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Influence of Drugs on Cognitive Functions

Claudia Juárez-Portilla, Tania Molina-Jiménez, Jean-Pascal Morin, Gabriel Roldán-Roldán and Rossana Citlali Zepeda

Abstract

Disorders related to the misuse of certain drugs represent not only a worldwide public health problem, but also an economic and social issue. Adolescents and children represent the most vulnerable population for drug consumption and addiction. At this early stage in life, a crucial phase of the neurodevelopmental process, substance abuse can induce brain plasticity mechanisms that may produce long-lasting changes in neural circuitry and ultimately behavior. One of the consequences of these changes is the impairment of cognitive functions, with academic negative impact in the acquisition of new knowledge. In this chapter, we will describe the effects of illicit substances of abuse, both stimulants and depressants as well as prescription drug misuse and its influence on learning and memory processes. Recent evidence on the new so-called smart drugs is also discussed.

Keywords: abuse, cognition, performance, nootropic, smart, stimulants, depressant, memory, impairment, adolescent

1. Introduction

According to United Nations Office on drugs and Crime, in 2015, around a quarter of a billion people used drugs, and approximately 29.5 million showed drug use disorders, including dependence [1]. Drug abuse produces health disruption. Disorders related to the use of certain drugs are associated with an important worldwide rate of morbidity. A wide range of drug-induced neurobiological modifications have been described; some of which can affect learning and memory functions. Stimulant drugs, like nicotine and amphetamine, improve cognitive function at lower doses but impair memory performance at higher doses. Depressant drugs, like alcohol, can cause long-term effects on prefrontal cortex function, disrupting cognitive abilities.
Several studies have suggested that the influence of psychoactive drugs on learning and memory might be explained, at least in part, because of the shared neurobiological mechanisms involved in learning and memory processes and the drug-induced structural and functional changes in the brain. Anatomically, there is an important overlap between the neural substrates of learning and memory and those of addiction. Some of the areas that show overlap include the cerebral cortex, hippocampus, amygdala and striatum [2]; all of them are components of the mesolimbic dopaminergic system.

Adolescence is a sensitive period in brain development characterized by a decrease in gray matter and an increase in white matter. The diminution of gray matter is thought to be due, at least in part, to the process of synaptic pruning, which is the developmental refinement of brain circuits by removal of superfluous synapses [3]. Early drug exposure is associated with frontal lobe damage, low cognitive performance and emotional learning, as well as other behaviors. Moreover, it has been demonstrated that adolescent exposure to both prescription and social drugs impairs cognition, as well as other behaviors, in the adulthood [4].

There is a clear bidirectional relationship between abuse of drugs and poor academic achievement. It has been suggested that cognitive deficits could make adolescents more vulnerable to substance abuse than others; conversely, other proposals argue that substance abuse is the source of cognitive impairments [5–7]. Of course the two possibilities are not mutually exclusive; teenagers with poor academic performance may be more prone to abusing illicit drugs, which may impair their results at school even further. While the several social science theories have been proposed to try to explain each of these phenomena [6], in the following text, we will focus on the cognitive consequences of adolescent substance abuse on the functioning of the nervous system that may have a deleterious impact on cognitive abilities, academic achievement and long-term satisfaction with life in general.

2. Stimulant drugs

Memory is the natural counterpart of learning; both are necessary for behavioral change that precedes survival of species. Substance abuse has been demonstrated to exert detrimental impact upon learning and memory. According to the United Nations Office on Drugs and Crime through World Drug Report 2017, 29.5 million people globally suffer from drug use disorders [8]. Cognitive impairment is a well-established consequence of long-term substance abuse, with stimulants as nicotine, methamphetamine (MA) and cocaine leading deficits in the area of executive function. Stimulants are a class of illicit drugs that can have negative impact on individuals who use them, although this impact might be masked by the believed benefits (Table 1) [9].

