Applied Neuropsychology: Child

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/hapc20

The benefit of long-term methylphenidate in childhood brain injury survivorship: A review

T. J. Harrison, P. Pornsukjantra, A. J. Hagan & S. J. Verity

To cite this article: T. J. Harrison, P. Pornsukjantra, A. J. Hagan & S. J. Verity (14 Oct 2024): The benefit of long-term methylphenidate in childhood brain injury survivorship: A review, Applied Neuropsychology: Child, DOI: 10.1080/21622965.2024.2413091

To link to this article: https://doi.org/10.1080/21622965.2024.2413091

APPLIED NEUROPSYCHOLOGY: CHILD
https://doi.org/10.1080/21622965.2024.2413091

Routledge
Taylor & Francis Group

The benefit of long-term methylphenidate in childhood brain injury survivorship: A review

T. J. Harrison[a], P. Pornsukjantra[a], A. J. Hagan[a] and S. J. Verity[a,b]

[a]Clinical Health Psychology, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [b]Newcastle University Centre for Cancer, Newcastle upon Tyne, UK

ABSTRACT

Survivors of childhood Acquired Brain Injury (ABI) often report chronic and debilitating neurocognitive late effects. While short-term clinical trials have demonstrated the efficacy of methylphenidate in improving neurocognitive performance within the early phases of recovery, its effectiveness over longer treatment periods remains largely unexplored. The present systematic review aims to evaluate whether methylphenidate may serve as a beneficial long-term rehabilitative strategy for improving neuropsychological outcomes in childhood ABI. Database searches were conducted in MEDLINE, PsycINFO, EMBASE, and Cochrane Library from their inception to March 2023. Studies containing a neurocognitive, psychosocial, or quality of life outcome measure were included. A purpose-developed evaluation tool was used to assess the quality of the evidence base. Six of the 1926 identified articles were included within this review. Results drew upon three clinical populations; brain tumor ($n=76$), acute lymphoblastic leukemia ($n=33$), and epilepsy and other EEG abnormalities ($n=166$). Study durations ranged between six to 12 months. Methylphenidate was associated with sustained improvements in attentional functioning, processing speed, social skills, and quality of life, with benefits extending beyond the initial recovery phase and into future development. Side effects of methylphenidate use were reported to be mild and temporary.

KEYWORDS

Brain injury; cognition; methylphenidate; quality of life

Introduction

Childhood acquired brain injury

Childhood Acquired Brain Injury (ABI) is a leading cause of mortality and morbidity globally. Beyond the acute neurological trauma, childhood survivors of ABI often experience chronic and multifaceted late effects that significantly impede age-appropriate cognitive, emotional and social development. Understanding this phenomenon is crucial not only for improving long-term outcomes but also for identifying effective rehabilitative interventions.

The term ABI encompasses any form of brain damage occurring after birth and not related to congenital, developmental, or neurodegenerative disorders (Spreij et al., 2014). Despite the wide variation in underlying causes, survivors of childhood ABI often experience comparable long-term physical, cognitive, and psychosocial consequences (Davis et al., 2019; De Ruiter et al., 2013; Gulati et al., 2014). Whilst the trajectory of these difficulties is dictated by the underlying mechanism of injury and age at time of injury, the longer-term neurocognitive profiles share several common features across ABI subgroups (Gordon & di Maggio, 2012; Greene et al., 2022; Keetley et al., 2020). Of these features, deficits in attentional function, executive function, and processing speed are frequently reported in traumatic brain injury (Gilboa et al., 2015; Gorman et al., 2015), brain tumor (Palmer et al., 2013), encephalitis (Gadian et al., 2022; Wilkinson-Smith et al., 2022), and epilepsy (Campiglia et al., 2014; Lopes-Santos et al., 2023).

Conceptual models suggest that difficulties with attention, memory, and processing speed contribute to broader systemic deficits in higher-order cognitive domains, which in turn lead to the plateauing of intellectual development (Mulhern et al., 2004; Palmer et al., 2007, Palmer, 2008). These deficits impede academic achievement (De Netto & McKinlay, 2020; Spiegel et al., 2021), future employment (Remes et al., 2021; Sato et al., 2018), adaptive functioning (Ashford et al., 2014; Neumane et al., 2021; Pulsifer et al., 2018; Vago et al., 2011), and self-esteem (Khan et al., 2023; Rosema et al., 2012), often leading to poorer quality of life outcomes (Puhr et al., 2021; Ryan et al., 2019). While appreciating the distinct pathophysiology of childhood ABI (e.g., brain tumor vs traumatic brain injury) is crucial for guiding appropriate treatment, the overlap in long-term neuropsychological outcomes across ABI subgroups suggests the potential advantages of exploring interventions that offer mutual benefits.

CONTACT Sarah J. Verity sarahjane.verity@nhs.net Newcastle Upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-Upon-Tyne NE1 4LP, UK.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/21622965.2024.2413091.

Methylphenidate & childhood ABI

Psychostimulant medications, such as methylphenidate, are increasingly utilized in managing post-ABI neurocognitive impairment (Hagan & Verity, 2023a). With an established role in the management of Attention Deficit Hyperactivity Disorder (ADHD) (Storebø et al., 2018, 2023), methylphenidate has demonstrated effectiveness in improving attention, memory, inhibitory control, processing speed, and the management of behavioral symptoms (Coghill et al., 2014; Vertessen et al., 2022). As many of the neuropsychological difficulties associated with childhood ABI share a degree of overlap with those observed in ADHD, recent research has aimed to evaluate the rehabilitative potential of methylphenidate in childhood ABI.

A number of short-term clinical trials have substantiated the role of methylphenidate in improving neurocognitive performance during the early stages of recovery post-ABI. The use of methylphenidate has been associated with improved attentional functioning in childhood traumatic brain injury (Ekinci et al., 2017; Mahalick et al., 1998), cerebrovascular complications (Daly et al., 2012), as well as improved cognitive flexibility, attention and processing speed in childhood survivors of brain tumor (Conklin et al., 2007; Verity et al., 2022a). Similarly, methylphenidate has been associated with improved self-esteem, emotional wellbeing and quality of life outcomes in childhood ABI (Johansson et al., 2020; Verity et al., 2022b; Yoo et al., 2009).

Long-term use of methylphenidate

While previous research has demonstrated the rehabilitative benefits of methylphenidate during the initial phases of recovery following childhood ABI, there has been limited robust investigation into whether these benefits extend beyond the "acute phase." Based upon previously proposed conceptual models of intelligence, the long-term use of methylphenidate may help preserve age-appropriate intellectual and academic development by enhancing the underpinning functions of attention, working memory, and processing speed (Palmer, 2008). The role of methylphenidate in preserving the functionality of attention and higher-order cognitive functions is particularly important for childhood survivors of ABI characterized by "*intermittent*" disease (i.e., epilepsy) or children who undergo long-term multimodality treatment (i.e., malignant brain tumors) in which survivors may be exposed to recurrent neurological insult. Specifically, childhood epilepsy is characterized by chronic neurocognitive difficulties, including attentional difficulties and impaired psychomotor ability (Piccinelli et al., 2010; Rathouz et al., 2014; Verche et al., 2018). Similarly, childhood survivors of brain tumor often show a trajectory of emerging neurocognitive impairment in the years following diagnosis and treatment (Wagner et al., 2020), with deficits persisting beyond 5 years post-diagnosis and impairing age-appropriate intellectual development (Palmer et al., 2013).

Examining the long-term benefits of methylphenidate is valuable for several reasons. Firstly, it may provide insights into whether continued use can offer sustained symptom relief and improvement in the core cognitive functions (e.g., attention) that underpin broader intellectual functioning (Palmer, 2008). While prior research has predominately focused on short-term outcomes, exploring the extended utility of methylphenidate can offer insight into it's potential to support age-appropriate intellectual, cognitive, and psychosocial development. Additionally, understanding long-term effects helps balance the knowledge of therapeutic benefits against adverse effects that may accumulate over time. This comprehensive perspective of longer-term use of methylphenidate is essential for developing guidelines and recommendations that ensure the safe and effective use of methylphenidate as a treatment option in childhood ABI.

