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REVIEW ARTICLE

Stimulant drugs to promote the awake state and cognitive performance: do they really work?

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Abstract

It is increasingly common for healthy people to seek means to improve their alertness, or to try to get better their performance in some cognitive functions; this with the aim of increasing their performance and productivity in the academic or work environment. Several stimulant drugs have been used for many decades and have recently become very popular especially among young people. However, general practitioners and even specialists are rarely informed of their real benefits or potential adverse effects. This review provides an updated overview of the effects (positive and adverse) of some stimulant drugs that have been used to maintain alertness or improve cognitive performance in healthy subjects. For stimulant drugs, the positive effects improving the subjective symptoms of sleep deprivation are well established. However, the cognitive effects of stimulant drugs are still highly variable and inconsistent, since there are few studies that have been carried out with adequate methodological design. In addition, there are several adverse effects, from mild to severe that can be observed and there is a concern of potential addiction effect to some of them. Some stimulant drugs can improve alertness, but their positive effects improving cognition are not yet fully proven.

Keywords: *Stimulant drugs. Alertness. Cognition. Sleepiness. Addiction.*

Fármacos estimulantes para promover el estado de alerta y el desempeño cognitivo: ¿realmente funcionan?

Resumen

Es cada vez más común que las personas sanas busquen medios para mejorar su estado de alerta o su desempeño cognitivo; esto con la finalidad de incrementar su productividad en los ámbitos académicos y laborales. Múltiples fármacos estimulantes han sido utilizados desde hace varias décadas y recientemente se han popularizado entre los jóvenes. Sin embargo, es poco común que los médicos generales e incluso los especialistas estén adecuadamente informados sobre sus beneficios reales y sus efectos adversos potenciales. El presente artículo realiza una revisión actualizada sobre los efectos tanto positivos como adversos de los fármacos estimulantes que han sido utilizados para mejorar el estado de alerta o la cognición en sujetos sanos. Para varios estimulantes, los efectos sobre el estado de alerta están bien establecidos. No obstante, los efectos cognitivos aún son muy variables e inconsistentes, en particular debido a que existen pocos estudios

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que se hayan llevado a cabo con rigor metodológico. Adicionalmente, existe la posibilidad de efectos adversos desde leves a severos y la preocupación sobre potenciales efectos adictivos para algunos de ellos. Algunos fármacos estimulantes pueden mejorar el estado de alerta, pero sus efectos sobre la cognición aún no están completamente probados.

Palabras clave: *Fármacos estimulantes. Alerta. Cognición. Somnolencia. Adicción.*

Introduction

The modern rhythm of life has become more and more demanding of individuals in every way; the availability of artificial light at any time of the day allows us to extend our social, work or school activities indefinitely; this has undoubtedly increased our productivity significantly in all areas, but it also represents a radical change in our biological rhythms, especially in normal sleep. Nowadays, no one hesitates to sacrifice a few hours or a whole night of sleep to carry out more activities and be more productive. These important changes in sleep habits are a global phenomenon, especially in the most industrialized nations[1]. All these changes have caused the quality and number of hours of nighttime sleep to be gradually reduced in the general population, and this effect being even more severe and evident in young people and students in general[2]. In this sense, recently it has begun to study the consequences that poor sleep quality (PSQ) and sleep disorders (SD) can have on the physical and mental health. At present, it is widely demonstrated that SD are related to various negative effects on health in the short term, including: depression, impaired concentration, poor school performance, irritability, eating disorders, and increased risk of accidents[3]. However, what is especially worrying is that these chronic SD are also a very important risk factor for suffering several chronic degenerative diseases in the future, for example, diabetes mellitus, arterial hypertension, obesity, myocardial infarction, and stroke[3]. It is for this reason that for several decades different drugs, which we know generically as "stimulants," have been used and developed to try to improve alertness and thus try to reduce or avoid the daytime hypersomnia due to SD or PSQ.

The stimulating effect of a cup of coffee is well known for all of us; however, currently there are some drugs that have a more selective and powerful action to try to counteract sleepiness during the day (daytime sleepiness). Most stimulant drugs were actually originally created for other therapeutic purposes (decongestant, antidepressant, attention deficit treatment, etc.), however, because some have shown effects by stimulating alertness, they are currently used also for this purpose[4].

