that included patients with TBI ($n = 1{,}221$),[28,29,36–57] whereas 15 studies (36.6%) included patients with stroke ($n = 3{,}213$).[58–71] **Table 1** provides an overview of the included number of studies (k) and participants (n) for each of the studied pharmacological agents, with pharmacological agents sorted according to the neuromodulatory system involved in the presumed mechanism of action. **Table 2** provides study characteristics of the included studies per pharmacological agent assessed.

Risk of bias

Figure 2 depicts a summary of the risk of bias assessment. Assessment of all individual studies can be found in **Figure S1**. Among the included studies, risk of bias (either some concerns or high risk) was observed in bias arising from the randomization procedure (21.1%); due to deviations from intended interventions (23.7%); due to missing outcome data (50.0%) and measurement of outcome (23.7%); and due to selection of the reported result (34.2%). A total of 13 articles (31.7%) had low risk of bias. These studies were classified as higher-quality studies and were used in the sensitivity analysis that studied the impact of risk of bias on the meta-analytic findings.

Main analysis

Meta-analytic effects were calculated according to the targeted neuromodulator system of pharmacological agents and for each individual pharmacological agent (**Table 1**; **Figure 3**). At the level of neuromodulator systems, the meta-analytic effect of

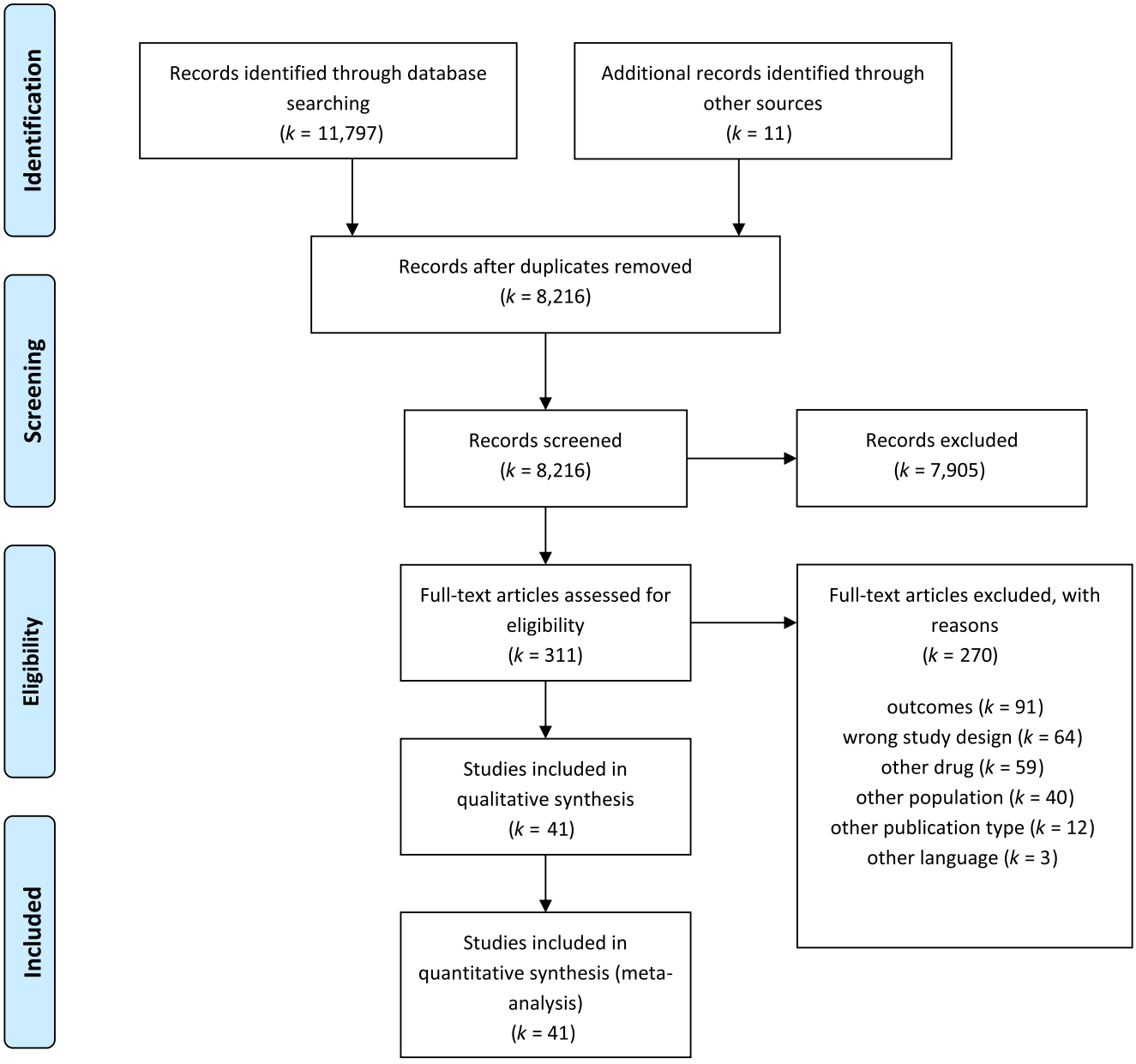

Figure 1 Prisma flow diagram.

noradrenergic agents on cognitive functioning was significant and small-sized ($k = 22$, $d = 0.22$, 95% CI: 0.10–0.35, $P = 0.001$), whereas the meta-analytic effects for all other neuromodulator systems were not significant (P values >0.09, ds: 0.002–0.35).