Aim

The current systematic review aims to evaluate the long-term utility of methylphenidate in alleviating neurocognitive late effects and improving quality of life in childhood ABI. Specifically, the review examines whether the use of methylphenidate for a minimum treatment period of six months offers a safe rehabilitative strategy for supporting age-appropriate cognitive development in childhood brain injury.

Method

This review was reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

Search strategy

A comprehensive literature search was performed in March 2023 using the following databases; PsycINFO, MEDLINE, EMBASE, and the Cochrane Library. Electronic search strategies combined MeSH terms and relevant keywords (Appendix A). Search terms consisted of an injury term (e.g., "brain tumour"), a treatment term (e.g., "methylphenidate") and an outcome term (e.g., "processing speed" or "quality of life"). No filters or limits were set when conducting the search. Relevant reference lists were hand-searched to identify eligible articles. Review articles with any relevance to pediatric neurorehabilitation or neurocognitive outcomes in childhood ABI were advanced to full-text review for the purpose of "snowball referencing."

Study selection

Articles were selected for inclusion based upon the following inclusion criteria:

Population

Children and young people aged ≤18 years old diagnosed with any form of acquired brain injury later than the perinatal period, and unrelated to an underlying congenital, developmental, or neurodegenerative disorder.

Intervention

Participants must be in receipt of any form of methylphenidate (e.g., immediate or sustained release).

Outcome

Studies must employ a neurocognitive, psychosocial, or quality of life outcome measure at baseline and follow up. The assessment period (from baseline to follow up assessment) must span a minimum of six months.[1]

Articles that did not meet the above outlined criteria were excluded. Studies solely including adult participants (aged ≥19 years), animal studies, letters to editors, and conference abstracts were excluded. Case studies were excluded as these often focus on unique and complex clinical scenarios that lack generalizability. Two reviewers independently assessed the eligibility of articles. Discrepancies between authors were uncommon. Where disagreements occurred, they were resolved through a two-stage process: (1) the reviewers engaged in discussions to reconcile conflicting articles and reach a consensus, and (2) in instances where consensus was unattainable, a third independent author settled the disagreement.

Data extraction and quality assessment

The following information was extracted from eligible articles: authors, year of publication, article title, location of study, sample size, sample characteristics (e.g. age, sex, ethnicity of participants), dosage of methylphenidate, duration of intervention, and outcome measure(s) used.

Assessment of risk of bias

The quality of included studies was assessed using the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016). The ROBINS-I assesses seven domains of bias, measured in three dimensions, pre-intervention, at intervention and post-intervention. The interpretation of risk of bias judgments in ROBINS-I can be classified as *"low risk," "moderate risk," "serious risk," "critical risk of bias"* or *"no information."*

Study quality assessment

The study quality was assessed using an adapted version of the Quality of Evidence Screening Tool: Methylphenidate and Attentional Performance (QuEST:MAP) (Appendix B) (Hagan & Verity, 2023b; Watts et al., 2016). For each criterion, a four-category system was utilized to evaluate the articles; "*Excellent,*" "*Satisfactory,*" "*Poor,*" and "*Not Reported.*" Overall, papers were classified as *"Decisive," "Convincing," "Fair,"* or *"Questionable"* evidence (Appendix C) (Hagan & Verity, 2023b). Interrater reliability for the quality of evidence assessments was reported as high (α=.77).

Results

Electronic database searches yielded 1926 articles, of which six articles met inclusion criteria and were included within the current review (Figure 1).

Characteristics of the evidence base

The main characteristics and QuEST:MAP ratings of each study are presented in Table 1. This review drew upon 275 participants[2] treated with methylphenidate across three clinical populations: epilepsy and other EEG abnormalities ($n=166$) (Gucuyener et al., 2003; Ray et al., 2019), brain tumor ($n=76$) (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022a; 2022b) and acute lymphoblastic leukemia ($n=33$) (Conklin et al., 2010; Netson et al., 2011). Of these participants, 195 (70.9%) were male, 80 were female (29.1%). The average age at study inclusion was 10.34 years (range = 5-18 years). The duration of methylphenidate intervention ranged between six – 12 months. Two articles included within the review drew upon the same participant population at different assessment points (Conklin et al., 2010; Netson et al., 2011).

For participants within the acute lymphoblastic leukemia and brain tumor groups, all oncological treatments (e.g. chemotherapy and proton beam therapy) were completed at least 12 months before the study commenced. Of the two studies that assessed the utility of methylphenidate in childhood epilepsy, only one detailed the anti-epileptic medications prescribed to participants. In this study, 80.9% of patients used valproate, 12.8% used carbamazepine, and 6.3% used other forms of antiepileptic medication (Ray et al., 2019).

Methylphenidate intervention

Immediate-release methylphenidate was used in two studies (Gucuyener et al., 2003; Verity et al., 2022a) whilst extended-release methylphenidate was used exclusively in one study (Ray et al., 2019). Both immediate-release and extended-release methylphenidate was used in three studies (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022b). The dosage of methylphenidate across studies ranged between 5 mg – 72 mg daily. The dosage was titrated in all six studies (Conklin et al., 2010; Gucuyener et al., 2003; Netson et al., 2011; Ray et al., 2019; Verity et al., 2022a; 2022b).

1. For the purpose of the current review, 'long-term' outcomes were defined as a minimum of six months post-baseline based upon the underlying trajectory of neurocognitive difficulties commonly reported in childhood ABI (Kurowski et al., 2019; Yeates et al., 2005).

2. To avoid overinflating results, pooled sample sizes excluded Netson et al. (2011) since this population was included within Conklin et al. (2010).

