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Systematic Review

The Use of Methylphenidate to Improve Executive Functioning in Pediatric Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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Abstract: Background/Objectives: This systematic review aimed to investigate the efficacy of methylphenidate medication in the treatment of cognitive problems, such as attention, following pediatric traumatic brain injury. Previous reviews have focused on a broader population of acquired brain injury in pediatrics. **Methods:** Six databases were systematically searched, and eleven relevant reports were included, of which five were randomised controlled trials (RCTs) and six were prospective cohort designs with no control arm. The risk of bias was assessed for each of the studies using appropriate tools. **Results:** Eleven studies were included in this study for data extraction consisting of 376 participants. Our primary outcome of the efficacy of methylphenidate in improving attention was assessed in the included studies using a variety of tools. A meta-analysis was only possible for studies using the continuous performance test data, which showed an overall insignificant reduction of 36.07 (95% CI [−96.94, 24.80], $p = 0.25$). Other outcomes, such as the Conners' rating scale and the behaviour rating interview of executive function, also did not show an overall difference after methylphenidate treatment. However, the risk of bias across all studies was judged as moderate to high. **Conclusions:** We conclude that there is currently no evidence to support the use of methylphenidate to improve cognitive outcomes in pediatric traumatic brain injury patients. Significantly larger high-quality studies are needed to determine an effect on executive functioning outcomes after methylphenidate treatment in pediatric traumatic brain injury.

Keywords: traumatic brain injury; pediatric; child; head trauma; methylphenidate; attention; behaviour; cognition

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1. Introduction

Traumatic brain injury (TBI) refers to an acquired brain injury in which an external physical force results in damage to the brain. There is a high incidence of TBI in the pediatric population, with head injury being one of the most common causes of hospital admission in this group [1]. One study calculated the crude incidence of pediatric TBI as 687 cases per 100,000 children per year [2]. Among the mechanisms accounting for injury are falls, sports-related injuries, and road traffic crashes [3]. It can result in symptoms like neurocognitive dysfunction. Specific neurocognitive consequences include loss of consciousness, confusion, and post-traumatic amnesia (PTA). The severity of the injury may be determined using factors including the duration of PTA, the Glasgow coma scale

(GCS), and the duration of the loss of consciousness [4]. Persistent neurocognitive outcomes of TBI include deficits in executive functioning, attention, and processing speed, as well as changes in behaviour and mood. These domains can be affected regardless of the severity of the injury. Diffuse injuries of the brain can impact vulnerable brain regions involved in attention, including the frontopolar, orbitofrontal, anterior temporal, and lateral temporal surfaces [5].

The neurocognitive consequences of TBI are significant in the pediatric population. One meta-analytical review [6] compared the effects of pediatric severe TBI to mild and moderate forms. Several neurocognitive domains, including attention, problem-solving, and visual perception, were examined. In longitudinal studies of moderate TBI, improvements in attention mainly occurred in the first two years after injury. Attention impairments persisted in both moderate and severe TBI groups. The results indicate that attention deficits following TBI may be persistent, with a slow recovery. Attention deficit is, therefore, a significant consequence of pediatric TBI, and in this setting, it may also be described as new-onset (or secondary) attention deficit hyperactivity disorder (ADHD) [7]. There are difficulties estimating its prevalence, with studies reporting a range of secondary ADHD rates [8]. A contributing reason might be that attention deficits do not necessarily appear immediately after injury. One study [9] concluded that secondary ADHD may occur up to ten years after childhood TBI, with around 62% developing 'secondary' ADHD in this period after severe TBI. However, this study excluded mild TBI data from their analysis [9], and the relevance of these results to the setting of mild TBI remains unclear.

Primary ADHD management has been well-researched in the pediatric population. Thus, these potential pre-existing management options might be explored in a 'secondary' ADHD context. Pharmacological treatment options for ADHD include methylphenidate (MPH) and dexamphetamine, with the medication choice depending on factors like co-morbid conditions. MPH is a central nervous system stimulant administered orally, acting as a noradrenaline and dopamine reuptake inhibitor (NDRI). Non-pharmacological ADHD treatment consists of psychological intervention, such as cognitive behavioural therapy (CBT), alongside lifestyle advice [10]. The focus of this systematic review is the utility of one ADHD medication, MPH, in the pediatric TBI context. Previous systematic reviews with some relevance to this topic exist, with one 2019 meta-analysis [11] demonstrating a significant reduction of -0.806 in the choice reaction time favouring MPH, although no significant effects on attention measures were observed. However, this meta-analysis was limited to adults. A 2022 review [12] studied the use of MPH in the pediatric population, addressing the outcome of attention, but investigated a broader population than TBI alone, including non-traumatic injuries such as brain tumours. Therefore, a systematic review that focuses on the use of MPH in a pediatric TBI population is justified to determine its efficacy in this context.

The overall review aimed to examine the effect of MPH compared to control on a broad range of cognitive outcomes in pediatric patients after TBI. The primary outcome was attention, with secondary outcomes relating to executive functioning and adverse effects. Based on previous reviews, the authors postulated that the review might reveal small improvements in cognitive outcomes, including attention, which favour MPH compared to control.

2. Materials and Methods

A systematic review was conducted following the guidance provided by the preferred reporting items for systematic reviews and meta-analysis (PRISMA) [13]. The review was registered with the international prospective register of systematic reviews (PROSPERO), CRD42024546406, prior to completing full-text screening.

2.1. Literature Searching

A systematic review was performed between 28 April and 15 August 2024. Six electronic databases were systematically searched with pre-defined search terms: MEDLINE, Embase, Web of Science, American Psychology Association (APA) PsycInfo, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed.

A research question was formulated after initial scoping searches using the MEDLINE and Embase databases. The population, intervention, comparator, outcome, and study design (PICOS) framework [14] was used to ensure that the question was specific and concise:

1. Population: pediatric population (aged below 18 years of age) with a history of TBI.
2. Intervention: MPH.
3. Comparator: placebo or standard medical care.
4. Primary outcome: attention.
5. Secondary outcomes: other aspects of cognitive function, behaviour, and adverse events.

Six electronic databases were used for the literature search. The Cochrane Handbook for Systematic Reviews of Interventions [15] recommends using two or more bibliographic databases to ensure optimal coverage. Here, the use of six was justified by the cross-disciplinary nature of the topic [16]. Grey literature was sourced through the OpenGrey website and through hand-searching citations of previously identified studies. Where the full text was unavailable, the authors were contacted via ResearchGate, and the results were excluded if these attempts were unsuccessful.

2.2. Search Terms

The search strategy was developed alongside advice from a University of Birmingham's specialist librarian. Search terms, shown in Table 1, were developed using the PICOS framework. Synonymous terms were used to broaden the results, including alternative terms for medication identified using the British National Formulary (BNF) website [17]. Synonyms were combined with the Boolean operator OR within the search fields.

Table 1. Terms used in the search strategy linked to aspects of the research question.

