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## Harm caused by the use of lisdexamfetamine to increase the academic performance of medical students: integrative review

*Danos causados pelo uso de lisdexanfetamina para aumentar o desempenho acadêmico de estudantes de medicina: revisão integrativa*

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### Abstract

Lisdexamfetamine (LIS) is a central nervous system stimulant used to treat Attention-deficit/hyperactivity disorder (ADHD), improving attention, concentration and reducing hyperactivity. However, it is important to highlight that the National Health Surveillance Agency (ANVISA), the regulatory body for medicines in Brazil, does not recognize the efficacy and safety of LIS outside of its indications contained in the medicine leaflet and, in addition, the inappropriate use of this substance becomes a risk factor for the occurrence of anxiety, cardiac arrhythmias and glaucoma. This is an integrative literature review carried out in PubMed, LILACS and SciELO databases searching the descriptors “Lisdexanfetamina”, “ADHD”, and “Students”. Around 23.3% of medical students use these substances to overcome fatigue and improve performance, with Ritalin and Venvanse being the most common. However, 57.1% use these medications without a prescription or diagnosis of ADHD, obtaining them illegally. In general, all medications should only be used after medical evaluation and verification of real need, however, in the case of psychostimulants, caution must be even greater. Therefore, it is crucial to raise awareness among patients who are not diagnosed with ADHD about the long and short-term implications of self-medication with LIS, seeking to combat this public health problem.

**Keywords:** Attention-deficit/hyperactivity disorder; lisdexanfetamina; university students; legal drugs; indiscriminate use of psychostimulants.

### Resumo

A lisdexanfetamina (LIS) é um estimulante do sistema nervoso central utilizado no tratamento do transtorno de déficit de atenção/hiperatividade (TDAH), melhorando a atenção, concentração e reduzindo a hiperatividade. Contudo, é importante destacar que a Agência Nacional de Vigilância Sanitária (ANVISA), órgão regulador de medicamentos no Brasil, não reconhece a eficácia e a segurança do LIS fora de suas indicações contidas na bula do medicamento e, além disso, a inadequação o uso dessa substância torna-se fator de risco para ocorrência de ansiedade, arritmias cardíacas e glaucoma. Trata-se de uma revisão integrativa da literatura realizada nas bases de dados PubMed, LILACS e SciELO com busca pelos descritores “Lisdexanfetamina”, “ADHD” e “Estudantes”. Cerca de 23,3% dos estudantes de medicina utilizam essas substâncias para superar a fadiga e melhorar o desempenho, sendo a Ritalina e o Venvanse os mais comuns. Porém, 57,1% utilizam esses medicamentos sem prescrição ou diagnóstico de TDAH, obtendo-os de forma ilegal. Em geral, todos os medicamentos só devem ser utilizados após avaliação médica e verificação da real necessidade, porém, no caso dos psicoestimulantes, o cuidado deve ser ainda maior. Portanto, é crucial sensibilizar os pacientes que não são diagnosticados com TDAH sobre as implicações a longo e curto prazo da automedicação com LIS, procurando combater este problema de saúde pública.

**Palavras-chave:** Transtorno de déficit de atenção/hiperatividade; lisdexanfetamina; Estudantes universitários; drogas legais; uso indiscriminado de psicoestimulantes.



## Introduction

The academic setting of universities fosters scientific advancement through study and research. Thus, students pursuing higher education must be highly motivated and dedicated, particularly those aiming medical school. Medical students who complete their education after six years must pass an exam to be eligible for residency, making medical school extremely competitive [1-7]. In these conditions, to maximize their academic effectiveness and enable them to study for extended periods of time, healthy college students have started turning to psychoactive substances [2-7]. Drugs known as stimulants are used to boost energy and focus, reducing the need for relaxation, among which methylphenidate and LIS stand out [2-7].

