Benefits and Harms of 'Smart Drugs' (Nootropics) in Healthy Individuals

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Abstract

'Smart drugs' (also known as 'nootropics' and 'cognitive enhancers' [CEs]) are being used by healthy subjects (i.e. students and workers) typically to improve memory, attention, learning, executive functions and vigilance, hence the reference to a 'pharmaceutical cognitive doping behaviour'. Whilst the efficacy of known CEs in individuals with memory or learning deficits is well known, their effect on non-impaired brains is still to be fully assessed. This paper aims to provide an overview on the prevalence of use; putative neuroenhancement benefits and possible harms relating to the intake of the most popular CEs (e.g. amphetamine-type stimulants, methylphenidate, donepezil, selegiline, modafinil piracetam, benzodiazepine inverse agonists, and unifiram analogues) in healthy individuals. CEs are generally perceived by the users as effective, with related enthusiastic anecdotal reports. However, their efficacy in healthy individuals is uncertain and any reported improvement temporary. Conversely, since most CEs are stimulants, the related modulation of central noradrenaline, glutamate, and dopamine levels may lead to cardiovascular, neurological and psychopathological complications. Furthermore, CEs' use can be associated with paradoxical short- and long-term cognitive decline; decreased potential for plastic learning; and addictive behaviour. Finally, the non-medical use of any potent psychotropic raises serious ethical and legal issues, with nootropics having the potential to become a major public health concern. Further studies investigating CE-associated social, psychological, and biological outcomes are urgently needed to allow firm conclusions to be drawn on the appropriateness of CE use in healthy individuals.

Key points

- Cognitive enhancers (CEs) are extensively and increasingly being used by healthy active subjects, with student use having been reported in the range of 1.3-33% across studies, with variations depending on country and definition of cognitive doping. However, their efficacy on non-impaired brains is uncertain and any reported improvement is temporary.
- Conversely, since most CEs are stimulants, the modulation of central neurotransmitter pathways could lead to severe complications and can be associated with paradoxical short- and long-term cognitive decline; decreased potential for plastic learning; and addictive behaviour.
- Finally, non-medical use of CEs raises serious ethical and legal issues, and CEs have the potential to become a major public health concern

1 Introduction

Cognitive enhancement is defined as an "amplification or extension of core capacity of the mind by improving the internal and external information processing systems" [1]. In healthy subjects it typically aims at improving memory, attention, learning, executive functions or alertness [1–3]. However, within the cognitive enhancement domain, there is a distinction between different constructs such as *processing speed* (e.g. referring to cognitive processing assessments that require rapid performance of tasks that range from very simple to complex) and *executive functioning* (e.g. those mental processes that enable subjects to plan, focus attention, and carry out multiple tasks successfully; see also Fan et al. [4]).
Pharmacological influence on processing speed does not necessarily associate, however, with levels of executive function improvement [5, 6]. Pharmacological enhancers, here referred to as 'smart drugs', 'nootropics' [7], or cognitive enhancers (CEs), are especially of interest to students and workers to increase concentration, motivation, accuracy, productivity, alertness, creativity and different aspects of performance e.g. intellectual [8].
Global demand for CEs is booming, being projected to reach USD 4.94 billion by 2025 [9]. CEs are made available over-the-counter (OTC) in some countries; on prescription; from the web; from dealers; and through diversion from friends and family [3].
CEs have a long tradition relating to the intake of specific nutritional components and herbs/plants (e.g. caffeine, Bacopa monnieri, Ginseng, Ginkgo biloba; [10, 11]). Nootropic research started at the time of World War II, when stimulants such amphetamine and modafinil were administered to/ingested by both soldiers and pilots to keep them awake/alert and to cope with fatigue-related issues [12]. Prescription CEs are typically used for attention deficit hyperactivity disorder (ADHD), narcolepsy/cataplexy and clinically relevant cognitive deficits [13].