2.1. Nicotine

Nicotine is the main psychoactive component of tobacco and the responsible agent of tobacco dependency. According to the World Health Organization, despite its severe health consequences, about one billion people smoke worldwide.
When nicotine is administered acutely, it produces positive effects improving cognitive functions, including sustained attention, vigilance, visuospatial selective attention, spatial working memory and associative memory, both in animal models [10, 11] and in humans [11]. Conversely, a vast amount of literature has showed that chronic nicotine use leads to tolerance, and 1 h after cessation of nicotine exposure, nicotine withdrawal syndrome emerges and it is characterized by mild cognitive deficits. In other words, nicotine tends to improve cognitive function at lower doses and impair performance at higher doses [12]. Furthermore, heavy smokers under acute abstinence from smoking experience decreased neurocognitive functions, including impairments in sustained attention, working memory and response inhibition [13]. Strong activation of memory-related brain regions that include the dorsolateral prefrontal cortex and hippocampus has been correlated with smoking-related cues in adult heavy smokers [14]. These areas are involved in emotional learning and reward-related learning.

Some reports have shown that nicotine and nicotinic agonists, as mecamylamine, evoked cognitive enhancement by potentiating the release of dopamine [12, 15]. Working memory is critically reliant on dopaminergic neurotransmission. In addition, rodent studies have revealed a direct relationship between dopamine release in the prefrontal cortex and on memory task accuracy [16]. Moreover, cholinergic systems and nicotinic receptors are essential for cognitive processes and have been implicated in diseases associated with cognitive impairment [17].

### Table 1. Effects of the stimulant and depressant drugs in cognitive functions.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cognitive process</th>
<th>Effect</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant drugs</td>
<td>Attention</td>
<td>Acute: Improving selective visuospatial attention, spatial working memory and associative memory</td>
<td>Monkey</td>
<td>[10, 11]</td>
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<tr>
<td></td>
<td>Vigilance</td>
<td></td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Memory</td>
<td></td>
<td>Mice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic: Withdrawal syndrome</td>
<td>Human</td>
<td>[13, 25-27, 29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild deficits in memory and inhibition response</td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disruption in prospective and visual memory, verbal ability, reasoning and decision making</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Depressant drugs</td>
<td>Attention</td>
<td>Acute/low doses: Facilitation in working memory, verbal fluency and executive functions</td>
<td>Human</td>
<td>[37, 38, 41, 55-57]</td>
</tr>
<tr>
<td></td>
<td>Memory</td>
<td>Impaired working memory, verbal fluency and executive functions</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic/high doses: Disruption in working and episodic memory, consolidation memory, attention and memory Also, presence of blackouts</td>
<td>Human</td>
<td>[39, 61-67]</td>
</tr>
</tbody>
</table>

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2.2. Methamphetamine (MA)

MA abuse represents a serious public health issue associated with a high likelihood of relapse. By 2008, nearly 25 million people worldwide were estimated to have used MA, with abuse being among younger age groups [18]. MA used is mainly for recreational purposes and it is known to induce a variety of desirable effects, including increased energy levels, positive mood, euphoria, reduced appetite, weight loss, enhanced mental acuity and social and sexual disinhibition [19]. In addition, MA-dependent individuals often claimed enhancement of cognitive function and ability to focus following drug administration. However, this drug induces long-term changes in the brain structure and function, changes in synaptic plasticity, cell death via apoptosis and neurotoxicity, and consequently, it causes dependence and withdrawal syndrome [20].

Anatomically, MA has a preferential neurotoxic effect on the frontostriatal systems that contributes to both emotion dysregulation and neurocognitive impairment [21]. For instance, MA addicts showed impaired performance on tests of cognitive flexibility, which measures the ability to modify behavior when presented with new information or changing outcomes. These deficits may impair MA addicts from altering their habitual drug abuse behavior, leading to an inability to initiate abstinence or resist relapse [22]. Cellular mechanism of this MA impairment has been associated with long-term downregulation of dopamine transporters, suggesting that there are structural changes in some of the dopamine nerve terminals [23]. Other findings suggest that MA use causes changes in the metabolism of the insula and striatum [24]. In a study in humans, MA-dependent participants had significantly lower results than control participants on memory tasks, including prospective memory and visual memory [25]. Accordingly, studies in young adult MA abusers have shown impaired verbal ability, deficits in psychomotor processing [26], reasoning deficits reflecting problematic decision-making abilities as well as retrospective memory task impairment [27].

The evidences pointed that acute administration of MA improves cognitive functions, while chronic consumption of MA deteriorates them.