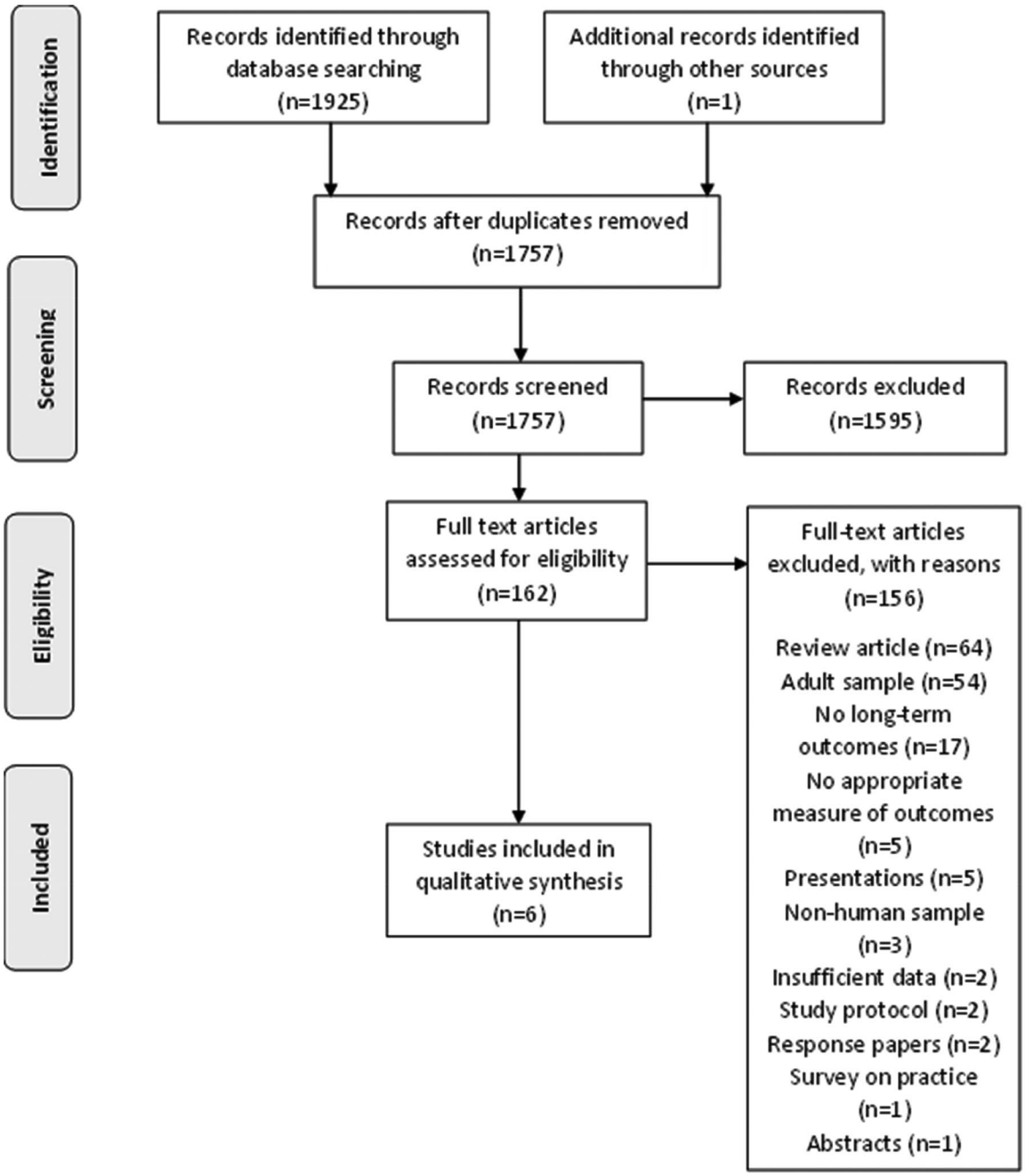

Figure 1. PRISMA flowchart of the literature search.

Attention

Five studies assessed attentional functioning, using a version of the Conner's Rating Scales (Gucuyener et al., 2003; Ray et al., 2019) or Conner's Continuous Performance Test (Conklin et al., 2010; Netson et al., 2011). One study assessed attentional functioning using the Test of Everyday Attention and SNAP-IV questionnaire (Verity et al., 2022b). Methylphenidate was associated with significant improvements in attentional performance across all five studies.

Methylphenidate was associated with long-term improvements in ADHD symptoms (inc., decreased hyperactivity, impulsiveness, emotional difficulties) reported by parents, as well as enhanced attentional performance on both teacher and parent rating scales at 12 months (Gucuyener et al., 2003). Similarly, methylphenidate was associated with higher mean Stroop scores (indicating better performance) at follow-up assessment (Ray et al., 2019).

Childhood survivors of brain tumor and acute lymphoblastic leukemia reported a significant benefit of methylphenidate on attentional functioning over a 12 month period (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022b).

Processing speed

Methylphenidate was associated with significant improvements in processing speed following methylphenidate in three studies (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022b).

Table 1. Characteristics of included studies.

Authors (date) Title	Location of study	Treatment group (Sample Size): Mean age (SD) Sex Ethnicity	Comparison group (Sample size): Mean age (SD) Sex Ethnicity	Methylphenidate intervention: Dosage Duration	Outcome measures	Assessment period	QuEST:MAP rating
Ray et al. (2019) Methylphenidate treatment outcomes and gender differences in attentional deficit and hyperactivity disorder with epilepsy: a follow-up study	Turkey	ADHD with epilepsy (47) 10.8 years (1.7) 30 males 17 females No ethnicity information provided	ADHD without epilepsy (47) 10.8 years (1.7) 30 males 17 females No ethnicity information provided	Dose range: 18-72mg/day once a day	Conners' Teacher Rating Scale Conners' Parent Rating Scale Stroop TBAG Form	6 Months	Fair
Conklin et al. (2010) Long-Term Efficacy of Methylphenidate in Enhancing Attention Regulation, Social Skills, and Academic Abilities of Childhood Cancer Survivors	United States of America	Brain tumor (35) and Acute lymphoblastic leukemia (33) 11.11 years (3.05) 37 males 31 females White (57) 84%, African American (10) 15% Other (1) 1%	Brain tumor (31) and acute lymphoblastic leukemia (23) 11.26 (3.16) 27 males 27 females White (43) 80% African American (11) 20%	Weight ≥ 30 kg Starting dose 18 mg extended-release daily, titrated upward to 27 mg daily, possibly 36 mg daily. Weight ≤ 30 kg Starting dose 5 mg once or twice a day, titrated upwards – immediate release 52 weeks	Conners' Parent Rating Scale Conners' Teacher Rating Scale Conners' Adolescent Self-Report Scale Conners' Continuous Performance Test Wechsler Intelligence Scale for Children – Third Edition Wechsler Adult intelligence Scale – Third Edition Wechsler Individual Achievement Test	12 months	Decisive
Gucuyener et al. (2003) Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities	Turkey	ADHD with either epilepsy (57) or EEG abnormalities without a defined seizure (62) 9.3 years (2.7) 98 male 21 female No ethnicity information provided	No comparison group	0.3-1mg/kg/day Started once daily, titrated to twice a day.	Conners' Parent Rating Scale Conners' Teacher Rating Scale	12 months	Fair
Netson et al. (2011) Parent and Teacher Ratings of Attention during a Year-Long Methylphenidate Trial in Children Treated for Cancer	United States of America	Brain tumor (35) and Acute lymphoblastic leukemia (33) 11.11 years (3.05) 37 males 31 females White (57) 84%, African American (10) 15% Other (1) 1%	No comparison group	Weight ≥ 30 kg Starting dose 18 mg extended-release daily, titrated upward to 27 mg daily, possibly 36 mg daily. Weight ≤ 30 kg Starting dose 5 mg once or twice a day, titrated upwards – immediate release 52 weeks	Conners' Continuous Performance Test Conners' Rating Scale-Revised Conners Parent Rating Scale Conners' Teacher Rating Scale	12 months	Decisive
Verity et al. (2022a) "I Feel Happy Again": Methylphenidate Supports Health-Related Quality of Life in Survivors of Pediatric Brain Tumor	United Kingdom	Brain tumor (12) 13.3 years (3.29) 8 male 4 female White British (22) 100%	No comparison group	Weight 15-20kg: Starting dose of 2.5 mg twice a day Weight 21-30kg: 5 mg twice daily Weight ≥ 30 kg: 10 mg twice daily Mean starting dose of MPH was 0.19 mg per kg	Pediatric Quality of Life Inventory	12 months	Convincing

(*Continued*)

Table 1. Continued.

Authors (date) Title	Location of study	Treatment group (Sample Size): Mean age (SD) Sex Ethnicity	Comparison group (Sample size): Mean age (SD) Sex Ethnicity	Methylphenidate intervention: Dosage Duration	Outcome measures	Assessment period	QuEST:MAP rating
Verity et al. (2022b) Methylphenidate improves cognitive function and health-related quality of life in survivors of childhood brain tumors	United Kingdom	Brain tumor (29) 10.6 years (3.55) 22 male 7 female White British (29) 100%	No comparison group	Weight 15-20kg: Starting dose of 2.5 mg twice a day Weight 21-30kg: 5 mg twice daily Weight ≥ 30 kg: 10 mg twice daily Mean starting dose of immediate release MPH was 0.19 mg per kg. Once appropriate level of immediate release MPH identified, patietns were converted to equivalent modified-release. Mean optimal dose was 0.34 mg per kg twice daily.	Test of Everyday Attention for Children, Second Edition Swanson, Nolan and Pelham Questionnaire (SNAP-IV) Pediatric Quality of Life Inventory	12 months	Fair

Quality of life

Two studies measured quality of life. Both of these studies used the Pediatric Quality of Life Inventory (PedsQL™; Varni et al., 2003) (Verity et al., 2022a; 2022b) and one study also used the Experience of Methylphenidate Treatment Questionnaire (Verity et al., 2022a). Findings indicate significant improvements in quality of life outcomes across multiple domains (inc., physical, emotional and social) with methylphenidate treatment over a 12 month assessment period.