1.1 Classification of cognitive enhancers (CEs)

Froestl et al. [14–16] proposed a classification of 1,705 molecules as nootropic agents, with a high proportion (42%) of them being putative beta-amyloid aggregation inhibitors that were tested for the treatment of dementia and/or molecules whose development was discontinued in Phase II or III clinical trials.
CEs may be classified consistently with the neurotransmitter involved in drug action (i.e. acetylcholinesterase inhibitors [AChEIs]; alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptor activators); the affected transduction mechanisms (e.g. specific phosphodiesterase inhibitors); and the potential to affect the brain blood flow [10, 17]. CEs can constitute neurotransmission substitutes (i.e. cholinergic modulators, biogenic amines and neuropeptides); central nervous system modulators (i.e. psychostimulants, excitatory amino acids [EAA]); and miscellaneous (i.e. nutrients and nutraceuticals, steroids, antioxidant, etc.) [15]. Finally, those CEs whose mechanism of action is unknown are classified either according to their chemical structure (e.g. peptides) or their source (e.g. herbal products) [15].
Those molecules most typically mentioned as being used/misused as CEs include methylphenidate, modafinil, piracetam, and amphetamine salts/mixtures [3]. Corticosteroids, sedative drugs, beta-blockers [18], vitamin E, oestrogens, nonsteroidal anti-inflammatory drugs, AChEIs, memantine, and citicoline [19], have also been mentioned as possessing a nootropic potential. A range of recreational (e.g. cannabis, amphetamines, cocaine, khat [20]), OTC (e.g. super strength caffeine-based tablets; energy drinks), and prescription (e.g. tianeptine [21]; tramadol [22]) drugs are anecdotally ingested as well with the aim of boosting core cognitive functions (for a review, see Sharif et al. [3]).

Napoletano et al. [8] recently classified 142 molecules identified by the e-psychonauts (i.e. subjects who experience intentionally drug-induced altered states of consciousness [23]) as possessing a nootropic potential. These were grouped into 10 categories, with the most popular ones including: plants/herbs/products (29%), prescription drugs (17%; including methylphenidate and modafinil), and psychostimulants (15%; including modafinil derivatives not licensed as prescribed drugs).

The aim of this article is to review available data on the prevalence, putative benefits and possible harms of smart drug use in healthy individuals, with a focus on amphetamine-type stimulants, methylphenidate, donepezil, selegiline, modafinil, piracetam, benzodiazepine inverse agonists, and unifiram analogues.

2 Literature Search Methods

To identify those studies that were here deemed as representative, between September and November 2021 we searched Medline/PubMed since inception, and in all languages available, for studies using the terms 'smart drugs'; ‘CEs’; ‘cognitive enhancers’; ‘amphetamine-type stimulants’; ‘methylphenidate’; ‘donepezil’; ‘selegiline’; ‘modafinil’; ‘piracetam’; ‘benzodiazepine inverse agonists’; ‘unifiram analogues’ AND ‘healthy individuals’. A range of key word strings were used, e.g. drugs AND neuroenhancement in healthy individuals; smart drugs OR neuroenhancers among healthy individuals AND cognition. Inclusion criteria related to both quantitative and qualitative studies relating to CEs’ use among healthy subjects. Conversely, studies focussing on the following: children, preclinical trials, or subjects with medical diagnoses using the selected drugs/substances for medical reasons, were excluded from the review.

3 Prevalence of CEs’ use

Over the last decades, the use of CEs has seen a substantial increase among both healthy high school/university students and professionals wanting to increase either their academic or competitive professional performances [24–27]. Strong need of optimal memory and academic performances, together with peer competition, are behind the occurrence of a ‘pharmaceutical cognitive doping behaviour’ in students [18].

Indeed, a popular UK newspaper reported about the high levels of online sales of modafinil, which was shipped to students from the universities of Cambridge, Oxford and Imperial College London more frequently at the time of the exams [28].

Consistent with this, amphetamine salts and ritalinic acid metabolites were quantified in campus wastewater using solid phase extraction (SPE) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) by Burgard et al. [29]. With respect to baseline low stress weeks, trends showed a possible increase in amphetamine levels during periods of high stress, with the highest increase over baseline (760%) having occurred during finals’ week of the second semester.

The prevalence of student use of CEs ranges from 1.3% to 33% across studies, with variations depending on both country and definition of pharmaceutical cognitive doping [18]. The Global Drug Survey carried out in 2015 and 2017 among healthy university students reported that the previous year’s CEs prescription drug use rates increased over time in all 15 countries for which data were analysed. Main reported sources of supply for CEs included friends (47.8%); the web (11.8%); family members (6.1%); and physicians (3.8%) [30].

Through a systematic review of nootropic intake in university students worldwide, Sharif et al. [3] identified 48 relevant papers; most popular molecules mentioned included methylphenidate, modafinil, amphetamine salt mixtures and caffeine-related compounds. Stimulant CEs’ intake was more prevalent among males than females.