Population	Intervention	Injury Type
p?ediatric *	Methylphenidate/	traumatic brain injury
child *	Concerta	brain injury
Child/	Ritalin	head injury
infan *	Delmosart	head trauma
Infant/	Equasym	concussion
adolescen *	Medikinet	Brain injuries, traumatic/
Adolescent/		Craniocerebral trauma/

* = wildcard symbol used to broaden the search.

The use of these search terms was adjusted to each database. The authors completed 'topic searches' using the Web of Science database and the title and abstract fields in databases such as MEDLINE and Embase.

2.3. Inclusion and Exclusion Criteria

The results from the searches were imported into the Covidence software [18] (Version 2, Veritas Health Innovation, Melbourne, Australia) for screening. Duplicates were excluded automatically by the software and manually by the reviewers (A.P.-F. and Z.A.).

Two screening stages were completed:

1. An initial title and abstract screening performed by two independent reviewers.
2. A full-text review.

The authors used the eligibility criteria in Table 2 to establish the inclusion and exclusion of studies. The criteria were based on the above PICOS framework. The Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence [19] were used to determine which study designs were to be included. Both retrospective and prospective literature were included to broaden the data collected. However, case reports and case series were excluded, as these are lower on the hierarchy of evidence. Studies needed to have available English language translations due to time and resource constraints. Each reviewer made inclusion and exclusion decisions independently based on the criteria, and any discrepancies were subsequently resolved through discussion.

Table 2. Eligibility criteria for inclusion and exclusion of studies with justification.

Inclusion Criteria	Exclusion Criteria	Justification
Including pediatric population aged 0–18 years	Only adult population	The focus of this review was to look at the efficacy in a pediatric population
History of traumatic brain injury	Other forms of brain injury	The focus of this review was the efficacy in a traumatic injury population
Studies in humans	Studies in animals	Scoping searches revealed that studies in humans were numerous enough to analyse and compare
Methylphenidate as intervention	Medications other than methylphenidate, including those in the same drug class	The focus of the review is to compare the efficacy of methylphenidate to placebo and standard care
Study designs meeting OCEBM levels one, two, or three, excluding reviews	Study designs meeting OCEBM level four or five and reviews	Low evidence levels would reduce the overall quality of the systematic review
English language translation available	No English language translation available	Time and resource constraints limited translation abilities
Full-text access available	Articles with abstract only, conference summaries, or no full-text available	Full-text was needed for a complete quality assessment and analysis of the data
No limitation on publication dates	Unpublished results	The field is novel, and previous systematic reviews did not focus on the same research question

Notes: OCEBM: Oxford Centre for Evidence-Based Medicine.

2.4. Data Extraction

One author (A.P.-F.) extracted relevant data from the study texts using a Microsoft Excel spreadsheet, and a second author (Z.A.) confirmed the process, with any discrepancies resolved through discussion. The study characteristics that were reported included the following: first author and year of publication, study origin, study design, number of participants, mean age and range of participants, female:male participant ratio, dosing regimen, and any measurements that were relevant to the primary and secondary review outcomes. This was used to formulate the study characteristics table, and additional tables for outcome measurements were created to collate comparable study results.

2.5. Quality Assessment

The risk of bias in the included studies was assessed using the Cochrane risk of bias tool 2 (RoB2) [20] for randomised controlled trials (RCTs) and the risk of bias in the non-randomised studies of interventions (ROBINS-I) tool [21] for non-randomised trials.

Two authors (A.P.-F and Z.A.) independently completed the relevant tool for each study. Any subsequent disagreements were settled through discussion.

The RoB2 tool is comprised of five domains assessing the risk of bias arising from the randomization process, the deviations from intended interventions, the missing outcome data, the measurement of the outcome, and the selection of outcomes reported. The RoB2 algorithms were used to determine each domain as low or high risk of bias or as having 'some concerns'. An overall risk of bias result was determined using a separate algorithm, dependent on the result for each domain.

The ROBINS-I tool is comprised of seven domains for risk-of-bias assessment based on the RoB2 tool. These include bias due to confounding, selection of participants, classification of the intervention, deviation from the intervention, missing outcome data, measurement of the outcome, and selection of the reported outcome. For each domain, a conclusion of low, moderate, serious, or critical risk was determined. An overall judgement was subsequently made based on the results across domains.

2.6. Statistical Analysis

A meta-analysis was performed on the outcome data reported in three or more studies using the RevMan software [22] (Version 5.4, The Cochrane Collaboration, London, UK), employing a random effects model. The heterogeneity of the results was assessed using the I^2, Chi^2, and Tau^2 statistics. A forest plot was created to visualize the results, including mean differences and confidence intervals, compared to the null line. In the current review, only one outcome measurement was suitable for meta-analysis. Narrative synthesis was used to analyse the other outcomes.

3. Results

3.1. Study Selection

Literature searching of the six electronic databases yielded 389 results. Embase yielded 153 results, MEDLINE yielded 54 results, 26 results were yielded from APA PsycInfo, the Cochrane CENTRAL database yielded 46 results, Web of Science yielded 78 studies, and 32 results were yielded from searching the PubMed database. Eight additional articles were identified by the authors outside of these databases: four from grey literature and four from hand-searching of citations. These additional results were excluded, as they were deemed irrelevant when the full text was obtained. The Covidence software removed 146 duplicates automatically, and an additional 11 studies were manually marked as duplicates. In total, 232 results underwent title and abstract screening by two independent reviewers. This process excluded 193 results due to lack of relevance. Full-text retrieval was sought for the remaining 39 papers. Of these, 35 full texts were obtained, while the other four papers were excluded as unavailable. The full-text screening process excluded 24 results, leaving nine studies (with eleven included reports) for data extraction [23–33]. The reasons for exclusion in the full-text screening stage are stated in the PRISMA flow diagram (Figure 1).

