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REVIEW ARTICLE

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Effect of psychostimulant medications on physical function in children with cerebral palsy: scoping review

Anwar B. Almutairi[1]✉, Naif Z. Alrashdi[2], Laura Vogtle[3] and Mansour M. Alotaibi[4]

The aim of this scoping review is to examine the extent and depth of the literature on effects of central nervous system (CNS) stimulant medications on physical function in children with cerebral palsy (CP). A systematic search for relevant peer-reviewed studies was conducted of PubMed, CINAHL, Cochrane, SPORTDiscus, Embase, & Scopus (January 2002 & August 2022). We included studies that examined the effects of CNS stimulants on physical function in children with CP. Four studies met our selection criteria. All studies explored the effect of Modafinil on physical function outcomes. Three studies of the four included studies reported positive effects of Modafinil on spasticity, motor performance, and gait, whereas one study reported no significant effects of Modafinil. Our findings suggest that there is very low-quality evidence that suggests that Modafinil may enhance physical improvements in body structure and function, including reduction in spasticity and improvements in gait parameters.

Pediatric Research (2024) 95:1217–1223; https://doi.org/10.1038/s41390-023-02933-3

IMPACT:

- Central nervous system stimulants were examined for efficacy on physical function and spasticity in children with cerebral palsy.
- The evidence on the effects of central nervous system stimulants on physical function in children with CP is limited and inconsistent.

INTRODUCTION

Cerebral palsy (CP) is a group of disorders that affects movement, posture, and balance in children.[1] Clinical features of CP result from an insult to the developing brain, which is permanent and non-progressive.[2] Globally, CP is one of the leading causes of physical disability, affecting 1.5 (high-income countries) to to 3.4 (low- and middle-income counties) for every 1000 children.[1,3] CP primarily impacts brain structure and function and could lead to significant functional impairments, such as gait abnormalities.[1,4] Clinically, CP is classified based on motor disorders into: spasticity (increased velocity-dependent muscle resistance to stretch),[5] dyskinesia (excessive involuntary and slow movement),[6] ataxia (inability to generate a coordinated voluntary movement),[7] or mixed movement disorders.[4]

Spasticity is the most common motor type of CP, impacting physical function and quality of life.[4] Several pharmacological treatments with different mechanisms of action are available and can be used to reduce spasticity in children with CP. For example, botulinum toxin type-A (BoNT-A) injections are efficacious in reducing upper[8] and lower[9] extremity spasticity and improving overall physical function in children with CP.[10] Several treatment guidelines recommend offering BoNT-A as a safe and effective intervention for spasticity management in children and adolescents with CP.[11–14] BoNT-A inhibits the release of acetylcholine from the presynaptic terminal, causing a decrease in muscle excitability.[10] However, BoNT-A targets only specific muscles and has a temporary effect. BoNT-A has been criticized for causing muscle weakness in a condition that is manifested with weakness as well as movement disorders.[10]

Other medications exist to manage spasticity in children with CP, including Baclofen (delivered as tablets or intrathecal injections) and Diazepam (oral medication).[13] These medications reduce spasticity by increasing the affinity of gamma-amino butyric acid (GABA) on its receptors which in turn blocks excitatory neurotransmitters.[15,16] These medications have been effective in reducing spasticity.[17,18] However, Baclofen and Diazepam have several side effects, including drowsiness and muscle weakness.[13] Therefore, there is a critical need to explore new medications that could reduce spasticity and have minimal side effects in this population.