Similar results were described by Nelson et al. [26] who conducted a quantitative anonymous web survey involving 2133 young Australian students. Almost 8% reported use of a prescription drug for CE purposes in the previous year; the nootropic intake was predicted by greater frequency of illicit drug use.
From the US, a meta-analysis estimated that the misuse of CEs among university students was 17% [31]. Similarly, a Belgian survey by Ponnet et al. [32] that recruited 661 students found that some 16% (n = 105) had previously taken stimulants for CE purposes.
Data from UK and Irish universities, relating to a sample of 877 students, found a lifetime prevalence of the use of modafinil, methylphenidate and amphetamine respectively of 6.2%, 5.9% and 2% [33].
Conversely, although in a Japanese undergraduates' sample cognitive enhancement study [34], no student had ever used prescription drugs for this purpose, about half of them had used energy drinks to improve their performance prior to an examination.
Some studies suggested that the propensity to use CEs may be a characteristic of specific course of studies. A Saudi Arabian study focussed on 1,177 medical students; some 29 (2.46%) were found to be using stimulants illicitly [35].
Micoulaud-Franchi et al. [36] submitted a validated questionnaire to a French sample of 206 medicine and pharmacology students; 5.8% reported to have used an illicit pharmaceutical neuroenhancer.
In Brazil, De Oliveira et al. [37] carried out a cross-sectional study focussing on 1,865 respondents; 4.2% had used methylphenidate, modafinil or piracetam in the previous 12 months, and the prevalence among law students reached 14.3%.

4 Evidence for potential benefits of CEs in healthy individuals

4.1 Amphetamine-type stimulants

In Zeeuws et al. [38], 36 male paid volunteers participated in a double-blind, placebo-controlled study in which the number of intermediate free recall tests was altered on purpose. A significant D-amphetamine facilitation effect on recall performance emerged 1 h and 1 day after list learning. No modulation of initial encoding, short-term memory (STM) processes, or even long-term retention enhancement were identified.
Dolder et al. [39] investigated the acute effects of single, high, equimolar doses of D-amphetamine (40 mg) and lisdexamfetamine (100 mg) using a randomised, placebo-controlled, double-blind, cross-over design in 24 healthy volunteers. Both D-amphetamine and lisdexamfetamine intake were associated with increased cognitive performance levels, as measured by the stop-signal task (SST) and Mackworth Clock Test (MCT); lisdexamfetamine increased the Digit Symbol Substitution Test (DSST) processing speed.
Roberts et al. [40] examined cognitive performance in healthy non-sleep-deprived adults following modafinil, methylphenidate, or D-amphetamine vs placebo in three meta-analyses. They used subgroup analysis by cognitive domain: executive functions (i.e. updating, switching, inhibitory control, access to semantic/long term memory), spatial working memory, recall, selective attention, and sustained attention; no effects associated with D-amphetamine on all these domains were identified.
Hoots et al. [41] carried out a secondary analysis of data previously collected from healthy adults who were administered, under controlled conditions and over 3 sessions, either with placebo or D-amphetamine (10 and 20 mg). Interestingly, since its positive subjective/hedonic effects were perceived as beneficial when working, subjects reported more desire to take 20 mg D-amphetamine again to improve their professional performances than for recreation.

Furthermore, Wardle et al. [42] administered either placebo or D-amphetamine (5, 10, and 20 mg) to 200 healthy volunteers, under counterbalanced double-blind conditions and over four sessions. Subjects executive functioning levels were assessed with the help of both the Wisconsin Card Sorting Task (WCST) and the N-Back working memory task. Better processing speed levels, but not executive functioning, were observed after active drug intake.

With the aim of assessing if variation in the catechol-O-methyltransferase (COMT) val(158)met polymorphism would be associated with executive cognition and working memory, Hamidovic et al. [5] assessed lapses in attention and visuo-spatial-motor speed of processing in 161 healthy subjects administered with either placebo or D-amphetamine (10 and 20 mg) in a double-blind, crossover design, study. When not administered with the active drug, val/val and val/met carriers showed greater lapses in attention on the reaction time task than met/met carriers, but the genotypic groups did not differ on the visuo-spatial-motor speed of processing task. With respect to placebo, both D-amphetamine dosages improved lapses in attention and visuo-spatial-motor speed of processing in val/val carriers, whilst the highest dose improved cognitive performance levels in both val/val and val/met carriers, but not in met/met carriers. They concluded that the presence of the val allele would be associated with poorer performance and greater improvement with a stimulant drug.

4.2 Substituted amphetamines

Most CEs mentioned by psychonauts in their fora included the substituted amphetamines phenethylamine-related compounds [8]. Phenethylamines include 3,4-methylenedioxymethamphetamine (MDMA/‘ecstasy’); different from amphetamine-type molecules targeting the dopamine transporter, MDMA targets the serotonin systems [43], Indeed, in humans levels of memory impairment, and not improvement, have been observed [44].

4.3 Methylphenidate

Linssen et al. [45] reviewed the effectiveness of single doses of methylphenidate in improving cognitive performance levels in the healthy population; levels of improvement were mainly observed in the domains of working memory (65% of included studies) and speed of processing (48% of included studies).