The high frequency of PSQ has led to the popularization of different "stimulant" products or beverages to combat daytime sleepiness or improve "energy." Some of these products actually have a placebo effect (vitamins, food supplements, antioxidants, etc.) since they do not have any stimulating properties, but others use combinations of different substances (including caffeine, taurine, and high amounts of sugar) that can show some stimulating effect[5,6].

In the same way that there is a growing need for some drugs that improve the symptoms of daytime sleepiness, there is also a growing demand for having some type of drug that improves or stimulates the cognitive or mental abilities. In general, these types of drugs have been called "Smart Drugs (SD)" or "Smart Pills." This type of drugs would offer (at least theoretically), the possibility of improving or combating the cognitive symptoms of different disorders characterized by lower cognitive performance such as: dementias, brain injuries, and intellectual disability[7].

However, it is important to note that due to the highly competitive environment that currently exists at work and school environments, the people who are most often interested in using or trying these types of drugs are healthy and young people who seek to enhance their normal cognitive abilities[8]. Studies carried out in this regard suggest that most of the users of this type of drugs are actually the most advantaged university students who seek to compete for a better academic place, opt for a scholarship or award, or simply stay in educational institutions with a high academic demand[9].

Unlike what happens with drugs that improve alertness, in which the positive effects are demonstrated for some substances, in the case of "SD" their possible positive effects on cognition are still very controversial, inconsistent or very scarce. However, even so, they are widely used and recommended[8]. In the same way that it happens with drugs that improve alertness, very few people know their real effects and their possible adverse effects or toxicity. Considering all the above, the objective of this article is to show an updated overview of stimulant drugs used to improve alertness or cognition, emphasizing their mechanism of action, the effects reported in clinical studies and their potential negative effects.

Drugs to improve alert or combat sleepiness

Regarding drugs to improve alertness, most of them are drugs that in some way, either directly or indirectly, increase the levels of brain catecholamines, especially dopamine (DA) and norepinephrine (NA), but can also increase the levels of other neurotransmitters such as acetylcholine, serotonin, or histamine[10].

Caffeine

Description

Caffeine is a xanthine (1,3,7-trimethylxanthine) derived from the seed of the coffee plant, it is a substance that is rapidly absorbed at the gastrointestinal level and that penetrates the brain in 80% of the blood levels, having its effect maximum in 30-45 min. The half-life of caffeine is 3-7 h. This substance is not only present in coffee, but can be found in a variety of commonly used beverages such as tea, cola sodas, some candies and desserts, energy drinks, as well as in medicines such as: anti-flu, analgesics, and anti-migraine formulations[11].

Mechanism of action

Caffeine exerts its action in the Central Nervous System (CNS) blocking the Adenosine receptors (A1 and A2). These receptors are widely distributed in different brain regions such as the cerebral and cerebellar cortex, the hippocampus, the striatum, and the *nucleus accumbens*. In a normal way, adenosine decreases the neuronal firing frequency and decreases the release of multiple neurotransmitters, in other words, it seems to have an inhibitory or depressant role on the neuronal firing in general; and it is for this reason that the consumption of caffeine by blocking this effect promotes neuronal activation and wakefulness[11].

Effects

It is well established that caffeine promotes alertness and improves some of the physical and cognitive symptoms of sleep deprivation in relation to the dose, having observed with doses from 50 to 75 mg, and this effect seems to be independent of whether the person consumes it regularly[12]. Here, it is important to note that this positive effect on alertness has been found in studies carried out mainly in healthy people, when it is administered during the morning. The administration of caffeine to avoid sleepiness or to avoid sleep during the night produces very different effects, since it seems to subjectively improve sleepiness but some studies suggest that cognitive performance does not actually benefit as it does during the morning[13]. In addition, there are multiple studies that show that caffeine intake during the night alters sleep latency, also reduces the efficiency of sleep, its total duration and also decreases the length of deep sleep stages[13]. However, some adaptation effect has been shown with chronic caffeine use[14]. On the other hand, there is some evidence that caffeine consumption can decrease appetite and contribute to generating a reduction in weight and body fat content, this because it has effects by increasing energy expenditure and lipolysis[15].