A few researchers have attempted to use off-label, central nervous system (CNS) stimulants such as Methylphenidate (MPH) for improving physical function in children with neurodevelopmental disease, such as Attention-Deficit/Hyperactivity Disorder (ADHD),[19,20] but not in children with CP. Furthermore, a previous case report study indicated that a 44-year old woman with CP (choreoathetosis with spasticity-mixed CP-type) consumed amphetamine (AMP) recreationally and noticed a remarkable

[1]Department of Physical Therapy, Faculty of Allied Health, Kuwait University, Jabriya, Kuwait. [2]Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Majmaah University, Al-Majmaah, Saudi Arabia. [3]Department of Occupational Therapy, School of Health Professions, Birmingham, The University of Alabama at Birmingham, Birmingham, AL, USA. [4]Department of Rehabilitation, Faculty of Applied Medical Sciences, Northern Border University, Arar, Saudi Arabia.
✉email: almutairi.anwar@ku.edu.kw

Received: 19 September 2023 Revised: 18 October 2023 Accepted: 14 November 2023
Published online: 9 December 2023

reduction in her spasticity, which encouraged her treating physician to prescribe her with MPH to reduce spasticity.[21] Using MPH resulted in substantial long-term reduction of spasticity and choreoathetosis in this 44-old woman.[21] Despite the design of this study, it documented positive effects of MPH on spasticity in a 44-old women with CP. Additionally, previous studies reported that MPH has positive effects on improving physical function in other populations such as individuals post stroke.[22,23] Side effects exist when treating children with MPH for long periods such as limiting body height.[24] However, researchers claim that CNS stimulants' effects on body height is minimal and lack sufficient longitudinal follow-up data.[25] To that end, CNS stimulants, including MPH and Modafinil may be used to manage spasticity and to improve physical function in children with CP because this medication alters neurochemicals in the brain, potentially produce changes in neuroplasticity.[26]

Neuroplasticity is a crucial factor in the success of any motor rehabilitation program in children with CP.[27] Specifically, motor training at early ages may increase the likelihood of better motor outcomes, partially due to improving sensory feedback plasticity.[28] Sensory feedback and sensory processing are integral component for motor learning on the basis of use or iteration, which strengthen connections between primary motor and somatosensory cortices.[29] However, it is unclear if CNS stimulants like MPH and Modafinil restore neuroplasticity impairments or augment motor training effects on neuroplasticity in children with CP. In addition, limited number of studies have examined the effects of CNS stimulants on spasticity and physical function, with or without rehabilitation programs, in children with CP. Therefore, this scoping review examined the extent and depth of the literature regarding the effects of CNS stimulant medications on spasticity and physical function in children with CP.

METHODS

To perform this scoping review, we followed both the Arskey and O'Malley (2005) framework for scoping reviews and the recommendation proposed by Levac et al. (2010).[30,31] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) Checklist was used for reporting this scoping review.[32]

Identifying the research question

Considering the breadth of research conducted using CNS stimulants on motor performance, this scoping review aimed to answer the question: "What is known from the existing relevant literature pertaining to the effects of CNS stimulants on spasticity and physical function in children with CP?"

Identifying relevant studies

We performed a comprehensive search of relevant peer-reviewed studies that were published over the past two decades (January 2002– August 2022) in PubMed, CINAHIL, Cochrane, SPORTDiscus, Embase, and Scopus databases (search conducted in August 2022). Our search included relevant keywords, synonyms, controlled vocabulary for CP, psychostimulant medications, CNS stimulants, motor performance, physical function, mobility, and spasticity. We further hand searched reference lists of all relevant articles to locate any potential studies.

Study selection

Our inclusion criteria for this scoping review are as follows: 1) studies conducted primarily on children with CP (i.e., excluding combined CP and ADHD), 2) studies used psychostimulant medications, 3) studies included one or more physical function outcome measures (gait, balance, mobility, or spasticity), and 4) studies published in a peer-reviewed journal. The exclusion criteria included: systematic reviews, theoretical frameworks, animal studies, or studies not available in English.

For all studies pooled from the search, two reviewers (MMA, ABA) independently performed title and abstract screening, as well as full texts review to determine studies that met our selection criteria. If a consensus was not met by the two authors (MMA, ABA), a third author (NZA) who was blinded to the two reviewer's' decision was consulted.[31] We used Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) to perform study screening and data charting and synthesizing.