Similarly, Batistela et al. [46] tested the effect of acute administration of varying doses of methylphenidate (10-40 mg vs placebo) on attention and both episodic and working memory in 36 students/graduates. No differences in performance were observed during any of the tests, although a dose-dependent (40 mg > placebo) effect on self-reported well-being was identified, suggesting that any possible cognitive performance modifications may in fact be related to drug-related improvements in subjective well-being.

Klinge et al. [47] investigated whether a cognitive test battery focussing on implicit cognition issues (e.g. location priming, contextual cueing, implicit task switching) was sensitive to the effects of 10 mg of methylphenidate vs placebo in 80 healthy volunteers. Whilst no evidence was reported for improved learning in any of the explicit measures, methylphenidate enhanced implicit learning on the location priming task. Conversely, the above-mentioned Roberts et al. [40] study, which examined cognitive performance in healthy adults given modafinil, methylphenidate, or D-amphetamine vs placebo, found an overall effect for methylphenidate ($p=0.0004$) as a result of improvements in recall ($p=0.0002$), sustained attention ($p=0.0004$), and inhibitory control ($p=0.03$).

More recently, from Germany and the Netherlands, Repantis et al. [48] carried out a multicentre, three-arm trial involving 48 male healthy volunteers comparing caffeine, methylphenidate, and modafinil with placebo; those given methylphenidate showed positive

effects on self-reported fatigue as well as on declarative memory 24 hours after learning. The few observed significant positive effects of the tested stimulants were, however, reported to be domain-specific and of rather low magnitude.

4.4 Donepezil

Donepezil hydrochloride is a piperidine derivative and a centrally acting, rapid, reversible inhibitor of acetylcholinesterase, thus increasing the availability of acetylcholine at the synapses [49]. Consistent with this, the molecule is approved in a range of countries for use in mild, moderate, and severe Alzheimer's disease (AD).

Although expectations about the clinical potential of donepezil may exceed its actual effects [48], according to Wade et al. [13], the molecule has been identified as a healthy subject 'smart drug' following the findings of a small study carried out in healthy aircraft pilots (30–70 years old), where it was found to be associated with better levels of retention of training for complex aviation tasks [50].

Donepezil was then compared with both placebo and no treatment in a double-blind, carry-over, study involving 27 healthy adults [51] administered over time with a cognitive test battery. Whilst no on-drug improvement in performance was identified at day 28, compared to the pooled control group on day 21, donepezil subjects performed significantly worse on some tests of speed, attention and memory ($p < 0.05$).

The opposite was observed by Ginani et al. [52] who performed a randomised controlled trial using donepezil 5-7.5 mg vs placebo in 42 young healthy male participants. They found that donepezil improved sustained attention, reaction times, dual-task performance and the executive component of digit span; indeed, these executive tasks' positive effects were not in correlation with the cholinergic system-regulated arousal/visuomotor/vigilance measures. Putative beneficial effects for donepezil would not, however, appear before peak-plasma concentrations (Tmax) are reached [53]. Since functional magnetic resonance imaging (fMRI) activation pattern modifications may serve as a sensitive metric, Balsters et al. [54] used a combination of electro-encephalogram (EEG) and simultaneous EEG/fMRI to examine the effects of 5 mg donepezil daily vs placebo on paired associates learning cognition at 6 hours, 2 and 4 weeks follow-up in healthy older participants. However, only significant negative effects of donepezil were identified.

4.5 Selegiline/l-deprenyl

(-)Deprenyl (selegiline) is metabolised to L-amphetamine and L-methamphetamine, with these compounds likely to present with a range of qualitatively different actions than their D-isomer counterparts on EEG and cognitive functioning [55]. Selegiline is a selective monoamine oxidase (MAO)-B inhibitor at lower doses; and of MAO-A as well at higher doses; whilst preventing the reuptake of norepinephrine, serotonin, and dopamine in the central nervous system (CNS). Furthermore, selegiline's positive clinical effects may be associated with gene expression to both maintain mitochondrial function and to decrease cytoplasmic oxidative radical levels (hence overall reducing apoptosis [56]), but also with activation of growth factors [57]. It is a US Food and Drug Administration (FDA)-approved molecule as an adjunct treatment in the management of patients with Parkinson's disease and as a treatment of major depressive disorders in adults.

It has been suggested that selegiline may possess potential therapeutic effects on improving the anti-amnesic activity in mice administered with scopolamine [58]. Furthermore, selegiline-related dopaminergic/noradrenergic enhancement may facilitate cognitive recovery after brain injury in rats [59]. When compared against donepezil in patients with AD, both molecules were found comparable in relieving AD symptoms [60].

In contrast, no controlled studies assessing the putative neuroenhancement effects of selegiline in healthy adults were here identified. However, consistent with its stimulant/dopamine enhancer profile [59], 'neurohackers' report that long-term use of 5 mg daily dose of selegiline helps in boosting mood, energy, and libido.