Adverse effects

Depends on the dose and the speed of administration, among the most frequent acute effects are: tachycardia, restlessness, agitation, tremors, chest pain, dizziness, fainting, epigastric pain, paresthesia, headache, and even respiratory distress. Recently, the ingestion of alcoholic beverages in combination with energy drinks with caffeine has become popular; because there is a belief that energy drinks counteract to some extent the depressant or sedative effects of alcoholic beverages[16]. There is ample evidence to support that this belief is completely false, this combination of substances can make the subject subjectively feel “better” but it has been shown that it does not improve their physical of cognitive performance, and some studies even suggest that impulsive or risky behaviors are increased, in addition to that promotes the increase in alcohol consumption[17]. Regarding its addictive potential, it is well established that caffeine can cause both symptoms of acute intoxication (very similar to other stimulant substances), as well as chronic effects: tolerance effect, dependence and abstinence, for which it should be considered as a potentially addictive substance[18].

Methylphenidate (MPH)

Description

It is a stimulant synthetic drug derived from piperidine, which was originally patented by CIBA and Novartis laboratories. In 1955 it was accepted by the United States FDA for the symptomatic treatment of attention deficit hyperactivity disorder (ADHD)[19].

Mechanism of action

It is related to the inhibition of DA and NA transporters, this inhibition increases the levels of DA and NA and increases the duration of their effect in the synaptic cleft, thus increasing their action. Although the stimulating effect of MPH on the dopaminergic and noradrenergic systems is completely unspecific, it is proposed that the therapeutic effects, improving alertness or attention and concentration, occur due to its effects at the level of the prefrontal cortex, especially in the meso-limbo-cortical circuit[19].

Effects

The current indication for MPH is the symptomatic management of Attention Deficit Hyperactivity Disorder (ADHD), and to combat daytime sleepiness in cases of narcolepsy, but it has also been used to treat symptoms such as fatigue in some systemic and neurological diseases and in the management of refractory depression[20]. The usual therapeutic dose is 10 mg to 60 mg/day. Its positive effects on improving alertness and reducing symptoms of daytime sleepiness are well documented. Due to its pharmacological characteristics, the effects usually occur in the short term because the action of the immediate-release formulations is approximately 4 h. Despite this positive effect during the day, there are some studies that suggest that the stimulating effects may also interfere with the duration and quality of night sleep; this has been especially studied in children with ADHD[21].

Adverse effects

Although in this sense there is an important individual susceptibility, used at therapeutic doses the most frequent adverse effects are nervousness, irritability, headache, insomnia, decreased appetite, loss of weight, and tachycardia. However, symptoms of acute overdose or intoxication may include: agitation, delirium, psychosis, hallucinations, cardiac arrhythmias, hypertension, hyperthermia, and seizures[22]. The addictive potential of MPH is considered high, although this is related to the dose and the route of administration, since it has been observed that intranasal and intravenous administration (as a recreational drug) exert a much more intense reinforcing effect than oral formulations; regarding pharmaceutical formulations, immediate-release tablets seem to have a higher addictive effect than prolonged-release formulations[23].

Modafinil

Description

Modafinil is a uniquely structured neuro-stimulant drug that has been accepted by the United States FDA for the treatment of narcolepsy, as an adjunct to the treatment of sleep apnea and in work shift SD. In addition, it has been used in the management of fatigue in neurological diseases, and as an adjunct to antidepressant treatment[24].

Mechanism of action

So far, the final mechanism of action of modafinil is not known with precision, but various physiological studies have shown that it produces an increase in DA and NA in the brain, it also seems to increase glutamate, serotonin and histamine levels, as well as orexin levels. For this reason, it is considered a “universal” brain stimulant. At the neuroanatomical level, it has been proposed that the effect of modafinil is preferentially exerted at the hypothalamic level, disinhibiting cortical neurons[25].

Effects

In therapeutic doses ranging from 200 to 400 mg/day, there are multiple studies that show a consistent effect reducing daytime sleepiness and fatigue, but also have a positive effect on the daily functionality of patients and even on quality of life, especially in patients with sleep apnea and narcolepsy[26]. Furthermore, as adjuvant treatment (along with other antidepressants) modafinil also seems to show a positive effect in patients with uni or bipolar depression[27]. On the other hand, its effects on fatigue caused by different neurological diseases (multiple sclerosis, Parkinson’s disease, and traumatic brain injury) have not been consistently observed, so its use is not recommended systematically for these indications[28]. Finally, a recent meta-analysis has also shown that modafinil has superior effects to placebo in the symptomatic management of ADHD, which is why it can be an alternative to first-line treatments in this disorder[29].

