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Smart drugs among students – multidimensional view on present ways of cognitive enhancement

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Abstract:

Background: Nootropic drugs, at the beginning of their career, were used in the treatment of diseases such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and narcolepsy. Nowadays, they are becoming more and more popular among students, where they are often called smart drugs or cognitive enhancers. Their properties that improve intellectual abilities and cognitive functions are used to, among other things, improve academic performance.

Aim of the study: The purpose of this article was to summarize the current state of knowledge relating to the use of smart drugs among students. This study discusses the multidimensional issues of using this group of drugs.

Material and methods: A cross-sectional search of relevant literature was performed in databases using accepted wording. Publications from 2003-2023 were included. The entire process has been supplemented with additional procedures to increase the reliability of this publication.

Results: In most sources, the most common representative of smart drugs turned out to be methylphenidate. Nootropics were most often obtained by obtaining a prescription from a doctor, online trading or from friends. The factors motivating the use of substances from this group are primarily the desire to improve academic results, competitiveness and the number of obligations at the university. There are many risks associated with their use, but students are more aware of the positive effects.

Conclusion: This paper presents various dimensions of the progressive spread of nootropic drugs. In addition to their undeniably positive effects, there are many risks, which are discussed in this article. Students' awareness should be formed through appropriate educational methods.

Keywords: nootropic agents; students; academic performance

Introduction:

Nootropic drugs have revolutionized the treatment of many disorders at the intersection of psychiatry and neurology. They were originally developed to treat a range of disorders, including attention deficit hyperactivity disorder (ADHD), Alzheimer's disease or narcolepsy [1]. Their multidirectional effects on improving cognitive brain function have been noticed and appreciated by many communities, thus gaining a lot of space for their off-label use. This had the foundation for defining a new group of drugs called smart drugs or cognitive enhancers. To complete their definition, it was assumed that these are prescription drugs, taken without indication and in doses above the recommended one, which enhance intellectual abilities and cognitive functions, such as concentration, alertness or memory [2]. Research on this group of substances originated during World War II, when stimulants (mainly amphetamine and modafinil) were administered to soldiers to keep them alert and counteract the fatigue that accompanied them [3]. In modern times, college students have become the main consumers, and the scale of their prevalence is shown by estimates that the demand and subsequent profits from their sale will reach nearly $5 billion by 2025 [4].

This paper focuses on pharmacological nootropic agents and takes a closer look at the contemporary problem of their prevalence, the motivation for their use and the resulting risks among the student population. The mechanism of action of the three most popular substances belonging to the aforementioned group was also described.

Material and methods:

Initially, a cross-sectional search was performed in PubMed database. For this purpose, the following formulations were used: ((Nootropic drugs[Title/Abstract]) OR (Nootropics[Title/Abstract]) OR (Smart drugs[Title/Abstract]) OR (Brain enhancers[Title/Abstract]) OR (Study aids[Title/Abstract]) OR (Cognitive enhancers[Title/Abstract])) AND ((students[Title/Abstract]) OR (student[Title/Abstract])). Publications from 2003-2023 were included. A complementary hand search of the literature cited in the preselected articles was also performed to find additional publications meeting the objectives of this review. Reviewers conducted an initial qualification of articles based on titles and abstracts to assess their suitability to meet all the objectives of this work. Those that clearly did not meet the inclusion criteria were excluded. The remaining publications were meticulously analyzed in full text for final qualification for inclusion in the literature items of this work.

Classification of smart drugs:

The term neuroenhancement can be considered multidimensionally. Substances to which such a term is attributed belong to a numerous and heterogeneous group, which includes methylphenidate, modafinil and piracetam, among others. Many authors complete the classification with stimulants such as amphetamine and its derivatives, explaining the enhancement of cognitive abilities through their effect of improving executive functions, as well as an increase in wakefulness or lack of feeling of fatigue.