Adrenergic agents. In the group of adrenergic agents, we found a significant and small-sized positive effect for methylphenidate on cognitive functioning ($k = 16$, $d = 0.28$, 95% CI: 0.11–0.45, $P = 0.001$). No significant effects were obtained for dextroamphetamine ($k = 2$, $d = 0.313$, 95% CI: −0.09 to 0.72, $P = 0.62$) and modafinil ($k = 3$, $d = 0.05$, 95% CI: −0.16 to 0.26, $P = 0.62$). Meta-analysis was not possible for atomoxetine because only one study was available.

Figure 4 displays the forest plot for the significant meta-analytic effect observed for methylphenidate, with a moderate between-study heterogeneity ($I^2 = 54.4\%$). The meta-analytic effect in a subgroup analysis on studies that included patients with stroke[60,63] was not significant ($k = 2$, $d = -0.14$, 95% CI: −1.03 to 0.73, $P = 0.74$). In the subgroup analysis on studies that included patients with TBI, a significant and positive small-sized effect was obtained ($k = 14$, $d = 0.34$, 95% CI: 0.12–0.56, $P = 0.003$). In a sensitivity analysis with the one-study-removed method, the meta-analytic effect remained significant after iterative exclusion of every single study. Likewise, the meta-analytic effect was replicated when including only the higher-quality studies with low risk of bias.[44,45,47,48,54] ($d = 0.185$, 95% CI: 0.028–0.341, $P = 0.021$). Finally, we found no evidence for publication bias in the visual inspection of the Funnel plot and Egger's Regression intercept ($P = 0.15$).

In-depth analysis of the meta-analytic effect size for methylphenidate in patients with TBI revealed significant positive small-sized effects of methylphenidate observed on Executive Memory ($k = 10$,

Table 1 Number of studies (*k*) and Meta-analytic effect sizes per neuromodulator system and pharmacological agent

Neuromodulator system	Pharmacological agent	Included trials (*k*) and participants (*n*)		Meta-analytic effect size			
		TBI	Stroke	*d*	95% CI	*P* value	I^2
Adrenergic	Atomoxetine	*k*=1 *n*=55	n/a	0.07	−0.210 to 0.351	0.62	
	Dextroamphetamine	*k*=1 *n*=64	*k*=1 *n*=32	0.31	−0.09 to 0.716	0.13	0.0
	Methylphenidate	*k*=14 *n*=385	*k*=2 *n*=50	0.28	0.107–0.451	**0.001**	51.7
	Modafinil	*k*=1 *n*=55	*k*=2 *n*=77	0.05	−0.158 to 0.263	0.62	0.0
	Overall effect size	*k*=17 *n*=559	*k*=5 *n*=159	0.22	0.095–0.347	**0.001**	41.3
Cholinergic	Donepezil	*k*=2 *n*=44	*k*=1 *n*=14	1.68	0.187–3.167	**0.03**	78.1
	Rivastigmine	*k*=3 *n*=355	*k*=1 *n*=50	0.04	−0.112 to 0.186	0.63	0.0
	Overall effect size	*k*=5 *n*=399	*k*=2 *n*=64	0.35	−0.053 to 0.755	0.09	78.0
Dopaminergic	Amantadine	*k*=2 *n*=144	n/a	0.07	−0.539 to 0.679	0.82	61.5
	Levodopa-Carbidopa	n/a	*k*=2 *n*=633	0.01	−0.152 to 0.138	0.89	0.0
	Overall effect size	*k*=2 *n*=144	*k*=2 *n*=633	0.002	−0.144 to 0.148	0.98	0.0
Serotonergic	(Es)citolapram	n/a	*k*=4 *n*=687	0.15	−0.128 to 0.435	0.29	62.8
	Fluoxetine	n/a	*k*=1 *n*=1,500	0.01	−0.098 to 0.123	0.82	
	Paroxetine	n/a	*k*=1 *n*=170	0.24	−0.076 to 0.560	0.14	
	Sertraline	*k*=2 *n*=119	n/a	−0.28	−0.726 to 0.177	0.23	0.0
	Overall effect size	*k*=2 *n*=119	*k*=6 *n*=2,357	0.07	−0.07 to 0.217	0.32	41.8
Total		*k*=26 *n*=1,221	*k*=15 *n*=3,213		*k*=41 4,434		

CI, confidence interval; TBI, traumatic brain injury; n/a, not applicable.
P values in bold (P<0.05) denote significant effect sizes.

d=0.346, 95% CI: 0.133–0.559, *P*=0.001), Baseline Speed (*k*=14, *d*=0.288, 95% CI: 0.126–0.450, *P*<0.001), Inhibitory Control (*k*=10, *d*=0.239, 95% CI: 0.012–0.466, *P*=0.04), and Variability in Responding (*k*=4, *d*=0.154, 95% CI: 0.007–0.301, *P*=0.04). Effects on Cognitive Flexibility (*k*=7, *d*=0.134, 95% CI: −0.016 to 0.285, *P*=0.08), and Non-executive Memory (*k*=5, *d*=0.091, 95% CI: −0.184 to 0.366, *P*=0.516) were not statistically significant.