Adverse effects

Since the initial clinical studies, it has been shown that the safety profile of modafinil appears to be different from that of other stimulants, since the frequency

and severity of adverse effects are lower compared to MPH or amphetamine. At therapeutic doses, effects such as restlessness, palpitations, irritability, headache, rhinitis, nausea, and dizziness have been reported; less frequently, elevations in systolic blood pressure and some events of cardiac arrhythmia have been reported. From the point of view of its addictive potential, modafinil seems to show a low addiction potential, although it has been shown that it can induce dependence and even withdrawal symptoms with prolonged use in some cases. However, compared to the case of MPH, with modafinil there are very few cases of severe intoxication or addiction[26].

Drugs to stimulate cognitive function

In a generic way, drugs that aim to increase some aspects of cognitive performance have been called "SD", although there are several synonyms: brain or cognitive enhancers or stimulants, brain boosters, nootropics, neurostimulants, etc. A "SD" is any drug or substance that increases the cognitive capacity of the individual who takes them, regardless of whether the user is cognitively affected or not.

Drugs that have been used for these purposes range from methamphetamines (illicit) to medical prescription drugs (modafinil, MPH, acetylcholinesterase inhibitors, etc.) and also stimulants such as caffeine, vitamins, antioxidants or natural products such as Gingko Biloba[30,31]. The use of prescription drugs is commonly oriented to the treatment of medical or psychiatric conditions; however, in recent years, some of these drugs have been used for other purposes than the original medical prescription in search that their effects may enhance some cognitive or physiological processes (non-medical use or without prescription)[31].

The prevalence of SD use not precisely known mainly because most users often do not freely accept that they consume them for that purpose, essentially because there is still an ethical and legal dilemma about their use[32]. However, some surveys of university students in the United States, Italy, and Great Britain reported that 34% agreed to use some medication; other authors mention that between 16% and 20% used some type of drug in order to improve their cognitive abilities[33]. On the other hand, these surveys have also been applied to health professionals (surgeons), where up to 8.9% agreed to use a prescription drug or an illicit drug exclusively to improve their cognitive performance[31].

These percentages may seem low, but in reality, there is great variability in the design of these surveys, for example: some surveys were not anonymous, some only question whether the subject is currently consuming, while others ask whether he has consumed them at some point in his life or only in the last year, or whether he has used them more than once, etc.[34] all of which can affect the response of individuals and underestimate the actual consumption of SD. On the other hand, some substances such as nicotine or caffeine are not usually considered as stimulants by most subjects but as a substance of habitual consumption, which may contribute to underestimating their frequency of use. The reasons for using these SD also vary in the results of these investigations. Some of the reasons for consumption that have been described are: "staying alert to study better," wanting to "enhance concentration," obtain better results in school tests, concentrate on work, to help memorize, as well as for "recreational" or "creativity purposes"[32,33].

In the following paragraphs, the most frequent drugs and substances that have been studied in their potential cognitive effects will be presented (since the pharmacology, adverse, and addictive effects of some of them have already been explained in the previous section, only their potential cognitive effects were discussed).

Caffeine

In a recent review of the subject, it was concluded that its effects can benefit sustained attention, alertness in simple tasks, as well as processing speed, which seems to be related to the administered dose and also depends on whether the individual are a regular or not a caffeine user; however, it has been reported that in high doses it can even interfere with cognitive performance[35].

Nicotine

It is an alkaloid isolated from the tobacco plant and its habitual route of consumption is in inhaled form in cigarettes. However, it must be taken into account that in this state its effect is also influenced by the other substances present in the cigarette (> 4000 isolated substances), in other words, talking about nicotine is not synonymous with tobacco or smoking. Nicotine is an agonist of the alpha 4ß2 type nicotinic acetylcholine receptors, these receptors increase calcium entry into *nucleus accumbens* neurons, which in turn promotes DA release in the cortical meso-limbic pathway, which is related to its high addictive potential and its stimulating effects[36].