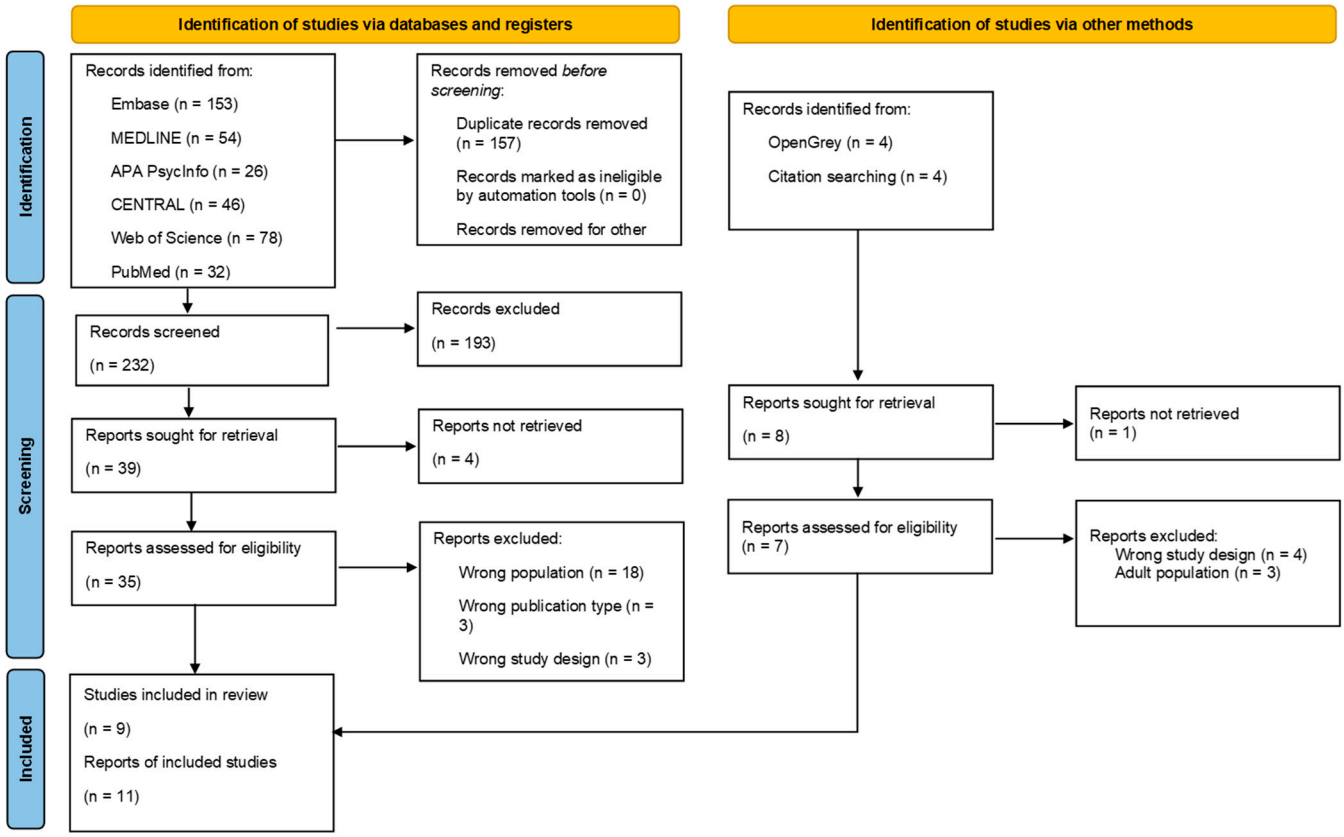

Figure 1. The PRISMA flow diagram representing the exclusion and inclusion of studies.

3.2. Study Characteristics

The main study characteristics of the eleven included papers were extracted and are summarised in Table 3. The publication dates of the studies span from 1990 to 2024, a 34-year period. Of the eleven studies, five [23–27] were reports of RCTs (two of which had two reports for separate data collected), one [28] had a prospective cohort design without a control, two [29,30] were prospective controlled trials, and three [31–33] were retrospective reviews of medical records. Nine [23,24,26,27,29–33] of the papers originated from the United States of America ('USA'), while the other two [25,28] originated from Australia and Turkey, respectively.

The sample size of the controlled trials ranged from eight to twenty-six participants. Of the retrospective reviews, one [31] was a multi-centre study comprising 234 patients; the other two medical record reviews [32,33] focused on 10 patients each. In total, this review included 376 participants, of which 251 (66.8%) patients were male.

In terms of dosing regimen, the seven controlled trials [23–27,29,30] used a crossover design involving exposure to one condition and then the other. The majority of the controlled studies compared MPH to placebo. Nikles et al. [25] compared two conditions (MPH and dexamphetamine) to a placebo control. Of the three retrospective reviews, one [33] examined the use of MPH on its own, one [31] looked at the use of MPH only and when combined with amantadine, and one [32] looked at the broader use of dopamine agonists including MPH.

In terms of patient characteristics, the severity of TBI in the participants was often documented using mean GCS. Six of the papers had a reported or calculable mean GCS [23,24,26,28,29,33]. Of these, two papers [29,33] reported a mean within the range for severe TBI (below eight), while the other four papers [23,24,26,28] had a mean GCS within the range for moderate TBI [34].

Table 3. Characteristics of the included studies.

Study	Study Origin	Type of Study	Number of Participants	Mean Age of Participants (Range)	Male:Female Ratio	Mean GCS (SD)	Dosing Regimen	Measurements Related to Primary and Secondary Outcomes
LeBlond et al., 2019 [23]	USA	RCT	26	11.25 (6–17)	20:6	11.9 (4.2)	Four weeks of one of MPH or placebo, followed by four weeks of the other condition	BRIEF parent-report and self-report CPT D-KEFS VF WISCIV-PSI
Kurowski et al., 2019 [24]	USA	RCT	26 (20 completed)	11.5 (6–17)	20:6 (15:5 completed)	11.9 (4.2)	Four weeks of one of MPH or placebo, followed by four weeks of the other condition	VADPRS PSERS Vital signs
Nikles et al., 2014 [25]	Australia	RCT	10	12.9 (6–16)	6:4	Moderate to severe	Three pairs of one week treatment periods (of placebo, MPH, and dexamphetamine)	Conners' 3 rating scales (parent and teacher) BRIEF parent-report, teacher-report, and self-report ECBI
Baker et al., 1990 [26]	USA	RCT	8	11 (7–15)	5:3	11.4 (4.9) at hospital admission	Two weeks of one of MPH or placebo, followed by two weeks of the other condition	MFFT CPT Stroop test Conners' abbreviated parent–teacher questionnaires Central-incidental method HRNB- seashore rhythm test, Trail making part A and B, progressive figures test ANSER PIC (short form)
Clark et al., 1990 [27]	USA	RCT	8	11 (7–15)	5:3	Unknown (had to meet baseline test requirements)	Two weeks of one of MPH or placebo, followed by two weeks of the other condition	MFFT CPT Stroop test Seashore rhythm test Trail making part A and B Abbreviated parent–teacher questionnaires
Ekinci et al., 2017 [28]	Turkey	Prospective cohort	20	12.7 (6–18)	15:5	8.6 (2.7)	IR-MPH, increased to a dose of 10 mg twice daily for first week and 10 mg three times a day for second week	Turgay DSM-IV disruptive behavior disorders rating scale parent and teacher forms Conners' 3 rating scale-revised (parent and teacher) CGI-S CGI-I Adverse effect scale
Mahalick et al., 1998 [29]	USA	Prospective controlled trial	14	10.7 (5–14.5)	11:3	8.1 (4.1)	14 days of either MPH or placebo with a washout period of 12 h, then crossed over	Gordon diagnostic system (model III) The Woodcock–Johnson psychoeducational test battery- revised Ruff 2 and 7 cancellation test
Williams et al., 1998 [30]	USA	Prospective controlled study	10	10.5 (8.3–16.7)	9:1	Unknown (had to meet baseline test requirements)	Two-week testing period, with four days of MPH or placebo and a three-day washout period before cross-over	Conners' 3 rating scale (parent and teacher) SDMT CPT SMRTT SRT RANT Psychomotor skills- Purdue pegboard, finger tapping test, developmental test of VMI

