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SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of methylphenidate on substance use disorders in children and adolescents with attention-deficit/hyperactivity disorder: a systematic review

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Abstract

Introduction and objectives: Attention-Deficit/Hyperactivity Disorder (ADHD) affects 2.2% of children and adolescents. The risk of substance use disorders (SUD) is twice as high among people with ADHD, requiring targeted approaches. This study aimed to evaluate the effect of methylphenidate on the development of substance use disorders among children and adolescents with ADHD, including alcohol, tobacco, and other drugs. **Methods:** A systematic search was conducted on January 26th, 2023. Characteristics of the study and participants were extracted and the risk of bias evaluated. **Results:** From the 2,854 articles identified and 14 registry entries, seven reports were included in the review, accounting for 860 participants, with 526 from intervention (61.2%) and 334 from control groups (38.8%). Treatment with methylphenidate was consistently protective against drug use. **Discussion:** Methylphenidate treatment may be effective in reducing SUD risk, especially in young drug users. Preventive measures are needed, including health promotion and interventions tackling health determinants, particularly in vulnerable groups. Further high-quality studies are required to strengthen our findings.

Keywords: ADHD. Child. Adolescent. Substance use. Methylphenidate.

Efeito do metilfenidato na perturbação de consumo de substâncias em crianças e adolescentes com perturbação de hiperatividade e défice de atenção: uma revisão sistemática

Resumo

Introdução e objetivos: A Perturbação de Hiperatividade/Défice de Atenção (PHDA) afeta 2,2% das crianças. O risco de Perturbação por uso de Substâncias (PS) é o dobro nesta população, exigindo abordagens direcionadas. Este estudo avaliou o efeito do metilfenidato no desenvolvimento de PS entre crianças e adolescentes com PHDA, incluindo álcool, tabaco e outras drogas. **Métodos:** Pesquisa sistemática realizada em 26/01/2023, com extração das características do estudo e dos participantes e avaliação do risco de viés. **Resultados:** Dos 2854 artigos identificados e 14 registos de ensaios clínicos, foram incluídos sete relatos, contabilizando 860 participantes, com 334 no grupo de controlo e 526 na intervenção (61,2%). O tratamento com metilfenidato foi consistentemente protetor contra o uso de drogas. **Discussão:** O tratamento com metilfenidato

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pode ser eficaz na redução do risco de PS, especialmente em jovens consumidores de drogas. São necessárias medidas preventivas, incluindo a promoção da saúde e intervenções nos determinantes da saúde. São necessários mais estudos de alta qualidade para fortalecer estes achados.

Palavras-chave: PHDA. Criança. Adolescente. Uso de substâncias. Metilfenidato.

Keypoints

What is known

– Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neuropsychiatric condition in children and adolescents, characterized by persistent patterns of inattention, hyperactivity, and impulsivity.
– Previous studies have established a strong association between ADHD and substance use disorders (SUD), with a substantially increased risk of developing SUD among individuals with ADHD and have as well explored the potential protective effect of methylphenidate (MPH) treatment against the development of SUD in individuals with ADHD.
– The neurobiological basis of this complex comorbidity remains largely unknown, but evidence suggests an interaction between dopaminergic and reward systems, contributing to impulsivity and reward-seeking behaviors associated with both disorders.
– Pharmacological interventions, such as methylphenidate, have been widely used to treat ADHD symptoms and have demonstrated, in some studies, a potential protective effect against the development of SUD in adolescents with ADHD.