The data charting

Two reviewers (MMA, ABA) performed data charting independently. The same reviewers met and discussed what data/items to extract. For all the included studies, we defined physical function outcome measures as any outcome measure that evaluates motor or functional performance, spasticity, balance, walking, gross motor function, mobility, neuromuscular, and/or functional independence. The data charting items included: authors' names, year of study publication, country where the study was performed, study design, sample size, age, gross motor function classification system (GMFCS) level, CNS stimulants used, dosage, physical function related measures used, and main results (i.e., significant findings reported).

Quality assessment and data synthesis

All included studies were classified based on the Clinical Practice Guideline Process Manual classification (Table 1) proposed by the American Academy of Neurology (AAN).[33] The AAN classification was used to characterize the quality of the existing evidence regarding the effects of CNS stimulant medications on motor performance in children with CP. AAN further classifies evidence into class I-IV based on internal validity aspects such as concealed randomization, blinding, and/or number of primary outcomes.[33] Class I indicates less threats to internal validity, whereas class IV indicates multiple threats to internal validity. Additionally, the reviewers (MMA, ABA) determined medication efficacy based on the reporting of statistical significance of results, where positive results (i.e., statistically significant differences) and negative results (i.e., non- significant differences) of the included studies were utilized.

RESULTS

Search results

The search from all databases produced 16 potential studies (Medline PubMed = 12, SPORTDiscus = 0, CINAHL = 0, Scopus = 1, Cochrane = 0, and Embase = 3). No duplicates were identified. Out of 16 potential studies, 9 studies were excluded during the title and abstract screening process. After full text review process ($n = 7$), 5 studies were excluded because of not using physical outcomes ($n = 3$), full-text article was not accessible ($n = 1$), and being a systematic review ($n = 1$). Two studies were included in the scoping review. The reference lists of these two included studies were searched and we included two further studies. Therefore, 4 studies were included in the final included studies in this scoping review (Fig. 1).

Characteristics of included studies

Among the final included studies ($n = 4$),[34–37] three were conducted in the United States of America[34–36] and one in Canada.[37] All of the included studies used Modafinil as a CNS stimulant to improve physical function among children with CP.[34–37] Of the included studies ($n = 4$), two were retrospective case-series,[34,35] one was a within-subject repeated measures study,[36] and one was a double-blind AB/BA cross-over RCT.[37] All of the included studies were conducted on children with CP. The age

Table 1. American Academy of Neurology Evidence Classification.

Classification	Criteria
Class I	Triple masked (i.e., the patient, treating provider, and outcome assessor) RCT in representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups or there is appropriate statistical adjustment for differences. In addition: a. Concealed allocation. b. Two or less specified primary outcomes. c. Clearly defined inclusion/exclusion criteria. d. Adequate account for dropout and cross-over with a minimum of 80% completion rate. e. For noninferiority and equivalence trials, claiming efficacy also requires: i. explicit statement of clinically meaningful difference by defining the threshold for noninferiority or equivalence. ii. Used a substantially similar standard intervention to that used in previous studies establishing efficacy of standard treatment. iii. inclusion/exclusion criteria for participant selection and outcomes of participants on the standard treatment are comparable with those of previous trials establishing efficacy of standard treatment. iv. The interpretation of study results is based on pre-protocol analysis that accounts for crossover or dropouts. v. For crossover trials, both carryover effects and periods are evaluated and statistical adjusted performed, if appropriate.
Class II	RCT that lacks one or two Class I criteria, Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics meeting Class I criteria b-e. Randomized crossover trial missing one of two following criteria: a. Period and carryover effects prescribed. b. Presenting baseline characteristics of treatment order groups. Relevant baseline characteristics are presented and substantially equivalent between treatment groups or there is appropriate statistical adjustment for differences. Masked or objective outcome assessment.
Class III	Controlled studies including studies with external controls such as well-defined natural history controls. Crossover trials missing both two criteria mentioned in Class II. Describing major confounding differences between treatment groups.
Class IV	Studies not meeting Class I, II, or III criteria.