LIS dimesylate is the most used medication. It functions by stimulating the central nervous system (CNS), preventing dopamine reuptake, and releasing dopamine and norepinephrine into the synaptic region. This medication is marketed as Venvanse® (Takeda) and Juneve® and Concertta® (Takeda) in Brazil [3,4]. Children with ADHD who benefit from LIS's improved attention are the only ones whose use is authorized legally. LIS is restricted in its prescription since it is a psychotropic substance that has a risk of misuse and dependence, according to the United Nations Psychotropic Substances Convention of 1971 [3,5]. LIS is widely used for non-medical purposes due to its potential cognitive benefits. University students utilize it regularly due to high academic standards and extended sleep requirements of their studies [1,6]. In addition, some patients have used LIS recreationally, as it acts on dopamine neurotransmitters directly or indirectly, being able to promote a feeling of euphoria [5].

On top of the known side effects such as tics, constant mood changes, signs of aggressiveness, dizziness, depression, irritability, nausea, vomiting, anxiety, shortness of breath, fatigue, drowsiness etc. [3], the indiscriminate consumption of LIS becomes even more serious due to divergent neural characteristics between people with ADHD and people who do not have the disorder, such as the size of the brain and specific regions, especially those related to dopamine, including changes in brain circuits [2].

## Objective

To examine LIS use among healthy medical students, covering its prevalence, demographic characteristics, motives for use, and potential positive effects on academic performance.

## Materials and Methods

Three databases – LILACS, PubMed, SciELO – were thoroughly searched, encompassing all English, Portuguese, and Spanish-language papers published in any of the three languages between 2010 and 2023. "Lisdexamfetamine", AND/OR "Medical students", "Lisdexamfetamine" AND/OR "Medical students", "Lisdexamfetamine" AND/OR "Medical students" were the key words used for the research. Publications prior to 2010, case reports, series case reports, articles analyzing populations other than college students, and articles lacking LIS analysis were some of the exclusion criteria that were used. The study's included articles were examined for information on the frequency of abuse of psychostimulant drugs, demographics of users (gender, age, graduates), reasons for usage, potential advantages, timing of LIS initiation, mode of administration, and familiarity with the medication.

## Eligibility criteria

Articles that did not mention LIS or attention deficit hyperactivity disorder in the title were discarded and articles that had a subject related to the use of the substance in relation to eating disorders were also discarded. Only fully available free articles published in the last 13 years were selected and among those selected were review articles such as bibliographical and systematic articles, case control articles and technical guidance, all others were discarded.

## Selection process

The study was conducted by two reviewers who analyzed the initial sample separately, applying the same filters and inclusion and exclusion criteria, and both arrived at the same final sample. For the analysis, the articles that contained the selected descriptors and were published in the last 13 years were subjected to detailed reading. All selection was done manually by reviewers without the use of additional tools. With the final sample, the author, title, year of publication and data on the mechanism of action of LIS, indications for use, adverse effects, harm from inappropriate use and long-term clinical outcomes were extracted.



## Results

This article reviewed a total of 7 papers that showed that ADHD is present in 5.3% of the population, being more common in childhood. However, 60% of these patients will present symptoms in adulthood and the cause of the disease is related to genetics in 75% of cases. The most used medications to treat the disorder are methylphenidate and LIS, which have been widely used incorrectly [2]. Students' justifications for its use included: improvement in academic performance by 51%, 48% due to exhaustion and 28% to compensate for sleep [3]. Table 1 presents the main information regarding findings from the database search.