What is added

– This systematic review and meta-analysis provide novel insights by synthesizing evidence from seven studies to comprehensively evaluate the effects of methylphenidate treatment on reducing the risk of substance use disorders (SUD) in children and adolescents with ADHD.
– Our findings consolidate evidence that methylphenidate treatment may have a positive impact on reducing the risk of SUD, particularly in youths already engaged in substance use.
– Additionally, we emphasize the importance of preventive measures, such as health promotion and interventions addressing social determinants of health, to mitigate the risks associated with ADHD and substance use.
– Through meticulous analysis of diverse treatment protocols and outcome measures, we have elucidated the heterogeneous nature of existing research. Therefore, this review underscores the need for further high-quality studies to validate and expand our findings, as well as the importance of adopting a multidisciplinary and personalized approach in managing ADHD and substance use disorders in children and adolescents.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common disorder among children and adolescents, with a mean worldwide prevalence of ADHD of 5.6% to 7.6% in this population[1]. ADHD is now acknowledged to persist into adulthood in ~ 50-65% of individuals[2-5]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), the presence of symptoms by age 12 is defined as the age of onset[6,7], with a recent European study showing an earlier onset between 2.3 years and 7.5 years, with an age of diagnosis between 6.2 and 18.1 years old[8]. ADHD shows high concurrent comorbidity of neurodevelopmental and mental health disorders, such as autism spectrum disorder, communication and intellectual disability, and depressive, anxiety, and bipolar disorders[9]. Earlier and more frequent use of alcohol, tobacco, and other drugs has also been linked with ADHD, with a risk of SUD twice as high among this group, making substance use disorders (SUD) one of the most problematic co-occurring disorders[10]. Individuals with ADHD who have low dopamine levels will experience impulsivity and inability to delay gratification, which represents the main developmental risk factors for early substance use and misuse[11]. On the other hand, substances of abuse increase the release of dopamine, reducing inattentive symptoms and inner restlessness.

Approved pharmacological agents for ADHD include stimulants[12]. Methylphenidate is an effective, safe, and well-tolerated psychostimulant and remains the first option of treatment[9]. The main mechanism of action of methylphenidate is the binding and blocking of dopamine transporters and norepinephrine transporters, leading to increased synaptic levels of these neurotransmitters. Adverse effects are sometimes present, with nervousness and insomnia being the most common[13].

Some studies suggest that stimulant treatment has a protective effect against the development of SUD in adolescence and early adulthood[14-16]. However, conflicting findings have been reported in other studies that did not find such a protective effect, with several adverse effects that led to its withdrawal[17,18]. These mixed results warrant further investigation and a comprehensive evaluation of the evidence.

Therefore, the main purpose of this review is to critically assess the existing studies and evaluate the overall evidence regarding the effect of methylphenidate treatment in children and adolescents with ADHD on the development of substance use disorders, including alcohol, tobacco, and other drugs.