Intelligence and academic performance

One study assessed intelligence over a 12-month period using the Wechsler Intelligence Scale for Children (Conklin et al., 2010). Findings indicated no long-term benefit of methylphenidate on intellectual performance at follow-up. Findings also reported no significant effect of methylphenidate on academic performance as measured by the Wechsler Individual Achievement Test (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022a).

Despite the non-significant effect of methylphenidate on academic performance, semi-structured interview findings described "improvement in academic performance" and an "increase in academic confidence" (Verity et al., 2022a).

Social skills and behavioral problems

Two studies (Conklin et al., 2010; Netson et al., 2011) measured social skills and behavioral problems using Social Skills Rating System and Child Behavior Checklist. Findings indicate significant improvements in both domains in the methylphenidate group compared to the control group over a 12-month period. Social function (as measured by the PedsQL) also reported significant improvements with methylphenidate (inc., peer relationships, engagement in social activities) (Verity et al., 2022a).

Side effects

Long-term side effects were measured in all included studies. Side effects observed included decreased appetite (Gucuyener et al., 2003; Verity et al., 2022b), stomach ache (Gucuyener et al., 2003; Verity et al., 2022b), headache (Gucuyener et al., 2003) and tics (Gucuyener et al., 2003). In one participant pool measured across two studies (Conklin et al., 2010; Netson et al., 2011), 23 childhood cancer survivors started a 12-month trial of methylphenidate, with eight discontinuing methylphenidate treatment due to adverse effects. Methylphenidate was not associated with any significant change in seizure threshold in patients with epilepsy or EEG abnormalities relative to baseline in one study (Gucuyener et al., 2003).

Quality of evidence and risk of bias

Overall, the quality of evidence was classed as "*satisfactory.*" No study was classed as "*critical*" on the risk of bias tool (ROBINS-I). Studies with a higher quality rating provided greater detail on eligibility criteria, potential confounding variables, and conducted appropriate adjustment for confounding factors. Common limitations across the studies included the lack of the study's power and lack of reporting certain statistical results such as certain effect sizes and confidence intervals.

Discussion

Survivors of childhood ABI commonly experience enduring neurocognitive late effects and poorer quality of life, with difficulties persisting beyond treatment and recovery. Whilst several studies have substantiated the utility of methylphenidate in improving neuropsychological outcomes during the early phases of recovery, little work has explored the potential long-term rehabilitative benefit of methylphenidate within childhood ABI. This review systematically evaluated the utility of methylphenidate on neurocognitive and quality of life outcomes in survivors of childhood ABI over a minimum treatment period of six months.

Neuropsychological outcomes

Methylphenidate was associated with long-term significant improvement in processing speed and attentional functioning at six and 12-month follow-up assessments (Conklin et al., 2010; Gucuyener et al., 2003; Netson et al., 2011; Ray et al., 2019; Verity et al., 2022b). Measures of quality of life (Verity et al., 2022a; 2022b), social skills, and behavioral problems (Conklin et al., 2010; Netson et al., 2011) also indicated significant improvements with methylphenidate in childhood brain tumor survivorship. These findings support previous suggestions that improvements in higher-order cognitive domains (i.e., processing speed) may mediate wider systemic benefits to functional outcomes, and in turn improve quality of life outcomes (Holland et al., 2018). It may be that improvements in processing speed in brain tumor survivorship enhance a child's ability to process social cues and information effectively, thus improving social interactions (Verity et al., 2022a).

However, the relationship between methylphenidate and academic performance presents a slightly different picture. Despite the reported cognitive benefits, no objective improvement was measured on academic subtests (Conklin et al., 2010; Netson et al., 2011; Verity et al., 2022a). A possible explanation for this could be that included studies lack sufficient power to detect subtle improvements in academic performance, which are often dependent upon improvements in multiple cognitive domains. Nonetheless, even in the absence of marked improvements in academic measures, childhood survivors receiving methylphenidate displayed increased engagement in academic-related behaviors (inc., increased academic confidence and exam preparation) (Verity et al., 2022a). As such, it may be that methylphenidate acts to improve related behaviors which in turn preserve academic ability and limit previously observed decline, rather than directly increasing performance on psychometric measures (Pelham et al., 2022).

Conner's rating scales

The Conner's Rating Scales are robust measures of attentional and cognitive difficulties, frequently used to monitor treatment outcomes (Conners et al., 1998; Ekinci et al., 2017; Helton et al., 2006). Previous work suggests that parental ratings of attentional ability offer a useful method of screening for poorer working memory and lower intellectual ability in childhood cancer survivors (Hardy et al., 2015). Of our findings, significant improvements on Conner's Rating Scales were reported in three studies (Conklin et al., 2010; Gucuyener et al., 2003; Netson et al., 2011). While these findings primarily indicate significant improvements in symptoms of attentional difficulties, they also potentially suggest a degree of stability in wider cognitive domains (i.e., working memory), which might otherwise be expected to decline following oncological treatment (Palmer at al., 2013; Stavinoha et al., 2018).

One paper reported a greater benefit of methylphenidate on parent rating scales compared to teacher scales (Conklin et al., 2010). One potential explanation for this may be that parents observe more subtle changes in their child's behavior and daily functioning that may not be as apparent in a structured school environment, thus providing a more accurate representation of a child's attentional ability (Narad et al., 2015). Nonetheless, findings may be influenced by parental expectations of methylphenidate and a greater desire for behavioral improvement, which could be a particularly important factor in open-label trials (Fageera et al., 2018).

Quality of the evidence base

Due to the scarcity of the current evidence base, studies drawing upon less robust methodologies (i.e., open-label designs – Conklin et al., 2010; Gucuyener et al., 2003; Netson et al., 2011) were included within this review. This in turn introduces several confounding variables, most notably the lack of blinding, which limits the validity and reliability of our findings. In cases where blinding isn't feasible, ensuring robust outcome measures is crucial (Kahan et al., 2014). Despite this, open-label studies do offer valuable insights into the real-world applicability of methylphenidate treatment and potential discontinuation rates.

This review included populations often receiving multiple concurrent therapies, most notably anti-epileptic medications (Gucuyener et al., 2003; Ray et al., 2019). Whilst methylphenidate may offer several neuropsychological benefits, the potential contributory influence of anti-epileptic medication could not be evaluated within this review due to unclear reporting. For instance, although methylphenidate may enhance attention and processing speed, certain anti-epileptic medications (inc., zonisamide and topiramate) have been reported to negatively impact performance on attention and verbal fluency measures (Moavero et al., 2017). This interaction may diminish the positive benefit of methylphenidate in this patient group. In contrast, medications such as lamotrigine have been associated with enhanced performance in selective attention tests (Moavero et al., 2017). This complexity underscores the importance of carefully considering drug interactions before evaluating the utility of methylphenidate for certain clinical groups.

Side effect profile

Of included studies, the reported side effects were predominately mild and led to the discontinuation of methylphenidate in 8.8% of participants in one participant sample measured across two studies (Conklin et al., 2010; Netson et al., 2011). Similar discontinuation rates (7%) have been reported within childhood brain tumor survivorship (Conklin et al., 2007). Of note, longer-term use of methylphenidate has been associated with a decrease in side effects within childhood ADHD samples. Findings from Deng et al. (2021) reported a greater proportion of children reported issues with height, weight and BMI within the first six months of treatment (Deng et al., 2021). The decrease in the prevalence of side effects during the course of treatment potentially supports the use of methylphenidate as a longer-term rehabilitative strategy.

Whilst the treatment-related risks remain relatively mild, they must be considered carefully when prescribing psychostimulants for long-term use in survivors of childhood ABI. Long-term methylphenidate use has historically been associated with reduced seizure threshold and increased seizure frequency (Feeney & Klykylo, 1997). However, this increase in seizure frequency was not reported by studies included in this review (Gucuyener et al., 2003; Ray et al., 2019).

