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USE OF METHYLPHENIDATE IN THE COGNITIVE ENHANCEMENT OF HEALTHY INDIVIDUALS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: The increased non-medical use of methylphenidate by healthy individuals raises ethical, safety, and efficacy issues. Understanding these issues is crucial in the face of societal pressures for performance and the potential impact on long-term mental health. Objective: To describe the risks, potential benefits, and ethical challenges of using methylphenidate in the cognitive enhancement of healthy individuals. To assess the effects of declarative memory, short-term and long-term memory, and to assess pharmacological risks. Methods: A systematic review of the literature was conducted including randomized controlled trials. The inclusion criteria include studies with healthy participants over 18 years of age, excluding those with recent use of psychoactive substances or sleep deprivation. The search was carried out in several electronic databases: MEDLINE/PUBMED, Lilacs, Scielo, using the keywords: methylphenidate, cognition, randomized clinical trial and its respective correlates in English, and Boolean operators. The selection of studies was carried out by multiple researchers, with duplicate checks and evaluation of titles, abstracts, and full texts. The quality of the selected studies was assessed using CONSORT and PRISMA checklists. Results: The review selected three articles after screening, and two studies suggest temporary improvements in memory and attention in healthy individuals using methylphenidate. In contrast, the third study showed cardiovascular impacts in patients, with no improvements in participants' memory and attention.

Keywords: Methylphenidate, Cognition, Randomized Clinical Trial.

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INTRODUCTION

Cognitive enhancement in contemporary society is a growing concern due to the constant pressure for academic, professional, and personal performance. In this context, methylphenidate, which has the trade name "Ritalin", has gained prominence as a central nervous system stimulant commonly prescribed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)[1]. However, there is considerable non-medical use of this substance by healthy individuals seeking improvements in cognitive performance, raising ethical, safety, and efficacy issues that deserve attention[2].

The pharmacology of methylphenidate reveals its action as an indirect agonist of dopamine and norepinephrine receptors, resulting in a stimulation of the central nervous system, which improves attention, concentration and focus. While these effects are beneficial for the treatment of ADHD, their use by healthy individuals can provide increased alertness and energy, sought to improve performance in several areas[3].

Although studies suggest temporary improvements in memory and attention in healthy individuals using methylphenidate, the magnitude of these effects and their long-term benefits are still debated [4]. In addition, results vary according to individual factors, such as dose and age, and raise concerns about their universality and potential risks[5].

The non-medical use of methylphenidate raises ethical issues related to equity of access, abuse, and health consequences. Understanding the risks, such as insomnia, anxiety, and addiction, as well as their long-term impact on mental health, is crucial for making informed decisions about cognitive enhancement[6].

Given this scenario, the discussion about the use of methylphenidate in healthy individuals is justified by social pressures for performance, ethical dilemmas, health risks, and future implications. Therefore, the continuous analysis of this topic is essential to guide public policies and individual practices, aiming to promote well-being and equity in society. The primary objective of this systematic literature review is to examine the effect of methylphenidate on the memory of healthy individuals. Secondarily, we also evaluate possible effects on attention and potential adverse effects7.

METHODOLOGY

TYPE OF STUDY

Systematic Review.

ELIGIBILITY CRITERIA

Randomised controlled trials (RCTs) and quasi-randomised controlled trials were included. RCTs were considered to be those who performed randomization through the use of coins, dice, or computer-based randomization. Studies that used other forms of randomization were classified as quasi-randomized.

TYPES OF INTERVENTION

Studies that evaluated the use of methylphenidate with a placebo or any other psychostimulant as a control group were included, whose outcomes included memory and/or attention tests.

STUDY POPULATION

Studies whose population is previously healthy (without psychiatric comorbidities) and is over 18 years of age were included.