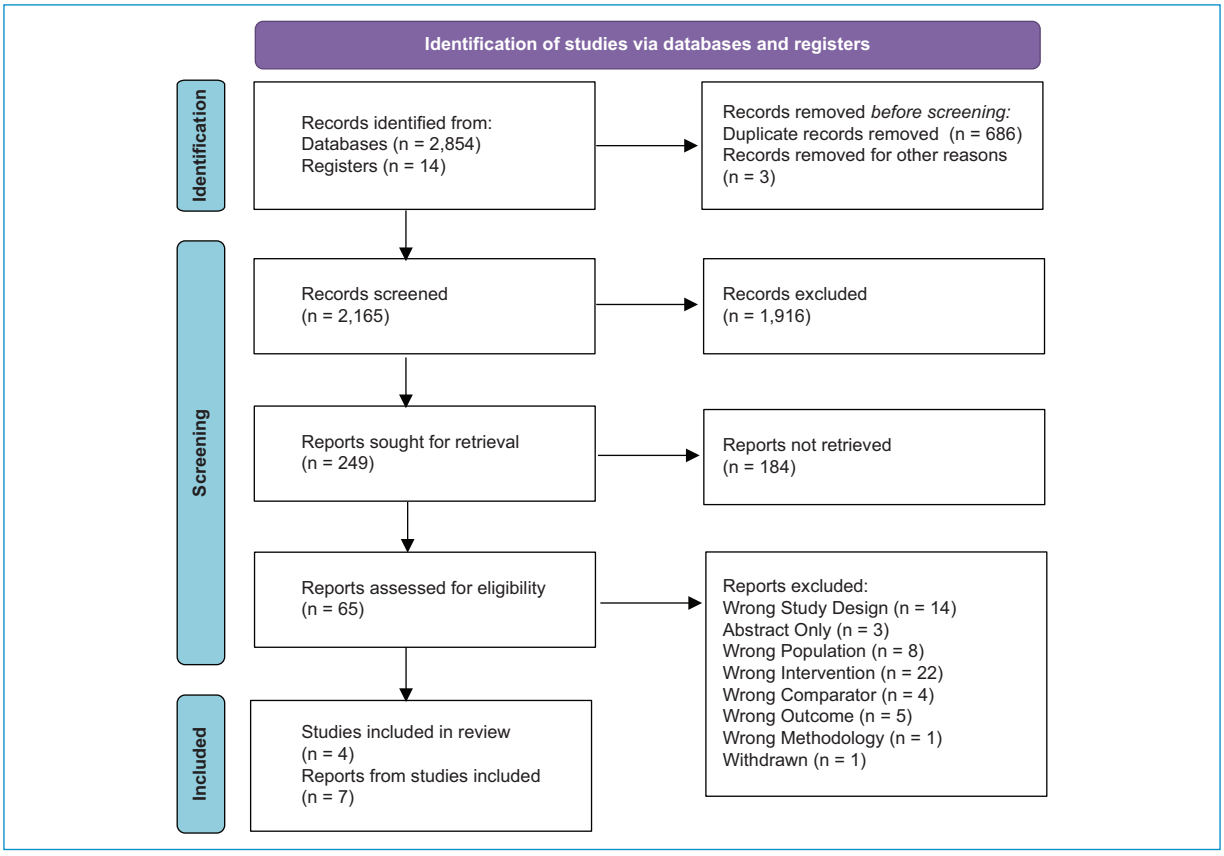

Figure 1. PRISMA flowchart of the studies reviewed in this systematic review.

Methodology

Search strategy

We defined the following patient, intervention, comparison, outcome (PICO) model: P) children and adolescents (< 18 years old) diagnosed with ADHD and with or without reported consumption of alcohol, tobacco, or drugs; I) treatment with methylphenidate; C) without any treatment or placebo; O) substance abuse disorder, including alcohol, tobacco, or other drugs.

We utilized Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) to define the search strategy. Studies were identified through a systematic search of four electronic databases: PubMed, ScienceDirect, Web of Science, and Embase. The search was conducted on January 26, 2023, using the following search query: (ADHD [MeSH Terms] AND (child OR adolescent* or kid*)) AND (methylphenidate [MeSH Terms]) AND (alcohol OR tobacco OR smoking OR drug* OR "drug abuse").

The search was also conducted in registries on January 26, 2023, namely the International Traditional Medicine Clinical Trial Registry and Clinicaltrials.gov. We filtered for the following terms: Population/Age Range: child (birth to 17 years old); Condition: ADHD; Intervention: methylphenidate. For Clinicaltrials.gov, we also applied the following: Outcome: tobacco OR smoking OR alcohol OR drug abuse OR substance use OR substance abuse.

Filters were applied to limit the search to studies involving children and adolescents (< 18 years old) and published between 1994 and 2023, as the consensual classification for ADHD was officially introduced in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in 1994[19]. We considered the following types of studies: Clinical trials, Drugs experiments/trials, Randomized controlled trials (RCTs), Cohorts and case-control studies, and other non-randomized studies, as quasi-experimental and natural experiment studies. Studies to be included must have not only the abstract, but also the full text.

We imposed no language or other restrictions on any of the searches.

Articles were screened by title, abstract, and full text, and data was extracted on the study and participants' characteristics, as well as odds ratio (OR) estimates and 95% confidence intervals (CIs).

The protocol of this review was registered in PROSPERO (ID: CRD42023394690).