In several studies, the acute effect of tobacco on cognition has been found to be related to improved selective attention, recognition memory, fine motor skills, and also episodic and working memory[37]. The effect that has been continuously replicated is an improved performance and reaction times in tasks that require sustained attention in smokers who are dependent on nicotine[38]. With this substance, it has also been found that the effect on cognitive processes is dependent on the dose and moment of evaluation, for example, participants in the tobacco withdrawal stage show, on the contrary, a significant reduction in their cognitive performance[39]. It is important to note that, in studies conducted in non-smoking subjects, nicotine had no positive effects on a prospective memory task[40]. In summary, most of the cognitive effects found are modest and have been observed in the nicotine-dependent population, so they cannot necessarily be extrapolated to non-smokers.

MPH, regarding its effects on cognition, improvements in memory (evocation), working memory, as well as reaction time (decreasing it), alertness, attention, executive function have even been found, effects have been found in mood where it increased subjective enthusiasm and some depressive symptoms in healthy patients[30].

Modafinil

On the results found in healthy population not deprived of sleep, contradictory results have been found, some studies suggest that it improves visual memory, spatial planning and reaction time[41]. In other studies, improvements have been found in visual memory, working memory and spatial planning tasks and it has also been suggested that their effects are related to an improvement in reaction time[38], and to a longer latency in more complex tasks[42].

It is important to mention that there are also multiple studies that found no differences in cognitive performance between modafinil and placebo[38,42] or that found differences in other time variables, but not in cognition[43], thus concluding that modafinil had no significant cognitive effects in healthy people without sleep deprivation.

Amphetamines

Amphetamines are non-catecholaminergic sympathomimetic amines with stimulating action on the CNS. Amphetamine acts to dramatically increase the amount of extracellular monoamines available in the brain, by blocking and/or reversing the DA, NE, and 5-HT reuptake transporters and regulating their surface expression levels[43].

Lisdexamfetamine (LDX)

Description

LDX is a prodrug of dextroamphetamine (DAM), developed for the treatment of ADHD[44]. LDX was approved in the United States for the treatment of ADHD in children 6-18 years of age in 2007 and 1 year later in adults up to 55 years[45].

Mechanism of action

It increases the release of DA and, to a lesser extent, NA to the intersynaptic space, and it blocks the reuptake of both neurotransmitters in the presynaptic neuronal terminal.

Effects

LDX decreases impulsivity in patients with binge eating disorder[46] and has a propensity to cause weight loss, which may be beneficial for obese patients with this disorder. This prodrug has other potential uses that are still off-label, and its use can be considered an intellectual enhancer[47], for example, LDX improves the cognitive performance in multiple sclerosis patients[48]. In relation to cognitive effects, in one clinical study was found to improve cognitive performance and processing speed[49].

Adverse effects

The potential for abuse of LDX is very low because it is extremely complex and expensive to extract DAM from the LDX molecule and it is not feasible to dissociate lysine through other routes of administration (nasal or injected) that could favor misuse and increase addictive risk[44]. Regarding safety, LDX is a well-tolerated drug[50]. The most frequent short-term adverse effects are loss of appetite (especially at mealtime, which may be associated with a decrease in the patient's weight) and insomnia. Less frequently, headache, dry mouth, cold extremities, anxiety/irritability, abdominal pain, increase of tics, among others, may occur[51].

Adderall

It is the commercial denomination that is used to name a drug composed of four different salts of amphetamine, the mixture contains equal parts of amphetamine and DAM and although all the components are stimulant they differ substantially in their pharmacological properties with respect to another type of formulations. Its mechanism of action is similar to another amphetamine.

Effects

Its ability to improve cognition in normal healthy people has been demonstrated by a series of laboratory studies with tests of problem solving and executive function[52,53]. In a 2008 study it was found that Aderall improved the performance of creative thinking, although it was found that the effect depended on the participant's baseline creativity; interestingly, the drug increased the creativity of the lower-performing participants and impaired it for the higher-performing participants[54].

Adverse effects

Appetite suppression, nausea, insomnia, and headaches were some of the side effects reported by parents of children taking Aderall[55].

Dextroamphetamine (DAM)

It is the dextro-isomer of amphetamine and is the most commonly administered form of amphetamine in human research studies, which is almost 2 times more potent in promoting alertness and wakefulness than the L-amphetamine[56].

