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SYSTEMATIC REVIEW: IS METHYLPHENIDATE EFFECTIVE IN THE TREATMENT OF SPECIFIC LEARNING DISABILITY - WITH IMPAIRMENT IN READING?

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ABSTRACT

Aim: To assess methylphenidate's efficacy and safety in dyslexia treatment. **Methods:** We conducted a literature search across MEDLINE, Cochrane Library, and Epistemonikos databases without restrictions on publication date, language, or publication status. The bias risk in RCTs was assessed via Cochrane instrument RoB 2.0. Evidence synthesis followed systematic review guidelines. **Results:** Three RCTs, totaling 91 children aged 6 to 13 years with reading scores 2 years below their chronological age, were included. Most studies had small sample sizes and tested different medications than methylphenidate (MTF) and placebo (PLB). Only one trial, Gittelman-Klein & Klein (1976), had a low risk of bias. Fagan et al. (1988) reported improved reading fluency (p=0.024) with methylphenidate. Gittelman-Klein & Klein (1976) noted a non-significant reading improvement trend after 4 and 12 weeks. Aman & Werry (1982) found no significant difference between methylphenidate, diazepam, and placebo. Overall, methylphenidate did not differ significantly from placebo in improving reading. **Conclusion:** Methylphenidate didn't significantly improve reading in dyslexia patients compared to placebo. Limited RCTs and a high risk of bias in most studies restrict the certainty level of this evidence. Further research is needed to establish efficacy and safety conclusively.

KEYWORDS: “Dyslexia”, “Specific Learning Disability”, “treatment” “Methylphenidate”, “Developmental Reading Disability”, “Bias assessment”, and “Effectiveness Assessment”.

INTRODUCTION

The International Dyslexia Association (IDA) establishes that this condition is characterized by “ difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities”[1] Dyslexia is recognized as one of the most common learning disabilities with an estimated prevalence of 7.1% in international studies.[2] This disorder generates great impact on the health and educational systems. One of the secondary consequences of dyslexia and limited reading experience is commonly named the Mattthew Effect, which refers to reduced vocabulary and knowledge base of individuals exposed to lower volume of text because of the learning disability.[3] Certainly, the impact of dyslexia is not limited to one specific academic domain but has widespread academic repercussions with a very high school dropout rate (approximately 45%) and a High School graduation rate of approximately 50%.[4] In addition, 60% of dyslexic children meet the criteria for at least one mental disorder.[5] Besides being highly comorbid with ADHD and disruptive disorders,[4] dyslexia also shows high comorbidity with anxiety and depression.[6,7]

Despite these psychosocial consequences, this condition often receives insufficient attention from healthcare professionals. Like other disabilities, it is unevenly distributed across social categories.[8] Therefore, it is crucial to search for evidence-based recommendations concerning its treatment to guide health policy makers.

There is currently no approved medical treatment for dyslexia,[4] with this disorder seen by many merely as a “school issue”. The core treatment approach to this disorder are educational interventions which provide explicit and systematic instruction in foundational literacy skills (i.e., phonological awareness, knowledge of phonetics, letter recognition, reading words and text) with simultaneous focus on vocabulary and comprehension.[9] Meta-analyses on the outcomes of

these interventions show small size effects in general (from 0.23 to 0.39).[9–12] Therefore, it is essential to search for therapeutic resources that can enhance these educational interventions.

Within this framework, Shaywitz et al., 2017.[13] showed that atomoxetine improved reading measures derived from the Woodcook-Johnson battery: "word attack" (i.e. pseudoword decoding), "basic reading skills" (i.e., identification of words and pseudowords) and "reading vocabulary" (i.e. semantic and synonyms/antonyms) in children with dyslexia without comorbidity with ADHD.

Despite the recent release of atomoxetine on Brazilian markets, only methylphenidate is publicly funded by the public unified health system (SUS) to treat ADHD in Brazil. Nevertheless, there are no systematic reviews investigating the effect of methylphenidate on dyslexia without the comorbidity with ADHD.

This review wanted to investigate the evidence on the effectiveness and safety of methylphenidate in the treatment of dyslexia without comorbidity with ADHD, considering that the comorbidity of dyslexia with ADHD would already indicate the use of methylphenidate or another stimulant. Our aim is to conduct a systematic review on the effectiveness of methylphenidate in Treatment of Specific Learning Disorder – with impairment in reading to provide evidence-based recommendations for healthcare professionals in the public health system.