Selection process

The retrieved articles were analyzed independently in pairs by the four authors (AC, DC, JCX, and MB) in line with pre-defined criteria in PICO to determine eligibility for inclusion. The screening phase comprises the analyses of the articles' titles, abstract, and full text. For the screening phase, possible classifications for the inclusion of the studies are: "Yes", "Unclear", and "No". If the paper is classified as "No" by both researchers, the paper is removed from the database. If it receives an "Unclear" or "Yes", it moves to the next selection phase.

The references of the studies selected which included the same outcome were also analyzed to find other eligible reports. When more than one report referred to the same study or clinical trial, the one presenting the results with more detail or providing data for the largest sample was considered, although any of the reports could be used to obtain information on the study characteristics. When there were disagreements between the reviewers in independent assessments, these were discussed in a specific meeting, and were resolved by consensus or after discussion with another researcher.

The qualitative analysis phase was carried out by 2 people (JC and MB). This step evaluated the existence of the outcome of interest and the completeness of the data, the control group (ADHD children and adolescents not medicated with methylphenidate or with placebo), any possible duplication of participants across studies, and the existence of other drugs utilized for ADHD.

If there was data related to inferential analysis, such as odds ratio or relative risk between the groups defined, these were also considered.

Data extraction and collection

The data was extracted independently by two people (AC and DC) and double-checked by JCX. Data was collected from the articles and entered in a Microsoft Excel spreadsheet, and included the following characteristics, including our defined PICO:

- Study design
- Location
- Population age
- Population gender
- Comparator group
- Duration of the study
- Duration of the follow-up
- Intervention characteristics
- Number of patients in the intervention group
- Number of patients in the control group
- Odds ratio, 95% confidence intervals (95% CI) and respective p values (if available). Due to their variability, these were converted to a logarithmic scale for data analysis purposes.

Risk of bias in individual studies

The Risk of Bias Assessment (RoB) was carried out by MB and JC, using the Cochrane Risk of Bias In Randomized Trials (RoB2), and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I). Robvis (National Institute for Health Research) was used for the graphic design of the RoB. The calculation of p values for Egger's test was used to assess publication bias.

The quality of evidence was evaluated using the GRADE approach. For RCTs, the evidence is downgraded from 'high' certainty by one level for serious (or by two levels for very serious) concerns for each study limitation. For non-randomized studies, the level of evidence starts from the lowest level of certainty, and is upgraded. The levels of certainty are defined according to the GRADE checklist[20].

Data synthesis

The qualitative synthesis was performed as a narrative review of the results of the studies, describing the effects of the variables and the main outcomes.

For the quantitative synthesis, we used the inconsistency index I^2 to assess statistical heterogeneity among studies in the meta-analysis. As heterogeneity was high, a subgroup analysis was attempted. OR were reported for each study included and a pooled estimate on forest plots, with a 95% confidence interval (CI), adopting a random-effects model. No treatment or placebo were considered as a reference.

Data synthesis was performed using OpenEpi[21] and IBM SPSS Statistics 28®.

Table 1. Summary of characteristics of the studies analyzed

Study	Type of study	Location	Total n	Mean age	SUD	Intervention	Duration	Dose	n Intervention	n Control	n Interv_ SUD+	n Control_ SUD+	Odds ratio	Confidence interval	p- value
S1	RCT	USA	303	16.5 y (SD = 1.3)	Drugs and alcohol	OROS-MPH	16 weeks	18 mg titrated up to 72 mg during the first two study weeks	151	152			*		
S2													*		
S3					Cigarette and cannabis use						71	82	0.76	0.48-1.19	0.228
S4	Non-randomized	Germany	215	8 y and 9 m	Smoking	Immediate release MPH	2 y and 3 m (SD = 1 y 1 m)	Cumulative total dose was 4.510 mg	106	109	21	29	0.68	0.36-1.30	0.244
S5					Alcohol abuse						15	21	0.69	0.33-1.43	0.323
					Other drugs						14	34	0.34	0.16-0.67	0.002
S6	Non-randomized	USA	141	15.7 (SD = 2.7)	Alcohol	OROS MPH	2 y	Mean of 64.6 ± 25.4 mg/day (1.02 ± 0.33 mg/kg/day)	115	26	12	9	0.22	0.08-0.60	0.003
					Marijuana						3	6	0.09	0.02-0.39	0.001
					Other drugs						2	6	0.06	0.01-0.31	0.001
S7	Non-randomized	USA	201	16.1 (SD = 3.2)	Smoking	OROS MPH	2 y	Daily mean of 61 ± 25 mg (0.97 ± 0.36 mg/kg/day)	154	57	11	11	0.32	0.13-0.79	0.013