**Table 1.** Authorship, article title, and key findings.

Authorship	Title	Type of study	Key findings
Nabar, M.J.M. et al., 2011 [2]	The use of psychoactive substances in Anatomy students and its implication in learning	Cross-sectional study	25.41% of the students included in the study answered that they used substances for sleeping and 41.8% used some substances to increase studying hours, such as: coffee, energy drinks, psychopharmacological medication (45.09% modafinil and methylphenidate) and acetylsalicylic acid. The numbers of hours working correlated with the number of substances consumed; students that were taking the subject again had less hours of sleep indirectly correlated with the use of psychoactive.
Barros, D. & Ortega, F., 2011 [3]	Methylphenidate and Pharmacological Cognitive Enhancement: social representations of university students	Qualitative and exploratory research	The study revealed that students had greater tolerance to methods that alter neurobiology in favor of the social ideal of improving the performance of people. Respondents expressed great concern about this procedure intensifying injustices and inequalities between people, especially in societies where there are already significant social differences.
Repantis, D. et al., 2010 [4]	Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review	Systematic review and meta-analysis	Expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomized controlled trials. For methylphenidate an improvement of memory was found, while modafinil was found to improve attention for well-rested individuals, while maintaining wakefulness, memory, and executive functions to a significantly higher degree in sleep deprived individuals.
Arria, A. & Wish, E.D., 2006 [5]	Nonmedical use of prescription stimulants among students	Literature review	College students are more likely to use prescription stimulants than their noncollege-attending counterparts and they may experience a need to stay awake to study given the high level of demands in the university environment. Data from the college studies presented here also suggest that, in addition to using prescription stimulants as a study aid, students use prescription stimulants to stay awake longer to party or drink more.
Habibzadeh, A. et al., 2011 [6]	Illicit methylphenidate use among Iranian medical students: prevalence and knowledge	Cross-sectional study	Methylphenidate users' mean knowledge score was higher than that of nonusers. Age, gender, and school year were positively correlated with knowledge score and 27 participants (8.7%) had taken methylphenidate at least once in their lifetime. The respondents believed that the most common motive for methylphenidate use among youths was that it aided concentration and therefore ability to study.
Urrego, M.A. et al., 2009 [7]	Use of amphetamines to improve the academic performance in students of the University of Manizales, 2008	Cross-sectional study	32,8 % of the students included informed consuming drugs like, marijuana, popper, and ecstasy. 14,6% consumed amphetamines to improve academic performance and 71% of the amphetamines consumers said to obtain good results. The alcohol and general

			drugs consumptions were associated factors to amphetamine consumption to improve academic performance.
Bogle, K.E. & Smith, B.H., 2009 [8]	Illicit methylphenidate use: a review of prevalence, availability, pharmacology and consequences	Literature review	Methylphenidate, a widely prescribed stimulant, has seen increased use for ADHD. Concerns about its illicit use among college students persist, though recent surveys indicate stable or decreasing rates, with potential demographic factors influencing misuse.

Source: Data collected by the authors.

### Discussion

Faced with an increasingly competitive job market, it is increasingly common to see students seeking academic excellence. To achieve this, many of them have used psychostimulants as supposed allies. The most used substances are methylphenidate and LIS, believing that they can overcome tiredness and achieve more satisfactory results, but more than half of these do not have a medical prescription and have a diagnosis of ADHD that would justify the use of these substances, that is, obtaining of these drugs occurs illicitly through friends, relatives and/or false prescriptions. As a result, self-medication of psychoactive drugs among students has become a public health problem that must be faced in proportion to its severity [2].

The intense search for the improvement of cognitive, emotional, and motivational functions by healthy individuals is intense and provoked by the much-desired pharmacological neuroenhancement, a term that is currently used to describe the cognitive improvement obtained with psychotropic drugs [4]. Pharmacological neuroenhancement has become more prevalent in the academic setting, particularly among college students. In fact, in many countries, using psychostimulant medications to boost academic performance is now regarded as a public health concern [1,7]. However, there is a dearth of Brazilian medical literature on this topic, with just a small number of papers appearing in specialized periodicals. In Brazil, popular media discusses this topic more frequently than scholarly publications do. Without any scientific basis to support consistent judgments about the Brazilian national standard of usage, the media publishes texts based on the opinions of non-specialists or on the opinions of a single expert [3].

The pharmacokinetic and pharmacodynamic characteristics of stimulants differ, and the benefits they provide for patients with ADHD diagnoses are not appropriately extended to healthy individuals who want to perform better academically. The use of a neurostimulation medication at a dosage that is not indicated by a doctor or by someone else without a prescription is considered a non-medical usage of the medication.5. Many college students who acknowledged abusing methylphenidate to improve their academic performance as well as their focus and alertness fall under the second category [6]. There is insufficient data in the available literature to draw firm conclusions on the medication's possible advantages for patients without ADHD. Studies to present do not consistently demonstrate beneficial effects on the central nervous system; one article, however, suggests that methylphenidate improves working memory [4]. There is no proof that methylphenidate improves attention span, despite what the public and college students think. The appropriate distribution of mental processes in response to pertinent inputs is known as attention [4].