Cholinergic agents. In the group of cholinergic agents, we found a significant and large-sized meta-analytic effect for donepezil on cognitive functioning (*k*=3, *d*=1.68, 95% CI: 0.19–3.17, *P*=0.03), whereas the meta-analytic effect for rivastigmine was not significant (*k*=4, *d*=0.04, 95% CI: −0.11 to 0.19, *P*=0.63).

Figure 5 displays the forest plot for the significant meta-analytic effect observed for donepezil, with a large between-study heterogeneity (I^2=78.14%). The meta-analytic effect in a subgroup analysis on studies that included patients with TBI[28,36] was not significant (*k*=2, *d*=2.13, 95% CI: −0.29 to 4.55, *P*=0.085). Only one study was available for patients with stroke, precluding meta-analytic aggregation.[58] In a sensitivity analysis with the one-study-removed method, the meta-analytic effect did not remain significant after iterative exclusion of Chang *et al.*[58] and Kim *et al.*[36] None of the studies assessing donepezil had low risk of bias. Publication bias analysis was not conducted because an insufficient number of studies was available.

Dopaminergic agents. In the group of dopaminergic agents, the meta-analytic effect sizes were not significant for the effect of amantadine (*k*=2, *d*=0.07, 95% CI: −0.54 to 0.68, *P*=0.82) and levodopa-carbidopa (*k*=2, *d*=0.012, 95% CI: −0.15 to 0.18, *P*=0.89).

Table 2 Characteristics of included studies

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Donepezil										
Chang *et al.* 2011	South Korea	14/7	55.6	36	Stroke Right hemisphere	454	5 mg/day	28	• MMSE • Rey-Osterreith Complex Figure Test • Verbal Learning Test	Some concerns
Kim *et al.* 2009	South Korea	26/13	41.2	50	TBI Severity N/A	161	5 mg/day for 3 weeks and then 10 mg/day for 3 weeks	42	• MMSE • Wechsler Memory Scale • Boston Naming Test • Raven's colored progressive matrixes	Some concerns
Zhang *et al.* 2004 (cross-over trial)	US	18	33	28	TBI Moderate to severe	127	5 mg/day for 2 weeks and then 10 mg/day for 8 weeks	70	• Wechsler Memory Scale III AII • Wechsler Memory Scale III VII • PASAT	Some concerns
Rivastigmine										
Brawman-Mintzer *et al.* 2021	US	94/49	41.3	4	TBI mild to severe	N/A	9.5 mg/24 hour (10 cm^2) transdermal rivastigmine patch	84	• Hopkins Verbal Learning Test Revised • Digit Span Raw Score • Letter-Number Sequencing • PASAT • Trail Making Test-A • Trail Making Test-B • COWAT	Some concerns
Narasimhalu *et al.* 2010	Singapore	50/25	68.8	66	Stroke	90	1.5 mg b.i.d. increased up to 4.5 mg b.i.d. if tolerated	168	• Ten-Point Clock Test • Color Trails Test 1 and 2 • ADAS-Cog • Symbol digit modalities • Digit cancellation • Maze • Verbal fluency • Visual memory • Frontal assessment battery	Low risk
Silver *et al.* 2006	US	157/80	37.0	32	TBI	959	1.5 mg b.i.d. increased up to 3.0 mg b.i.d. if tolerated	84	• Cambridge Neuropsychological Test Automated Battery • Hopkins Verbal Learning Test • COWAT • Wechsler Adult Intelligence Scale Digit Span	Low risk
Tenovuo *et al.* 2009 (crossover trial)	Finland	102	45.5	39	TBI	2.920	1.5 mg/day Increased up to 6.0 mg b.i.d.	56	• 10CRT • Subtraction tests • Vigilance tests	High risk

(Continued)

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Amantadine										
Hammond *et al.* 2018	US	119/59	38.6	N/A	TBI	2,263	100 mg b.i.d.	28	• Digit Span, Wechsler Memory Scale—III • Trail Making Test-A • Trail Making Test-B • COWAT • CVLT-II • Rey Complex Figure Test	Some concerns
Meythaler *et al.* 2002 (crossover trial)	US	35	31	26	TBI Moderate to severe Subacute	Within first 6 weeks	200 mg/day	42	• MMSE	Some concerns
Levadopa-Cardidopa										
Delbari *et al.* 2011	Iran	40/20	64.0	30	Stroke Sub-acute	68	125 mg per day	15	• MMSE	Some concerns
Ford *et al.* 2019	UK	593/308	68.5	39	Stroke Post-acute	18	Intermittent (before therapy) 125 mg (100 mg of levodopa and 25 mg of carbidopa)	42	• MoCA	Low Risk
Atoxemetine										
Ripley *et al.* 2014 (cross-over trial)	US	55	40.6	25	TBI	2,847	40 mg b.i.d.	14	• CDR Computerized Cognitive Assessment System: ○ POA ○ COA • Stroop Color and Word Test	Low risk
Dexamphetamine										
Goldstein *et al.* 2018	US	64/32	66	45	Stroke Subacute	N/A	10 mg every 4 days	21	• MMSE	Low risk
Hart *et al.* 2017	US	32/17	39.2	38	TBI Moderate to severe Subacute	57	10 mg/day	21	• Finger tapping test • Symbol Digit Modalities Test	Some concerns
Methylphenidate										
Delbari *et al.* 2011	Iran	39/19	64.0	41	Stroke Sub-acute	66	20 mg per day	15	• MMSE	Some concerns
Dymowski *et al.* 2016	Australia	11/6	34.0	36	TBI Mild to severe for more than 6 months	293	0.6 mg/kg q.d. extended-release MPH (equivalent to 0.3 mg/kg b.i.d.)	49	• Symbol Digit Modality Test (raw score) • Trail Making Test-A • Trail Making Test-B • Hayling A (raw score) • Hayling B (raw score) • Hayling error (raw score) • Digit Span	Some concerns