2.3. Cocaine

Cocaine has long been one of the most common recreational stimulants, especially for adolescents. A recent estimate indicates that half a million of United States habitants use this drug weekly; in this sense, cocaine addiction represents a substantial burden for societies worldwide, linked to adverse outcomes such as violence, suicide and disability, as well as high rates of chronic relapse [28]. In the brain, crack cocaine use has been shown to cause toxic effects, particularly in the prefrontal cortex. These abnormalities are associated with neuropsychological impairments.

Abundant evidence has shown that cocaine withdrawal induces memory decline after its chronic use. It has been reported that chronic cocaine users showed significant harm on verbal memory and fluency as well as deficits in cognitive flexibility, but not in spatial memory, after acute withdrawal. Further, Briand and colleagues observed that object recognition was disturbed after withdrawal from chronic exposure to cocaine by an object recognition task in 2-week abstinent rats [29]. Several reports have shown that the insular and prefrontal cortices, involved in cognitive control, show reduced activity on selective attention and inhibitory
control tasks in cocaine addicts [30]. These brain areas may be involved in the maintenance and relapse of drug use [31]. Individuals with cocaine abuse and dependence show higher insula, frontal and/or striatum activation in response to cocaine-related cues, reflecting heightened attention in response to this drug [32, 33]. Furthermore, imaging data have revealed that gray matter volume loss over time is twice as fast among cocaine addicts as in healthy individuals. Given that gray matter volume in prefrontal cortex has been related to working memory performance, these findings are in keeping with the idea that long-term cocaine use may cause sustained deleterious effect on working memory.

3. Depressant drugs

Adolescence is the critical period for initiation of alcoholic beverage consumption. Epidemiologic studies reveal that alcohol use is remarkably common among teenagers, with increasing rates of alcohol abuse in the US including heavy episodic drinking [33]. After alcohol and tobacco, marijuana is the social drug most frequently consumed by this cohort. Additionally, a high percentage of alcohol abusers also consume marijuana [34]. Several studies have shown that both alcohol and marijuana tend to alter the structure and function of the brain and are associated with impaired decision-making, memory and impulsivity in young adults and adolescents (Table 1).

3.1. Ethanol

Evidence shows a direct correlation between early onset of alcohol intake and alcohol-related problems in adulthood, suggesting that adolescent exposure to the reinforcing properties of this drug increases the probability of its abuse later [35]. However, as for other addictive substances, the effect of exposure to alcohol depends to a great extent on how much and for how long it is consumed.

Acute alcohol intake has a biphasic effect on brain activity, causing excitation and euphoria at low blood concentration and depression as it increases [36]. However, regarding cognitive functions, experimental data have been inconsistent using a variety of cognitive tests. Thus, low or moderate doses of alcohol, relative to placebo, produced facilitation [37, 38], deficits [39] or no change [40] in memory performance at subtoxic amounts (<65 mg/dl). Moreover, it apparently does not produce adverse effects and may even slightly improve working memory in nonproblem drinkers, regardless of sex [41]. However, as the dose of alcohol increases, confusion, loss of awareness and selective attention begin to occur, significantly diminishing the execution of working memory and its long-term consolidation. The effect of alcohol on long-term memory formation is much greater than its impact on the capacity to remember previously consolidated memories or to retrieve short-term memory. It is well known that if subjects are asked to repeat newly acquired information following short delays (seconds) after its presentation while intoxicated, they often do fine [42]. Likewise, they are able to retrieve information acquired before acute intoxication. On the contrary, subjects perform very poorly using delays longer than 20 min, particularly if they are distracted between the stimulus presentation and testing [43].
As studies indicate that the extent of alcohol-induced memory deficits increases with the dose but maintains the same pattern (i.e., greater difficulty at forming new long-term memories than recalling the existing ones), it appears that this drug mostly affects memory consolidation.