EXCLUSION CRITERIA

Studies with participants who used any medication or caffeine in the last 24 hours before the application of the cognitive tests, who have a history of psychoactive substance use (alcohol, nicotine, cannabis, cocaine and opioids), who have concomitant psychiatric disorders or who have a history of sleep deprivation in the last 72 hours were excluded.

Methods for study identification

Electronic search

The search was carried out by three researchers separately, who subsequently held a consensus meeting to verify whether there was homogeneity among the findings. In the presence of disagreement with the findings, a fourth researcher (the advisor) was consulted. The search for articles was carried out in the following databases: MEDLINE/PUBMED, Lilacs, Scielo, Embase without restriction of year or language.

To identify relevant articles in the electronic databases, the following keywords were used: methylphenidate, cognition, randomized clinical trial and their respective correlates in

English, in addition to the use of Medical Subject Headings (MeSH). As a search filter, the following were used:

- Boolean operators – AND and OR.

RESULTS

SELECTION OF STUDIES

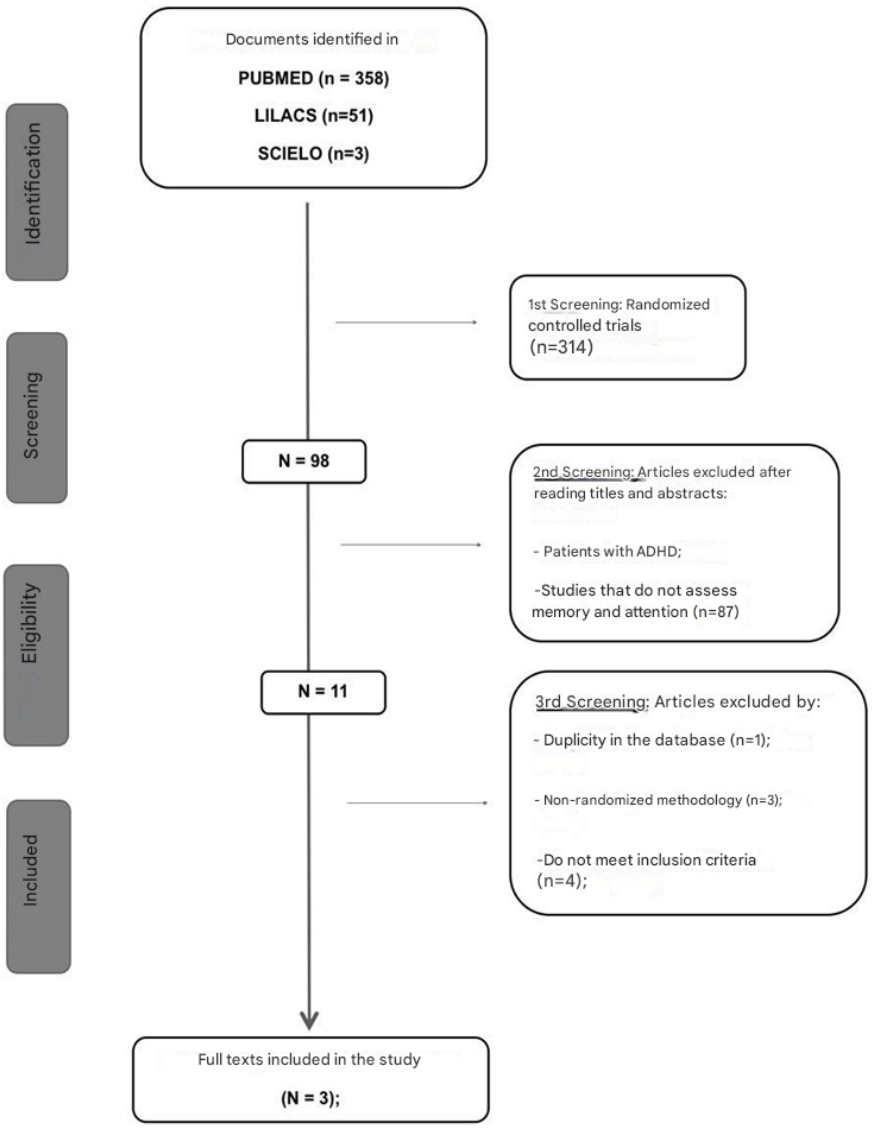
Initially, duplicates of articles were checked using Microsoft Office Access 2013 database management. After this stage, the articles selected only through the title and abstract were evaluated according to the eligibility criteria, excluding irrelevant articles. The selected articles were read in full to decide on their inclusion. Then, the researchers separately performed the data extraction and, after collection, a new consensus meeting was held to verify the degree of agreement among the authors. When disagreements occurred in the consensus meetings, the fourth researcher (advisor) was asked to reach an agreement. To evaluate the quality of the selected articles, the Consolidated Standards of Reporting Trials (CONSORT) checklist was applied, and the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was applied to evaluate the final quality of the systematic review.