LIS is thought to improve aim and focus on stimuli by increasing dopamine release in the CNS. When ingested, the drug is enzymatically hydrolyzed, producing the active fraction of d-AMP. This primarily occurs in the blood, and thus, this production is not affected by gastrointestinal pH. Its effects, with just a single dose, are observed after 13 hours in children and adolescents and after 14 hours in adults, significantly improving ADHD symptoms [6]. The fact that most trials employed doses of 12-20 mg of LIS may be one of the reasons for the drug's modest effectiveness as a neuroenhancement therapy for healthy individuals. This is most likely a sub-dose of the medication compared to what is anticipated. Nevertheless, no scientific study has compared the impact of various dosages on academic achievement [4].

In conditions where LIS has been shown to be helpful, patients with narcolepsy should take 20-30 mg of the drug daily; this amount can be increased to a maximum of 40-60 mg daily. The recommended starting dose for children diagnosed with ADHD is 5-10 mg per day; if the child's condition calls for greater dosages, this should be gradually increased to a maximum of 60 mg per day. Taking the medicine three days prior to an exam is likely another factor contributing to academic failure. Academic performance is negatively impacted by this study strategy because students are



exposed to more information in the weeks leading up to tests than they can learn in that short of a time [2]. Furthermore, under these situations, stimulating agents exacerbate learning difficulties by causing euphoria and wakefulness, which interfere with getting the necessary sleep for memory consolidation.

In addition to the paucity of scientific evidence supporting the use of methylphenidate in healthy adults without a medical justification, even fewer studies have examined any potential negative effects. The adverse consequences, which include tachycardia without subsequent hypertension, are characterized by some who assess this matter as benign [4].

Only one study mentioned the possibility of serious side effects, such as Tourette's syndrome, dyskinesias, mania syndromes being triggered, and visual hallucinations [8]. In addition, a few additional less serious adverse effects of the medication include headaches, vertigo, nausea, anxiety, stomachaches, and sleep disturbances. The potential for long-term intellectual impairment, psychological suffering, and pharmaceutical addiction was not covered in any scholarly publication [2].

College students' opinions of stimulating medicine, including its potential advantages and applications, are shaped by knowledge gleaned from friends' and lay media opinions [3]. As a result, the degree of understanding regarding the physiological, psychological, and legal ramifications of its unlawful use is lower than one might anticipate, indicating that this subject has not received enough attention in the curriculum of contemporary medical schools [6, 9-11].

It is also important to understand that, due to self-medication and often the lack of necessary medical supervision while using the drug, the lack of necessary medical supervision while using the drug, many patients are unaware that LIS can induce severe reactions when interacting with monoamine oxidase inhibitors (MAOIs), serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), potentially leading to serotonin syndrome. Additionally, interactions with sodium bicarbonate, which alkalizes urine, reduces urinary excretion, and prolongs the half-life of amphetamines, should be considered [7].

Another point that underscores the seriousness of the situation is related to the potential for dependence on LIS, as the drug increases the concentration of extra neuronal dopamine and norepinephrine in the prefrontal cortex [5]. Furthermore, the way many students use the medication can exacerbate issues, as they often take it during exam periods and abruptly cease intake without the necessary tapering, leading to the withdrawal of LIS, accentuating insomnia, and giving rise to depression, evening exhaustion, and cardiovascular effects [2].

## Conclusions

Any medication should only be used following medical assessment and confirmation of a genuine necessity. When it comes to psychostimulants, caution should be exercised even more diligently. Additionally, it is crucial to raise awareness among the population about the short and long-term consequences of unauthorized use of LIS, which is an issue that deserves to be addressed in further studies.

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