Unfortunately, during adolescent life, repeated intoxication with high doses of alcohol becomes more frequent and memory impairments are more profound, commonly resulting in blackouts, that is, a complete incapability to remember all or part of a drinking event [44]. Heavy alcohol drinking associated with blackouts [45] does not necessarily involve loss of consciousness, but rather a failure to transfer information from short- to long-term memory [46]. Individuals with a history of blackouts show episodic memory impairments while intoxicated [47], particularly at retrieving the spatiotemporal context of events [48]. Moreover, long-term (3 years) heavy alcohol intake in adolescents between 15 and 19 years of age induced memory deficits [49] as well as volume reduction in subcortical and temporal regions [50].

The mechanisms underlying alcohol-induced memory disruption are still elusive. Throughout several decades, it was supposed that alcohol produces a nonspecific general depression of brain activity. Later, research led to assumption that alcohol depressed the activity of neurons by altering the fluidity of the neuronal membrane and consequently the activity of proteins, including ion channels that might, in turn, produce synaptic dysfunctions [51].

It was not until recently that new pharmacological information regarding the effects of alcohol on neural cells revealed that this drug has actually very selective effects on various neurotransmitter systems, both excitatory, e.g., glutamatergic and cholinergic, and inhibitory, such as GABAergic, glycineergic and serotonergic among others. Alcohol could alter the activity of specific receptor subtypes as well [52]. All these neurotransmission mechanisms have a deep impact on cognitive functions. Paradoxically, repeated alcohol exposure might promote the formation of a particular drug-reward–associated implicit memory that could underlay its addiction [53].

The main risk of alcohol ingestion early in life is that the adolescent brain is still in a maturation period and drug intoxication greatly affects its development and the individual’s future life.

### 3.2. Cannabis

Recently, endocannabinoids, endogenous ligands that bind to and activate the same receptors as 9-delta-tetrahydrocannabinol (THC), the psychoactive component of cannabis, were found to play an important role in the diminution of gray matter [3]. Cannabis is the third most prevalent drug of abuse among teenagers, behind alcohol and tobacco [54]. Many studies in humans have shown that chronic cannabis consumption, especially when initiated early in life, correlates with a range of cognitive impairments in adulthood, including learning and memory deficits. Meanwhile, the evidence remained equivocal, partly due to the myriad of confounding factors, characteristic of human studies, as well as different methodology employed by the distinct studies, some unveiling clear effects, while others finding marginal or no effects [55]. However, in recent years, a clearer picture is emerging, which seems to suggest that teenage cannabis consumption may indeed have long-term detrimental effects on cognitive processes, including memory. The present section surveys the evidence linking adolescent cannabis consumption...
and prevailing memory deficits. We will further discuss the present state of knowledge on such questions as how is it that cannabis consumption can affect memory? Is memory homogeneously affected or are there certain types of memory more impaired? Also, if cannabis intake during adolescence affects brain function in the long-term, are such sequelae reversible?

First, as for the acute effects of marijuana consumption, impaired working memory during the acute phase of cannabis intoxication has been observed in several studies [55, 56]. For instance, randomized clinical trials with dronabinol, a synthetic derivate of THC, revealed impaired verbal fluency, working memory and executive functions in healthy subjects during and in the hours following intoxication [57]. On the other hand, other works on healthy subjects found that performance on verbal working memory was left unaffected but that the tasks elicited a higher activation of parahippocampal areas, which may indicate either “neurophysiological inefficiency” or alternate/compensatory neural mechanisms in these subjects [58]. This is consistent with another fMRI study that was conducted on otherwise healthy adults that were current marijuana users and that showed hyperactivation during a verbal working memory challenge, which the authors suggest may be related to suboptimal efficiency during cognitive challenge in this group [59]. Finally, another study by the same group showed that the frequency of cannabis use is positively correlated to blood oxygenation level–dependent signal in the left parahippocampal gyrus during a visual associative memory task, regardless of the age of onset (early vs. late adolescence) [60].

But beyond the acute intoxication phase, one obvious question is whether cannabis consumption produces long-term sequelae on cognition. Working memory performance appears to be especially sensitive to cannabis consumption in the early teenage years (before the age of 16–17). Testing 122 long-term heavy cannabis users on a corroborated 28-day abstinence period and 87 control subjects, Pope and collaborators showed that although adult-onset cannabis users hardly differed from controls, those that started before the age of 17 were impaired in a series of cognitive tests, most especially in verbal memory [61]. Further research has shown that the observed cannabis-induced deficits may prevail even after 6 weeks of discontinuation; although after 3 months of complete discontinuation, no difference was observed between previous heavy users and controls [62]. However, a more recent study in adolescents 18–20 years old with a history of chronic, heavy cannabis use, while performance in a verbal memory test was comparable to that of age-matched controls, a significant bilateral atrophy was observed, even after 6 months of supervised drug abstinence [63]. The putative detrimental effects of cannabis use appear to be dose-dependent. For example, performance in the Rey Auditory Verbal Learning Test correlated negatively with the number of years of cannabis misuse [64].