Table 3. *Cont.*

Study	Study Origin	Type of Study	Number of Participants	Mean Age of Participants (Range)	Male:Female Ratio	Mean GCS (SD)	Dosing Regimen	Measurements Related to Primary and Secondary Outcomes
Caliendo et al., 2024 [31]	USA	Retrospective review	234	11.6 median (2 months–21 years)	146:88	Unknown	Had been given MPH	Demographic data MPH dosing patterns, adverse events Cognitive state (at admission, discharge, and other time points)
Patrick et al., 2003 [32]	USA	Retrospective review	10	13.7 (8–19)	7:3	'Low response state' for 30 days or more	Given a dopaminergic agonist (amantadine, pramipexole, bromocriptine, levodopa, or MPH)	WNSSP scores before and on medication
Hornyak et al., 1997 [33]	USA	Retrospective review	10	10.9 (3–16)	7:3	6.2 (range 5 to 9)	Had been given MPH	Ranchos Los Amigos level of cognitive functioning Subjective/qualitative comments on results

Notes: ANSER: aggregate neurobehavioral student health and educational review; BRIEF: behaviour rating interview of executive function; CGI-I: clinical global impression-improvement; CGI-S: clinical global impression-severity; CPT: continuous performance test; D-KEFS VF: Delis–Kaplan executive function system verbal fluency; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ECBI: Eyberg child behaviour inventory; GCS: Glasgow coma scale; HRNB: Halstein–Reitan neuropsychological battery; IR-MPH: immediate-release methylphenidate; MFFT: matching familiar figures test; MPH: methylphenidate; PIC: personality inventory for children; PSERS: Pittsburgh side effects rating scale; RANT: rapid automatized naming test; RCT: randomised controlled trial; SD: standard deviation; SDMT: symbol digit modalities test; SMRTT: Sternberg memory and reaction time test; SRT: sentence repetition task; TBI: traumatic brain injury; USA: United States of America; VADPRS: Vanderbilt attention deficit hyperactivity disorder diagnostic parent rating scale; VMI: visual–motor integration; WISCIV-PSI: Wechsler-Intelligence Scale for Children, 4th Edition, Processing Speed Index; WNSSP: Western neuro sensory stimulation profile.

3.3. Risk-of-Bias Assessment

Risk-of-bias tools were used to assess quality in all eleven included studies. The RoB2 tool was used for the five RCTs [23–27] (Figure 2A,B), while the six remaining non-randomised studies [28–33] were assessed using the ROBINS-I tool (Figure 3A,B), and summary charts, as well as the risk of bias in each of the individual domains, are also shown for the included studies. Overall, nine of the eleven included studies [23,24,27–33] had a high/serious risk of bias, while the remaining two [25,26] were deemed to have 'some concerns'. For the RCTs, much of the high risk of bias resulted from missing outcome data and bias in the selection of the reported results. Some studies also had some concerns in the randomisation process, missing outcome data, and bias in the selection of the reported results. For the non-RCTs, a high risk of bias resulted from bias due to confounding, participant selection, classification of interventions, and outcome measurement.

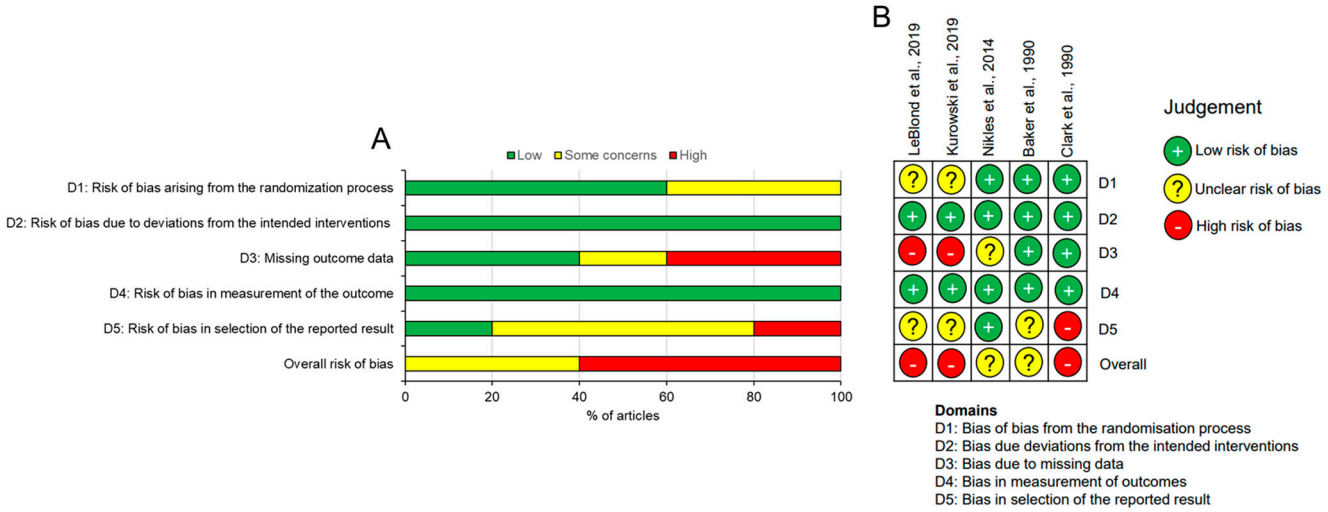

Figure 2. Risk of bias assessments for the included RCTs [23–27]. (**A**) Summary chart and (**B**) risk of bias in individual studies.

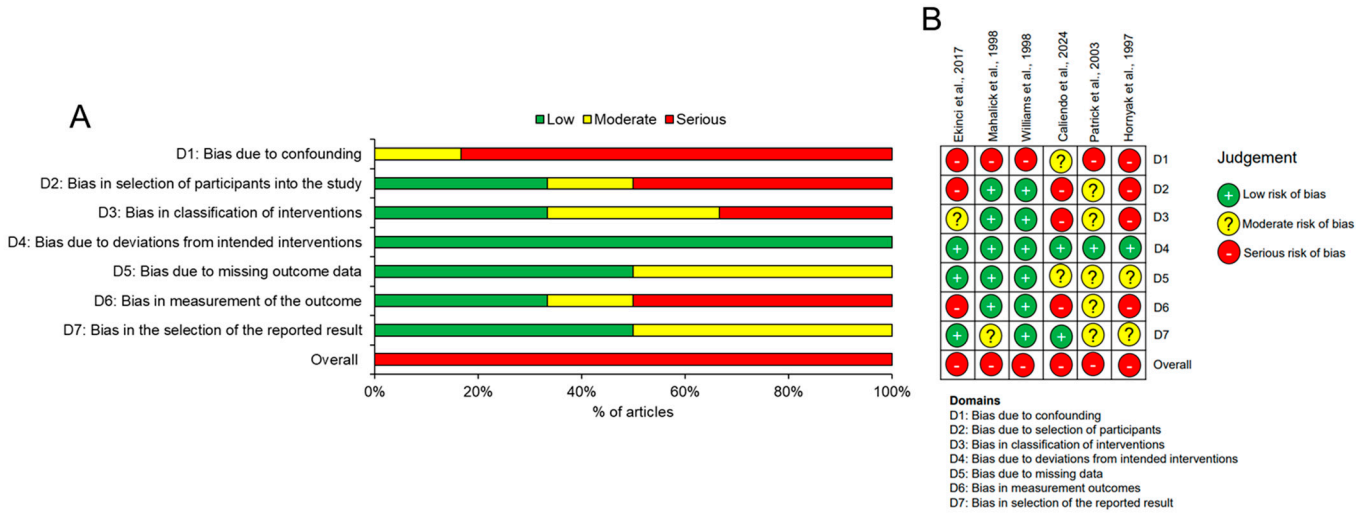

Figure 3. Risk of bias assessments for the included non-randomised studies [28–33]. (**A**) Summary chart and (**B**) risk of bias in individual studies.