RCT randomized controlled trials.
Adopted from the 2017 Edition of Clinical Practice Guideline Process Manual published by the American Academy of Neurology.

range among all included studies was 0-18 years. Only one study[37] reported mean age (11.4 ± 1.4) and was the only study that reported GMFCS levels (III-IV). Sample size varied between 8-116 participants. Table 2 provides further details on studies' characteristics. Finally, all of the included studies lacked high-quality methodology features, such as detailed sample description and information about received rehabilitation.

Reported outcomes

One of the included studies[34] evaluated children with CP before and after 4-weeks of modafinil intervention (retrospective case-series study). Outcomes evaluated included: neurological exam, vital signs (i.e., blood pressure and pulse rate), weight, modified Ashworth scale (MAS) score for the hip adductors, gait speed, and blinded review of a videotape of the participants' gait. The authors did not operationally define gait improvements. Overall, positive results observed were reduction in MAS score of adductor spasticity and improvement in gait speed after Modafinil intervention.

The same authors of the previous study conducted two other retrospective case-series,[35,36] with an overall goal of identifying cases of children with spastic CP who used Modafinil. One study (2004)[35] aimed to examine reduction in spasticity, parent-reported side effects, and compliance of Modafinil. Children with CP exhibited positive results reflected by a reduction in spasticity and continuation of Modafinil beyond the chart review period, which could indicate that this medication may have positive long-lasting effects on spasticity. The study reported some side effects, including decreased appetite, less sleep time, and hyperactivity. In the second study (2006),[36] the authors examined gait improvements in children with CP receiving Modafinil, in comparison to children with CP who did not receive Modafinil. Positive results were reflected through gait improvement in children in the Modafinil group. The authors also did not operationally define gait improvements or report other co-interventions (e.g., physical therapy).

Finally, Murphey and colleagues (2008)[37] aimed to replicate the results obtained by Hurst and his team by conducting a randomized double blind AB/BA cross-over trial. In this clinical trial, authors examined spasticity, function and quality of life in children with CP while being treated with modafinil. The outcomes reported were MAS, Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD), visual analog scale (VAS) for pain intensity, gross motor function measure (GMFM), Quality of Upper Extremity Skills Test (QUEST), and Pediatric Evaluation of Disability Inventory (PEDI).[37] Quality of life (QoL) was measured using the QoL subset of CPCHILD. The use of Modafinil yielded decreased QoL, however, this decrease was not statistically significant.

DISCUSSION

The current scoping review aimed to answer the question of "What is known from existing literature regarding the effects of CNS stimulants on physical function in children with CP?" The final four included studies[34–37] have identified evidence on only one medication class (Modafinil) that met our selection criteria. Across all included studies,[35,36] two were retrospective chart reviews included children with CP who were previously treated with Modafinil, one was within subjects repeated-measures,[34] and the remaining one was RCT[37] study design. Among the four included studies, three[34–36] reported positive effects of Modafinil on physical function and spasticity; these three studies were published by the same research group. In contrast, one study[37] reported no significant effects of Modafinil on physical function outcomes. The findings from the included studies were inconsistent. Notably, three out of the 4 identified studies were done by the same group of researchers.