On the other hand, the definition of neuroenhancement also includes drugs with sedative effects. For many researchers, it is clear that substances with sedative potential are not used directly to improve learning performance, but they can affect performance. A state of rest and relaxation can increase the likelihood of more effective learning. Thus, for example, taking cannabis to relax, stop recurring thoughts and facilitate falling asleep would allow one to remain more alert and focused the next day [5]. Mention should also be made of those natural and everyday counterparts to the aforementioned, also known by some as soft enhancers. There is no doubt that products such as coffee, energy drinks, dietary supplements and caffeine pills find many consumers in a much more representative group than the previously mentioned drugs. This is not surprising looking at their widespread availability and low addictive potential. Many authors include them in their publications and report data with them in mind. Soft enhancers are common among students in everyday life, and also their use seems to be socially acceptable [6].

Mechanism of action:

The group of substances collectively referred to as nootropics is not homogeneous. They differ in chemical structure, mechanism of action and effects on the body, producing different clinical effects. Considering social aspects, they are characterized by varying prevalence and popularity, the greatest of which is attributed to the drugs presented below, where their mechanism of action is discussed.

Methylphenidate

Methylphenidate is a representative of compounds in the phenylethylamine group. It stimulates the noradrenergic and dopaminergic systems in the central nervous system. Its action takes place through the release, sensitive to reserpine, of the contents of synaptic vesicles [7]. Methylphenidate increases dopamine and norepinephrine concentrations in the synaptic space by blocking the dopamine transporter (DAT) and the norepinephrine transporter (NET). It has been shown to improve cognitive function, enhance planning skills and improve working memory. However, it worsens local blood flow in various brain regions [8]. Methylphenidate's effects are also based on its agonist function toward serotonergic receptor 1A (HTR1A) [9,10]. In addition, it affects neurotrophic effects on neural tissue via brain-derived neutrophic factor (BDNF), which influences neuronal survival and plasticity. The evidence for the above actions is unclear, as some studies suggest inhibition [11], while others show activation and an increase in plasma BDNF levels in children with ADHD [12]. It has also been reported that methylphenidate affects the regulation of apoptosis-related proteins, which may have a role in neuronal survival [13]. Moreover, studies suggest the immunomodulatory properties of methylphenidate by triggering inflammation via the release of interleukin 1 (IL-1) and tumor necrosis factor (TNF) [14]. Methylphenidate's range of action also includes regulation of mediators and transcription factors such as adenylyl kinase isoenzyme 1 (AK-1), mitogen-activated protein kinase 3 (MAPK-3), c-Fos protooncogene (FOS), calcium and calmodulin-dependent kinase type IV (CAMK-4) [15].

Modafinil

Modafinil stimulates the noradrenergic system of the thalamus, frontal cortex and hypothalamus. It also activates dopaminergic receptors of the nucleus accumbens, striatum, frontal cortex and locus coeruleus [16]. It causes an increase in the concentration of norepinephrine and dopamine in the synaptic gap [17,18]. Modafinil also exhibits neuroprotective and antioxidant effects, which may affect excitatory properties [19,20]. In other studies, modafinil has been shown to reduce the release of gamma-aminobutyric acid. Unlike amphetamine and its derivatives, modafinil exhibits weaker dopaminergic activity, which has a tidal effect on its weaker addictive potential. An additional mechanism of action of modafinil involves the hypocretin system. Hypocretin, also known as orexin, regulates appetite. One study found reduced levels of hypocretin in dogs with narcolepsy, so it is speculated that it may be responsible for wakefulness. Hypocretin peptides stimulate histamine release in the tuberomammillary nucleus, affecting the sleep-wake cycle. In one study, hypocretin administered to rats caused a prolongation of the wakefulness phase [21].

Piracetam

Piracetam is another nootropic drug used to improve cognitive abilities. It belongs to the pyrrolidone group and is a derivative of gamma-aminobutyric acid (GABA). It improves memory, concentration and psychomotor performance. It has also been proven to enhance memory and thinking processes in patients after a stroke or head injury. It also improves cognitive function in patients who have experienced memory loss as a result of coronary artery bypass graft (CABG) surgery. [22]. Piracetam improves brain nerve cell metabolism, increases oxygen and glucose utilization, and improves cerebral blood supply [23]. Moreover, it protects mitochondria from oxidative stress and aging. Although the protective properties of piracetam in in vitro studies are modest, which can be explained by unnatural and overly demanding conditions. Leuner et al. report that in the pathophysiological view of the slowly progressive changes that occur during aging, these processes are sometimes completely inhibited by treatment with piracetam. This is likely to happen through an increase in the fluidity of mitochondrial membranes, which may be the most important factor regulating their function [24]. It should be added that piracetam does not exhibit free radical scavenging activity [25], so it can be assumed that its action is limited directly to the mitochondria.