Strengths and limitations

To the best of our knowledge this is the first review to explore the long-term utility of methylphenidate within the pediatric ABI population. This systematic review utilized a comprehensive search strategy and rigorous inclusion criteria drawing upon a range of clinical etiologies. A limitation of the present review is that included studies were relatively small, and two studies gathered data from the same sample. As such, the generalizability of the findings to the wider ABI sphere (i.e., TBI and CNS infections) should be interpreted cautiously. It is possible that database results may have been impacted by publication bias, with positive results concerning the utility of methylphenidate more likely to be published (Easterbrook et al., 1991). A common limitation of systematic reviews is the potential for publication bias, where negative or non-significant findings are less likely to be published, resulting in an overestimation of positive results in the literature. This could perhaps distort the perceived efficacy of long-term methylphenidate use. Authors attempted to overcome this by intentionally keeping eligibility criteria broad in the hope of offering a balanced perspective. Also, despite our search including various terms for neuropsychological outcomes, it is possible that we did not account for every measure.

Another limitation of this systematic review is the variability in medication regimens used across different pediatric ABI populations. Children with ABI may be prescribed various medications alongside methylphenidate depending on specific medical needs and comorbid conditions. This heterogeneity in pharmacological interventions can complicate the interpretation of methylphenidate's long-term effects. Examining the complex pharmacological interactions that may occur in this patient group sits beyond the scope of the current review, nonetheless we have attempted to acknowledge this where possible.

Conclusion

This review systematically evaluates the current evidence base on the utility of long-term methylphenidate use in childhood ABI. Our findings indicate that methylphenidate may pose a beneficial long-term rehabilitative strategy by preserving neurocognitive function and improving quality of life outcomes. The review does however highlight a notable limitation in the current evidence base, with many pediatric ABI subgroups (inc., TBI and CNS infections) insufficiently represented. The current literature gap highlights the need for further research to assess the potential therapeutic benefit of methylphenidate across a wider range of pediatric ABI etiologies. Compiling case series that describe patients' experiences of long-term methylphenidate use may offer valuable clinical insight and potentially enhance rehabilitation strategies for these underrepresented clinical groups.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work of AJH was supported by funding from the OSCAR's Pediatric Brain Tumor Charity (2023), SR101122. Data write-up by SJV was supported by funding from the Children with Cancer UK (2022–2023), PGTaSFA/100008.

ORCID

T. J. Harrison http://orcid.org/0009-0008-6524-3886
P. Pornsukjantra http://orcid.org/0000-0002-2265-860X
A. J. Hagan http://orcid.org/0000-0002-3622-3949
S. J. Verity http://orcid.org/0000-0001-9111-780X

Data availability statement

The data used in this review is published within the literature base and as such no new data was created or stored.

References

Ashford, J. M., Netson, K. L., Clark, K. N., Merchant, T. E., Santana, V. M., Wu, S., & Conklin, H. M. (2014). Adaptive functioning of childhood brain tumor survivors following conformal radiation therapy. *Journal of Neuro-Oncology*, *118*(1), 193–199. https://doi.org/10.1007/s11060-014-1420-7

Campiglia, M., Seegmuller, C., Le Gall, D., Fournet, N., Roulin, J.-L., & Roy, A. (2014). Assessment of everyday executive functioning in children with frontal or temporal epilepsies. *Epilepsy & Behavior: E&B*, *39*, 12–20. https://doi.org/10.1016/j.yebeh.2014.07.023

Coghill, D. R., Seth, S., Pedroso, S., Usala, T., Currie, J., & Gagliano, A. (2014). Effects of methylphenidate on cognitive functions in children and adolescents with attention-deficit/hyperactivity disorder: Evidence from a systematic review and a meta-analysis. *Biological Psychiatry*, *76*(8), 603–615. https://doi.org/10.1016/j.biopsych.2013.10.005

Conklin, H. M., Khan, R. B., Reddick, W. E., Helton, S., Brown, R., Howard, S. C., Bonner, M., Christensen, R., Wu, S., Xiong, X., & Mulhern, R. K. (2007). Acute neurocognitive response to methylphenidate among survivors of childhood cancer: A randomized, double-blind, cross-over trial. *Journal of Pediatric Psychology*, *32*(9), 1127–1139. https://doi.org/10.1093/jpepsy/jsm045

Conklin, H. M., Reddick, W. E., Ashford, J., Ogg, S., Howard, S. C., Morris, E. B., Brown, R., Bonner, M., Christensen, R., Wu, S., Xiong, X., & Khan, R. B. (2010). Long-term efficacy of methylphenidate in enhancing attention regulation, social skills, and academic abilities of childhood cancer survivors. *Journal of Clinical Oncology: official Journal of the American Society of Clinical Oncology*, *28*(29), 4465–4472. https://doi.org/10.1200/jco.2010.28.4026

Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, *26*(4), 257–268. https://doi.org/10.1023/a:1022602400621

Davis, A. G., Nightingale, S., Springer, P. E., Solomons, R., Arenivas, A., Wilkinson, R. J., Anderson, S. T., & Chow, F. C. (2019). Neurocognitive and functional impairment in adult and paediatric tuberculous meningitis. *Wellcome Open Research*, *4*, 178. https://doi.org/10.12688/wellcomeopenres.15516.1

De Netto, R. K., & McKinlay, A. (2020). Impact of childhood traumatic brain injury on educational outcomes and adult standard of living. *Disability and Rehabilitation*, *42*(17), 2444–2450. https://doi.org/10.1080/09638288.2019.1637948

De Ruiter, M. A., van Mourik, R., Schouten-van Meeteren, A. Y., Grootenhuis, M. A., & Oosterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. *Developmental Medicine and Child Neurology*, *55*(5), 408–417. https://doi.org/10.1111/dmcn.12020

Deng, L., Zhou, P., Zhu, L., Zhang, Y., Yang, T., Zhao, Q., Chen, J., Li, T., Cheng, Q., & Chen, L. (2021). Methylphenidate and atomoxetine treatment negatively affect physical growth indexes of school-age children and adolescents with attention-deficit/hyperactivity disorder. *Pharmacology, Biochemistry, and Behavior*, *208*, 173225. https://doi.org/10.1016/j.pbb.2021.173225

Easterbrook, P. J., Gopalan, R., Berlin, J. A., & Matthews, D. R. (1991). Publication bias in clinical research. *Lancet (London, England)*, *337*(8746), 867–872. https://doi.org/10.1016/0140-6736(91)90201-Y

Ekinci, O., Direk, M. Ç., Gunes, S., Teke, H., Ekinci, N., Yıldırım, F., & Okuyaz, Ç. (2017). Short-term efficacy and tolerability of methylphenidate in children with traumatic brain injury and attention problems. *Brain & Development*, *39*(4), 327–336. https://doi.org/10.1016/j.braindev.2016.11.005

Fageera, W., Traicu, A., Sengupta, S. M., Fortier, M.-E., Choudhry, Z., Labbe, A., Grizenko, N., & Joober, R. (2018). Placebo response and its determinants in children with ADHD across multiple observers and settings: A randomized clinical trial. *International Journal of Methods in Psychiatric Research*, *27*(1), e1572. https://doi.org/10.1002/mpr.1572

Feeney, D. J., & Klykylo, W. M. (1997). Medication-induced seizures. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(8), 1018–1019. https://doi.org/10.1097/00004583-199708000-00007

Gadian, J., Eyre, M., Konstantoulaki, E., Almoyan, A., Absoud, M., Garrood, I., & Lim, M. (2022). Neurological and cognitive outcomes after antibody-negative autoimmune encephalitis in children. *Developmental Medicine and Child Neurology*, *64*(5), 649–653. https://doi.org/10.1111/dmcn.15101

Gilboa, Y., Kerrouche, B., Longaud-Vales, A., Kieffer, V., Tiberghien, A., Aligon, D., Mariller, A., Mintegui, A., Canizares, C., Abada, G., & Paule Chevignard, M. (2015). Describing the attention profile of children and adolescents with acquired brain injury using the Virtual Classroom. *Brain Injury*, *29*(13-14), 1691–1700. https://doi.org/10.3109/02699052.2015.1075148