In addition, an active search was carried out for other studies cited in the references of the selected articles.

Following the initial search strategy, 412 articles were found in the PubMed, Scielo and LILACS databases. After careful selection and evaluation, only randomized controlled studies were filtered and, thus, 314 articles were excluded. The articles were filtered considering the year of publication.

After this stage, 98 articles were selected. Of these, 87 were excluded based on the title and abstract, because the composition of the patients in the study was diagnosed with psychiatric disorders, especially ADHD, or because they did not aim to assess the participants' memory and attention. At the end of this process, 11 articles were fully read and analyzed. Of these, six more articles were excluded: one for duplication in the databases, three for the type of non-randomized study, and another four for not meeting the inclusion criteria. Thus, three articles were included and make up the present study.

Figure 1: Schematic representation of the methods of identification, screening, eligibility and inclusion of articles in the review, adapted according to the PRISMA Flow Diagram



CHARACTERIZATION OF THE SELECTED STUDIES

The study by Maxi Becker et al aimed to investigate the use of stimulants (methylphenidate, modafinil, and caffeine) and repeatedly evidenced the improvement of cognitive processes, such as attention and memory. The study included 48 healthy and right-handed male participants, with a mean age of 26.27 years.

The study was conducted by an in-house, placebo-controlled, randomized, double-blind, three-arm study in which each stimulant was tested and compared to a placebo. Each participant received only one stimulant (and placebo) in the form of a white capsule for oral ingestion and was tested at two different times, at the same time of day, at the beginning of the day. The sessions were separated by a one-week break. In the case of

methylphenidate, the extended-release formulation at a dose of 20 mg was used. Participants coded the memory task with functional magnetic resonance imaging (fMRI) scanner visual material, and completed the rest of the tasks (including memory task retrieval) afterward outside of the scanner. The fMRI procedure was started 90 minutes after oral ingestion of substances.

The results of the study indicate that, in the memory task with visual material, on average, participants correctly remembered 35.21 words after the administration of the stimulant and 31.69 in the placebo ($p = 0.008$). After 24 hours, participants correctly recalled an average of 21.53 words with the stimulant and 16.77 words with placebo ($p < 0.001$).

As for the results related to the memory task with audio material, the participants recorded around 40.60 words correctly with the stimulus and 37.21 words in the placebo condition, with the early memory retrieval statically significant ($p < 0.001$). The results of the study also indicate that in the implicit memory task, the recording in the stimulant condition was approximately 2.29, while in the placebo it was 2.01 ($p = 0.0015$).

The limitations of the study should be emphasized that may reduce the generalizability and interpretation of the results. Only male participants were recruited. Similarly, only participants with low/irregular caffeine consumption were included in the study to avoid confounding effects on cognitive outcomes – which may not represent the reality of the population in the face of more severe caffeine consumption. Second, the small sample size per stimulant group ($n = 16$). Finally, only self-report was used to select participants for confounding variables, such as caffeine, consumption of prescription stimulants, use of illicit substances, or sleep quality. Objective measures, such as a sleep diary or actigraphy to assess participants' sleep patterns, as well as a urine test to detect drugs before testing, were not applied.