However, these results did not allow to determine whether cannabis had long-term detrimental effects on the cognitive abilities and brain functioning of these youths once they reached adulthood or whether a preexisting set of slight cognitive deficiencies such as lower verbal memory somewhat predisposed these youths to maladaptive behaviors including early-onset cannabis consumption. More to the point, as the authors pointed out, even if the toxic effects of cannabis were the culprit, it was impossible to determine in the light of these results, whether the observed differences were due to long-term effects of cannabis on these subjects or more short-term effects during adolescence that made them perform poorly at school and therefore made them less prone to develop these cognitive skills through adulthood.
In this regard, a recent widely reaching analysis from the Cannabis Cohorts Research Consortium using data from three distinct longitudinal studies started to shed light on this issue [57]. The study found that young adults that were cannabis users as teenagers were more likely to experience adverse outcomes as diverse as cannabis addiction, suicide attempt and high-school dropout. Importantly, the authors report that controlling for the potential confounding factors present, both before and during adolescence and spanning individual, parental and peer factors, failed to abolish most of the associations observed. Along with the fact that they also observed a dose-response relation, heavy users having the poorest outcomes as adults, the findings support the hypothesis that teenage marijuana consumption has long-term detrimental effects on cognition, memory and general well-being. Finally, preclinical research brought further support for a causal relationship between teenage cannabis consumption and adult cognitive impairments; chronic consumption of cannabis in rats during adolescence, but not adulthood, impaired spatial working memory when tested as adults [65, 66].

4. Prescription drugs

According to the Anxiety and Depression Association of America, mental disorders are common among children in the United States. Anxiety and major depression disorders are usually diagnosed in children between 8 and 15 years of age (National Health and Nutrition Examination Survey). The treatment of mental disorders in children and adolescents depends on the impairment degree. However, these treatments usually include drugs that affect cognitive functions. On the other hand, during childhood and adolescence, sports activities, especially at college levels, are frequently a cause of painful injuries that requires acute or chronic treatment of anti-inflammatory and/or analgesic drugs. All these treatments that are administered to school students could have an impact on cognitive functions and therefore on academic achievement. In this section, we will discuss the effects of nonsteroidal anti-inflammatory, anxiolytic and antidepressant drugs (Table 2).