(Continued)

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Grade *et al*. 1998	US	21/10	71.3	48	Stroke Sub-acute	18	5 mg increased gradually to 30 mg	21	• MMSE	Some concerns
Jenkins *et al*. 2019a and b (crossover trial)	UK	40	39.5	15	TBI Moderate to severe for more than 3 months	2,250	0.3 mg/kg b.i.d.	14	• CRT intra individual variability • CRT median response time • People Test Delayed Recall • People Test Forgetting • People Test Immediate Recall • Stroop Color Naming and Word Reading Composite Score • Stroop Inhibition • Stroop Inhibition-Switching • Stroop Inhibition-Switching verses Baseline Contrast • Trail Making Test-A • Trail Making Test-B • Trail Making Test B-A • WASI Matrix Reasoning	Low risk
Johansson *et al*. 2015 (crossover trial)	Sweden	44	38.9	57	TBI Mild to moderate for more than 6 months	2,993	Gradually increased to 20 mg t.i.d.	28	• Trail Making Test-A • Trail Making Test-B • Trail Making Test-C • Trail Making Test-D • Digit Symbol Coding Test • Digit Span • Computer Test, Simple • Computer Test, Complex	Low risk
Kim *et al*. 2006	South Korea	18/9	34.2	11	TBI TBI for more than 6 months	949	20 mg one dose	1	• Two-back working memory task (accuracy) • Trail Making Test-A • Trail Making Test-B • Trail Making Test B–A • WASI Matrix Reasoning	Some concerns
Kim *et al*. 2012 (crossover trial)	US	23	34.2	22	TBI Moderate to severe for more than 3 months	1,533	0.3 mg/kg one dose	1	• Visuospatial attention task (reaction time) • Visuospatial attention task (accuracy) • 2-back working memory task (reaction time) • 2-back working memory task (accuracy)	Low risk

(Continued)

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
LeBlond *et al*. 2019 (crossover trial)	US	26	11.5	22	TBI Mild to severe for more than 6 months	1,898	Participants weighing <25 kg received 18 mg (low), 27 mg (medium), and 36 mg (high) dosages; participants weighing above 25 kg received 18 mg (low), 36 mg (medium), and 54 mg (high) dosages during the trial	28	• WAIS PSI overall (standard score) • WAIS coding overall (scaled) • WAIS Symbol search overal (scaled) • Continuous Performance test II coefficient of variation overall • Continuous Performance Test II mean reaction Time overall • Continuous Performance Test II SD reaction Time overall • D-KEFS Verbal Fluency switch accuracy • D-KEFS Verbal Fluency correct switches	Low risk
Lee *et al*. 2005a	South Korea	20/10	35.4	20	TBI Mild to moderate for 2 months to 1 year	32	starts at 5 mg/day to 20 mg/day in a week	28	• MMSE • Critical Flicker Fusion Threshold (Hz) • Recognition Reaction Time (ms) • Motor Reaction Time (ms) • Total Reaction Time (ms) • Compensatory Tracking Task (pixel) • Compensatory Tracking Task (ms) • Mental Arithmetic Test (ms) • Sternberg Memory Scanning Task (ms) • Digit Symbol Substitution Test	Some concerns
Mahalick *et al*. 1998 (crossover trial)	US	14	10.7	21	TBI Mild to severe	424	0.3 mg/kg b.i.d.	14	• Gordon Diagnostic System (delayed efficiency ratio) • Gordon Diagnostic System (Distractibility commission) • Gordon Diagnostic System (vigilance commission) • Ruff 2 and 7 cancellation test (letters) • Ruff 2 and 7 cancellation test (numbers) • Woodcock Johnson test (processing speed)	Some concerns
McDonald *et al*. 2017	US	76/38	39.8	36	TBI Mild to severe for more than 4 months	2,759	0.3 mg/kg b.i.d.	42	• CVLT-II • Continuous Performance Test Distractibility trial (reaction time) • PASAT • WAIS -III Digit Symbol-Coding number correct • Delis–Kaplan Trail Making Test, trial 2 completion time • MASQ • Craft Stories immediate recall total score • Brown location Test initial encoding over trials 1–5 number correct • DKEFS Sorting Test-Free Sorting Description total score	Some concerns

(Continued)