*Not possible to calculate due to utilizing different outcome measures.
RCT: randomized controlled trial.

Results

A total of 2,854 articles were identified through searching databases, of which 402 were from PubMed, 487 from ScienceDirect, 1,684 from Web of Science, and 169 from Embase. Searches conducted in the International Traditional Medicine Clinical Trial Registry and Clinicaltrials.gov retrieved three and 11 hits, respectively. After removing duplicates, 2,165 articles remained for screening. Of these, 12 were Cochrane Reviews and 249 were selected for abstract screening. Sixty-five articles were selected for full-text review. Ultimately, seven reports from four studies met the inclusion criteria and were included in the review and meta-analysis.

Specific characteristics of each of these articles are presented in table 1. From the articles selected, three were randomized controlled trials, while the remaining four were non-randomized trials. Two studies were retrospective; these were conducted in Germany. The other studies were prospective and carried out in the United States. Out of the prospective studies, three were conducted for 16 weeks, while the remaining two had an overall intervention duration of two years.

Most of the studies presented a mean age of around 16 years old, except for two, which included children with a mean age of around eight years old. The settings where the studies were conducted varied greatly between referral sources, such as juvenile justice and social services agencies, as well as primary care and mental health clinics, schools, and media advertising.

When accounting for the studies included, there were 862 participants with ADHD, with 526 participants (61.0%) across the intervention groups.

Regarding the intervention, five studies adopted OROS-MPH[22-24;27-28], whereas two others utilized immediate release MPH[25-26].

The dosage also varied among studies. Three studies reported having an initial dose of 18 mg titrated up to 72 mg (or highest dose tolerated) during the first two study weeks[22-24]. Two different studies, conducted by Hammerness et al., employed varying dosage regimens. In the study from 2013, participants received daily doses of OROS MPH that were clinically adjusted during a six-week acute phase, with increments of 9-18 mg/day and a maximum of 1.5 mg/kg/day or 126 mg/day[28]. The mean exposure to OROS-MPH was 10 months, culminating in a mean dose at the endpoint of 61 ± 25 mg. Conversely, in the 2017 study, OROS MPH was prescribed under open-label conditions for up to 24 months, with clinically adjusted doses reaching a maximum of 1.5 mg/kg/day or 126 mg/day. The mean exposure to OROS-MPH in this study was 13 months, with a mean dose at the endpoint recorded as 64.6 ± 25.4 mg/day (1.02 ± 0.33 mg/kg/day)[27].

The remaining two retrospective studies presented a mean cumulative total dose of 4.510 mg MPH per child[25-26].

As for the outcome, three studies defined smoking as the main outcome[24,26,28], one analyzed alcohol dependence[25], and three studies analyzed drug abuse (cannabinoids and other drugs)[22,23,27]. Different studies reported outcomes in various parameters, described below:

- S1: Riggs et al. (2011) defined utilized substance-adolescent reported number of days of use in the past 28 days, while also conducting weekly urine drug screens[22];
- S2: Tamm et al. (2013) utilized reported reduction in substance use days from baseline to week 16[23];
- S3: Gray et al. (2011) analyzed smoking tobacco and cannabis use after a 16-week follow-up period[24];
- S4: Huss et al. (2007) first evaluated self-reported consumption of alcohol and drugs, while also measuring urine sampling[25];
- S5: Huss et al. (2008) analyzed the prevalence of nicotine use disorders, while also recording the ages at first cigarette and at regular smoking (10 cigarettes per day for at least four weeks)[26];
- S6: Hammerness et al. (2017) also utilized urine sample screening, together with self-reported use of alcohol or substances, including marijuana[27];
- S7: Hammerness et al. (2013) evaluated smoking tobacco initiation and persistence, which was self-reported by participants[28].

In the studies analyzed, dependence levels on marijuana and other drugs were as low as 1.7% to 2.6%, whereas cigarette and cannabis dependence combined presented the highest dependence levels, with 47.0%.

Prior to delving into inferential analyses, a risk of bias assessment was conducted using both ROBINS-I and ROB2. The findings unveiled notable concerns across most studies, particularly in the domain of confounding (refer to Fig. 2). Despite these concerns, the overall quality of evidence was deemed moderate according to the GRADE approach. Furthermore, the Egger's test presented a p value of 0.013, denoting publication bias.

A forest plot was conducted (Fig. 3) to understand the various studies and their outcomes. The data was analyzed using a random effects model. However, owing to the substantial heterogeneity observed ($I^2 = 79\%$), we refrained from conducting a meta-analysis on the results.

Figure 2. Risk of bias assessment for the studies analyzed: for S1-S3, ROB2 was applied (top), whereas for S4-S7 ROBINS-I was the indicated framework for evaluation (bottom).

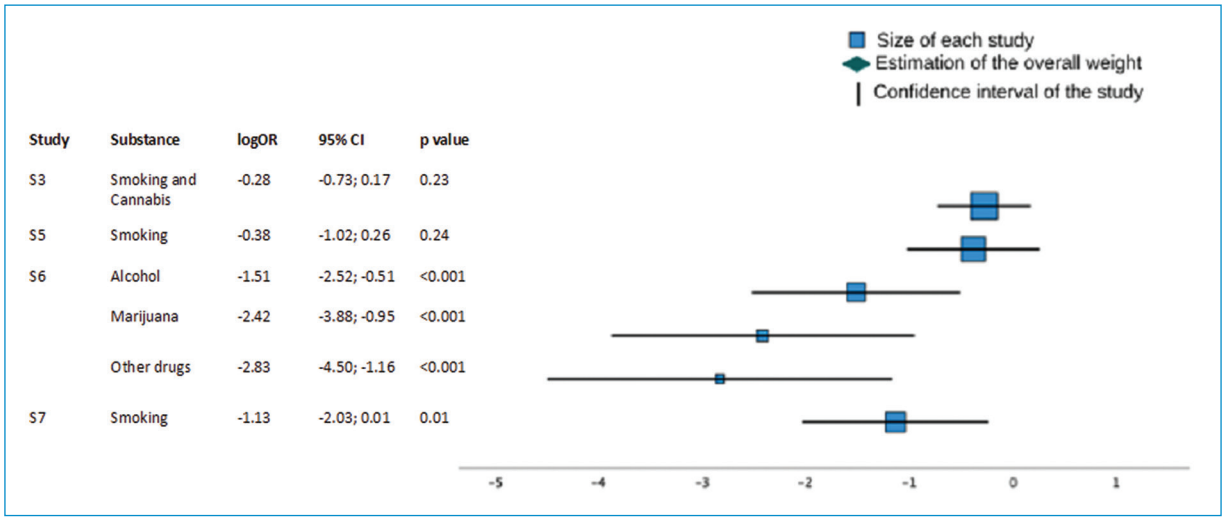

Figure 3. Forest plot with a summary of the papers included.

To comprehend the reasons for this heterogeneity, another forest plot was carried out, taking into account the country of origin, which also separates studies on randomized versus non-randomized.