4.6 Modafinil

Modafinil is a non-amphetamine CNS stimulant being prescribed for the treatment of narcolepsy, sleep work shift disorder and obstructive sleep apnoea. Modafinil may provide positive outcomes [61], including cognition, in sleep-deprived subjects.

Although modafinil's pharmacodynamics are somewhat unclear, the binding of modafinil to the dopamine reuptake pump can prevent reuptake of dopamine, resulting in a boost in extracellular dopamine [62]; from this point of view, the molecule may be similar to other recreational stimulants. However, its neurochemical effects, anatomical pattern of brain area activation, and propensity for causing euphoric effects may differ from such molecules [63].

In non-sleep deprived subjects, modafinil's potential as a CE may be limited [64]. The above-mentioned Repantis et al. [48], three-arm (caffeine, methylphenidate, modafinil) trial vs placebo found no significant effect of modafinil in any of the instruments of the cognitive test battery.

In line with this, Fernandez et al. [65] carried out a randomised, double-blind, placebo-controlled, cross-over trial to evaluate the effect of modafinil vs placebo on the cognitive functions of 160 healthy students with the means of the Stroop; Biber Cognitive Estimation (BCET); and digit span tests. Whilst a significant difference favouring modafinil vs placebo was identified in the proportion of Stroop Test correct answers, no differences were found in digit span or BCET tests. It was concluded that the molecule was not associated with neuroenhancement relating to those mental processes that are relevant to studying tasks in healthy, non-sleep deprived, students.

By contrast, Turner et al. [66] conducted a 100-200 mg modafinil vs placebo randomised trial in 60 healthy young males administered with a range of memory- and attention-related tasks. Subjects were more alert, attentive and energetic whilst on drug; this significantly enhanced performance on tests of digit span, visual pattern recognition memory, spatial planning and stop-signal reaction time.

Furthermore, Gilleen et al. [67] carried out a 14-day, 200 mg modafinil vs placebo, randomised controlled trial involving 33 healthy volunteers provided on a daily basis with cognitive training on tasks of new-language learning, working memory and verbal learning. Whilst no enhancement in other areas was observed, modafinil facilitated levels of within-day learning, as opposed to between-day retention.

Battleday and Brem [68] suggested that only about half of modafinil-related studies were associated with better attention, learning, and memory levels. With modafinil, complex assessment-related executive functions' improvement levels may be observed as well [69]. To this respect, a 28-healthy volunteer, modafinil 200 mg vs placebo, randomised controlled cross-over study [70] reported that modafinil significantly improved the Cambridge Neuropsychological Test Automated Battery (CANTAB); the CANTAB Rapid Visual Processing; Intra-Extra Dimensional Set Shifting; the MATRICS Consensus Cognitive Battery (MCCB) scores; and verbal recall accuracy performance levels.

In the Roberts et al. [40] study, the cognitive performance levels associated with modafinil, methylphenidate, or D-amphetamine vs placebo healthy adult intake was assessed in three meta-analyses. An overall effect for modafinil ($p=0.01$) was identified, supported by improved memory updating ($p=0.03$) levels.

4.7 Racetams, including piracetam

The γ-aminobutyric acid (GABA) cyclic derivative piracetam, possibly the first 'nootropic' drug not associated with either sedation or stimulation [7], has long been abused by healthy individuals to enhance performance [71]. Its neuroenhancement effects may be the result of restored neurotransmission [72] and enhanced neuroplasticity [73]. Furthermore, piracetam can act at the AMPA receptor as an allosteric modulator binding in six different positions, thus leading to increased calcium influx, which results in an excitatory action [74]. Recent docking studies have confirmed that racetams, including piracetam and coluracetam, are AMPA receptor agonists [75].

In both AD and age-associated memory impairment, piracetam dosage is in the 2.4-8 g daily range [72]. Michel and Lehmann [76] carried out a double-blind, piracetam (2.4, 4.8 or 9.6 g) vs placebo trial. Six healthy young men were asked to watch single digits presented in a pseudorandom order whilst 42-channel event-related EEG potential maps (ERP) were recorded; the strongest positive effects in terms of information processing were observed after the 4.8 g dosage.

Similarly, Kondakor et al. [77] studied the 47-channel resting EEG complexity of 12 healthy volunteers administered with either 2.4, 4.8, 9.6 g piracetam or placebo. Only the 2.4 dosage affected the spontaneous EEG in volunteers; this was interpreted as increased cooperativity of brain functional processes.