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Plenger *et al*. 1996	US	23/10	29.4	26	TBI Moderate to moderately severe subacute	N/A	0.3 mg/kg b.i.d.	30	• Galveston Orientation and Amnesia Test • Continuous Performance Test (Vigil) • 2 and 7 Test • PASAT • Digit Span & Attention/Concentration from WMS-R • Selective Reminding • Delayed, Verbal, and Visual Memory from the WMS-R • Porteus Maze • Pursuit Rotor	Some concerns
Speech *et al*. 1993 (crossover trial)	US	12	27.6	58	TBI	1,455	0.3 mg/kg b.i.d.	7	• Gordon Diagnostic System • Digit Symbol • Digit Span • Stroop Interference Task • Two-choice complex reaction time task • The Sternberg High Speed Scanning Task • Selective Reminding Test • Serial Digit Test	Some concerns
Willmott and Ponsford, 2009 (crossover trial)	Australia	40	26.3	30	TBI Moderate to severe Subacute to chronic	68	0.3 mg/kg b.i.d.	14	• Ruff 2 and 7 Selective Attention Test Automatic (raw speed score) • Ruff 2 and 7 Selective Attention Test Controlled (raw speed score) • Selective Attention Task Simple (reaction time) • Selective Attention Task Complex (reaction time) • Selective Attention Task Complex (errors) • Selective Attention Task Complex (misses) • Four Choice Reaction Time Task DC (reaction time) • Four Choice Reaction Time Task DI (errors) • Four Choice Reaction Time Task DI (reaction time) • Four Choice Reaction Time Task SC (reaction time) • Four Choice Reaction Time Task SI (reaction time) • Symbol Digit Modalities Test (no correct in 90 seconds) (SDMT) • Sustained Attention to Response Task (SART) 3 errors • Sustained Attention to Response Task (SART) non-3 errors • LNS scaled score	Low risk

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Whyte *et al*. 1997 (cross-over trial)	US	19	30.8	21	TBI	514	0.25 mg/kg b.i.d.	2	• Go/no-go task (sustained arousal task) • Phasic arousal task • Distraction task • Behavioral inattention • Choice reaction-time task	Some concerns
Zhang *et al*. 2017	China	36/18	35.6	25	TBI Mild to severe, subacute	45	Starting from 5 mg/ day and gradually titrated to 20 mg/day	210	• Choice Reaction Time • Compensatory Tracking Task • Mental Arithmetic Test • Digit Symbol Substitution Test • MMSE	Some concerns
Modafinil										
Bivard *et al*. 2017 (crossover trial)	Australia	36	63	39	Stroke	270	200 mg/day	42	• MoCA	Low risk
Jha *et al*. 2008 (crossover trial)	US	51	38.3	31	TBI Mild to severe	2,106	400 mg/day	70	• ImPACT Verbal Memory • ImPACT Visual Memory • ImPACT Visual Motor Speed • ImPACT Reaction Time • Conners' Continuous Performance Test II	Some concerns
Poulsen *et al*. 2015	Denmark	41/21	70	53	Stroke	8	400 mg/day 200 mg/ day if 65 years or older	90	• MoCA	Some concerns
(Es)citalopram										
Kim *et al*. 2017	South Korea	478/241	63.6	39	Stroke	Within 21 days	10 mg/day	90	• MoCA	Low risk
Cao *et al*. 2020	China	97/49	62	51	Stroke	2–7	5–10 mg/day	90	• MMSE	Some concerns
Cao *et al*. 2020	China	99/52	N/A	N/A	Stroke	N/A	5–10 mg/day	90	• MMSE	Some concerns
Jorge *et al*. 2010	US	88/43	62.5	38	Stroke	32	10 mg/day escitalopram 5 mg/ day for patients >65 years	365	• RBANS • Trail Making Test-B • Trail Making Test B–A • COWAT • Stroop Color and Word Test • WAIS Similarities	Some concerns

(Continued)

Table 2 (Continued)

Study	Location	Sample size, total/ drugs	Mean age, years	Females, %	ABI	Mean time since ABI, days	Treatment protocol	Duration, days	Outcomes	Overall risk of bias according to ROB 2
Fluoxetine										
Lundström *et al.* 2020	Sweden	1500/750	70.8	38	Stroke	5	20 mg/day	180	• MoCA	Low risk
Paroxetine										
Pan *et al.* 2018	China	170/85	65.9	25	Stroke	2	20 mg/day	90	• MoCA	Some concerns
Sertraline										
Lee *et al.* 2005	South Korea	20/10	35.4	20	TBI Mild to moderate for 2 months to 1 year	32	100 mg/day	28	• MMSE • Critical Flicker Fusion Threshold (Hz) • Recognition Reaction Time (ms) • Motor Reaction Time (ms) • Total Reaction Time (ms) • Compensatory Tracking Task (pixel) • Compensatory Tracking Task (ms) • Mental Arithmetic Test (ms) • Sternberg Memory Scanning Task (ms) • Digit Symbol Substitution Test	Some concerns

10CRT, Ten-Choice Reaction Time; AAI, Auditory Immediate Index; ABI, acquired brain injury; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Portion; CDR, Cognitive Drug Research; COA, Continuity of Attention; COWAT, Controlled Oral Word Association Test; CVLT-II, California Verbal Learning Test-II; DKEFS, Delis-Kaplan Executive Function System; LNS, Letter Number Sequencing Task; MASQ, Mood and Anxiety Symptom Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; N/A, not applicable; PASAT, Paced Auditory Serial Addition Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TBI, traumatic brain injury; VII, Visual Immediate Index; WAIS, Wechsler Adult Intelligence Scale; WMS-R, Wechsler Memory Scale Revised.