Gordon, A. L., & di Maggio, A. (2012). Rehabilitation for children after acquired brain injury: Current and emerging approaches. *Pediatric Neurology*, *46*(6), 339–344. https://doi.org/10.1016/j.pediatrneurol.2012.02.029

Gorman, S., Barnes, M. A., Swank, P. R., Prasad, M., Cox, C. S., & Ewing-Cobbs, L. (2015). Does processing speed mediate the effect of pediatric traumatic brain injury on working memory? *Neuropsychology*, *30*(3), 263–273. https://doi.org/10.1037/neu0000214

Greene, R. K., Rich-Wimmer, N., Williams, C. N., & Hall, T. A. (2022). Social functioning and autistic behaviors in youth following acquired brain injury. *Children*, *9*(11), 1648. https://doi.org/10.3390/children9111648

Gucuyener, K., Erdemoglu, A. K., Senol, S., Serdaroglu, A., Soysal, S., & Kockar, I. (2003). Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. *Journal of Child Neurology*, *18*(2), 109–112. https://doi.org/10.1177/08830738030180020601

Gulati, S., Yoganathan, S., & Chakrabarty, B. (2014). Epilepsy, cognition and behavior. *Indian Journal of Pediatrics*, *81*(10), 1056–1062. https://doi.org/10.1007/s12098-014-1530-4

Gurbuz, F., Gurbuz, B. B., Celik, G. G., Yildirim, V., Ucakturk, S. A., Seydaoglu, G., Ucakturk, E. M., Topaloglu, A. K., & Yuksel, B. (2016). Effects of methylphenidate on appetite and growth in children diagnosed with attention deficit and hyperactivity disorder. *Journal of Pediatric Endocrinology & Metabolism: JPEM*, *29*(1), 85–92. https://doi.org/10.1515/jpem-2015-0171

Hagan, A. J., & Verity, S. J. (2023a). The influence of methylphenidate on sustained attention in paediatric acquired brain injury: a meta-analytical review. *Child Neuropsychology: a Journal on Normal and Abnormal Development in Childhood and Adolescence*, *29*(5), 710–741. https://doi.org/10.1080/09297049.2022.2112559

Hagan, A. J., & Verity, S. J. (2023b). Translating methylphenidate's efficacy on selective and sustained attentional deficits to those reported in childhood cancer survivors: A qualitative review. *Applied Neuropsychology. Child*, *12*(1), 74–87. https://doi.org/10.1080/21622965.2022.2025538

Helton, S. C., Corwyn, R. F., Bonner, M. J., Brown, R. T., & Mulhern, R. K. (2006). Factor analysis and validity of the conners parent and teacher rating scales in childhood cancer survivors. *Journal of Pediatric Psychology*, *31*(2), 200–208. https://doi.org/10.1093/jpepsy/jsj010

Huang, C.-H., Huang, C.-C., Sun, C.-K., Lin, G.-H., & Hou, W.-H. (2016). Methylphenidate on cognitive improvement in patients with traumatic brain injury: A meta-analysis. *Current Neuropharmacology*, *14*(3), 272–281. https://doi.org/10.2174/1570159x13666150514233033

Johansson, B., Andréll, P., Rönnbäck, L., & Mannheimer, C. (2020). Follow-up after 5.5 years of treatment with methylphenidate for mental fatigue and cognitive function after a mild traumatic brain injury. *Brain Injury*, *34*(2), 229–235. https://doi.org/10.1080/02699052.2019.1683898

Kahan, B. C., Cro, S., Doré, C. J., Bratton, D. J., Rehal, S., Maskell, N. A., Rahman, N., & Jairath, V. (2014). Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomised trials. *Trials*, *15*(1), 456. https://doi.org/10.1186/1745-6215-15-456

Keetley, R., Westwater-Wood, S., & Manning, J. C. (2020). Exploring participation after paediatric acquired brain injury. *Journal of Child Health Care: For Professionals Working with Children in the Hospital and Community*, *25*(1), 81–92. https://doi.org/10.1177/1367493520905673

Khan, N., Ryan, N. P., Crossley, L., Hearps, S., Catroppa, C., & Anderson, V. (2023). Associations between peer relationships and self-esteem after childhood traumatic brain injury: exploring the mediating role of loneliness. *Journal of Neurotrauma*, *40*(19-20), 2100–2109. https://doi.org/10.1089/neu.2022.0420

Kurowski, B. G., Epstein, J. N., Pruitt, D. W., Horn, P. S., Altaye, M., & Wade, S. L. (2019). Benefits of methylphenidate for long-term attention problems after traumatic brain injury in childhood: A randomized, double-masked, placebo-controlled, dose-titration, crossover trial. *The Journal of Head Trauma Rehabilitation*, *34*(2), E1–E12. https://doi.org/10.1097/HTR.0000000000000432

Lopes-Santos, L. E., de Angelis, G., Nakano, F. N., Thome, U., Velasco, T. R., Santos, M. V., Machado, H. R., Hamad, A. P. A., Sakamoto, A. C., & Wichert-Ana, L. (2023). Executive functioning in children with posterior cortex epilepsy compared to temporal and frontal lobe epilepsies. *Epilepsy Research*, *192*, 107141. https://doi.org/10.1016/j.eplepsyres.2023.107141

Moavero, R., Santarone, M. E., Galasso, C., & Curatolo, P. (2017). Cognitive and behavioral effects of new antiepileptic drugs in pedi-

atric epilepsy. *Brain & Development*, *39*(6), 464–469. https://doi.org/10.1016/j.braindev.2017.01.006

Mulhern, R. K., Merchant, T. E., Gajjar, A., Reddick, W. E., & Kun, L. E. (2004). Late neurocognitive sequelae in survivors of brain tumours in childhood. *The Lancet. Oncology*, *5*(7), 399–408. https://doi.org/10.1016/S1470-2045(04)01507-4

Narad, M. E., Garner, A. A., Peugh, J. L., Tamm, L., Antonini, T. N., Kingery, K. M., Simon, J. O., & Epstein, J. N. (2015). Parent–teacher agreement on ADHD symptoms across development. *Psychological Assessment*, *27*(1), 239–248. https://doi.org/10.1037/a0037864

Netson, K. L., Conklin, H. M., Ashford, J. M., Kahalley, L. S., Wu, S., & Xiong, X. (2011). Parent and teacher ratings of attention during a year-long methylphenidate trial in children treated for cancer*. *Journal of Pediatric Psychology*, *36*(4), 438–450. https://doi.org/10.1093/jpepsy/jsq102

Neumane, S., Câmara-Costa, H., Francillette, L., Araujo, M., Toure, H., Brugel, D., Laurent-Vannier, A., Ewing-Cobbs, L., Meyer, P., Dellatolas, G., Watier, L., & Chevignard, M. (2021). Functional outcome after severe childhood traumatic brain injury: Results of the TGE prospective longitudinal study. *Annals of Physical and Rehabilitation Medicine*, *64*(1), 101375. https://doi.org/10.1016/j.rehab.2020.01.008

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., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery (London, England)*, *88*, 105906. https://doi.org/10.1016/j.ijsu.2021.105906

Palmer, S. L. (2008). Neurodevelopmental impact on children treated for medulloblastoma: a review and proposed conceptual model. *Developmental Disabilities Research Reviews*, *14*(3), 203–210. https://doi.org/10.1002/ddrr.32

Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., Schreiber, J., Swain, M., Chapieski, L., Mabbott, D., Knight, S., Boyle, R., & Gajjar, A. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: An international, prospective, and longitudinal study. *Journal of Clinical Oncology: official Journal of the American Society of Clinical Oncology*, *31*(28), 3494–3500. https://doi.org/10.1200/JCO.2012.47.4775

Palmer, S. L., Reddick, W. E., & Gajjar, A. (2007). Understanding the cognitive impact on children who are treated for medulloblastoma. *Journal of Pediatric Psychology*, *32*(9), 1040–1049. https://doi.org/10.1093/jpepsy/jsl056