Whilst no controlled studies assessing the putative beneficial neuroenhancement effects of racetams in healthy adults were identified, Corazza et al. [71] carried out a range of exploratory qualitative searches of 227 websites commenting on piracetam as a CE. Most users reported satisfactory improvements in different cognitive functions including learning, memory, concentration, and verbal intelligence. Piracetam, at daily dosages of up to 9.6 g, was often ingested in combination with other recreational psychotropics and supplements. Finally, oxiracetam's therapeutic effects were initially suggested to be both discriminated from placebo and better than piracetam in terms of memory improvement [78].

4.8 Miscellaneous: inverse agonist benzodiazepines and unifiram derivatives

Imidazo[1,5-a][1,2,4]-triazolo[1,5-d][1,4]benzodiazepines, which are GABA-A receptor α5 selective inverse benzodiazepine agonists, have been reported as possessing neuroenhancement properties whilst not being associated with the related anxiety/agitation common with other non-selective inverse agonists such as FG7142 [79].

Out of some 101 designer benzodiazepine compounds, Catalani et al. [75] recently carried out a range of docking/in silico studies and identified a total of 12 molecules, including fluadinazolam, pyclazolam, pynazolam, and tofisopam, showing potential binding levels consistent with being GABA-A receptor α5 selective inverse agonists.

Gualtieri [80] described how, in the 1980s, he had identified two potential, not patent protected, not toxicologically-assessed, CEs (e.g. unifiram [DM 232] and sunifiram [DM 235]), which are now popular on the web. Together with sapunifiram (MN19 [81]), these may constitute novel anti-amnesic compounds structurally related to ampakines [82, 83].

5 Evidence for potential harms of CEs in healthy individuals

The lack of safety data for short-and long-term CE use in healthy individuals is a reason for concern. Whilst the modulation of central noradrenaline, glutamate, and dopamine levels in healthy individuals seeks to enhance CE users' cognitive functions beyond baseline levels, this may well lead to a range of both medical (e.g. cardiovascular; neurological [84–86]), and psychopathological [87] complications, with this being especially true for psycho-biologically vulnerable, but otherwise healthy, individuals [88, 89] (see Table 1).

Since most popular CEs are stimulants, they are associated with tolerance, dependence, and withdrawal with the related glutamate modulation, per se, facilitating the occurrence of addictive behaviour [90].
Conversely, the stimulant-related increased dopaminergic and noradrenergic levels may well be associated with a paradoxical cognitive decline. In fact, the relationship between the prefrontal cortex cognition enhancement and the levels of both dopamine and noradrenaline is an inverted U-curve, with high/very high levels of neurotransmitters' enhancement being associated with poorer cognitive performance [45, 91].
Urban and Gao [92, 93] have also emphasised that the use of CEs such as methylphenidate and modafinil can have short- and long-term impacts on plasticity in the pre-frontal cortex that may affect the potential for plastic learning, and especially so in children and adolescents [91]. It has been suggested that modifying some parameters of an healthy cognitive neural system with a non-medical, irregular, use of CEs may negatively affect and alter the balance of the whole system [86, 94].

5.1 Amphetamine-type stimulants

Since amphetamine-type stimulants are selective noradrenaline/dopamine reuptake inhibitors, they produce euphoria, hallucinations, increased alertness and sexual arousal. This may be associated with loss of appetite, nausea/vomiting, tachycardia, hypertension, flushing, anxiety, headache, dizziness, skin irritation, difficulty urinating and hangover effects (for an overview, see Schifano et al [87]).

5.2 Substituted amphetamines

Conversely, with MDMA-like drugs, enhanced mood, increased energy, openness and perceptual alterations are typically reported, together with a range of serotonergic and sympathomimetic toxicity effects which include tachycardia, hypertension, metabolic acidosis, convulsions, rhabdomyolysis, mydriasis, vomiting, diarrhoea and thrombocytopenia. Acute renal failure and hyperthermia are a reason of particular concern [43]. Finally, De Sousa Fernandes Perna et al. [44] found that memantine did not reverse MDMA-induced memory impairment and mood in their 15 subjects who participated in a double-blind, placebo-controlled, within-subject design.

5.3 Methylphenidate and methylphenidate derivatives and analogues

Regarding methylphenidate, Kis et al. [95] carried out a prospective, randomized controlled trial comparing methylphenidate with placebo over the period of 1 year. Comparing 205 patients who received ≥1 dose of methylphenidate with 209 patients who received placebo, adverse effects occurring significantly more frequently in the stimulant group were decreased appetite (22 vs. 3.8%), dry mouth (15 vs. 4.8%), palpitations (13 vs. 3.3%), gastrointestinal infection (11 vs. 4.8%), agitation (11 vs. 3.3%), restlessness (10 vs. 2.9%), hyperhidrosis, tachycardia, and weight loss (all 6.3 vs. 1.9%).
According to Weiss et al. [96] the most frequent (e.g. >10% of participants) adverse events included decreased appetite (20.1%) and headache (15.0%).
Koren and Korn [97] calculated that the relative risk of methylphenidate causing sudden death/arrhythmia would be 1.46 (95% confidence interval, 1.03-2.07); with an estimated 20 million college/university students in the United States in 2020, these figures suggest an excess of 146 deaths caused by methylphenidate per year considering postsecondary US students only.
A range of novel methylphenidate derivatives are widely discussed online and have recently been anecdotally identified as CEs [8, 98], including: 3,4-dichloromethylphenidate, 4-fluoromethylphenidate, 4-fluoroethylphenidate, 4-methylmethylphenidate,