4.1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are therapeutic agents commonly used in clinical practice for their analgesic, anti-inflammatory and antipyretic activity [67]. Although these chemical compounds are structurally different, they all inhibit both isoforms of the cyclooxygenase enzyme, COX-1 and COX-2, an enzyme responsible for inflammation and pain, which is necessary for prostaglandins and prostanoids synthesis [68]. Normally, COX-2 is expressed in dendritic spines of hippocampal and cortex neurons and has been implicated in synaptic modification, because its expression increases during long-term potentiation [69]. Moreover, astrocytes express prostaglandin E2 receptors (EP) and prostaglandin E2 (PGE2), which regulate membrane excitability, synaptic transmission and synaptic plasticity implicated in learning and memory processes [70]. Also, the administration of misoprostol, an agonist of PGE2 receptors, ameliorates the long-term deficits observed in Huntington disease R6/1 mice by increasing the branching in hippocampal neurons and stimulating the synthesis of brain-derived neurotrophic factor (BDNF) [71].
Furthermore, subchronic administration of acetylsalicylic and ascorbic acids increases expression of receptors related with cognitive function such as learning and memory, while chronic treatment of acetylsalicylic acid lessens the spatial memory impairment observed in an experimental model of Alzheimer’s disease [72]. Several reports indicate that celecoxib, a selective COX-2 inhibitor, reduces oxidative stress in a model of hypoxia reoxygenation, reducing the activation of microglia and astrocytes in the neonatal rat brain and improving cognitive function, suggesting that celecoxib may have neuroprotective actions [73]. In addition, multiple exposures to sevoflurane, a model that mimics the neurotoxicity induced by anesthesia, produces an increase in proinflammatory cytokines and deterioration in cognitive function in young mice, effects that were attenuated by the administration of ketorolac [74].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cognitive process</th>
<th>Effect</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription drugs</td>
<td>Spatial memory impairment</td>
<td>Acute administration: Neuroprotection</td>
<td>Rat</td>
<td>[70–75]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subchronic administration: improving cognitive functions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Chronic administration: improve spatial memory impairment</td>
<td>Mouse</td>
<td></td>
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<tr>
<td></td>
<td>Cognitive and emotional alterations</td>
<td>Reestablishment of the deterioration in memory and spatial learning</td>
<td>Human</td>
<td>[78, 81–86]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminish despair and memory impairment</td>
<td>Rat</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Chronic administration: increase cell proliferation in hippocampus</td>
<td>Mouse</td>
<td>[88–90]</td>
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<tr>
<td></td>
<td></td>
<td>Increase of BDNF levels</td>
<td></td>
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<tr>
<td>Memory and learning impairment</td>
<td>Restore cognitive impairment</td>
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<tr>
<td></td>
<td>Improve executive function</td>
<td></td>
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<tr>
<td></td>
<td>Increase spatial memory</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cognition-enhancing drugs</td>
<td>Formation of memories and performing tasks</td>
<td>Enhancing cognitive performance in Alzheimer’s disease patients</td>
<td>Human</td>
<td>[95, 96]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improve cognitive functions as: verbal memory, attention memory, information processing, executive function and memory mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alertness and enhance cognition</td>
<td>Improves attention, memory and executive function in sleep-deprived individuals</td>
<td></td>
<td>Human</td>
<td>[101–105]</td>
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<td></td>
<td>Limited effects in nonsleep deprived individuals</td>
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<td></td>
<td>Mental performance of subjects with low baseline performance</td>
<td></td>
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</tr>
<tr>
<td>Attention deficit/ hyperactivity disorder</td>
<td>Improve cognition processes as: working memory, speed of processing, verbal learning and memory and attention</td>
<td></td>
<td>Human</td>
<td>[107–109, 111]</td>
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<td></td>
<td></td>
<td></td>
<td>Rat</td>
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Table 2. Effects of the prescription and cognition-enhancing drugs in cognitive functions.
4.2. Antidepressant drugs

Major depression is a common mental disorder affecting adolescents in the United States. According to the National Institute of Mental Health, in 2015, an estimated of 3 million adolescents aged 12–17 in the United States had, at least, one major depressive episode. Major depressive disorder is a long-term disabling condition occurring with relapse and recurrences, which could become a chronic condition [76]. Among all the symptoms presented in this psychopathology, memory and attention deficits are considered an important clinical manifestation of major depressive disorder [77]. Furthermore, cognitive and emotional alterations observed in depressive patients have been associated with changes in neuronal activity of prefrontal cortex, cingulate cortex and hippocampus. In major depressive disorder, orbitofrontal, ventromedial and prefrontal cortices are hypoactive, and postmortem evidence indicates histopathological changes in orbitofrontal and prefrontal cortex [78]. Additionally, significant hyperactivity in anterior cingulated cortex, inferior frontal gyrus and occipitoparietal regions has been observed in adolescents with major depressive disorder [79]. Also, a reduction in the volume of the hippocampus was reported, which is related to the severity and the duration of the major depressive disorder [80]. All these alterations were shown to contribute to changes in cognitive and emotional processing in depressive patients. Nevertheless, antidepressant treatment contributed to reestablish mood and cognitive functions. For instance, the chronic administration of deprenyl, a monoamine-oxidase-B inhibitor, reestablished the deterioration in memory and spatial learning and also diminished the lipid peroxidation and the neuronal loss in prefrontal cortex, striatum and hippocampus [81]. Moreover, treatment with desipramine, a norepinephrine reuptake inhibitor, caused reestablished long-term potentiation and diminished despair and memory impairment, through activation of CREB in the hippocampus [82]. Similar effects were observed with fluoxetine (serotonin reuptake inhibitor); rats receiving a chronic treatment of fluoxetine increased cell proliferation and BDNF in hippocampus associated to a memory and learning improvement [83]. These studies suggest that antidepressants revert memory and learning deterioration observed in animal models of depression.