Effects

DAM in cognitive and memory function follows an inverted U-shaped curve relationship, in which moderate doses are beneficial for cognition, while excessive activation may lead to cognitive impairment[57]. DAM has been found to further improve performance in subjects with poor baseline performance[58] or sleep deprived subjects[59]. In contrast, in a study conducted on the modification of neurocognitive performance during sleep loss, DAM in doses of 5 mg had no effects on cognitive performance[60].

Adverse effects

In one classical study with increasing doses from 5 mg to 10 mg of DAM administered hourly reported the following adverse reactions: increased blood pressure, postural hypotension, tachycardia, increased oral temperature, premature ventricular contractions, decreased appetite/anorexia, paraesthesia, and SD. Psychological adverse experiences included depression, hypochondria, lack of interest in surroundings or activities, irritability, fault-finding, dependence on clinical staff, negativity, paranoia, and delusions; however, the doses at which they were observed they were not indicated on the article[61].

Other sleep disorders without scientific evidence

As previously mentioned, in addition to the drugs that have a truly stimulating action, increasing the levels of brain monoamines neurotransmitters, very often other types of drugs or substances have been used as "cognitive enhancers;" however, unlike stimulant drugs, their pharmacological actions are very varied and non-specific, for example, they are antioxidants, anti-inflammatory, neuroprotective, vitamins, and dietary supplements. These active principles include Ginkgo Biloba, Ginseng, green tea, omega 3 and 6 fatty acids, vitamin-antioxidants such as Vitamin E and Vitamin C, resveratrol, B-complex vitamins, lipid precursors such as lecithin, citicoline, piracetam, L-carnitine, amino acids such as tyrosine and tryptophan, some minerals such as magnesium, zinc, selenium, and a long etcetera[8]. Although some of them have been rigorously studied in terms of their possible effects on cognition, for example, omega 3 fatty acids in Alzheimer's disease[62], their results have been mild or inconsistent in the best of cases and in many cases of these there is no real or direct evidence that their effects as antioxidants or anti-inflammatories have a positive effect on cognition, so they should not be considered as true "cognitive enhancers"[8].

Table 1 summarizes the most significant effects on alertness and cognition of stimulant drugs.

Final comments and conclusions

The high demands of modern life have led more and more people to seek the means to improve their performance in many personal, school, and professional fields. As previously discussed, different stimulant substances have been used and tested to improve alertness or combat the effects of sleep deprivation (sleepiness) or decrease the effects of some SD.