dexmethylphenidate, ethylphenidate, ethylnaphthidate, methylmorphenate, methylnaphthidate, 3,4-dichloroethylphenidate, isopropylphenidate, propylphenidate, 4-methylmethylphenidate, and N-benzylethylphenidate. Few data are currently available for these molecules, but a number of fatalities/near misses involving some of these analogues have been reported [98]. To date, ethylphenidate has been involved in 28 fatalities, although it was reportedly directly related to the cause of death in only 7 cases; 3,4-dichloroethylphenidate was involved in 1 death [98].

5.4 Donepezil

When used as a nootropic, the anecdotally reported donepezil side effects include diarrhoea, nausea, vomiting, insomnia, muscle cramps and loss of appetite [99].

5.5 Selegiline

Selegiline intake is anecdotally associated with irritability, insomnia, nausea, and stomach upset [99]. Furthermore, selegiline may potentiate the 'highs' of various recreational drugs [100].

5.6 Modafinil and modafinil derivatives and analogues

Regarding modafinil, the most reported adverse effects (less than 10% of users) are headache, nausea, and decreased appetite. Other commonly reported adverse effects include anxiety and insomnia [101].

Kaplan et al. [102] examined the potential risk of cardiovascular (CV) events associated with modafinil. They carried out a retrospective, inception cohort, design of patients who initiated treatment in the US with modafinil between 2006 and 2008; users were matched with nonusers. Endpoints of interest, including myocardial infarction (MI), stroke, CV hospitalizations, and all-cause death, were assessed using incidence rates and Cox proportional hazard ratios (HRs), adjusted for potential confounding factors. No increased risk for MI in the cohorts was observed; the risk of CV hospitalization was overall not different between modafinil users and nonusers. For the sub-category of obstructive sleep apnoea patients with prior stroke, an adjusted HR of 1.96 (95% CI, 1.02 to 3.76) was however observed for stroke among modafinil users compared with nonusers.

Furthermore, although modafinil was initially said to comprise no risk for abuse, there are now indications that modafinil works on the same neurobiological mechanisms as other addictive stimulants [103]. Indeed, Murillo-Rodriguez et al. [104] emphasized both the putative modafinil dependence liability issues and the possible occurrence of a range of modafinil-associated neurobiological functions' changes.

The molecule is widely available for online purchase [105] and it is of interest that a range of modafinil derivatives are actively being discussed on web fora, including: adrafinil, fladrafinil, flmodafinil, and N-methyl-4,4′-difluoro-modafinil [8]. Finally, the modafinil R-enantiomer armodafinil, which is being used to improve wakefulness in patients with excessive sleepiness [106], is currently the subject of an anecdotal debate relating to its properties as a CE [107].

5.7 Racetams and racetam derivatives

Finally, the unwanted side-effects anecdotally reported by piracetam misusers included psychomotor agitation, dysphoria, 'feeling weird', tiredness, dizziness, memory loss, headache, and severe diarrhoea; moreover, several users did not experience any cognitive improvement at all [71]. A range of putatively nootropic racetam derivatives are currently being discussed online, including: aniracetam, coluracetam, fasoracetam, nefiracetam, oxiracetam, phenylpiracetam, and pramiracetam [8].

6 Discussion

In this review, we have provided an up-to-date summary of the evidence of possible benefits and harms for a select list of the most commonly discussed CEs. Increasing levels of interest relating to the use of 'smart drugs' by healthy subjects have recently been reported [108], with most putative cognitive beneficial effects being around achieving better productivity levels. CEs are a wide and diverse group of molecules, differing in pharmacological activity, duration and mode of action, targeted cognitive domain, pharmacodynamic and pharmacokinetic properties, as well as possible short- and long-term side-effects [8].

The effectiveness of a range of medications has been demonstrated in patients with AD [109]. Furthermore, the benefits of stimulant CEs has been confirmed in patients suffering from specific diagnosed conditions, such as ADHD [110], or narcolepsy [111]. Whether CEs improve cognition in healthy individuals is however either quite unclear [26, 112] or minimal at best [40], with any putative improvement being transient, lasting only until the index CE metabolism and elimination is completed [113].