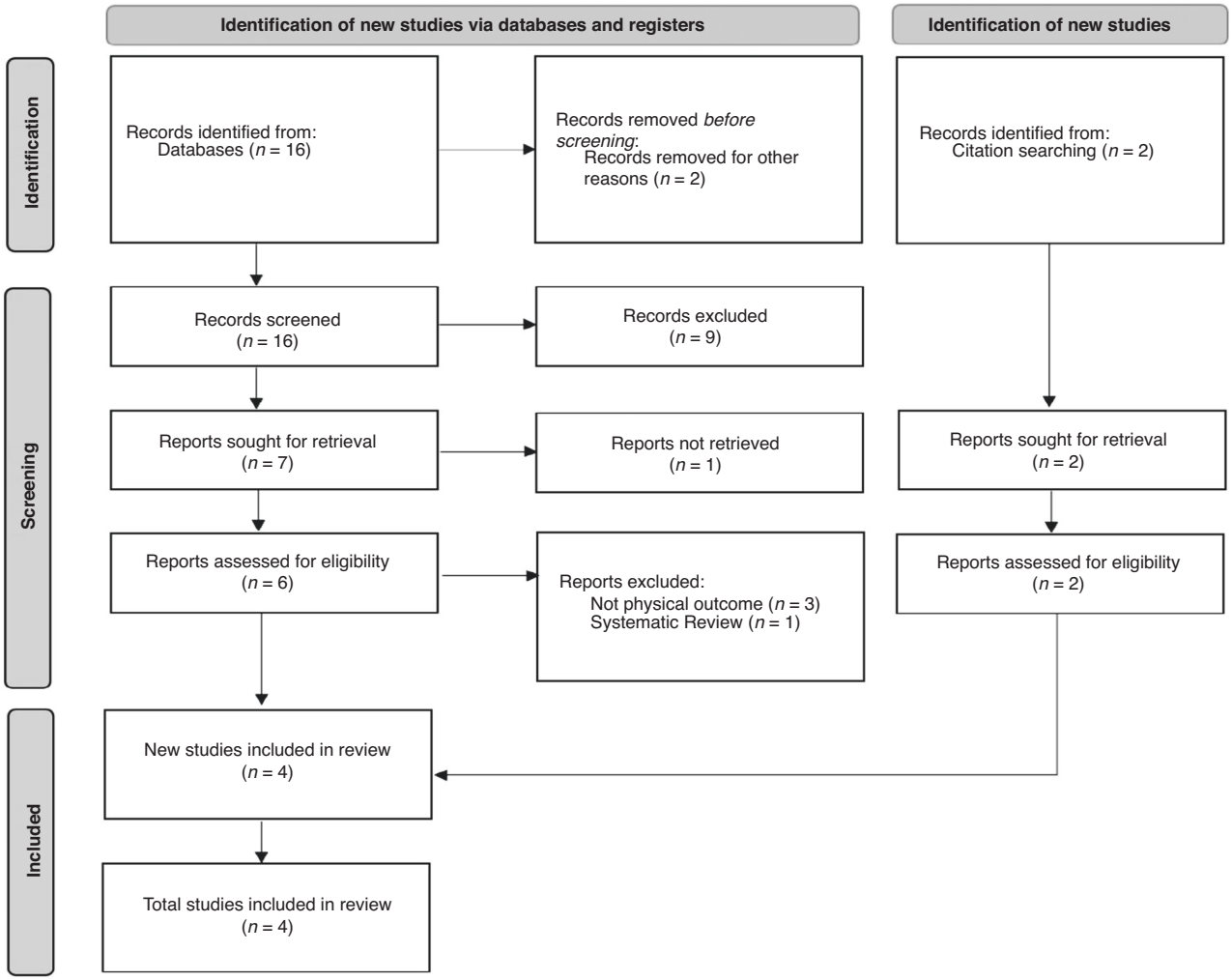

Fig. 1 PRISMA flow diagram for scoping review - the selection process of eligible papers through screening of title, abstract, and full text.

This scoping review revealed that limited evidence exists regarding effects of CNS stimulants on physical function in children with CP, yielding an unexplored, important research area. The currently-available evidence presents with several limitations that hindered drawing a solid conclusion, such as poor sample description, use of retrospective study designs, and lack of control for significant confounders. None of the included studies have examined psychostimulant medications (e.g., MPH or AMP) while controlling for rehabilitation interventions received by the participants. Across all included studies,[34–37] there was no description of any other received treatments, including rehabilitation programs. Rehabilitation programs could provide a cointervention with CNS stimulants and contribute to improvements in motor performance and reducing spasticity in children with CP.[38] Except for MAS, none of the included studies used consistent outcome measures. All included studies only focused on measures of structure and function, and activities (i.e. description of gait) domains of the of functioning, disability and health children and youth version (ICF-CY). Finally, among all included studies, there was only one double-blinded cross-over RCT.[37] Importantly, this RCT was underpowered as reported in the study, which limited drawing solid conclusions regarding the effects of Modafinil on motor performance and spasticity in children with CP. The findings of this RCT did not favor the use of Modafinil.