Regarding clinical studies, patients with major depressive disorder showed lower levels of BDNF in plasma, which correlates with memory function deficits; hence, BDNF levels increased after the antidepressant treatment [84]. Nevertheless, the impairment in psychomotor and memory processes observed in depressed treated patients has no significance for clinical purposes [85]. Moreover, some evidence has shown that conventional antidepressant treatment selectively diminishes cognitive dysfunction [86].

The involvement of antidepressant drugs in cognitive functions is not clear; however, animal model studies have shown that synaptic plasticity is increased in neuronal regions involved in mood and memory processing [81–84].
4.3. Anxiolytics

Cognitive impairments have been consistently reported in anxiety disorders. Benzodiazepine, which acts in a specific site of the GABA A receptor, has been, for many years, the first-line therapy for the treatment of anxiety disorders. Although benzodiazepines are attractive for their rapid therapeutic effect, these drugs have undesirable side effects both in the short term (e.g., sedation) and in the long-term (e.g., dependence and memory impairment [87]). Some reports have indicated that GABAergic neurotransmission in the hippocampus is involved in the modulation of learning and memory functions [88]. Also, the administration of an inverse agonist of α5 subtype GABA A receptors (RO4938581) enhances long-term potentiation in hippocampus, restores the cognitive impairment caused by the scopolamine treatment and improves the executive function in monkeys without affecting emotional state [89]. Furthermore, a partial inverse agonist of α5 subtype GABA A receptors increased spatial memory [90]. These studies indicate that GABAergic neurotransmission regulates memory and learning processes, which opens the possibility of designing new selective molecules with clinical utility, not just for treating anxiety disorders, but also for improving cognitive functions.

5. Cognition-enhancing drugs

The search for drugs that improve cognitive functions to treat several diseases, including Alzheimer disease (AD), attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), has derived a wide number of synthetic drugs that, in turn, increase learning, executive functions, or creativity in healthy people. These drugs, also named “smart drugs” or “nootropics,” have different chemical origins and mechanisms and in general have showed little or no effect in improving learning and memory tasks. There is a growth in the consumption of these drugs by adolescents [91, 92], mainly due to academic demands and competitiveness [93]. According to the Federal Substance Abuse and Mental Health Services Administration, every year around 137,000 college students in the US begin to use psychostimulants. Furthermore, consumption of stimulant drugs of abuse increases in key academic dates (Table 2) [94].

Nootropics have focused their targets on modulation of neurotransmission, hormones, transduction systems and neuron metabolism. However, we will focus on legal stimulants commonly used by students to improve academic performance: acetylcholinesterase inhibitors, memantine, modafinil and methylphenidate.

5.1. Antidementia drugs

5.1.1. Acetylcholinesterase inhibitors (AChEIs)

Most of the drugs that are used to enhance cognitive functions, both in patients and in healthy volunteers, work through acetylcholine (ACh) neurotransmission. ACh is a neurotransmitter closely involved in synaptic transmission and also in the formation of memories and performing tasks. Donepezil, rivastigmine or galantamine had good results enhancing cognitive
performance in patients with mild to moderate AD, when compared with placebo [95]. However, diverse studies conducted in healthy volunteers have showed that AChEIs lightly improve verbal memory after semantic processing of words, attention memory, information processing, executive function and memory mood [96].

5.1.2. Memantine

Memantine is a psychostimulant used to treat moderate to severe AD. It acts on the glutamatergic system by antagonizing N-methyl-α-aspartate (NMDA) receptors. This drug has been showed to slightly improve cognitive functions as monotherapy of AD [97]. There are few studies about the cognitive-enhancing capacity of memantine on healthy volunteers. The studies published were tested with acute single dose of memantine, finding that this drug does not increase mental performance significantly [96].