METHODS

This work is a literature review aimed at addressing the clinical question outlined below. Subsequently, the systematic methods of search, study selection process, risk of bias assessment in RCTs, and synthesis of results will be presented.

Clinical question: Is Methylphenidate Effective And Safe For The Management Of Reading Difficulty In Dyslexia?
The PICO structure for this question was
Population: Individuals diagnosed with Dyslexia.
Intervention: Methylphenidate.
Comparison: Placebo or alternatives available in the SUS (Brazilian Unified Health System).
Outcomes: Improvement in reading accuracy and fluency according to standardized assessments for age and incidence of drug side effects.

Search and study selection process

A systematic literature search was conducted in MEDLINE (via PubMed), Cochrane Library, and Epistemonikos databases by two independent reviewers (LSTM and VSS) on July 3th, 2023. No restrictions on date, language, or publication status (abstract or full text) were applied. The search strategies for each database are described in Table 1.

The eligibility screening step for studies was conducted in two stages by two independent reviewers at each step. The first stage involved evaluating the title and abstract of each study. In the second stage, the full text was read, retaining randomized clinical trials (RCTs) that evaluated the medication for the analyzed indication. The discrepancies, when present, were discussed until reaching a consensus.

The eligibility criteria were considered as follows

(a) Participant Types: Patients diagnosed with Dyslexia or Reading Disability or a diagnosis compatible with that described in DSM-5,[14] as Specific Learning Disorder - with impairment in reading, at any age.
(b) Type of Intervention: Methylphenidate, as monotherapy, administered at any dosage.
(c) Study Types: Randomized clinical trials comparing methylphenidate to placebo or a pharmacological alternative.
(d) Outcomes: Improvement in reading accuracy and fluency according to standardized assessment for age and incidence of adverse drug events.
(e) Language: Only texts published in English, Portuguese, or Spanish were retained.

Risk of Bias Assessment

The risk of bias assessment of included RCTs was conducted using a validated instrument, employing the Cochrane Risk of Bias assessment tool (RoB 2.0)[15] and the Cochrane Risk of Bias for cross-over design.[16]

Evidence Synthesis

We adopted a criterion for evidence synthesis described in,[17] This method was based on: vote counting based on the direction of the effect in relation to the clinical question (favoring placebo x favoring methylphenidate), p-value for the evaluated outcomes, bias assessment of each trial, sample size of each study, and intervention effect size.

RESULTS

Initially, 175 publications were identified. After excluding duplicates (n = 41), 133 articles remained. Following the screening by title and abstract reading, only 4 publications were screened for full-text reading, as can be seen in Figure 1. Of these, the study by,[18] was not included because it did not make comparisons with a placebo group.

Three publications referring to three RCTs were included,[19,20,21] The main characteristics of the included studies are described in Table 2. These studies date back to the 1970s and 1980s and use a different diagnostic nomenclature for Specific Learning Disorders: Specific Learning Disability, reading retardation, and dyslexia.

The studies were identified through database searches, resulting in a total of 175 references. After removing duplicates and screening titles and abstracts, 4 references were selected for full-text evaluation. Among these, 3

studies met the inclusion criteria and were included in the review. The included studies generally have relatively small sample sizes, utilize a crossover design, have short duration, and test additional substances besides methylphenidate and placebo. The total population of the studies consists of 91 children aged between 6 and 13 years old, who performed standardized reading tests at a level two years below the expected level for their age.

Bias Assessment

All assessed studies were double-blind, placebo-controlled randomized clinical trials, which tends to provide higher quality evidence regarding the intervention. Using the Rob2 tool, the trials were assessed as "low risk" for Gittelman-Klein & Klein (1976)[21] and as "high risk" for bias for Aman & Werry (1982)[19] and Fagan et al., (1988)[20] as per Chart 1. Comments on the evaluation process are described in Chart 2.

Gittelman-Klein & Klein (1976)[21] used a traditional double-blind placebo-controlled RCT design. Data analysis was conducted per randomization ('modified intention-to-treat analysis'). Outcome data were available for almost all participants, and apparently, all evaluated data were analyzed according to the initial plan.