The exact mechanism of how Modafinil might improve physical function in children with CP has not been well investigated. Modafinil increases dopamine concentration at the synaptic cleft of different areas in the brain such as the basal ganglia, potentially leading to improvements in motor performance.[39] Furthermore, Modafinil, similar to MPH, could improve physical function indirectly by improving executive functioning.[40] Modafinil has also shown beneficial effects on reducing fatigue in other populations such as persons with multiple sclerosis.[41] In contrast, Modafinil had limited effects on corticospinal excitability and alpha motoneuronal excitability.[42] These findings from previous published work suggest that research is needed to examine potential associations between Modafinil and motor systems in children with CP.[4] Our findings encourage examining the effects of Modafinil on physical function and spasticity in children with CP using rigorous research design, such as RCT.

The effects of CNS stimulants like MPH on physical function were expected to be positive. However, we located no studies that examined such effects on children with CP. MPH increases dopamine and norepinephrine concentration in the synaptic cleft by blocking their reuptake in areas of the brain that regulate motor planning and execution.[43] This hypothesis is supported by previous research that showed positive effects of MPH on physical function measured by the Fugl-Meyer Scale (FMS) and modified functional independence measure (M-FIM) in adults post-stroke.[23] Another study reported significant improvements in physical function in individuals poststroke who received physical therapy and MPH when compared to a placebo group.[44] Thus, we

Table 2. Summary of selected articles.

Authors	Design	N	Age	Functional Level	Drug/ Dose	Outcomes	Results	Overall Effect	AAN Classification
Hurst et al. (2002)	Within-subject repeated measures	10	3–18	N/A	Modafinil/wt <35 kg - 50 mg/day for 4 weeks wt >35 kg & 100 mg/day for 4 weeks	Neurological evaluation, vital signs, MAS rating of hip adductors, blinded videotaped evaluation of gait & gait speed (ft/sec)	- 7 out of 9 showed statistically significant decrease in spasticity - 6 out of 9 had statistically significant improvement in gait speed	+	IV
Hurst et al. (2004)	Case-series	30	≤18	N/A	Modafinil/ Not reported	Benefit on spasticity, side effects & compliance with therapy	23 (76%) out of 30 showed diminished spasticity in clinical examination	+	IV
Hurst et al. (2006)	Case-series	116 (Modafinil-treated = 59 & Control = 57)	≤18	N/A	Modafinil/ Not reported	Gait improvements	73% showed gait improvement in group receiving Modafinil	+	IV
Murphy et al. (2008)	Randomized double blind AB/BA cross-over	8	11.4 ± 1.4	GMFCS level III to V	Modafinil/<35 kg - 50 mg/day for 4 weeks >35 kg & 100 mg/day for 4 weeks with 4 weeks washout period	MAS, CPCHILD, VAS for pain, GMFM, QUEST, PEDI	Statistically significant improvement of the mean CPCHILD score (quality of life) after the placebo period	-	II

CP Cerebral Palsy, *N/A* Not Applicable, *GMFCS* Gross Motor Classification System, *wt* weight, *kg* kilogram, *mg* milligram, *MAS* modified Ashworth Scale, *ft/sec* feet per second, *CPCHILD* Caregiver Priorities and Child Health Index of Life with Disabilities, *VAS* visual analog scale, *GMFM* Gross Motor Function Measure, *QUEST* Quality of Upper Extremity Skills Test, *PEDI* Pediatric Evaluation of Disability Inventory, *AAN* American Academy of Neurology.