Commonness of cognitive enhancement:

There are conflicting data on the prevalence of smart drugs among students. Esposito et al. report that it ranges from 2-80%, with an average of 22.81% [26]. In the United States, on the other hand, Teter et al. found that 24.5% of students included in the study confirmed taking methylphenidate [27]. In another American study, this percentage is as high as 96% [28]. The number of users of brain enhancers is steadily increasing, and men are more likely to admit to using them [26]. In contrast, Miranda et al. published the results of their study, in which women were more likely to use coffee, tea and dietary supplements [29]. According to some sources, the largest number of students used smart drugs without a prescription or medical consultation. The most common ways to obtain them were through friends and e-commerce [26]. Data on the prevalence of student use of nootropics varies depending on the source. This is influenced by the nationality of the study group, the year of the study, the field of study and the country in which the study was conducted. Among the French population of medical and pharmacy students, Franchi et al. proved that 5.8% of the study group admitted to having used substances from the aforementioned group. Methylphenidate was the most popular (3.6%), followed closely by amphetamine and piracetam, whose use was confirmed by 2.9% of respondents each, respectively [30]. The popularity of methylphenidate was also reflected among the Portuguese academic community, where, of the drugs used, methylphenidate again had the highest percentage (35.1%). The next choices were modafinil (10.4%) and idebenone (2.6%), indicating a different preference than noted by Franchi et al [29].

Despite the greatest popularity of methylphenidate among smart drugs, which was demonstrated in most of the studies included in the literature of this paper, there are substances that legitimize greater prevalence in some academic communities. Among Western Australian students, dextroamphetamine was the most common pharmaceutical of choice, with 5.3% of respondents admitting to using it. This is more than three times the rate for methylphenidate, whose prevalence was put at 1.5% [31]. The vast majority of users of these drugs did not have a prescription or medical recommendation for their use, and all of them began consumption during their first year of school [30]. In comparison, other sources found no statistically significant relationship between the frequency of use of enhancers and the year of study [29]. In one large study involving 6725 students, 13.8% of respondents indicated that they had used prescription drugs or narcotics at least once for cognitive enhancement. The most common drugs were again methylphenidate (4.1%), and surprisingly sedatives (2.7%) and beta blockers (1.2%). The above results were more applicable to those students who reported higher levels of perceived stress at the same time. Consumption of soft enhancers, which included coffee, energy drinks and vitamins, was found to be much more common. These were consumed daily in the month leading up to the exam, while their aforementioned pharmacological counterparts were used relatively infrequently and more sporadically, mainly immediately before a pass. The highest predilection for the use of smart drugs was among architecture students (19.6%), and the lowest in mathematics (8.6%).

A very important aspect is the source from which young people obtain the mentioned substances. It turns out that they most often get them from a doctor who writes a prescription [6]. This is also confirmed by Miranda et al. where they detailed the exact medical professions where students realize their needs. It was proven that 33% of the respondents, despite the lack of a diagnosis, manage to get a prescription from a family doctor, another 22% from a psychiatrist. On the other hand, they mainly get their knowledge and information from websites and medical books [32].

Motivation for using smart drugs:

Finding a common denominator to comprehensively explain what motivates students to decide to take the above measures seems impossible, due to the complexity of the issue at hand. Esposito et al. in their systematic review showed that smart drugs are most often taken for their effects on better concentration, greater cognitive abilities, reduced stress levels, more efficient time optimization and curiosity [26]. What is more, students who reported feeling more pressure to perform in their studies, at work or among their families were more likely to admit to experiencing nootropics [6]. One study on a group of UK students aimed to examine the relationship between attitudes toward using aids. They proved that the most important positive predictors for their use were competitiveness and superficial motives, understood as the need to work enough to meet only minimum requirements.