Pelham, W. E., III, Altszuler, A. R., Merrill, B. M., Raiker, J. S., Macphee, F. L., Ramos, M., Gnagy, E. M., Greiner, A. R., Coles, E. K., Connor, C. M., Lonigan, C. J., Burger, L., Morrow, A. S., Zhao, X., Swanson, J. M., Waxmonsky, J. G., & Pelham, Jr., W. E. (2022). The effect of stimulant medication on the learning of academic curricula in children with ADHD: A randomized crossover study. *Journal of Consulting and Clinical Psychology*, *90*(5), 367–380. https://doi.org/10.1037/ccp0000725

Piccinelli, P., Beghi, E., Borgatti, R., Ferri, M., Giordano, L., Romeo, A., Termine, C., Viri, M., Zucca, C., & Balottin, U. (2010). Neuropsychological and behavioural aspects in children and adolescents with idiopathic epilepsy at diagnosis and after 12 months of treatment. *Seizure*, *19*(9), 540–546. https://doi.org/10.1016/j.seizure.2010.07.014

Puhr, A., Ruud, E., Anderson, V., Due-Tønnessen, B. J., Skarbø, A. B., Finset, A., & Andersson, S. (2021). Executive function and psychosocial adjustment in adolescent survivors of pediatric brain tumor. *Developmental Neuropsychology*, *46*(2), 149–168. https://doi.org/10.1080/87565641.2021.1900191

Pulsifer, M. B., Duncanson, H., Grieco, J., Evans, C., Tseretopoulos, I. D., MacDonald, S., Tarbell, N. J., & Yock, T. I. (2018). Cognitive and adaptive outcomes after proton radiation for pediatric patients with brain tumors. *International Journal of Radiation Oncology, Biology, Physics*, *102*(2), 391–398. https://doi.org/10.1016/j.ijrobp.2018.05.069

Rathouz, P. J., Zhao, Q., Jones, J. E., Jackson, D. C., Hsu, D. A., Stafstrom, C. E., Seidenberg, M., & Hermann, B. P. (2014). Cognitive development in children with new onset epilepsy. *Developmental Medicine and Child Neurology*, *56*(7), 635–641. https://doi.org/10.1111/dmcn.12432

Ray, P., Çelik, G., Tahiroğlu, A., Gamlı, İ., & Hergüner, Ö. (2019). Methylphenidate treatment outcomes and gender differences in attentional deficit and hyperactivity disorder with epilepsy: A follow-up study*. *Anatolian Journal of Psychiatry*, *20*(0), 1. https://doi.org/10.5455/apd.28181

Remes, T. M., Hovén, E., Ritari, N., Pohjasniemi, H., Puosi, R., Arikoski, P. M., Arola, M. O., Lähteenmäki, P. M., Lönnqvist, T. R. I., Ojaniemi, M. K., Riikonen, V. P., Sirkiä, K. H., Winqvist, S., Rantala, H. M. J., Harila, M., & Harila-Saari, A. H. (2021). Neurocognitive impairment, employment, and social status in radiotherapy-treated adult survivors of childhood brain tumors. *Neuro-Oncology Practice*, *8*(3), 266–277. https://doi.org/10.1093/nop/npab004

Rosema, S., Crowe, L. M., & Anderson, V. (2012). Social function in children and adolescents after traumatic brain injury: a systematic review 1989 - 2011. *Journal of Neurotrauma*, *29*(7), 1277–1291. https://doi.org/10.1089/neu.2011.2144

Sato, I., Higuchi, A., Yanagisawa, T., Murayama, S., Kumabe, T., Sugiyama, K., Mukasa, A., Saito, N., Sawamura, Y., Terasaki, M., Shibui, S., Takahashi, J., Nishikawa, R., Ishida, Y., & Kamibeppu, K. (2018). Employment status and termination among survivors of pediatric brain tumors: a cross-sectional survey. *International Journal of Clinical Oncology*, *23*(5), 801–811. https://doi.org/10.1007/s10147-018-1279-2

Spiegel, J. A., Goodrich, J. M., Morris, B. M., Osborne, C. M., & Lonigan, C. J. (2021). Relations between executive functions and academic outcomes in elementary school children: A meta-analysis. *Psychological Bulletin*, *147*(4), 329–351. https://doi.org/10.1037/bul0000322

Spreij, L. A., Visser-Meily, J. M. A., van Heugten, C. M., & Nijboer, T. C. W. (2014). Novel insights into the rehabilitation of memory post acquired brain injury: A systematic review. *Frontiers in Human Neuroscience*, *8*(780), 993. https://doi.org/10.3389/fnhum.2014.00993

Stavinoha, P. L., Askins, M. A., Powell, S. K., Pillay Smiley, N., & Robert, R. S. (2018). Neurocognitive and psychosocial outcomes in pediatric brain tumor survivors. *Bioengineering*, *5*(3), 73. https://doi.org/10.3390/bioengineering5030073

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., Carpenter, J. R., Chan, A.-W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., … Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical Research ed.)*, *355*, i4919. https://doi.org/10.1136/bmj.i4919

Storebø, O. J., Pedersen, N., Ramstad, E., Kielsholm, M. L., Nielsen, S. S., Krogh, H. B., Moreira-Maia, C. R., Magnusson, F. L., Holmskov, M., Gerner, T., Skoog, M., Rosendal, S., Groth, C., Gillies, D., Buch Rasmussen, K., Gauci, D., Zwi, M., Kirubakaran, R., Håkonsen, S. J., … Gluud, C. (2018). Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. *The Cochrane Database of Systematic Reviews*, *5*(5), CD012069. https://doi.org/10.1002/14651858.CD012069.pub2

Storebø, O. J., Storm, M. R. O., Pereira Ribeiro, J., Skoog, M., Groth, C., Callesen, H. E., Schaug, J. P., Darling Rasmussen, P., Huus, C.-M. L., Zwi, M., Kirubakaran, R., Simonsen, E., & Gluud, C. (2023). Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *The Cochrane Database of Systematic Reviews*, *3*(3), CD009885. https://doi.org/10.1002/14651858.CD009885.pub3

Vago, C., Bulgheroni, S., Usilla, A., Biassoni, V., Serra, A., Gentile, S., Ajovalasit, D., Leonardi, M., Massimino, M., Fidani, P., & Riva, D. (2011). Adaptive functioning in children in the first six months after surgery for brain tumours. *Disability and Rehabilitation*, *33*(11), 953–960. https://doi.org/10.3109/09638288.2010.520804

Varni, J. W., Burwinkle, T. M., Seid, M., & Skarr, D. (2003). The PedsQLTM* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambulatory Pediatrics*, *3*(6), 329–341. https://doi.org/10.1367/1539-4409(2003)003<0329:TPAAPP>2.0.CO;2

Verche, E., San Luis, C., & Hernández, S. (2018). Neuropsychology of frontal lobe epilepsy in children and adults: Systematic review and meta-analysis. *Epilepsy & Behavior: E&B*, *88*, 15–20. https://doi.org/10.1016/j.yebeh.2018.08.008

Verity, S. J., Bell, L., Ryles, J., & Hill, R. M. (2022a). "I feel happy again": Methylphenidate supports health-related quality of life in survivors of pediatric brain tumor. *Children*, *9*(7), 1058. https://doi.org/10.3390/children9071058

Verity, S. J., Halliday, G., Hill, R. M., Ryles, J., & Bailey, S. (2022b). Methylphenidate improves cognitive function and health-related quality of life in survivors of childhood brain tumours. *Neuropsychological Rehabilitation*, *34*(1), 133–153. https://doi.org/10.1080/09602011.2022.2157446

Vertessen, K., Luman, M., Staff, A., Bet, P., de Vries, R., Twisk, J., & Oosterlaan, J. (2022). Meta-analysis: Dose-dependent effects of methylphenidate on neurocognitive functioning in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *61*(5), 626–646. https://doi.org/10.1016/j.jaac.2021.08.023