3.4. Primary Outcome

Data for the primary outcome of attention were extracted, including mean scores and standard deviations (SDs). The attention measurement scales used varied between

the included studies. These included the following: the continuous performance test (CPT) [23,26,27,30]; the Vanderbilt attention deficit hyperactivity disorder diagnostic parent rating scale (VADPRS) [24]; Conners' 3 rating scale [25,28,30]; the matching familiar figures test (MFFT) [26,27]; the Stroop colour and word test [27]; the central-incidental method [26]; the seashore rhythm test [27]; the trail-making test (parts A and B) [26,27]; the Turgay Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV) the disruptive behavior disorders rating scale [28]; the Gordon diagnostic system (model III) [29]; and the Ruff 2 and 7 cancellation test [29].

Of the above measures, only the CPT was used to generate comparable data across three or more studies, and therefore, only one meta-analysis was possible, represented as a forest plot in Figure 4. The CPT is an administered test that measures reaction times to targets as well as responses to 'non-targets' [35]. From this, the reaction times and number of errors made are recorded. The CPT reaction times (in milliseconds) were available for three studies [23,26,30], with a lower reaction time indicative of a better cognitive result. The studies measured CPT scores at a range of follow-up times: regularly over a four-week period [26], after one week of treatment [30], and at optimal MPH dose [23]. All three studies reported a reduction in the mean CPT score for the MPH condition compared to placebo, meaning that MPH treatment led to an improvement in CPT performance. A meta-analysis was conducted on pooled data from the three studies, demonstrating a pooled reduction of −36.07 ms ((95% CI −96.94, 24.80)); $p = 0.25$). However, this result was not statistically significant. Scores for CPT were also measured by Clark et al. [27], but only the overall trends were reported, and hence, they could not be used in the meta-analysis.

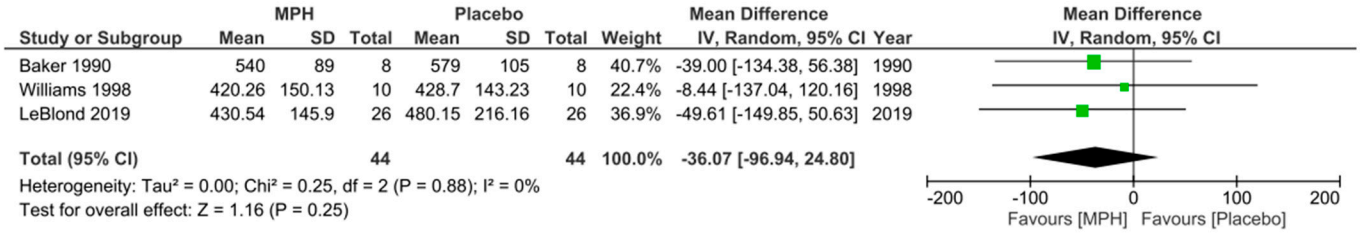

Figure 4. Forest plot for the primary outcome of attention, using CPT reaction time (ms) data in MPH and placebo groups [23,26,30].

The heterogeneity for the three studies included in this CPT meta-analysis was calculated at 0% using the I^2 test, suggesting that further studies are needed to accurately calculate heterogeneity. Additionally, the low number of total participants, 44, means that statistical power is decreased for this result.

The Conners' 3 rating scale is an alternative measure of attention, using parent- or teacher-reported questionnaires as a proxy measure. This scale was used by four included studies. However, the outcomes were not measured consistently, and therefore, a meta-analysis was not possible. For example, Nikles et al. [25] and Williams et al. [30] compared scores in stimulant and placebo groups, but Williams et al. [30] reported the scores from the global index subscale only. Clark et al. [27] reported trends in the data rather than numerical values. Ekinci et al. [28] reported mean changes in ratings at the endpoint of intervention compared to baseline scores. Table 4 demonstrates the Conners' data comparing MPH and placebo in parent and teacher reports. All mean scores are lower for the stimulant groups compared to placebo. However, none of these differences were statistically significant.

Additional attention measures were each used by a single study only. Data tables for these measures are included in the supplementary materials (Supplementary Materials, Tables S1–S11).

Table 4. Conners' 3 rating scale results for MPH compared to placebo groups.

Study	Type of Score	Stimulant Group (Mean ± SD)	Placebo Group (Mean ± SD)
Nikles et al., 2014 [25]	Parent-rated	10.9 ± 4.9	13.3 ± 5.4
	Teacher-rated	6.5 ± 4.4	11.0 ± 5.2
Williams et al., 1998 * [30]	Parent-rated	56.50 ± 14.71	56.90 ± 24.69
	Teacher-rated	53.83 ± 13.78	61.29 ± 10.68

* Global index subscale.

3.5. Secondary Outcomes

Several secondary outcomes were examined by the authors. In terms of broader executive functioning, the behavior rating interview of executive function (BRIEF) was compared across two of the studies (Table 5). This is a self-, teacher- or parent-reported questionnaire. LeBlond et al. [23] compared sub-components of the parent- and self-reported scores between MPH and placebo groups. Nikles et al. [25] examined both parent- and teacher-reported scores. Table 6 demonstrates that mean scores for the groups not treated with stimulants were consistently higher than those for the stimulant group, indicating poorer executive functioning in the untreated groups. However, the findings of Nikles et al. [25] all included the null value in their 95% credible region and thus were not statistically significant at a 5% significance level.

Table 5. BRIEF scale results for MPH and placebo groups.

Study	Type of Score	Stimulant Group (Mean ± SD)	Placebo Group (Mean ± SD)
LeBlond et al., 2019 [23]	Self-rated (GEC)	41.10 ± 3.53	46.03 ± 3.53
	Parent-rated (BRI mean)	58.49 ± 1.84	62.88 ± 1.84
Nikles et al., 2014 [25]	Parent-rated	147.8 ± 29.8	152.3 ± 27.4
	Teacher-rated	127.4 ± 24.1	143.2 ± 20.2

Notes: BRI: behavior rating index; GEC: global executive composite.

Table 6. Adverse events in MPH and placebo groups.