As for the articles by Aman & Werry (1982)[19] and Fagan et al., (1988)[20], which used a different type of RCT modality (crossover design), the adaptation of the Rob2 tool for crossover design was utilized. Aman & Werry (1982)[19] study was assessed as high risk for residual effect bias because it used a short washout period considering the long half-life of Diazepam. Thus, participants who used Diazepam in the first period and methylphenidate or placebo in the second period could still be under the influence of Diazepam during the performance assessment for the second substance. This effect is attempted to be minimized with statistical analysis controlling for "substance order factor," which was performed in the study. Also, only the result of the statistical analysis for the "drug factor" was reported, not the "order of drug factor." However, the authors reported that only one variable was affected by the "order of drug factor."

On the other hand, the article by Fagan et al., (1988)[20] article uses an appropriate washout period but does not report statistical analysis controlling for the influence of the drug order factor. This limitation can generate biases related to the "residual effect." Furthermore, the authors reported that "the data were evaluated in several ways"; they did not report the means of different groups or their standard deviations and only reported the p-value of these analyses. This raises doubts whether the data were analyzed according to a pre-established plan, increasing the risk of selection bias of the outcome to be reported.

The Intervention Effect

As the mean values of the groups in the Fagan et al., (1988)[20] study were not described, the p-value was used as a parameter to evaluate the intervention outcome, which was classified into two categories: "favors placebo" or "favors methylphenidate" as per Table 3.

In the Gittelman-Klein & Klein (1976)[21] study, reading scores on the WRAT showed a non-statistically significant improvement trend in the methylphenidate group after 4 weeks of MPH treatment (mean= 2.87 SE= 0.09 $p>0.05$) and PLB (mean=2.72 SE=0.09 $p>0.05$). This trend of improvement in the methylphenidate group was also observed after 12 weeks of treatment, but it was also not statistically significant (MPH (mean= 2.94 SE= 0.08 $p>0.05$) and PLB (mean=2.76 SE=0.08 $p>0.05$)). The improvement in GOR scores - "Gray Oral Reading Test" observed in the MPH group was not statistically significant either at 4 weeks of treatment (Standardized Mean Difference= 0.36, t= 0.28, df= 57 and $p>0.05$) or at 12 weeks (SMD=1, t= 0.65, df= 55 and $p>0.05$). The TRGI scores - Global Rating of Improvement in Reading Scores given by the Teacher tended to be higher in the methylphenidate group $\chi2=1.98$, $p = 0.08$, one-tailed test at 4 weeks, but not at 12 weeks.

In the Aman & Werry (1982)[19] study, there was no statistically significant difference between the methylphenidate, diazepam, and placebo groups in the Neale analysis scores: MPH - mean: 84.6; DZP-mean: 84.53 and PLB- mean: 83.13 ($F= 1.83$ df= 2 and 24 $p= 0.181$, Newman-Keuls test). In the psycholinguistic analysis, the self-correction rate, error rate, and repetition rate showed a non-significant improvement trend in the methylphenidate and diazepam groups. MPH and DZP resulted in small non-significant gains in the letter recognition test and slight deterioration in the high-frequency word recognition test. The tests of Combination of familiar figures and A-V Integration were also not statistically significant.

In the[20] study, reading fluency ($p=0.024$) and motor accuracy for the dominant hand ($p=0.01$) improved in the methylphenidate group. Balance did not change in any medication group compared to placebo. Eye movement fixation errors tended, non-significantly, to decrease in the methylphenidate and meclizine groups.

Side Effects

The Gittelman-Klein & Klein (1976)[21] study only mentions that two children did not tolerate the dose of methylphenidate at 5mg and were therefore excluded from the trial. There is no specification of the reason for intolerance. The Aman & Werry (1982)[19] and Fagan et al., (1988)[20] trials do not report the rate or specification of adverse events.

RESULTS SYNTHESIS

Using the criteria: vote counting based on the direction of the effect in relation to the clinical question (favors

placebo x favors methylphenidate), p-value for the evaluated outcomes, bias assessment of each trial, and sample size of each study (Table 3), it was decided to prioritize the results of Gittelman-Klein & Klein (1976)[21] and Aman & Werry (1982)[19] These two trials indicate no difference between the placebo group and the methylphenidate group in the sample of dyslexic children regarding reading improvement assessed by standardized instruments.