Wagner, A. P., Carroll, C., White, S. R., Watson, P., Spoudeas, H. A., Hawkins, M. M., Walker, D. A., Clare, I. C. H., Holland, A. J., & Ring, H. (2020). Long-term cognitive outcome in adult survivors of an early childhood posterior fossa brain tumour. *International Journal of Clinical Oncology*, *25*(10), 1763–1773. https://doi.org/10.1007/s10147-020-01725-7

Watts, S. J., Rodgers, J., & Riby, D. (2016). A systematic review of the evidence for hyporesponsivity in ASD. *Review Journal of Autism and Developmental Disorders*, *3*(4), 286–301. https://doi.org/10.1007/s40489-016-0084-y

Wilkinson-Smith, A., Blackwell, L. S., & Howarth, R. A. (2022). Neuropsychological outcomes in children and adolescents following anti-NMDA receptor encephalitis. *Child Neuropsychology: a Journal on Normal and Abnormal Development in Childhood and Adolescence*, *28*(2), 212–223. https://doi.org/10.1080/09297049.2021.1965110

Yeates, K. O., Armstrong, K., Janusz, J., Taylor, H. G., Wade, S., Stancin, T., & Drotar, D. (2005). Long-term attention problems in children with traumatic brain injury. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(6), 574–584. https://doi.org/10.1097/01.chi.0000159947.50523.64

Yoo, H. K., Park, S., Wang, H.-R., Lee, J. S., Kim, K., Paik, K.-W., Yum, M. S., & Ko, T.-S. (2009). Effect of methylphenidate on the quality of life in children with epilepsy and attention deficit hyperactivity disorder: an open-label study using an osmotic-controlled release oral delivery system. *Epileptic Disorders: international Epilepsy Journal with Videotape*, *11*(4), 301–308. https://doi.org/10.1684/epd.2009.0278

Appendix A. Database Search Results

Search conducted 14.03.2024					
Database	Treatment Concept (OR)	Outcome Concept (OR)	Medical Diagnostic Concept (ORG)	Age Concept	Number of studies identified
PsycInfo	Methylphenidate Concerta Ritalin	Fatigue Function* Ataxi* Quality_of_Life IQ Cogniti* Verbal_intelligence VIQ Processing_Speed PSI Social*	Brain_Injury ABI TBI Tumo* Epilep* Infectio* Stroke Arteriovenous_malformation Bleed* Hypox* Anox* Hydrocephalus	Child Young Person Adolescent Young Adult	138
Medline	Methylphenidate Concerta Ritalin	Fatigue Function* Ataxi* Quality_of_Life IQ Cogniti* Verbal_intelligence VIQ Processing_Speed PSI Social*	Brain_Injury ABI TBI Tumo* Epilep* Infectio* Stroke Arteriovenous_malformation Bleed* Hypox* Anox* Hydrocephalus	Child Young Person Adolescent Young Adult	248
EMBASE	Methylphenidate Concerta Ritalin	Fatigue Function* Ataxi* Quality_of_Life IQ Cogniti* Verbal_intelligence VIQ Processing_Speed PSI Social*	Brain_Injury ABI TBI Tumo* Epilep* Infectio* Stroke Arteriovenous_malformation Bleed* Hypox* Anox* Hydrocephalus	Child Young Person Adolescent Young Adult	1535
Cochrane	Methylphenidate Concerta Ritalin	Fatigue Function* Ataxi* Quality_of_Life IQ Cogniti* Verbal_intelligence VIQ Processing_Speed PSI Social*	Brain_Injury ABI TBI Tumo* Epilep* Infectio* Stroke Arteriovenous_malformation Bleed* Hypox* Anox* Hydrocephalus	Child Young Person Adolescent Young Adult	4

Appendix B. Adapted version of the quality of evidence screening tool: Methylphenidate and attentional performance (QuEST:MAP)

Criterion	Quality Assessment	Rating Criteria
A) Participants recruitment		
1. Eligibility criteria is reported:	Excellent	Eligibility criteria is comprehensively reported, including the key areas of; age at study inclusion, sex, IQ, clinical diagnosis.
	Satisfactory	Eligibility criteria is clearly reported but lacks one key area.
	Poor	Some information regarding eligibility criteria is provided, but at least two key areas are missing.
	Not reported	Eligibility criteria is not clearly reported.
2. Demographic information is provided:	Excellent	Demographic information is comprehensively reported for the key areas of; age at diagnosis/injury, age at study inclusion, sex, IQ, clinical diagnosis, and comorbidities (e.g., ADHD).
	Satisfactory	Demographic information is clearly reported, but lacks one key area.
	Poor	Demographic information is not clearly reported, and at least two key areas are missing.
	Not reported	No demographic information has been reported.
3. Where a matched control is employed, the matching process is detailed:	Excellent	The matching process is appropriately detailed and includes the key areas of; age at diagnosis/injury, age at study inclusion, sex, IQ, and diagnosis. Or, any potential confounds associated with the key areas have been appropriately acknowledged and controlled (e.g., appropriate use of post-hoc analyses). Crossover designs - eligibility criteria and demographic information relevant to the matching process is extensively outlined.

(*Continued*)

Appendix B. Continued

Criterion	Quality Assessment	Rating Criteria
	Satisfactory	Groups are matched on at least three key areas. Or, where matching of every key area is not possible, some attempt to control potential confounds is made. Crossover designs - eligibility criteria and demographic information is described but omits relevant finer details.
	Poor	Groups are not appropriately matched on any of the key areas. Or, while groups are matched on one key area, there is minimal evidence of attempts to control for relevant confounding variables (e.g., no evidence of post-hoc analyses). Crossover designs - minimal information is provided regarding relevant matching variables (e.g., IQ).
	Not reported	The matching process has not been reported.
	Not applicable	The study does not employ a matched control.
B) Appropriate adjustment for potential confounds		
Appropriate adjustments are made as a result of potential confounds (e.g. discontinuation rates, bias from informed intervention and assessment, adherence of medication):	Excellent	Where appropriate, confounds are thoroughly discussed and adjustments applied (e.g. adjustment for discontinuation, blinding to intervention, blinding to assessment, adjustment for adherence of medication, etc.).
	Satisfactory	Confounds are appropriately addressed but differ from an "*Excellent*" rating due to the associated adjustments being less robust.
	Poor	Confounds are not discussed and no evidence of necessary management is provided.
C) Analysis process		
The study is sufficiently powered:	Excellent	Appropriate power analysis is comprehensively reported.
	Satisfactory	Power calculations are provided showing the study to be only moderately well powered/ powered only to detect a large effect.
	Poor	Power calculations are inadequately reported. Or, demonstrates the design to be insufficiently powered.
	Not reported	Power calculations have not been reported.
D) Statistical results		
Reporting of statistical results:	Excellent	The results were described comprehensively and thoroughly allowing readers to gain a clear understanding of study finding (e.g., appropriate reporting of effect sizes).
	Satisfactory	Statistical reporting of outcomes is appropriately thorough but leaves out some key details that would have provided additional insight (e.g., effect sizes or confidence intervals).
	Poor	Only basic statistical outcomes are provided (e.g., means), providing very limited insight into study findings.
	Not reported	Statistical findings are not reported.

Appendix C. Summary table: Overall quality rating utilizing the quality of evidence screening tool: Methylphenidate and attentional performance (QuEST: MAP)

Key Area	
Participant recruitment	
Appropriate adjustment for potential confounds	
Analysis process	
Statistical results	
Decisive Evidence	The majority of key areas warrant an "Excellent" rating. No key areas being evaluated as "Poor." Any areas assigned a rating of "Not Reported" are highly unlikely to negatively influence the quality of evidence
Convincing Evidence	The majority of key areas are covered to a "Satisfactory" or "Excellent" level. No key areas are evaluated as "Poor." Any areas assigned a rating of "Not Reported" are highly unlikely to negatively influence the quality of evidence.
Fair Evidence	Most key areas warrant a "Satisfactory" rating, but few attain "Excellent." There are few key areas evaluated as either "Poor" or "Not Reported."
Questionable Evidence	Many key areas are "Poor" or "Not reported." The evidence provided is questionable.