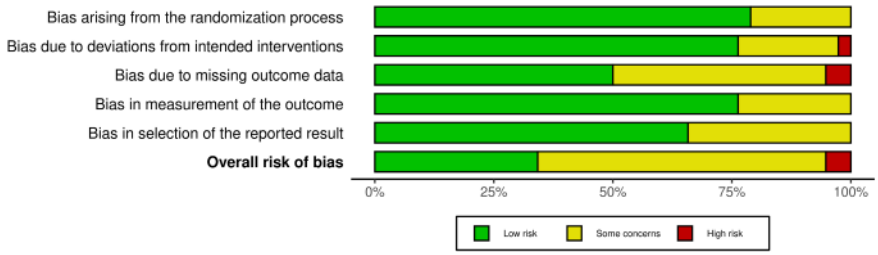

Figure 2 Summary of risk of bias assessment.

	Effect size			Sample size	
Neuromodulator system	***d***	**[95% CI]**	***P*-value**	***k***	**Std diff in means and 95% CI**
Adrenergic	0.22	[0.095–0.347]	0.001	22	
Cholinergic	0.35	[–0.053–0.755]	0.09	7	
Dopaminergic	0.002	[–0.144–0.148]	0.98	4	
Serotonergic	0.07	[–0.070–0.217]	0.32	8	

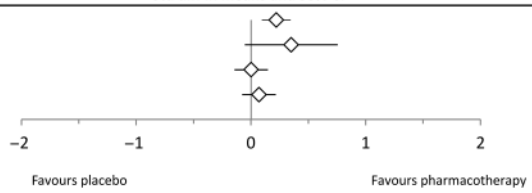

Figure 3 Forest plot of effect sizes on neuromodulator systems. CI, confidence interval.

	Effect size			Sample size	Weight	
Study	***d***	**[95% CI]**	***P*-value**	***n***		**Std diff in means and 95% CI**
Delbari 2011	0.250	[–0.380–0.880]	0.437	39	4.73%	
Dymowski 2016	–0.423	[–1.745–0.900]	0.571	10	1.49%	
Grade 1998	–0.654	[–1.533–0.225]	0.145	21	2.95%	
Jenkins 2019 (high caudate) *	–0.079	[–0.404–0.246]	0.634	22	8.91%	
Jenkins 2019 (low caudate) *	0.022	[–0.338–0.383]	0.903	18	8.30%	
Kim 2006	0.566	[–0.389–1.522]	0.245	18	2.58%	
Kim 2012 *	0.427	[0.065–0.788]	0.021	20	8.28%	
LeBlond 2019 *	0.387	[–0.013–0.788]	0.058	25	7.65%	
Lee 2005	0.155	[–0.731–1.042]	0.731	20	2.91%	
Johansson 2015 *	0.310	[0.075–0.545]	0.010	44	10.53%	
Mahalick 1998 *	0.684	[0.098–1.270]	0.022	14	5.18%	
McDonald 2017 a	0.406	[–0.249–1.060]	0.224	37	4.50%	
McDonald 2017 b	0.319	[–0.359–0.996]	0.356	34	4.30%	
Plenger 1996	1.142	[–0.181–2.464]	0.091	11	1.49%	
Speech 1993 *	0.139	[–0.446–0.724]	0.641	12	5.19%	
Willmott & Ponsford 2009 *	0.088	[–0.153–0.329]	0.475	40	10.42%	
Whyte 1997 *	0.222	[–0.201–0.644]	0.304	14	7.31%	
Zhang 2017	1.957	[1.137–2.777]	0.000	34	3.28%	
Total	0.279	[0.108–0.451]	0.001		100%	

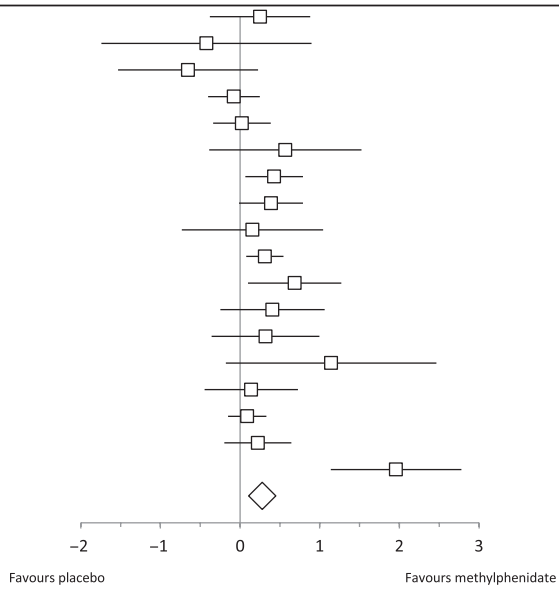

Figure 4 Forest plot of effect sizes (SMD) of studies on methylphenidate. *Crossover trial. CI, confidence interval.