Study	Stimulant Group (%)	Placebo Group (%)
Clark et al., 1990 [27]	37.5	25.0
Ekinci et al., 2017 [28]	55	-
Caliendo et al., 2024 [31]	8.0	-

Additional secondary outcomes are recorded in supplementary data tables. These include executive functioning (Supplementary Materials, Tables S12–S18), behaviour (Supplementary Materials, Table S19), psychomotor function (Supplementary Materials, Table S20), hyperactivity (Supplementary Materials, Tables S21 and S22), and responsiveness (Supplementary Materials, Table S23) measures. Each of these measures was used by a single study only.

Four of the eleven studies [24,27,28,31] examined the adverse events of MPH and placebo, as shown in Tables 6 and 7. Three of the studies [27,28,31] measured the number of adverse events and the percentage of the sample that these represented (Table 6). Clark et al. [27] found a higher percentage of participants experiencing side effects in the stimulant group (37.5%) compared to control (25.0%). Kurowski et al. [24] used the Pittsburgh side effects rating scale (PSERS), which rates the severity of various side effects from a score of zero (none) to three (severe), recording a mean value and standard deviation for each subcategory (Table 7). One of the highest mean scores in the stimulant group was in the 'change in appetite' subcategory.

Table 7. Adverse events in MPH and placebo groups using the PSERS (at week 4).

Study	Type of Event	Stimulant Group (Mean ± SD)	Placebo Group (Mean ± SD)
Kurowski et al., 2019 [24]	Change in appetite	0.3 ± 0.5	0.2 ± 0.4
	Extreme sadness	0.0 ± 0.0	0.1 ± 0.2
	Headache	0.1 ± 0.3	0.2 ± 0.4
	Irritability	0.2 ± 0.4	0.3 ± 0.6
	Listless	0.1 ± 0.3	0.1 ± 0.3
	Picking at	0.3 ± 0.6	0.4 ± 0.6
	Repetitive movements	0.1 ± 0.2	0.1 ± 0.2
	Sees/hears things	0.0 ± 0.0	0.0 ± 0.0
	Shaky	0.1 ± 0.2	0.1 ± 0.4
	Socially withdrawn	0.0 ± 0.0	0.1 ± 0.2
	Stomach-ache	0.2 ± 0.5	0.0 ± 0.0
	Suicidal/homicidal ideation	0.0 ± 0.0	0.1 ± 0.2
	Trouble sleeping	0.2 ± 0.4	0.2 ± 0.5

4. Discussion

This systematic review evaluated the use of MPH following pediatric TBI, with attention as the primary outcome. Literature searching resulted in 11 included studies. The findings of one meta-analysis conducted on CPT data favoured MPH, but this was not statistically significant. Other measures of attention and secondary outcomes demonstrated a trend in the expected direction but were not statistically significant, and methodological weaknesses were considered to impact this. The adverse events of MPH and placebo were examined, but only Clark et al. [27] compared the percentage of side effects in MPH and placebo groups. The risk of bias was moderate to serious in all included studies.

Therefore, the evidence in this review does not support the use of MPH in the treatment of the cognitive impacts on pediatric TBI. Elsewhere in the literature, a previous review [12] regarding a broader pediatric population of acquired brain injury found a small benefit in sustained attention in MPH groups compared to control. This was based on a meta-analysis of CPT results and results from the Conners' scales. Importantly, the previous study also found that the efficacy of the intervention depended on the previously diagnosed ADHD status of the participants. This may be a confounding factor in the current study, as not all 11 studies recorded previous ADHD status. Other factors, such as the timing and severity of injury, may have influenced the utility of MPH, as neuroinflammation is postulated to be an important mechanism in experiencing neurocognitive symptoms such as attention issues [36]. However, it is possible that the non-significant results found by the current study might be the result of a lack of efficacy for MPH in treating cognitive outcomes in pediatric TBI patients. In ADHD, however, MPH acts as an NDRI, but much is still unknown about its specific mechanism on attention [37].

In future research on this topic, there is a need for RCTs with larger sample sizes and better-quality study designs to eliminate potential risks of bias. Larger studies would allow subgroup analysis to be performed, allowing beneficial characteristics and confounding factors to be identified.

Limitations of Individual Studies

The included studies in this study have several limitations. Only 11 studies were included, with high-quality studies lacking. Quality assessments of the studies revealed bias in the RCTs resulting from missing data. Confounding was a key contributor to bias in the non-randomised trials. This resulted from differing injury characteristics, such as time since injury, as well as different lengths of follow-up. Many studies did not use analysis methods that adjusted for confounding factors. In terms of study designs, three of the

studies [31–33] were retrospective reviews of medical records, meaning that they were non-selective and lower on the hierarchy of evidence. These studies had less consistency in the intervention in terms of dosing and timings. The small sample size of many of the controlled studies means that there is low statistical power. Additionally, subgroup analysis could not be performed, which would account for factors such as the age range of participants. In terms of TBI characteristics, there were differences between the studies. The anatomical location of the injury was included in the analysis in some studies, such as Ekinci et al. [28], but this was not measured across all 11 studies. Some trials had a baseline requirement for executive functioning, such as intelligence quotient (IQ) scoring. In addition, studies that included both adult and pediatric patients, without separation of the data, were subsequently excluded from the analysis.

The outcomes of interest were not measured in a consistent and comparable way, which made it more difficult to analyse the studies. Multiple scales were used across the studies. Some used direct assessments, while others used parent and teacher reports as a proxy. The pediatric study population meant that proxy measures were often needed, as participants below a certain age are less able to express their behaviours or to complete direct assessments. However, the use of these indirect measures increased the subjectivity of the results. In direct measures, the test–retest intervals were not consistent between the studies, which may be a factor in the improvement of the results. More recent research in adults has included functional magnetic resonance imaging (fMRI) data alongside observed behavioural outcomes. This enables researchers to observe how brain activity and the underlying brain anatomy are affected [38]. Most of the studies did not consistently measure additional important secondary outcomes, including behavioural problems, mental fatigue, and aggression. It would be useful to also be able to compare these outcomes in future studies.

The intervention and control conditions varied between the trials. Different dosing regimens and formulations of MPH were used. Some studies also assessed the effect of combinations of medication, for example, amantadine with MPH [31]. The use of a placebo as a control may lead to a placebo effect, causing improvement in participants. This is partially accounted for by Kurowski et al. [24] through using higher tolerated MPH doses, but not all included trials explicitly stated methods to account for a placebo effect. The length of follow-up of the participants was not consistent between the studies. Many studies measured short- and medium-term outcomes, up to eight weeks, while longer-term outcomes were lacking. Therefore, tolerance effects such as those hypothesised by Gualtieri et al. [39] might not have been observed.

Many of the RCTs had a crossover design, which has limitations due to the carryover effects of the intervention [40]. Additionally, this design does not eliminate confounders such as the order and timing of treatment. Some of the limitations were expected due to the nature of undertaking trials of interventions. Additional ethical issues resulted from studying a pediatric population, where parental consent was often an additional obstacle in the recruitment stages. This may contribute to the lack of available research in the pediatric population compared to adults. The willingness of parents and ethical requirements in recruitment may have varied geographically, with Ekinci et al. [28] encountering a culture of stigma around ADHD in Turkey. This review, by the nature of the research question created from initial scoping searches, only examined the utility of one ADHD medication. However, it would be useful to look at the effectiveness of other ADHD medications in this context. Additionally, research into non-pharmacological therapies, such as cognitive behavioural therapy, would add utility to the holistic care of these patients [41].