The study by Repantis et al aims to explore the effects of several popular stimulants on cognition. The study was a randomized, double-blind, placebo-controlled, within-subject clinical trial. The sample consisted of forty-eight healthy right-handed male volunteers, with a mean age of 26.27 years. The inclusion criteria were: Male volunteers, aged between 21 and 36 years, right-handed, healthy general health status, absence of current and previous medical, neurological and psychiatric disorders, absence of known family history of psychiatric disorders, absence of prescription medications, nicotine or illicit substances. Habitual consumption of small amounts of caffeinated beverages was allowed, while regular and excessive consumption (> 4 cups/day) was not allowed.

Participants were randomized to receive either of three stimulants (20 mg immediate-release methylphenidate, 200 mg modafinil, 200 mg caffeine) or placebo, in two sessions separated by approximately one week. Each session was scheduled for the same time in the early afternoon. Participants were evaluated for the presence of side effects regularly and before discharge. After each session, they were contacted by telephone 24 hours later to assess for late side effects and perform a delayed recall test of memory tasks.

The tests used in the study were: Declarative memory task: Participants learned a list of 72 words and then were tested to remember them; BOMAT (Bochum Advanced Matrix Test): A logical reasoning test where participants selected geometric figures according to patterns in matrices; Trail Test (ZVT): Participants connected numbers in ascending order as quickly as possible, measuring the speed of information processing; Reverse Digit Sequence Test: Participants had to remember and write in reverse order the digits presented; Alternative uses task: Participants reported unusual and creative uses for an object; False memory test: Participants heard words and were tested to remember and recognize correctly, including words not previously presented; Psychomotor Vigilance Test (PVT): A visual reaction time test to measure sustained attention; Subjective affect assessment: Using items from the Positive and Negative Affect Scale (PANAS) to measure feelings of fatigue and serenity; Motivation assessment: Done through visual analog scales filled in after different cognitive tests; Late free recall test: An information retention test conducted over the phone 24 hours after the session.

In addition, participants were evaluated for side effects regularly throughout the study. The study was conducted using linear mixed-effects analysis to control for within-subject effects. A separate analysis was performed for each type of stimulant (methylphenidate, modafinil, and caffeine) compared to the placebo group. The significance of the data was set at $p < 0.05$ (bilateral), and the Benjamini-Hochberg (BH) correction was applied for multiple comparisons.

For methylphenidate (MPH), the following results were found: Delayed recall of visual material ($p = .003$); Retention of audio material from the second declarative memory task ($p = .032$); early recall of visual material after ingestion of MPH ($p = .029$); Early recall of audio material after MPH ingestion ($p = .047$); implicit memory for audio material after MPH ingestion ($p = .023$); creativity after MPH ingestion ($p = .029$); reduction of fatigue after MPH ingestion ($p = .001$); motivation after MPH ingestion ($p = .034$).

Results for modafinil (MOD): Reduction of fatigue after ingestion of modafinil ($p = .023$).

Results for caffeine (CAF): better performance in the sustained attention task after caffeine ingestion (p = .002); trend of better early recall of audio material after caffeine ingestion (p = .044); follow-up analysis to determine the differential effect between MPH and LEEP on declarative memory performance (p = .48); second follow-up analysis to determine differences between stimulants in fatigue (p = .80).

There are some limitations to the study, such as the small sample size, correction for multiple comparisons, relatively low to moderate doses of stimulants, and the lack of individual measurements of plasma concentrations of the substances.

In summary, the article shows specific, albeit subtle, effects of the different stimulants tested. Methylphenidate (MPH) improved declarative memory, especially in delayed recall.