The students who use CEs tend however to perceive them as effective, hence the related positive bias being reported [3, 13]. One could then argue about the role of possible personality issues to better explain some of the students/workers' enthusiasm in ingesting CEs. Indeed, recently abstinent CE users may show higher levels of trait impulsivity and novelty seeking, combined with lower levels of social reward dependence and cognitive empathy, a personality profile being shared with illegal stimulant users [114].

The ethical issues raised by cognitive enhancement have been debated for over a decade [115]. Mohamed and Sahakian [116] pointed out that CE use in healthy people might have some advantages, such as helping reduce disparity in society by mitigating the possible adverse environmental effects (e.g. economic disadvantages) on the brain. According to Sahakian et al. [117], society may need to debate if pharmacological neuroenhancement is acceptable, and for which groups (e.g. military at war; doctors/surgeons doing their shifts). In line with this, Beyer et al. [118] have suggested that if long-term research can prove that the risks are negligible and the outcomes positive, then the use of 'smart' drugs may be philosophically defendable. However, with the paucity of good quality trials carried out in healthy subjects, nootropic-related discussions should here be considered premature and should be addressed carefully so as not to mislead both nootropic users and the general public [119].

Ram et al. [120] assessed the knowledge and attitudes of professionals in New Zealand towards CEs and willingness to use a hypothetical CE. Although the survey response rate was only 34.5% (414/1200), participants strongly disagreed with statements that it was fair or ethical for students to ingest non-prescribed CEs for cognitive enhancement.

Indeed, with all psychostimulants, cognitive enhancement would be obtained with low stimulant doses, whereas high/very high dosages are arguably associated with cognitive deficits, psychomotor agitation, and addiction [45, 94, 120–122]. Hence, the hypothetical need of a 'tailored dose' [123] is being debated, to facilitate a benefit on an individual basis dependent on the domain of cognition in which an improvement is required. Finally, the use of CEs by healthy individuals poses a range of legal issues as well, since a range of stimulant CEs are controlled and/or prescription drugs [124–126]

7 Conclusions

Prevalence of CEs' use in healthy individuals, including students, is significant and likely rising; this may be facilitated by the wide range of psychotropics available and ease of online

access [8, 127–129]. Such use is at odds with the evidence for little to no benefit of CEs for neuroenhancement in healthy subjects, and the significant associated harms [122]. With recent societal (bio)medicalisation and 'pharmacologization' [127], pharmaceutical CEs have the potential to become a major public health concern [115, 121, 130]. Hence, raising awareness levels about CE-related harms in academic settings is essential. Further studies targeting social, psychological, and biological outcomes associated with CEs are needed; in this area of 'cosmetic neurology' [1] even research papers producing null results and/or evidence of task-specific impairments should be published [131] to allow firmer evidence-based decisions to be made on appropriate use of these agents.

Declarations

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Table 1 *Evidence of potential benefits and harms of 'smart drug' use in healthy subjects*

Cognitive enhancer	Efficacy / Effectiveness Study Conclusions	Possible Harms/Safety issues
D-amphetamine	Significant facilitation effect on recall performance emerged 1 h and 1 day after list learning. No modulation of initial encoding, STM processes, or long-term retention enhancement [38] Increase of cognitive performance levels, as measured by the SST and MCT [39] No effect on executive functions (updating, switching, inhibitory control, access to semantic/long term memory), spatial working memory, recall, selective attention, and sustained attention [40] Positive subjective/hedonic effects perceived as beneficial when working with subjects reporting increase desire towards further usage to improve their professional performances [41] Better processing speed levels, but not executive functioning, after active drug intake vs placebo [42] Improved lapses in attention and visuo-spatial-motor speed of processing in val/val carriers, improved cognitive performance levels in both val/val and val/met carriers, but not in met/met carriers. [5]	Euphoria, hallucinations, increased alertness and sexual arousal levels, associated with loss of appetite, nausea/vomiting, tachycardia, hypertension, flushing, anxiety, headache, dizziness, skin irritation, difficulty in urinating and hangover effects [87-89]
Lisdexamfetamine	Increased cognitive performance levels (as measured by SST and /MCT) and increased DSST processing speed [39]	Similar to other amphetamine-type substances; see D-amphetamine [87-89]
3,4-Methylenedioxymethamphetamine	Memory impairment, and not improvement, in humans [44]	Enhanced mood, increased energy, openness and perceptual alterations; serotonergic and sympathomimetic toxicity effects, including hyperthermia, tachycardia, hypertension, metabolic acidosis, convulsions, rhabdomyolysis, mydriasis, vomiting, diarrhoea and thrombocytopenia. Acute renal failure may be observed as well [43] Memantine did not reverse MDMA-induced memory impairment and mood [44]