Serotonergic agents (5-HT). In the group of serotonergic agents, the meta-analytic effect sizes were not significant for the effect of (es)citalopram ($k = 4$, $d = 0.15$, 95% CI: −0.10 to 0.12, $P = 0.287$) and sertraline ($k = 2$, $d = -0.28$, 95% CI: −0.73 to 0.18, $P = 0.23$). Meta-analysis was not feasible for fluoxetine[70] and paroxetine,[70] because only one study was available per agent.

Meta-regression analysis

Considering the number of observations available, meta-regression was only feasible for the meta-analytic effect of methylphenidate, see **Figures S2–S5**. We found no significant relations between the magnitude of effect sizes and any of the following moderator variables: mean age (in years, range = 10.7–71.3, $\beta = -0.0074$, $P = 0.51$ df = 14), sex (in percentage of female subjects, range = 11%–58%, $\beta = -0.0009$, $P = 0.90$, df = 14), time since injury (in days, range = 18–2,993, $\beta = -0.0001$, $P = 0.43$, df = 13), or treatment duration (in days, range = 1–210, $\beta = 0.0027$, $P = 0.5073$, df = 14). The moderator variable dosage was not available for meta-regression due to difference in reporting between studies.

DISCUSSION

This meta-analysis and meta-regression representing 4,434 patients with ABI aimed to provide aggregations of the available

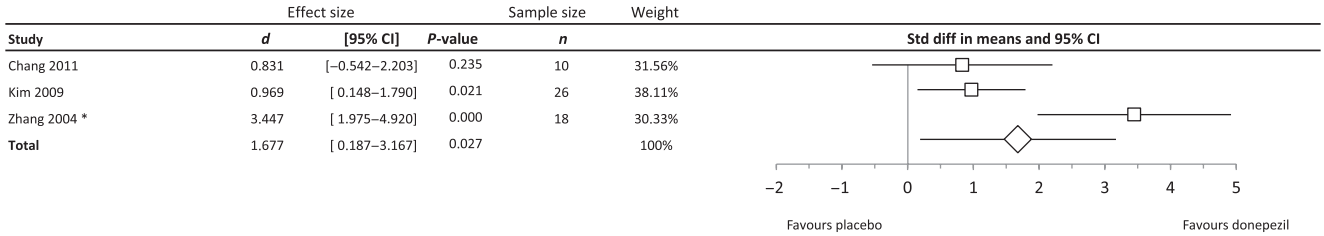

Figure 5 Forest plot of effect sizes (SMD) of studies on donepezil. *Crossover trial. CI, confidence interval.

randomized controlled trials regarding the effects of pharmacotherapy on cognitive functioning. The results indicate that methylphenidate has a small-sized beneficial effect on cognitive functioning in patients with TBI. Thanks to the meta-analytic approach, we were able to provide robust evidence for the beneficial effect of methylphenidate based on a much larger sample than previously reported, encompassing 12 RCTs representing 385 patients with ABI. Thereby, this study strengthens the evidence-base from the fragmented literature to support the consideration of methylphenidate for patients with TBI and cognitive impairment. The results further suggest that cholinergic modulation with donepezil may hold promising value, although no robust evidence was found for beneficial effects of other neuromodulating agents.

In the group of adrenergic agents, we found a robust small-sized meta-analytic effect of methylphenidate on cognitive functioning in patients with TBI. In-depth analysis revealed that small-sized positive effects of methylphenidate may be expected for cognitive functions related to executive memory, baseline speed, inhibitory control, and variability in responding. These findings are in line with a recent narrative systematic review,[72] which reported that methylphenidate may improve cognitive abilities, particularly working memory, processing speed, and/or aspects of attention. Our findings relating to executive memory and inhibitory control also align with the findings of studies showing that methylphenidate may enhance cognitive functioning by affecting neural networks related to working memory[73] and inhibitory control.[74] Two recent considerably smaller meta-analyses that aggregated up to 6 studies representing up to 148 patients that previously reported a positive effect of methylphenidate on processing speed,[75] and attention.[76]

In the group of cholinergic agents, we identified a large-sized and statistically significant effect for donepezil, suggesting that donepezil may be a promising pharmacological agent for the treatment of cognitive impairment in patients with ABI. However, it should be noted that this meta-analytic effect was based on only three very small studies ($n = 14–26$) with substantial heterogeneity in terms of patient characteristics (e.g., mean age, type of injury, and mean time since ABI). The meta-analytic effect also showed considerable instability in sensitivity analysis. Consequently, the results suggest promising value, yet further research is needed to determine the efficacy of donepezil in the treatment of cognitive impairment in ABI.[77,78] Currently, a large multicenter trial (NCT02255799) examines the effect of donepezil on memory impairments in individuals with TBI.