The main objective of the article by Turner et al is to characterize the dose-related effects of methylphenidate on a variety of neuropsychological functions in healthy elderly volunteers. Sixty healthy elderly male volunteers were given a single oral dose of placebo, 20 mg, or 40 mg of methylphenidate before performing a variety of tasks designed to assess memory, attention, and executive function. A randomized, double-blind design was used, between subjects.

Exclusion criteria included any significant psychiatric history, visual or motor impairment, or the concomitant use of any psychotropic medication or any contraindicated medication in addition to methylphenidate. In addition, participants with a history of hypertension, cardiac disorders, epilepsy, or drug or alcohol abuse were also excluded. All subjects underwent the Folstein Mini Mental State Examination (MMSE) to exclude undiagnosed mild dementia. All volunteers were advised not to consume alcohol or caffeinated beverages in the 12 hours prior to the study.

The volunteers were submitted to the following tests: Physiological measurements: Recording of blood pressure and pulse at four different times; Psychological measures: Use of validated tests, including the CANTAB battery, with variants of some original tasks to increase sensitivity in normal volunteers. The tests were performed on an Advantech personal computer, with responses recorded via the touchscreen or an answer key; Visual Analog Scale: Participants completed visual analog scales to assess their feelings toward 16 dimensions at three different time points; Digitized Spanish: A test taken from the Wechsler Adult Intelligence Scale, in which participants were asked to repeat longer and longer sequences of digits, both forward and backward; Computerized tests taken from the CANTAB battery: Several computerized tests were performed, including spatial working memory, visual memory, attention, attention shifting, spatial planning, and decision-making

tasks; Decision-making task (Gamble): Participants were presented with a task in which they had to decide which box the computer had hidden a token in, as well as place bets to increase their total score; Stop signal task (STOP): A classic task to measure pre-potent response inhibition, in which participants were required to respond quickly to certain stimuli but also to inhibit their response at other specific times. Five blocks of trials were performed, and participants received visual feedback after each block.

Some limitations present in the study: design between subjects, as the use of this design may have reduced the statistical power of the study. An within-subject design could have been more effective for controlling for confounding variables, especially in a study with a smaller sample where each subject serves as their own control. When looking at the dosage used: The study used relatively high doses of methylphenidate (20-40 mg), which may have contributed to the cardiovascular effects observed. The use of lower doses could have allowed for a better assessment of cognitive effects, especially in an elderly population that is more sensitive to these effects. Concomitantly, therefore, there was a lack of evaluation of lower doses: The study did not evaluate doses lower than 20 mg methylphenidate, which could have revealed improvements in cognitive performance without the cardiovascular adverse effects associated with higher doses. It is noteworthy that there was no evaluation of long-term effects: the study did not consider the effects of methylphenidate on prolonged administration. An assessment of cognitive and cardiovascular effects after a period of continuous use could provide additional insights into the safety and efficacy of the drug in the elderly. Another point was the sample size: the study does not mention the sample size, which makes it difficult to assess the representativeness of the results and generalize it to the elderly population in general. In addition, there were limitations in cognitive assessment: although the study evaluated several measures of cognitive performance, there may have been limitations in the sensitivity or specificity of these measures for detecting subtle changes in cognitive function in older adults.

The study concludes that oral administration of 20-40 mg of methylphenidate in an elderly population of healthy volunteers produces significant cardiovascular effects, but does not have an overall positive impact on most monitored cognitive functions.

Table 1. General data of the studies included in the systematic review, ordered by year of publication.

References	Year	Goal	Study design	Inclusion Criteria
Turnes *et al*	2003	To characterize the dose-related effects of methylphenidate on a variety of	Randomized, double-blind clinical trial	Healthy elderly adult males

		neuropsychologic functions		
Repantis *et al*	2020	Explore the effects of several popular stimulants on cognition	Randomized, double-blind clinical trial	Male volunteers, aged 21-36 years, right-handed, generally healthy health status
Maxi Becker *et al*	2021	Investigate the use of stimulants (methylphenidate, modafinil, and caffeine)	Randomized double-blind clinical trial	Male, healthy and right-handed with an average age of 26 to 27 years

Table 2. General data of the studies included in the systematic review, ordered by year of publication.