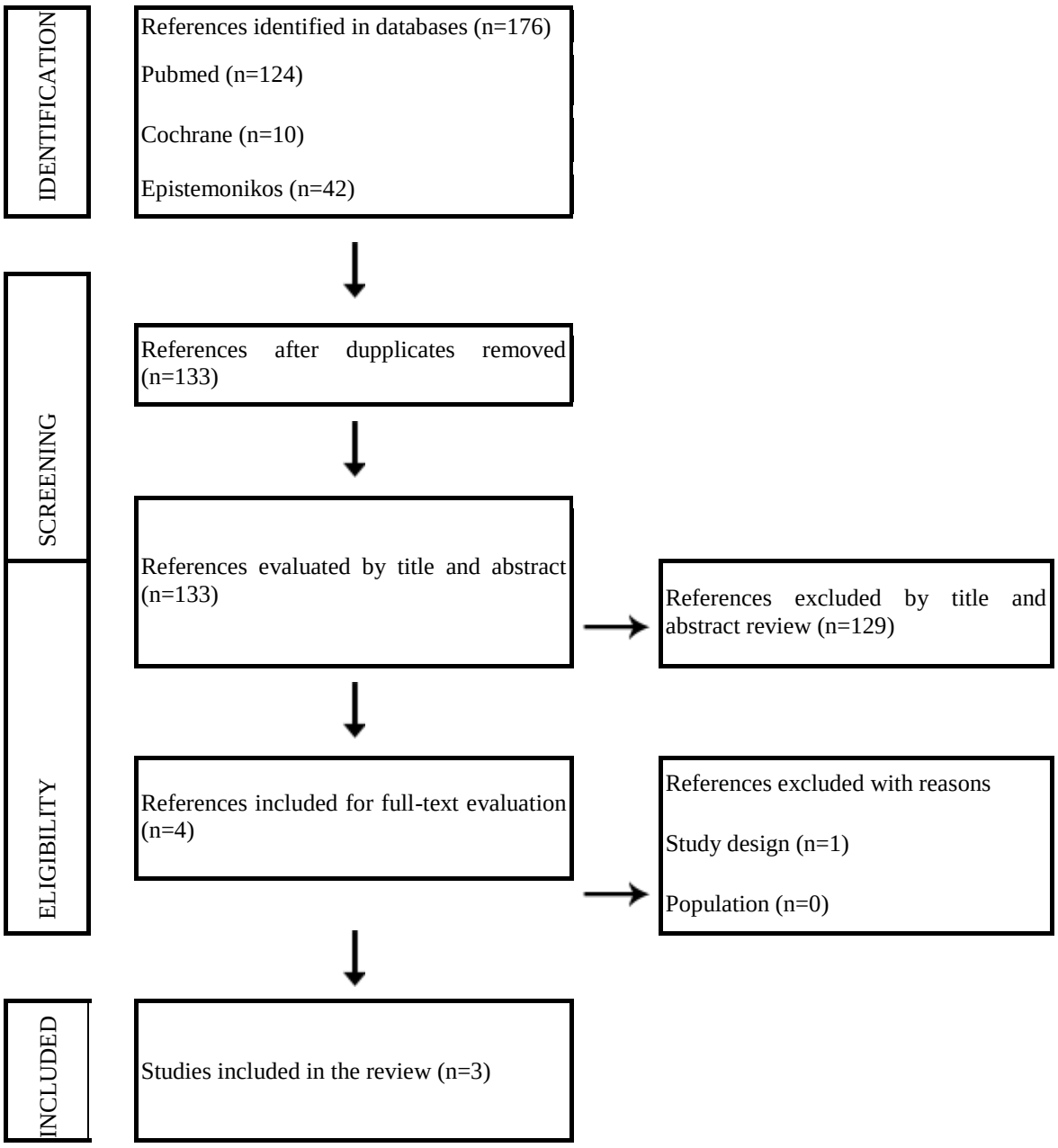

Fig. 1: Flowchart outlining the study selection process.

Table 2: Characteristics of clinical studies evaluating methylphenidate compared to placebo in reading performance in the studied population.