However, heterogeneity still remained high, with I^2 = 76%. As such, we proceeded with the narrative synthesis of the results reported in the inferential analyses of the selected studies.

Regarding OR values, two of the studies showed diverse significant results, depending on the SUD analyzed, ranging from 0.06 (0.01-0.31; p = 0.001) to 0.32 (0.13-0.79; p = 0.013). Two other studies had non-significant results, mostly related to nicotine dependence.

In reviewing studies that investigated tobacco use, ADHD patients treated with MPH exhibited varying results:

Hammerness, 2013 reported an OR = 0.32 (0.13-0.79; p = 0.013) when compared to non-medicated patients[28], while Huss, 2008 showed a non-significant OR of 0.68 (0.36-1.30; p = 0.244)[26].

The alcohol group also showed benefits on being medicated with MPH, with an OR = 0.22 (0.08-0.60; p = 0.003) in the Hammerness study[27], whereas the study by Huss et al. showed non-significant OR = 0.69 (0.33-1.43; p = 0.323)[25]. The marijuana group had significant results, with an OR = 0.09 (0.02-0.39; p = 0.001), despite its smaller sample[31]. Similarly, other drugs analyzed in the same study by Hammerness also had a small number of individuals with SUD after the intervention, with an OR = 0.059 (0.01-0.31; p = 0.001)[27]. The study by Huss et al. also reported significant outcomes, albeit slightly higher OR = 0.34 (95% CI 0.16-0.67; p = 0.002)[26].

The studies from Riggs, Tamm, Gray et al. reported combined factors - smoking and cannabis, which reported a non-significant OR = 0.76 (0.48-1.19; p = 0.228)[22-24].

Discussion

In this systematic review, we aimed to evaluate the impact of methylphenidate (MPH) treatment on children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) and co-occurring substance use disorders (SUD). We included a total of seven studies, comprising 862 participants, and provided a comprehensive perspective. Among these, three were randomized controlled trials (RCTs) involving 303 participants, while four were non-randomized trials encompassing 559 participants. The average age of participants was approximately 16 years, except for two studies that focused on younger children with a mean age of about eight years.

These studies employed varied formulations and durations of MPH treatment. The majority utilized OROS-MPH (n = 5), while others utilized immediate-release MPH (n = 2). The treatment duration ranged from a minimum of 16 weeks to a maximum of two years and three months. The outcomes assessed were diverse, with three studies concentrating on smoking, one on alcohol dependence, and three on drug abuse, including marijuana, cannabis, and other substances.

Our findings suggest that the administration of MPH to children and adolescents with comorbid ADHD and SUD demonstrated a discernible impact, particularly in the context of drug use. However, it is important to note that the effect of MPH on smoking outcomes was less evident, potentially indicating nuanced perceptions of smoking compared to other substance use disorders.

In caring for adolescents and young adults facing both SUD and ADHD, it is crucial to address both conditions simultaneously. A thorough assessment of their substance use and ADHD is crucial before initiating treatment. Research underscores the significant benefits derived from a combination of family and individual interventions for adolescents and young adults with SUD[29]. An initial emphasis on addiction control is advised[30,31].

Addressing ADHD, the guidelines from the National Institute for Health and Care Excellence (NICE) advocate for the use of stimulant medications, particularly methylphenidate and other amphetamines, as the primary intervention for both children and adults[32]. These medications have exhibited effectiveness in ameliorating core ADHD symptoms and functional impairments, including in adolescents grappling with ADHD and SUD[33].

For school-aged children and young individuals with mild symptoms of ADHD, NICE recommends behavioral therapy as the initial course of action[32]. However, when medication is warranted, methylphenidate stands as the first-choice medication for those with moderate to severe ADHD symptoms and functional impairment. In children and adolescents with concurrent ADHD and SUD, the timing of pharmacological intervention appears to be a critical consideration[33].