References	Sample size	Denouement	Limitations
Turner *et al*	60	Spatial working memory, visual memory, attention, attention shifting, spatial planning, and decision-making tasks	The study used only high doses of methylphenidate (20-40mg), which may have contributed to the cardiovascular effects observed. Lack of evaluation of lower doses, absence of evaluation of long-term effects, did not evaluate the subtle changes in cognitive function
Repantis *et al*	48	Declarative memory, false memory, and working memory tasks	Small sample size per arm, correction for multiple comparisons, relatively low to moderate doses of stimulants, and lack of individual measurements of plasma concentrations of substances
Maxi Becker *et al*	48	Memory tasks with visual material, memory with audio material, false memory, implicit memory, and measurement model for latent memory change factor	Only male participants, small sample size per stimulant group, only self-report was used to select participants

QUALITY OF SELECTED STUDIES

Regarding the evaluation of the quality of the selected studies, considering the items proposed by CONSORT, none of the articles analyzed met the ideal scoring criterion for systematic review. Although the studies did not present at least 29 items fully met, due to the lack of studies in the literature, it was decided to keep them among those selected.

The study by Repantis et al complied with 23 (69.7%) of the proposed items, while Maxi B. et al complied with 21 (63.6%) and Turner et al 20 (60.6%), as described in Table 3. Four of the 37 total items of the CONSORT were not analyzed because they were not applicable to the studies, namely: important changes in the methods after the start of the clinical study; any changes in outcomes after the clinical study has been initiated; explanation of any interim analysis and closure guidelines; Say the reasons why the study was terminated or stopped.

Eight items were fully complied with by 100% of the studies: item 5, related to the description of the study intervention; item 12, related to the description of the statistical method used in the study; item 13, related to the flow of participants; item 17, related to outcomes and estimates; item 18, related to auxiliary analyses; item 20, related to the limitations of the study; item 22, related to the consistent interpretation of the results; and, finally, item 25, characterized by the description of the study incentives.

Table 3. Evaluation of the quality of the studies selected through CONSORT

CONSORT		Repantis *et al*	Maxi B. *et al*	Turner *et al*
Title and Abstract				
	1st			
	1b			
Introduction				
Rationale and objectives	2nd			
	2b			
Methods				
Study design	3rd			
	3b			
Participants	4th			
	4b			
Interventions	5			
Outcomes	6a			
	6b			
Sample sizes	7a			
	7b			
Randomization				
Sequence generation	8a			
	8b			
Allocation mechanism	9			
Implementation	10			
Blinding	11a			
	11b			
Statistical methods	12a			
	12b			
Findings				
Participant flow	13th			
	13b			
Recruitment	14th			
	14b			
Baseline data	15			
Numbers analyzed	16			
Outcomes and estimation	17a			
	17b			
Ancillary Analyses	18			
Damage	19			
Discussion				
Limitations	20			
Generalization	21			
Interpretation	22			
Other information				
Register	23			
Protocol	24			
Fomentation	25			
Total (percentage)		69,7%	63,6%	60,6%

Legend: Present; Absent;

Tabela 4. Desfechos de memória e atenção estatisticamente significantes

Desfechos avaliados	Maxi Becker et al	Repantis et al	Turner et al
Memória de curto prazo			
Memória visual	p < 0,001		
Memória com material de áudio	p < 0,001		
Memória explícita	p < 0,001		
Memória de longo prazo			
Lembrança tardia do material visual		p < 0,004	
Atenção			
VAS (Alerta)			p < 0,005
Latência de resposta			p < 0,004

VAS = Visual Analogue Scales (Escala Analógica Visual)

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