Trial	Study Design	N°	Age (years)	Aim	Diagnostic Nomenclature	Tested Dosis	Study Duration
Gittelman-Klein & Klein (1976)[21]	RCT, double-blind, placebo controlled	64	7-13	to evaluate the effectiveness of methylphenidate in improving reading performance and cognition.	Specific Learning Disability	MPH (Target Dose: 60mg/day on the 4th week).	12 weeks. Testing at 4 and 12 weeks of medication use
Aman & Werry (1982)[19]	RCT, double-blind, crossover design, placebo controlled, with 3 arms: MPH, diazepam and placebo	15	6-12	to evaluate the effectiveness of methylphenidate and diazepam in improving reading performance and cognition.	Reading Retardation	MPH: 0,35mg/kg. Diazepam: 0,1mg/kg	3 weeks. Testing on the 5th day of use of each substance
Fagan et al., (1988)[20]	RCT, double-blind, crossover design, placebo controlled, with 4 arms: MPH, meclizine, combination of the above medications and placebo	12	8-13	to evaluate the effectiveness of methylphenidate and meclizine in reading fluency, balance, coordination, and eye movements.	Developmental Dyslexia	MPH: 10mg. Meclizina: 12,5mg	4 weeks. Testing on the 2nd day of use of each substance. Washout period of one day.
Note: RCT= Randomized Controlled Trial, MPH= methylphenidate							

Chart 1: Bias Assessment for Clinical Trials Comparing Methylphenidate to Placebo Evaluated by the RoB 2.0 Tool for Improvement in Reading Measures.

	Randomized Clinical Trial		
Bias Domain	**Gittelman-Klein & Klein (1976)**	**Aman & Werry (1982)**	**Fagan et al., (1988)**
Bias arising from the randomization process	Low Risk	Low Risk	Low Risk
Bias due to residual effect or period effect	Not applicable	High Risk	Some concerns
Bias due to deviations from intended interventions	Low Risk	Low Risk	Some concerns
Bias due to missing outcome data	Low Risk	Low Risk	High Risk
Bias in measurement of the outcome	Low Risk	Low Risk	Low Risk
Bias in selection of the reported result	Low Risk	High Risk	High Risk
Overall risk-of-bias judgement	Low Risk	High Risk	High Risk

Chart 2: Comments on the Bias Assessment Process of Trials Using the RoB 2 Tool.

	Randomized Clinical Trial		
Bias Domain	**Gittelman-Klein & Klein (1976)**	**Aman & Werry (1982)**	**Fagan et al., (1988)**
Bias arising from the randomization process	There is mention that the study was randomized and double-blind.	There is only mention that the study was randomized and double-blind and used a Latin square design to assist in determining the treatment order. The tested substances were released in identical capsules with individual, dated envelopes.	There is only mention that the study was randomized, double-blind, and used a Latin square design to assist in determining the treatment order. There is no available information regarding the variables assessed in the pre-medication phase and the difference between the groups. The tested substances were released by a central pharmacy that kept the medication sequence code.
Bias due to residual effect or period effect	Not applicable	Period effects were taken into account in the analysis. There are risks of residual effects; the washout period was relatively	Statistical analysis controlling for the influence of the drug order factor on the outcome is not reported. Adequate washout period.

		short, considering the long half-life of diazepam. Only one variable, the speed of the auditory-visual integration test, was affected by the drug order factor.	
Bias due to deviations from intended interventions	Data analysis according to randomization.	Data analysis according to randomization. Data from one participant who was unable to read at any time during the Neale analysis was excluded. However, it is unlikely that this was an effect of the intervention type.	There is no mention of missing data. Apparently, the analysis used does not have a substantial impact on the outcome.
Bias due to missing outcome data	Outcome data for almost all participants were available for analysis. There is no evidence that missing data influenced the outcome.	The outcome data for almost all participants were available for analysis. There is no evidence that the data from the excluded participant influenced the outcome.	There is no mention of missing data.
Bias in measurement of the outcome	The outcome assessment methods are comparable for all groups.	The outcome assessment methods are appropriate and comparable for all groups.	The outcome assessment methods are appropriate and comparable for all groups.
Bias in selection of the reported result	All evaluated results were reported according to the initial plan.	There was a difference between the groups based on the Drug Order factor, so ANCOVA was performed, controlling for the effect of the drug order. Only the analysis values for the drug factor are reported, and the analysis for the drug order factor is not reported.	It is reported that "the data were evaluated in various ways." Apparently, no analysis was conducted considering the order of substance use. The study does not report the means of the different groups, mean differences, or their standard deviations. It only reports the p-values of these analyses.
Overall risk-of-bias judgement	Low Risk	High Risk	High Risk

Table 3: Criteria for synthesis of findings.