In contrast, among the negative predictors, students' academic performance was found to be the most significant [33]. Among the French population of medical and pharmacy students, the desire to improve academic performance was the most common motivation for their use, as confirmed by all respondents. Increasing arousal and concentration, as well as reducing body weight and achieving a state of euphoria were found to be the next most common reasons [30]. Students who admitted to using pharmacological cognitive enhancers presented higher levels of perceived stress and lower coping abilities. As a strategy to cope with the demands of academic life, they chose the one based on coping with emotions, and the closer they got to their deadlines, they focused directly on their chosen goals [34]. In turn, Merwid-Ląd et al. report that among the Polish population of medical and dental students, the most common reasons for reaching for reinforcers were feeling overwhelmed by the number of tasks (68% of respondents), followed by stress during studies (50%). What is more, nearly 20% of respondents answered that the mentioned means were recommended by their friends, who suggested the effectiveness of these substances, although it is questionable according to some studies. One of these is an experiment on the potential of methylphenidate at different doses (10 mg, 20 mg, 40 mg and placebo) in affecting a wide range of cognitive functions in healthy and young adults. Participants were subjected to tests of attention and episodic and working memory. No differences in performance were observed in any case, thus negating the cognitive effects of methylphenidate in this group of subjects [35].

Despite the increasing percentage of students who choose to supplement with the above drugs, there is still a group that believes the benefits of their use are overestimated. Students who have never used smart drugs are more likely to argue that their colleagues' reasons for reaching for them are due to insufficiently well-planned work. They also add that the above pharmaceuticals even hinder the formation of planning and learning skills. Some work argues that users of brain enhancers overestimate the benefits associated with their potential intellectual enhancement effects [36]. Nevertheless, participants in one study agreed that the decision to use them should be individual and autonomous. Only those who had no experience with these substances supported the finding of unregulated access to them, indicating that they may cause more pressure among the student population and that it may result in inequality in educational and professional development. Interesting findings also came from those students who were in the process of preparing their presentations for scientific conferences. A significant percentage (13.41%) responded that speaking and communication skills were most important to them, and the desire to improve them was the main motivator for using smart drugs [29].

In addition to the reasons, understood as the goals that individuals want to achieve with the help of pharmacology, it has been proven that there are certain personality traits that predispose to this. It turned out that low extroversion, low agreeableness, high conscientiousness are conducive to reaching for them. In addition, circumstances such as alcohol consumption and anxiety intensify the consumption of nootropic drugs [37].

Risks and side effects:

Many studies demonstrate the lack of knowledge regarding the side effects of smart drugs and their addictive potential [38]. Many authors agree that this awareness can be built through educational campaigns [39]. In one study, the most commonly reported side effects of this group of agents include nervousness (27.1%), sleep disturbances (26.4%) and headaches (25%). Participants also reported experiencing depression (18.1%), loss of appetite (17.9%) and tachycardia (15.8%). A less numerous but socially important group of side effects included problems with family (6.3%) or friends (3.8%). Some students experienced anxiety attacks (7.4%) or fits of aggression (6.6%). Several respondents admitted to financial problems (2.4%), problems with the police (2.3%), accidents (0.9%), and even unconsciousness (2.5%) [6]. Students were generally more knowledgeable about the benefits and possibilities of using nootropic drugs than about their potential side effects, which is a significant predictor of abuse. The potential for addiction was the most frequently cited problem resulting from their consumption. In contrast, respondents confirmed the lack of available information on health effects as a source of the aforementioned risks [40]. In another study, respondents who were not interested in enhancing their intellectual abilities with this group of drugs unanimously answered that the main factors that kept them from doing so were lack of need to do so (73.23% of respondents) and fear of their health consequences (37%).

The dangers of using enhancers are generally well understood and widely reported in the literature. Among both students who have used and those who have not had experience with them, there is a belief that such substances cannot be considered without negative consequences. The frequency and type of side effects that accompanied those who used drugs from the group in question depended, among other things, on the type of pharmaceutical. For the aforementioned dextroamphetamine, popular among Australians, almost two-thirds of students experienced negative effects, where, in contrast to modafinil, their frequency was less than half. Respondents mainly complained of insomnia, anxiety and loss of appetite [31].