5. Conclusions

This systematic review examined the effects on cognition of MPH in pediatric TBI. A trend towards reduced scores favouring the intervention was observed using a meta-analysis of continuous performance test results, but the results did not reach significance. Additional outcomes regarding attention and executive functioning also found similar trends in improvement of scores after MPH intervention but, again, did not reach statistical significance. Therefore, this review does not support the use of MPH in pediatric TBI management. Higher-quality studies with larger sample sizes, consistent dosing and outcome measurement scales, and powered subgroup analyses are needed. However, the authors recognise the challenges of designing trials of interventions in a pediatric population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/traumacare5010001/s1, Table S1: VADPRS primary outcome data for attention, comparing MPH and placebo groups; Table S2: Conners' rating scale primary outcome data for attention, comparing baseline and endpoint scores in MPH groups; Table S3: MFFT primary outcome data for attention, comparing MPH and placebo groups; Table S4: Stroop colour and word test colour–word score primary outcome data for attention, comparing MPH and placebo groups; Table S5: Central-incidental method primary outcome data for attention, percentage of correct responses, comparing MPH and placebo groups; Table S6: Seashore rhythm test primary outcome data for attention, comparing MPH and placebo groups; Table S7: Trail making test part A times (seconds) primary outcome data for attention, comparing MPH and placebo groups; Table S8: Trail making test part B times (seconds) primary outcome data for attention, comparing MPH and placebo groups; Table S9: Turgay DSM-IV Disruptive behavior disorders rating scale primary outcome data for attention, comparing baseline and endpoint scores in MPH groups; Table S10: Gordon diagnostic system (model III) primary outcome data for attention, comparing MPH and placebo groups; Table S11: Ruff 2 and 7 cancellation test primary outcome data for attention, comparing MPH and placebo groups; Table S12: Delis–Kaplan executive function system ('D-KEFS') verbal fluency secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S13: Weschler processing speed index secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S14: The Woodcock–Johnson psychoeducational test battery for processing speed secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S15: Symbol digit modalities test ('SDMT') score at phase, secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S16: Sternberg memory and reaction time test ('SMRTT') at phase, secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S17: Sentence repetition task ('SRT') at phase, secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S18: Rapid automatized naming test ('RANT') at phase, secondary outcome data for executive functioning, comparing MPH and placebo groups; Table S19: Eyberg child behaviour inventory ('ECBI') secondary outcome data for behaviour, comparing MPH and placebo groups; Table S20: Purdue pegboard, finger tapping test, developmental test of visual-motor integration ('VMI') test scores at phase, secondary outcome data for psychomotor function, comparing MPH and placebo groups; Table S21: VADPRS parent hyperactivity rating secondary outcome data for hyperactivity, comparing MPH and placebo groups; Table S22: Turgay DSM-IV disruptive behavior disorders rating scale hyperactivity score, comparing baseline and endpoint scores in MPH groups; Table S23: Western neurosensory stimulation profile ('WNSSP') secondary outcome data for responsiveness, comparing the score pre- and post-medication.

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References

1. Forsyth, R.; Kirkham, F. Predicting outcome after childhood brain injury. *Can. Med. Assoc. J.* **2012**, *184*, 1257–1264. [CrossRef] [PubMed]
2. Bruns, N.; Trocchi, P.; Felderhoff-Müser, U.; Dohna-Schwake, C.; Stang, A. Hospitalization and morbidity rates after pediatric traumatic brain injury: A nation-wide population-based analysis. *Front. Pediatr.* **2021**, *9*, 747743. [CrossRef] [PubMed]
3. Dewan, M.C.; Mummareddy, N.; Wellons, J.C.; Bonfield, C.M. Epidemiology of global pediatric traumatic brain injury: Qualitative review. *World Neurosurg.* **2016**, *91*, 497–509. [CrossRef] [PubMed]
4. Menon, D.K.; Schwab, K.; Wright, D.W.; Maas, A.I.; Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: Definition of traumatic brain injury. *Arch. Phys. Med. Rehabil.* **2010**, *91*, 1637–1640. [CrossRef] [PubMed]
5. Stierwalt, J.A.G.; Murray, L.L. Attention impairment following traumatic brain injury. *Semin. Speech Lang.* **2002**, *23*, 129–138. [CrossRef]
6. Babikian, T.; Asarnow, R. Neurocognitive outcomes and recovery after pediatric TBI: Meta-analytic review of the literature. *Neuropsychology* **2009**, *23*, 283–296. [CrossRef] [PubMed]
7. Narad, M.E.; Riemersma, J.; Wade, S.L.; Smith-Paine, J.; Morrison, P.; Taylor, H.G.; Yeates, K.O.; Kurowski, B.G. Impact of secondary ADHD on long-term outcomes after early childhood traumatic brain injury. *J. Head Trauma Rehabil.* **2020**, *35*, E271–E279. [CrossRef] [PubMed]
8. Stojanovski, S.; Scratch, S.E.; Dunkley, B.T.; Schachar, R.; Wheeler, A.L. A systematic scoping review of new attention problems following traumatic brain injury in children. *Front. Neurol.* **2021**, *12*, 751736. [CrossRef] [PubMed]
9. Narad, M.E.; Kennelly, M.; Zhang, N.; Wade, S.L.; Yeates, K.O.; Taylor, H.G.; Epstein, J.N.; Kurowski, B.G. Secondary attention-deficit/hyperactivity disorder in children and adolescents 5 to 10 years after traumatic brain injury. *JAMA Pediatr.* **2018**, *172*, 437–443. [CrossRef]
10. Nazarova, V.A.; Sokolov, A.V.; Chubarev, V.N.; Tarasov, V.V.; Schiöth, H.B. Treatment of ADHD: Drugs, psychological therapies, devices, complementary and alternative methods as well as the trends in clinical trials. *Front. Pharmacol.* **2022**, *13*, 1066988. [CrossRef] [PubMed]
11. Chien, Y.J.; Chien, Y.C.; Liu, C.T.; Wu, H.C.; Chang, C.Y.; Wu, M.Y. Effects of methylphenidate on cognitive function in adults with traumatic brain injury: A meta-analysis. *Brain Sci.* **2019**, *9*, 291. [CrossRef] [PubMed]
12. Hagan, A.J.; Verity, S.J. The influence of methylphenidate on sustained attention in paediatric acquired brain injury: A meta-analytical review. *Child Neuropsychol.* **2022**, *29*, 710–741. [CrossRef] [PubMed]
13. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Br. Med. J.* **2021**, *372*, n71. [CrossRef] [PubMed]
14. Amir-Behghadami, M.; Janati, A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. *Emerg. Med. J.* **2020**, *37*, 387. [CrossRef] [PubMed]
15. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. Searching for and selecting studies. In *Cochrane Handbook for Systematic Reviews of Interventions*; Version 6.4; Cochrane: London, UK, 2023.
16. Bramer, W.M.; Rethlefsen, M.L.; Kleijnen, J.; Franco, O.H. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Syst. Rev.* **2017**, *6*, 245. [CrossRef] [PubMed]
17. British National Formulary. Available online: https://bnf.nice.org.uk/drugs/methylphenidate-hydrochloride/ (accessed on 29 July 2024).
18. Covidence Systematic Review Software. Available online: https://www.covidence.org/ (accessed on 29 July 2024).
19. The Oxford Levels of Evidence 2. Available online: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence/ (accessed on 29 July 2024).

20. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.-Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *Br. Med. J.* **2019**, *366*, l4898. [CrossRef] [PubMed]
21. Sterne, J.A.; Hernán, M.A.; Reeves, B.C.; Savović, J.; Berkman, N.D.; Viswanathan, M.; Henry, D.; Altman, D.G.; Ansari, M.T.; Boutron, I.; et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *Br. Med. J.* **2016**, *355*, i4919. [CrossRef]
22. Review Manager (RevMan), Version 4.0. The Cochrane Collaboration. Available online: https://revman.cochrane.org (accessed on 10 August 2024).
23. LeBlond, E.; Smith-Paine, J.; Riemersma, J.J.; Horn, P.S.; Wade, S.L.; Kurowski, B.G. Influence of methylphenidate on long-term neuropsychological and everyday executive functioning after traumatic brain injury in children with secondary attention problems. *J. Int. Neuropsychol. Soc.* **2019**, *25*, 740–749. [CrossRef] [PubMed]
24. Kurowski, B.G.; Epstein, J.N.; Pruitt, D.W.; Horn, P.S.; Altaye, M.; Wade, S.L. Benefits of methylphenidate for long-term attention problems after traumatic brain injury in childhood: A randomized, double-masked, placebo-controlled, dose-titration, crossover trial. *J. Head Trauma Rehabil.* **2019**, *34*, E1–E12. [CrossRef] [PubMed]
25. Nikles, C.J.; McKinlay, L.; Mitchell, G.K.; Carmont, S.A.; Senior, H.E.; Waugh, M.C.; Epps, A.; Schluter, P.J.; Lloyd, O.T. Aggregated n-of-1 trials of central nervous system stimulants versus placebo for paediatric traumatic brain injury—A pilot study. *Trials* **2014**, *15*, 54. [CrossRef]
26. Baker, B.K. The Effect of Methylphenidate on the Attending Behavior of Children with Closed Head Injuries. Ph.D. Thesis, The University of Utah, Salt Lake City, UT, USA, 1990.
27. Clark, E.; Baker, B.K.; Gardner, M.K.; Pompa, J.L.; Tait, F.V. Effectiveness of stimulant drug treatment for attention problems: A look at head-injured children. *Sch. Psychol. Int.* **1990**, *11*, 227–234. [CrossRef]
28. Ekinci, O.; Direk, M.; Gunes, S.; Teke, H.; Ekinci, N.; Yıldırım, F.; Okyuaz, C. Short-term efficacy and tolerability of methylphenidate in children with traumatic brain injury and attention problems. *Brain Dev.* **2017**, *39*, 327–336. [CrossRef]
29. Mahalick, D.M.; Carmel, P.W.; Greenberg, J.P.; Molofsky, W.; Brown, J.A.; Heary, R.F.; Marks, D.; Zampella, E.; Hodosh, R.; von der Schmidt, E., 3rd. Psychopharmacologic treatment of acquired attention disorders in children with brain injury. *Pediatr. Neurosurg.* **1998**, *29*, 121–126. [CrossRef] [PubMed]
30. Williams, S.E.; Ris, M.D.; Ayyangar, R.; Schefft, B.K.; Berch, D. Recovery in pediatric brain injury: Is psychostimulant medication beneficial? *J. Head Trauma Rehabil.* **1998**, *13*, 73–81. [CrossRef] [PubMed]
31. Caliendo, E.; Lowder, R.; McLaughlin, M.J.; Watson, W.D.; Baum, K.T.; Blackwell, L.S.; Koterba, C.H.; Hoskinson, K.R.; Tlustos, S.J.; Shah, S.A.; et al. The use of methylphenidate during inpatient rehabilitation after pediatric traumatic brain injury: Population characteristics and prescribing patterns. *J. Head Trauma Rehabil.* **2024**, *39*, E122–E131. [CrossRef] [PubMed]
32. Patrick, P.D.; Buck, M.L.; Conaway, M.R.; Blackman, J.A. The use of dopamine enhancing medications with children in low response states following brain injury. *Brain Inj.* **2003**, *17*, 497–506. [CrossRef] [PubMed]
33. Hornyak, J.E.; Nelson, V.S.; Hurvitz, E.A. The use of methylphenidate in paediatric traumatic brain injury. *Pediatr. Rehabil.* **1997**, *1*, 15–17. [CrossRef]
34. Mena, J.H.; Sanchez, A.I.; Rubiano, A.M.; Peitzman, A.B.; Sperry, J.L.; Gutierrez, M.I.; Puyana, J.C. Effect of the modified Glasgow Coma Scale score criteria for mild traumatic brain injury on mortality prediction: Comparing classic and modified Glasgow Coma Scale score model scores of 13. *J. Trauma Acute Care Surg.* **2011**, *71*, 1185–1193. [CrossRef] [PubMed]
35. Roebuck, H.; Freigang, C.; Barry, J.G. Continuous Performance Tasks: Not just about sustaining attention. *J. Speech Lang. Hear. Res.* **2016**, *59*, 501–510. [CrossRef]
36. Kumar, A.; Loane, D.J. Neuroinflammation after traumatic brain injury: Opportunities for therapeutic intervention. *Brain Behav. Immun.* **2012**, *26*, 1191–1201. [CrossRef]
37. Faraone, S.V. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci. Biobehav. Rev.* **2018**, *87*, 255–270. [CrossRef]
38. Peattie, A.R.D.; Manktelow, A.E.; Sahakian, B.J.; Menon, D.K.; Stamatakis, E.A. Methylphenidate ameliorates behavioural and neurobiological deficits in executive function for patients with chronic traumatic brain injury. *J. Clin. Med.* **2024**, *13*, 771. [CrossRef]
39. Gualtieri, C.T.; Evans, R.W. Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. *Brain Inj.* **1988**, *2*, 273–290. [CrossRef] [PubMed]
40. Lim, C.Y.; In, J. Considerations for crossover design in clinical study. *Korean J. Anesthesiol.* **2021**, *74*, 293–299. [CrossRef] [PubMed]
41. Lee, H.Y.; Hyun, S.E.; Oh, B.M. Rehabilitation for impaired attention in the acute and post-acute phase after traumatic brain injury: A narrative review. *Korean J. Neurotrauma* **2022**, *19*, 20–31. [CrossRef] [PubMed]