Study	Risk of Bias	Outcome of Interest	n° of subjects per analysis	Statistical Parameter	Direction of the effect
Gittelman-Klein & Klein (1976)	Low Risk	Reading Measured by WRAT and GOR at 4 and at 12 weeks	61 at 4 weeks.	p>0.05	Favors Placebo
			60 at 12 weeks	p>0.05	
Aman & Werry (1982)	High Risk	Reading Measured by Neale Analysis (accuracy).	15	p=0.181	Favors Placebo
		Reading Measured by psycholinguistic analysis.	14	p>0.05	
		Reading Measured by letter and word recognition	15	p>0.05	
Fagan et al., (1988)	High Risk	Reading Measured by the Elkwall Inventory	12	p=0.024	Favors Methylphenidate

DISCUSSION

The present study aimed to provide evidence-based recommendations for healthcare professionals in the Brazilian public health system regarding the effectiveness and safety of methylphenidate, a publicly funded medication in Brazil, for the treatment of dyslexia

without comorbidity with ADHD. This review demonstrated that there are few and outdated randomized clinical trials on the present clinical question, and most of the selected trials have a high risk of bias. Nevertheless, based on the chosen evidence synthesis method, methylphenidate did not differ from placebo in improving reading in the studied sample of dyslexic patients.

This finding is consistent with the absence of a medication specifically approved for dyslexia by the Brazilian Anvisa and the major regulatory agencies worldwide, such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency).

This is the first systematic review evaluating the effectiveness of methylphenidate for this condition, and therefore, comparisons with previous reviews are not possible. Since the study by[13] motivated the present work, some differences between that study and the current one will be highlighted. The study by Shaywitz et al., 2017[13] used the GOR-4 test - "Gray Oral Reading Test"[22] in an updated version of the measure also used in the study by[21] In the former study, intergroup variability detected by the GOR-4 was not significant, as in the latter study. Nevertheless the study by Shaywitz et al., 2017[13] demonstrated the superiority of the tested drug over placebo in measures derived from the Woodcock-Johnson battery. Therefore, it is possible that the negative result of the reviewed studies is due to the absence of sensitive tests to detect the effect of methylphenidate. This hypothesis was not tested; however, it is noteworthy that the reviewed studies used standardized and validated reading measures. The longest reviewed study lasted 12 weeks, while the study by[13] lasted 16 weeks. Thus, it is suggested that future clinical trials use standardized tests for word and pseudoword decoding, as well as vocabulary assessment for reading, in a parallel placebo-controlled and long-term design.

In this review, it was not possible to calculate the intervention effect size because the mean scores of the groups in the Fagan et al., (1988)[20] study were not described, and therefore, a meta-analysis of the results was not performed. However, in order to provide transparency in reporting the results, a criterion for evidence synthesis described in[17] was adopted. Similarly, it was not possible to assess the safety of methylphenidate in the population with dyslexia without comorbidities because this outcome was not reported in all trials. One limitation of the present work is that the review protocol was not registered. However, all the steps of this review followed a predefined method and relevant information, such as study risk of bias, effect measures, and synthesis methods are thorough reported.

Due to the aforementioned limitations, the certainty level of the summarized evidence is limited, and therefore, more studies on methylphenidate in dyslexia are needed, preferably using updated reading skill measures that have proven to be sensitive to intervention by other drugs as seen in.[13]

Methylphenidate is effective in ADHD comorbid with dyslexia, and this comorbidity is significant. Cross-prevalence estimates of ADHD in children diagnosed with dyslexia range from 25 to 45%.[23] Therefore, it is necessary to assess the presence of psychiatric comorbidities, and when present, proceed with their corresponding therapeutic approach. For all children with dyslexia with or without ADHD, educational interventions, which provide explicit and systematic instruction in foundational reading skills with simultaneous focus on vocabulary and comprehension, are still considered the first-line therapy.[9]

CONCLUSION

This literature synthesis is limited due to the scarcity of randomized trials, the fact that the trials are outdated, and the majority have a high risk of bias. However, based on the chosen synthesis method, it was concluded that methylphenidate did not differ from placebo in improving reading in the studied sample of dyslexic patients.

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The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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