Conclusions:

This paper presents various dimensions of the progressive spread of nootropic drugs used as pharmacological cognitive enhancement. It may entail many risks due to the lack of sufficient knowledge and awareness of how smart drugs can harm health. Unfortunately, the measures being taken to curb these problems are not keeping pace with the rate at which brain enhancers are gaining popularity among students. What is needed, therefore, are targeted strategies and the dissemination of information about the effects of smart drugs and their risks. Universities should be responsible in educating students in this area. Promising results have been noted using an education methodology referred to as "peer to peer," in which people with similar levels of experience learn from each other and exchange knowledge [40]. The aspects considered in this article focus on off-label use of the aforementioned substances. It is important to remember that the treatment of many neurological diseases would not be possible without them, which thus puts them in a completely different light.

Author Contributions:

Conceptualization, Piotr Pisera and Aleksandra Kiełkowicz; methodology, Daniel Ślusarczyk and Bartłomiej Żmuda; software, Filip Pactwa and Zuzanna Popińska; check, Wiktoria Jakubowska and Michał Żuberek; formal analysis, Piotr Pisera and Daniel Ślusarczyk; investigation, Aleksandra Kiełkowicz and Zuzanna Popińska; resources, Bartłomiej Żmuda, Wiktoria Jakubowska and Michał Żuberek; data curation, Filip Pactwa, Daniel Ślusarczyk and Wiktoria Jakubowska; writing - rough preparation, Piotr Pisera; writing - review and editing, Piotr Pisera and Aleksandra Kiełkowicz; visualization, Piotr Pisera, Bartłomiej Żmuda and

Michał Żuberek; supervision, Filip Pactwa and Zuzanna Popińska; project administration, Piotr Pisera.

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References:

1. Sahakian BJ, Morein-Zamir S. Pharmacological cognitive enhancement: treatment of neuropsychiatric disorders and lifestyle use by healthy people. Lancet Psychiatry. 2015 Apr;2(4):357-62.

https://doi.org/10.1016/s2215-0366(15)00004-8

2. Hildt E. Cognitive enhancement–A critical look at the recent debate. Cognitive enhancement. Netherlands: Springer; 2013. pp. 1–14. https://doi.org/10.1007/978-94-007-6253-4_1
3. Morelli M, Tognotti E. Brief history of the medical and non-medical use of amphetamine-like psychostimulants. Exp Neurol. 2021 Aug;342:113754. https://doi.org/10.1016/j.expneurol.2021.113754
4. Schifano F, Catalani V, Sharif S, Napoletano F, Corkery JM, Arillotta D, Fergus S, Vento A, Guirguis A. Benefits and Harms of 'Smart Drugs' (Nootropics) in Healthy Individuals. Drugs. 2022 Apr;82(6):633-647. https://doi.org/10.1007/s40265-022-01701-7
5. Mache S, Eickenhorst P, Vitzthum K, Klapp BF, Groneberg DA. Cognitive-enhancing substance use at German universities: frequency, reasons and gender differences. Wien Med Wochenschr. 2012 Jun;162(11-12):262-71. https://doi.org/10.1007/s10354-012-0115-y
6. Maier LJ, Liechti ME, Herzig F, Schaub MP. To dope or not to dope: neuroenhancement with prescription drugs and drugs of abuse among Swiss university students. PLoS One. 2013 Nov 13;8(11):e77967. https://doi.org/10.1371/journal.pone.0077967
7. Scahill L, Carroll D, Burke K. Methylphenidate: mechanism of action and clinical update. J Child Adolesc Psychiatr Nurs. 2004 Apr-Jun;17(2):85-6. https://doi.org/10.1111/j.1744-6171.2004.00085.x
8. Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, Malison RT, Carson RE, Ding YS. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psychiatry. 2010 Nov 1;68(9):854-60. https://doi.org/10.1016/j.biopsych.2010.06.017
9. Markowitz JS, DeVane CL, Pestreich LK, Patrick KS, Muniz R. A comprehensive in vitro screening of d-, l-, and dl-threo-methylphenidate: an exploratory study. J Child Adolesc Psychopharmacol. 2006 Dec;16(6):687-98. https://doi.org/10.1089/cap.2006.16.687
10. Carlier J, Giorgetti R, Varì MR, Pirani F, Ricci G, Busardò FP. Use of cognitive enhancers: methylphenidate and analogs. Eur Rev Med Pharmacol Sci. 2019 Jan;23(1):3-15.