Table 1. Summary of the main effects of stimulant drugs on alert and cognition

Substance	Description	Mechanism of action	Positive effects	Negative effects
Caffeine	– Present in coffee, tea, cola, sweets, desserts, energy drinks, medicines (anti-flu, analgesic, anti-migraine).	– Blocks adenosine A1 and A2 receptors, which promotes neuronal activation and wakefulness.	– Promotes alertness (in healthy and administered during the day). – Improves physical and cognitive symptoms of sleep deprivation. Insomnia – Decreased appetite and body fat content.	– Tachycardia, restlessness, agitation, tremors, chest pain, dizziness, fainting, epigastric pain, paresthesia, headache and even respiratory distress. – Causes tolerance, dependence and withdrawal. – Potentially addictive.
Methylphenidate	– Since 1955 it has been used for the symptomatic treatment of ADHD.	– Inhibition of DA and NA transporters. This inhibition increases the levels of DA and NA and increases the duration of their effect in the synaptic space, thus increasing their action.	– Combats daytime sleepiness in cases of narcolepsy. – Management of fatigue in some systemic and neurological diseases. – Management of treatment-refractory depression. – Neuroplasticity stimulant in patients who have suffered some type of brain damage. – Improves alertness. – Reduces the symptoms of daytime sleepiness.	– Nervousness, irritability, headache, insomnia, decreased appetite, weight loss and tachycardia. – Overdose: agitation, delirium, psychosis, hallucinations, cardiac arrhythmias, hypertension, hyperthermia and seizures. – Potentially addictive.
Modafinil	– Useful in the treatment of narcolepsy, adjuvant for the treatment of OSAHS, sleep disorder due to change of work schedule and antidepressant treatment, management of fatigue in neurological diseases.	– Produces an increase in brain DA and NA, glutamate, serotonin and histamine and brain orexins ("generic" brain stimulant). – Neuroprotective and antioxidant effect.	– Reduces daytime sleepiness and fatigue. – Improves functionality and quality of life in patients with OSAHS and narcolepsy. – It seems to improve uni or bipolar depression. – Alternative to first-line treatments in ADHD.	– Restlessness, palpitations, irritability, headache, rhinitis, nausea and dizziness; less frequent elevations of systolic blood pressure, and some events of cardiac arrhythmia. – Low addictive potential. – Induce dependency and withdrawal. – Latent possibility of intoxication.
Amphetamines	– Amphetamines are non-catecholaminergic sympathomimetic amines with stimulating action on the central nervous system.	– Acts to dramatically increase the amount of extracellular monoamines available in the brain, by blocking and/or reversing the DA, NE, and 5-HT reuptake transporters and regulating their surface expression levels.	– Depend on the formulation (D or L isomer, or derivatives), among its positive effects are the decrease in impulsivity in patients with binge eating disorder, intellectual enhancer, improve cognitive performance, and processing speed, improve creativity.	– Anorexia, sleep disorders (insomnia), headache, dry mouth, cold extremities, anxiety, gastrointestinal disturbances (abdominal pain), nausea, increased blood pressure, tachycardia, increased oral temperature, premature ventricular contractions, paraesthesia, visual disturbances and fatigue, among others.
Cognitive effects				
Caffeine	**Methylphenidate**	**Modafinil**	**Nicotine**	**Amphetamines**
– Sustained attention.	– Improvement in memory (evocation), working memory, decreases reaction time, improves alertness, increases subjective enthusiasm and improves some depressive symptoms.	– Improves visual memory, spatial planning and reaction time.	– Improved selective attention, recognition memory and working memory; better performance and reaction times on tasks that require sustained attention.	– The effects may depend on the formulation (D or L isomer).

(*Continues*)

Table 1. Summary of the main effects of stimulant drugs on alert and cognition *(continued)*

Cognitive effects				
Caffeine	**Methylphenidate**	**Modafinil**	**Nicotine**	**Amphetamines**
– Improves alertness and processing speed. – In high doses it can interfere with cognitive performance.		– Improvements in visual memory tasks, working memory, spatial planning, improvement in reaction time and longer latency in complex tasks.	– The recognition memory effect is dose dependent – Cognitive effects observed in nicotine-dependent population, so they cannot necessarily be extrapolated to non-smokers.	– Improve performance in subjects with poor baseline performance or sleep deprived subjects. – Improve performance in solving problems and executive functions. – May improve the creative thinking.

ADHD: attention deficit hyperactivity disorder; DA: dopamine; NA: noradrenaline; OSAHS: obstructive sleep apnea hypopnea syndrome.

The initial indications for these drugs were restricted to patients with some type of SD, but today healthy people are increasingly looking for ways to reduce their sleep time (to continue studying or working) or to lessen the effects of voluntary sleep deprivation (daytime sleepiness).

The effects on alertness of multiple drugs and substances are well established. However, it is very important to mention that reducing the feeling of subjective fatigue or sleepiness does not necessarily mean that your work, school, or cognitive performance also improves by the same magnitude.

In this sense, as mentioned in the text, some drugs have been shown to improve some cognitive abilities; however, there are very few studies that have been carried out in healthy people, and that have adequately ruled out the "placebo" effect of drugs; therefore, the results on the cognitive stimulation of these drugs and substances are still contradictory and inconsistent.

It is relevant to note that the stimulating effects are variable from person to person. In the same way, all these drugs and substances have different adverse effects that can range from mild to serious, and that do not necessarily depend on the dose and frequency of use, that is, there also seems to be an individual susceptibility to adverse reactions, in such a way that not exist a type of stimulant that should be recommended generally for all individuals.

Finally, there is still an important ethical debate about its use in academic, school, and work environments, and in this sense, there is still no adequate regulatory framework on its use and/or restriction, so the issue of the effects of stimulant drugs still have multiple aspects that must be investigated and clarified in the future before their use can be recommended or promoted in healthy individuals.

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Conflicts of interest

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