postulate that MPH may reduce spasticity and improve physical function in individuals post a brain injury. Future research should examine if using MPH would yield reduction in spasticity and improvements in physical function in children with CP. In contrast, a previous published study found no significant effects of dextroamphetamine (AMPH), another CNS stimulant, on physical function in individuals post stroke.[22] The effects of MPH were also examined in patients with moderate to moderately severe TBI.[45] MPH significantly improved physical function measured by the disability rating scale.[45] This study included a wide age range of adolescents and adults (16-64 years).[45] In this study, researchers also found that at 90-days after MPH discontinuation, motor improvements vanished.[45] These findings suggest that MPH may not have a long-lasting effect on improving disability level. It is worth noting that this study did not control for rehabilitation interventions nor were potential interfering effects reported,[45] which might limit the strength of these findings. Overall, MPH seems a promising candidate for improving physical function in children with CP, but there are many confounders that could interfere with MPH effects such as receiving rehabilitation and disability severity.

Based on AAN classification criteria, there is limited high-quality evidence regarding the effects of CNS stimulants on physical function in children with CP. Only one study[37] had a good-quality classification (class II) where the authors used an RCT design but lacked a few AAN features of rigorous designs such as triple blinding and adequate accounting for dropouts. Two[35,36] out of the final 4 included studies were retrospective study designs such an inferior evidence level compared to prospective study designs. Low evidence level could lead to major concerns such as lack of controlling for major confounders and inability to determine causal effects/relationships. Finally, the within-subject repeated measures study[34] was classified as weak evidence (class IV) due to multiple methodological concerns, including lack of sample size justification and lack of a control group. Future research should consider using rigorous study designs to allow for improved internal validity when examining the effects of CNS medications on physical function in a larger sample of children with CP.

Clinical implications and future research directions

Our findings in the current scoping review support the need for further studies to test the effects of different CNS stimulants on reducing spasticity and improving physical function in children with CP. Low-quality evidence with major methodological concerns recommended using Modafinil for physical function improvement and reduction of spasticity in children with CP. Out of the four included studies in this review, one study reported negative effects of Modafinil on spasticity and physical function. However, this study had low sample size which could inflate the likelihood of type II error. Thus, CNS stimulants, Modafinil in particular, should be examined using a larger sample size with strong research study designs while controlling for major confounders, such as receiving rehabilitation. Finally, examining CNS stimulants, including Modafinil in children with CP should also include assessment of safety and tolerability elements.

CONCLUSIONS

This scoping review revealed that limited low-quality evidence has examined the effects of CNS stimulants on reducing spasticity and improving physical function in children with CP. While using CNS stimulants like Modafinil for reducing spasticity and improving physical function in children with CP is promising, using these medications currently cannot be recommended due to the lack of high-quality evidence. Future studies with high-quality research designs should examine if Modafinil and other CNS stimulants

would reduce spasticity and improve physical function in this population.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

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ACKNOWLEDGEMENTS

The authors extend their appreciation to the Deanship of Scientific Research at Northern Border University, Arar, KSA for funding this research work through the project number "NBU-FFR-2023-0121". The author would like to thank Deanship of Scientific Research at Majmaah University for supporting this work under project number "R-2023-827".

AUTHOR CONTRIBUTIONS

A.B.A. had a substantial contribution to the conceptualization and design of the article. She also helped with the acquisition, analysis, and interpretation of data. Finally, she drafted the article. N.Z.A. helped with the acquisition, analysis, and interpretation of data. He also revised the draft critically for important intellectual content. L.V. had a substantial contribution to the conceptualization and design of the article. She also revised the draft critically for important intellectual content. M.M.A. had a substantial contribution to the conceptualization and design of the article. He also helped with the acquisition, analysis, and interpretation of data.

COMPETING INTERESTS

The authors report there are no competing interests to declare.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Anwar B. Almutairi.

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