https://doi.org/10.26355/eurrev_201901_16741

11. Wetzell BB, Muller MM, Cobuzzi JL, Hurwitz ZE, DeCicco-Skinner K, Riley AL. Effect of age on methylphenidate-induced conditioned taste avoidance and related BDNF/TrkB signaling in the insular cortex of the rat. Psychopharmacology (Berl). 2014 Apr;231(8):1493-501. https://doi.org/10.1007/s00213-014-3500-y
12. Amiri A, Torabi Parizi G, Kousha M, Saadat F, Modabbernia MJ, Najafi K, Atrkar Roushan Z. Changes in plasma Brain-derived neurotrophic factor (BDNF) levels induced by methylphenidate in children with Attention deficit-hyperactivity disorder (ADHD). Prog Neuropsychopharmacol Biol Psychiatry. 2013 Dec 2;47:20-4. https://doi.org/10.1016/j.pnpbp.2013.07.018
13. Réus GZ, Scaini G, Jeremias GC, Furlanetto CB, Morais MO, Mello-Santos LM, Quevedo J, Streck EL. Brain apoptosis signaling pathways are regulated by methylphenidate treatment in young and adult rats. Brain Res. 2014 Oct 2;1583:269-76. https://doi.org/10.1016/j.brainres.2014.08.010
14. Motaghinejad M, Motevalian M, Falak R, Heidari M, Sharzad M, Kalantari E. Neuroprotective effects of various doses of topiramate against methylphenidate-induced oxidative stress and inflammation in isolated rat amygdala: the possible role of CREB/BDNF signaling pathway. J Neural Transm (Vienna). 2016 Dec;123(12):1463-1477. https://doi.org/10.1007/s00702-016-1619-1
15. Coelho-Santos V, Socodato R, Portugal C, Leitão RA, Rito M, Barbosa M, Couraud PO, Romero IA, Weksler B, Minshall RD, Fontes-Ribeiro C, Summavielle T, Relvas JB, Silva AP. Methylphenidate-triggered ROS generation promotes caveolae-mediated transcytosis via Rac1 signaling and c-Src-dependent caveolin-1 phosphorylation in human brain endothelial cells. Cell Mol Life Sci. 2016 Dec;73(24):4701-4716. https://doi.org/10.1007/s00018-016-2301-3
16. Lynch G, Palmer LC, Gall CM. The likelihood of cognitive enhancement. Pharmacol Biochem Behav. 2011 Aug;99(2):116-29. https://doi.org/10.1016/j.pbb.2010.12.024
17. Ishizuka T, Sakamoto Y, Sakurai T, Yamatodani A. Modafinil increases histamine release in the anterior hypothalamus of rats. Neurosci Lett. 2003 Mar 20;339(2):143-6. https://doi.org/10.1016/s0304-3940(03)00006-5

18. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med. 2012 Jul;83(7):685-90. https://doi.org/10.3357/asem.3212.2012
19. Sousa A, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of the cognitive enhancer modafinil: Relevant clinical and forensic aspects. Subst Abus. 2020;41(2):155-173. https://doi.org/10.1080/08897077.2019.1700584
20. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006 Oct;40(10):1829-33. https://doi.org/10.1345/aph.1h024
21. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. J Clin Psychiatry. 2006 Apr;67(4):554-66. https://doi.org/10.4088/jcp.v67n0406
22. Malykh AG, Sadaie MR. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. Drugs. 2010 Feb 12;70(3):287-312. https://doi.org/10.2165/11319230-000000000-00000
23. Marisco PC, Carvalho FB, Rosa MM, Girardi BA, Gutierres JM, Jaques JA, Salla AP, Pimentel VC, Schetinger MR, Leal DB, Mello CF, Rubin MA. Piracetam prevents scopolamine-induced memory impairment and decrease of NTPDase, 5'-nucleotidase and adenosine deaminase activities. Neurochem Res. 2013 Aug;38(8):1704-14. https://doi.org/10.1007/s11064-013-1072-6
24. Leuner K, Kurz C, Guidetti G, Orgogozo JM, Müller WE. Improved mitochondrial function in brain aging and Alzheimer disease - the new mechanism of action of the old metabolic enhancer piracetam. Front Neurosci. 2010 Sep 7;4:44. https://doi.org/10.3389/fnins.2010.00044
25. Keil U, Scherping I, Hauptmann S, Schuessel K, Eckert A, Müller WE. Piracetam improves mitochondrial dysfunction following oxidative stress. Br J Pharmacol. 2006 Jan;147(2):199-208. https://doi.org/10.1038/sj.bjp.0706459
26. Esposito M, Cocimano G, Ministrieri F, Rosi GL, Nunno ND, Messina G, Sessa F, Salerno M. Smart drugs and neuroenhancement: what do we know? Front Biosci (Landmark Ed). 2021 Aug 30;26(8):347-359. https://doi.org/10.52586/4948

27. Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy. 2006 Oct;26(10):1501-10. https://doi.org/10.1592/phco.26.10.1501
28. White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. J Am Coll Health. 2006 Mar-Apr;54(5):261-8. https://doi.org/10.3200/jach.54.5.261-268
29. Miranda M, Barbosa M. Use of Cognitive Enhancers by Portuguese Medical Students: Do Academic Challenges Matter? Acta Med Port. 2022 Apr 1;35(4):257-263. https://doi.org/10.20344/amp.14220
30. Micoulaud-Franchi JA, MacGregor A, Fond G. A preliminary study on cognitive enhancer consumption behaviors and motives of French Medicine and Pharmacology students. Eur Rev Med Pharmacol Sci. 2014 Jul;18(13):1875-8.
31. Nelson M, Jensen C, Lenton S. Study drug use among university students in Western Australia: Results of a web survey and their policy and practice implications. Drug Alcohol Rev. 2021 May;40(4):530-539. https://doi.org/10.1111/dar.13190
32. Merwid-Ląd A, Passon M, Drymluch P, Głuszyński M, Szeląg A, Matuszewska A. Do Medical Universities Students Use Cognitive Enhancers while Learning?-Conclusions from the Study in Poland. Life (Basel). 2023 Mar 17;13(3):820. https://doi.org/10.3390/life13030820
33. Adamopoulos P, Ho H, Sykes G, Szekely P, Dommett EJ. Learning Approaches and Attitudes Toward Cognitive Enhancers in UK University Students. J Psychoactive Drugs. 2020 Jul-Aug;52(3):248-254. https://doi.org/10.1080/02791072.2020.1742949
34. Jensen C, Forlini C, Partridge B, Hall W. Australian University Students' Coping Strategies and Use of Pharmaceutical Stimulants as Cognitive Enhancers. Front Psychol. 2016 Mar 1;7:277. https://doi.org/10.3389%2Ffpsyg.2016.00277
35. Batistela S, Bueno OFA, Vaz LJ, Galduróz JCF. Methylphenidate as a cognitive enhancer in healthy young people. Dement Neuropsychol. 2016 Apr-Jun;10(2):134-142. https://doi.org/10.1590/s1980-5764-2016dn1002009

36. Schelle KJ, Faulmüller N, Caviola L, Hewstone M. Attitudes toward pharmacological cognitive enhancement-a review. Front Syst Neurosci. 2014 Apr 17;8:53. https://doi.org/10.3389/fnsys.2014.00053
37. Myrseth H, Pallesen S, Torsheim T, Erevik EK. Prevalence and correlates of stimulant and depressant pharmacological cognitive enhancement among Norwegian students. Nordisk Alkohol Nark. 2018 Oct;35(5):372-387. https://doi.org/10.1177/1455072518778493
38. Franke AG, Lehmberg S, Soyka M. Pharmacological Neuroenhancement: teachers' knowledge and attitudes-Results from a survey study among teachers in Germany. Subst Abuse Treat Prev Policy. 2016 Sep 20;11(1):32. https://doi.org/10.1186/s13011-016-0077-y
39. Pacifici R, Palmi I, Vian P, Andreotti A, Mortali C, Berretta P, Mastrobattista L, Pichini S. Emerging trends in consuming behaviours for non-controlled substances by Italian urban youth: a cross sectional study. Ann Ist Super Sanita. 2016;52(1):104-13. https://doi.org/10.4415/ann_16_01_17
40. London-Nadeau K, Chan P, Wood S. Building Conceptions of Cognitive Enhancement: University Students' Views on the Effects of Pharmacological Cognitive Enhancers. Subst Use Misuse. 2019;54(6):908-920. https://doi.org/10.1080/10826084.2018.1552297