In alignment with NICE, the American Academy of Pediatrics (AAP) also designates stimulant medications as the preferred first-line treatment for elementary school-aged students with ADHD[34]. Stimulants have demonstrated considerable efficacy in mitigating ADHD core symptoms. Selective norepinephrine reuptake inhibitors, such as atomoxetine, and selective α-2 adrenergic agonists, including extended-release guanfacine and extended-release clonidine, are also considered available pharmacological options, although some studies point to the need for further investigations due to safety concerns[35,36].

The European ADHD Guidelines Group (EAGG) aligns with the AAP and NICE, endorsing stimulant medications, such as methylphenidate and amphetamines, as the primary treatment modality for ADHD in children and adolescents. Non-stimulant medications, like atomoxetine, are suggested as a second-line option for those who do not respond well to stimulants or have side effects or contraindications to their use[37].

Cognitive behavioral therapy (CBT) has also demonstrated utility in combination with pharmacotherapy. Several studies have reported a reduction in ADHD scores with combined therapies, underscoring the

augmentative role of CBT in improving ADHD symptomatology[37]. Structured psychotherapies emerge as the preferred treatment approach for addressing both ADHD and SUD[33,38]. Motivational interviewing has also exhibited promise in ameliorating ADHD symptoms, encompassing structured and goal-oriented sessions[39,40].

Given the limited availability of literature specifically addressing psychotherapy for adolescents and young adults with concomitant SUD and ADHD, additional research examining the efficacy of CBT in treating both active disorders and preventing relapse is essential.

Limitations

The mixed results observed in our review and the existing literature emphasize the need for further studies and a comprehensive evaluation of the evidence regarding the use of MPH in ADHD and SUD. Future research should consider larger sample sizes, longer follow-up periods, and standardized outcome measures to provide more robust evidence on the potential benefits and risks of MPH treatment in this specific population.

It is also important to acknowledge the limitations of the studies included. The heterogeneity in study designs, participant characteristics, treatment protocols, and outcome measures across the studies may have contributed to the variability in the observed results. Additionally, the reliance on self-report measures and the potential for selection bias in non-randomized trials should be considered when interpreting the findings.

Furthermore, we presented a publication bias, which can be tackled by investing in the development of high-quality research and thorough literature reviews, which will allow meta-analyses. Additionally, journals should strive to publish legitimate trials regardless of their results, requiring peer reviewers and authors to disclose their conflicts of interest[41].

Conclusion

Overall, these findings suggest that methylphenidate treatment may be effective in reducing the risk of substance use disorders in children and adolescents with ADHD, especially in drug users.

Despite our limited conclusions, further high-quality studies are needed to confirm these results and address potential sources of bias.

Preventive measures for this population are required, by tackling social determinants of health and working closely with vulnerable groups. Health promotion and interventions in the community are needed to decrease the use of substances in this age group.

Authors' contribution

Andreia Coutinho: Conceived and designed the study, report, review, or other type of work or paper; Analyzed or interpreted data from patients, research studies, or literature; Drafted the article; Critically reviewed the article for important intellectual content; Provided final approval of the version to be published; Agreed to be accountable for the accuracy or integrity of the work; Maria Bento: Conceived and designed the study, report, review, or other type of work or paper; Analyzed or interpreted data from patients, research studies, or literature; Drafted the article; Critically reviewed the article for important intellectual content; Provided final approval of the version to be published; Agreed to be accountable for the accuracy or integrity of the work; Dídia Cruz: Conceived and designed the study, report, review, or other type of work or paper; Analyzed or interpreted data from patients, research studies, or literature; Drafted the article; Critically reviewed the article for important intellectual content; Provided final approval of the version to be published; Agreed to be accountable for the accuracy or integrity of the work; José Chen-Xu: Conceived and designed the study, report, review, or other type of work or paper; Acquired data from patients, research studies, or literature; Analyzed or interpreted data from patients, research studies, or literature; Drafted the article; Critically reviewed the article for important intellectual content; Provided final approval of the version to be published; Agreed to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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