We found no evidence for beneficial effects of rivastigmine (4 studies), amantadine (2 studies), levodopa-carbidopa (2 studies), atomoxetine (1 study), dextroamphetamine (2 studies), modafinil (3 studies), or any of the serotonergic agents (8 studies). Due to the sparse literature for these pharmacotherapeutic options, our negative findings do not rule out potential value for cognitive functioning, or other treatment indications in this population. For example, a recent systematic review suggests that levodopa may have positive effects on motor function, mood, and promote wakefulness in stroke survivors.[79] Similarly, amantadine is the most commonly prescribed medication for patients with prolonged disorders of consciousness after TBI and is considered to promote functional recovery.[80]

The current study has limitations and strengths. According to our knowledge, this is the first study to examine the effects of all available pharmacotherapeutic agents aimed at improving cognitive functioning following both TBI as well as stroke, whereas aggregating the evidence across cognitive outcome measures. The majority of studies included in this review was limited by moderate to severe bias affecting the validity of their findings. Nevertheless, the meta-analytic effect of methylphenidate was replicated when including only those studies that had low risk of bias. Furthermore, aggregating evidence from a fragmented research field with a relatively large number of small and underpowered studies increases the risk of publication bias. This risk may be particularly high in the field of pharmacotherapy for TBI, as a recent analysis of registered trials on ClinicalTrials.gov found that the majority of completed trials had negative findings and only six were published.[81] However, it should be noted that the majority of the included methylphenidate studies in the current study also did not report a statistically significant effect. Moreover, we found no evidence of publication bias in the meta-analytic effect of methylphenidate. Last, it has been hypothesized that placebo effects may imitate the therapeutic effect of certain pharmacological agents, in particular, dopaminergic agents used in ABI populations.[82] Dopaminergic cortical circuits may in fact be sufficiently upregulated by placebo treatment alone to produce a therapeutic response, complicating the effort to identify a medication-specific effect in patients with TBI. Finally, it should be noted that the manifestation of cognitive impairment after ABI as well as the response to treatment is not only the result of the brain injury sustained, but is also influenced by risk factors such as age, prior brain injury, exposure to neurotoxic substances, and pre-existing conditions. Such factors should be taken into account when considering pharmacological treatment for cognitive impairment after ABI.

Future directions

The results of this study support the beneficial effects of methylphenidate for patients with TBI at the group level. Our meta-regression analysis was an attempt to identify factors that

predict the heterogeneity in the treatment response across studies, revealing no evidence for a modulating influence of sex, age, time since injury, or treatment duration. Indeed, meta-analytic techniques do not allow thorough investigation of interindividual differences in the treatment response. The distinct heterogeneity in the ABI population, with regard to the type, severity, and location of neuropathology, but also premorbid functioning and genetic make-up, are likely to influence the sensitivity of individuals to treatment with differential pharmacotherapeutic agents.[83] Matching the treatment at an individual level may therefore increase efficacy. Consequently, we suggest that future studies aimed at the efficacy of pharmaceutical treatments acknowledge that interindividual differences between patients can importantly influence the treatment response, and such differences should in fact be utilized to select the optimal treatment at the individual patient level. For example, the included study by Jenkins *et al*. stratified patients into groups with a hypodopaminergic or normo-dopaminergic state using neuro-imaging in an attempt to selectively target a subgroup of patients with optimal treatment response for a given neuromodulating agent.[44] Other options could involve the use of predictive and pharmacodynamic biomarkers,[84] as well as the integration of data from multiple sources, such as medical history, phenotypic genetic, and imaging data in combination with data-mining techniques. Likewise, careful stepwise dosage titration should also be considered in future studies, given the emerging evidence for complex non-linear dose–response relationships, which may also differ between patients.[33] Future research might also look into the synergistic effects of combinations of pharmacological agents and non-pharmacological treatments. For example, the use of pharmacotherapy alongside structured rehabilitation programs and combining pharmacological treatments with cognitive therapy,[51] noninvasive brain stimulation techniques[85] or physical exercise programs.[60,86] Moreover, treatment of cognitive impairment may also involve targeting other underlying factors, such as treating sleep disturbances through cognitive behavior therapy[87] or pharmacological agents,[88] highlighting the multifaceted nature of handling cognitive impairment in ABI. Last, future research should extend to understanding how pharmacological improvements in cognition translate into daily life functioning and quality of life for patients with ABI.[89]

CONCLUSION

This study provides meta-analytic evidence for a small, beneficial, and robust effect of methylphenidate on cognitive functioning of patients with TBI. Donepezil may hold promising value, but the evidence is based on a small number of studies with heterogeneous results. We found no robust evidence for positive effects of other neuromodulating agents in patients with ABI. Methylphenidate can be recommended as an effective treatment option for improving cognitive functioning in patients after TBI. The results of this study may aid in clinical decision making for off-label treatment options, can be used for the development and updates of practice guidelines, and may inform future pharmacotherapeutic studies.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank Wichor Bramer from the Erasmus MC Medical Library for developing and updating the search strategies.

FUNDING

This work was supported by “Daan Theeuwes Fonds” and “Daan Theeuwes Centrum voor Intensieve Neurorevalidatie.”

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.vdV., M.K., A.vl., S.P., P.M.B., and J.O. wrote the manuscript. R.vdV., M.K., S.P., P.M.B., and J.O. designed the research. R.vdV. and S.B. performed the research. R.vdV., M.K., S.B., P.M.B., and J.O. analyzed the data.

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