5.2. Modafinil

Modafinil is a psychostimulant indicated in the treatment of narcolepsy, shift work sleep disorder and excessive daytime sleepiness [98]. Since approval by FDA, in 1998, modafinil has been widely used not only to treat wakefulness disorders, but also to increase alertness and enhance cognition. Modafinil exhibits advantages among other psychostimulants, including the lack of unwanted side effects (e.g., tolerance, abuse potential, sleep rebound and locomotor excitability) [99], and, in most countries, it is not a controlled substance; therefore, it can be easily purchased online. Modafinil exerts its actions through an unknown mechanism. Still, it is recognized that modafinil inhibits dopamine and noradrenaline uptake, elevates catecholamine’s levels, therefore raises extracellular serotonin, glutamate, histamine and orexin and reduces GABA’s concentration [100]. Although the effects of modafinil as a wakefulness promoter have been proven [101], its properties as cognitive enhancer are still controversial. In sleep-deprived individuals, modafinil improves attention, memory and executive function [102], while the effects of modafinil in non–sleep-deprived adolescents are limited [103]. Other reports have found that modafinil actually improves several cognitive functions [104]. Interestingly, modafinil has showed to enhance mental performance of subjects with low baseline performance or IQ on several tasks evaluated [105].

5.3. Methylphenidate (MPH)

MPH (Ritalin®) is a psychostimulant approved for the treatment of attention deficit/hyperactivity disorder (ADD/ADHD) [106]. Additionally, MPH is one of the most effective cognitive enhancers used by healthy people [107], because it acts through a mechanism analogous to that of cocaine: increases the levels of the catecholamines, dopamine, norepinephrine and serotonin, by blocking their transport [108]. This drug improves working memory, speed of processing, verbal learning and memory and attention [102]. Nevertheless, MPH effects are not restricted to spatial problems, since it also improves digit span test score [109]. Although MPH has demonstrated to be effective and safe in most of the patients when used in the short term, several side effects have been reported: decrease of appetite, insomnia, headache, irritability, weight loss, sadness, abdominal pain, nausea, somnolence, dizziness, among others.
Several studies have reported that MPH treatment during childhood produces “permanent” changes in behavioral responses to other psychostimulants [110]. Moreover, a recent study made on rats has showed that acute and long-term exposure of adolescents to MHP has important effects on reward-dependent learning and decision [111].

5.4. Considerations about use and misuse of cognition-enhancing drugs

There are some difficulties evaluating the efficacy of smart drugs, mainly due to the heterogeneity of subjects and the differences in the cognitive evaluation methods. Besides, the disparities in the design of the studies have been challenging the evaluation of smart drugs in healthy subjects. However, there are some studies that have used systematic methodology to analyze the literature published on healthy volunteers [96, 97]. According to these reviews, antide mentia drugs, AChEIs and memantine enhance cognitive functions in patients with AD; nevertheless, their effects on healthy volunteers appear to be very poor [107]. Another aspect to consider is the interindividual variability of volunteers, because it could be an important reason that masks the cognitive effect of these drugs.

There are also several ethical considerations about the use of psychostimulants in healthy people. Currently, caffeine is the stimulant most commonly used to get alertness. However, the misuse of MPH and modafinil is growing among students, since these drugs are cheap and easy to obtain illegally.

6. Perspectives

Drug abuse and addiction to legal and illegal substances have become a major challenge in western developed and developing societies. Growing evidence has shown that the onset age of drug consumption is around 15 years. At this age, the central nervous system is still under maturation. Childhood and adolescence are critical stages for neural and social development. Therefore, worldwide increasing prevalence of drug abuse among teenagers will certainly have an effect on scholar performance. All the evidence described in the present review suggests that teenagers that consume drugs risk deleterious consequences in their academic growth, since the neural mechanisms targeted by these drugs may have long-term impacts on cognitive functions. Therefore, prevention initiatives and public health programs must be implemented in schools to protect children and teenagers from escalating drug use.

7. Conclusion

In summary, the evidence regarding the possible long-term detrimental effects of teenage drug consumption on learning and memory adds to the increased risk of developing mental disorders, and therefore it should be included in public health information campaigns that seek to encourage delaying and/or reducing drug consumption at this stage of life. The scientific information obtained from studies such as those described above will be of little use without adequate public policies aimed at alleviating this serious problem.
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