REPORT 9 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-16)
Increasing Awareness of Nootropic Use
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. This report evaluates the use of nootropics (also called "smart drugs") which are prescription drugs, supplements, or other substances that are claimed to improve cognitive functions of healthy individuals, particularly executive function, memory, learning, or intelligence.

Methods. English-language articles were selected from a search of the PubMed database through April 30, 2016 using the search terms for putative nootropics according to the following format (for example): "methylphenidate" AND "cognition," excluding "Alzheimers" and "ADHD." In some cases, alternate disease exclusions were applied (e.g., "narcolepsy" when searching for modafinil). The Cochrane Controlled Trial register and library of systematic reviews also was searched using specific nootropic candidate names. Additionally, articles were selected from a search of the PubMed and Google Scholar databases using the search terms "nootropic," "smart drug," and "cognitive enhancement." Various internet sites managed by manufacturers and purveyors of nootropic "products and formulations" also were consulted and the Consumer Healthcare Products Association was contacted in search of market information. Additional articles were culled from the reference lists contained in the pertinent articles and other publications.

Results**.** Short term use of prescription stimulants (i.e., methylphenidate and mixed amphetamine salts) and wakefulness-promoting agents such as modafinil is associated with modest improvements on various laboratory measures of cognitive function; effects are more evident in individuals with lower baseline performance. Prescription stimulants are used in an off-label fashion by a subset of high school and college students in an attempt to improve academic performance, and some colleges have implemented policies equating this practice with cheating. More than 100 substances from amino acids to botanical preparations are advertised on websites as having the ability to improve cognitive performance, and many sites offer products containing multiple ingredients. Little is known about the actual efficacy or safety of virtually any of these ingredients, individually or in combination. Additionally, no reliable information is available on the extent of consumer use.

Conclusion. Existing evidence suggests that putative nootropics are used by otherwise healthy individuals in an attempt to pursue a competitive advantage at school or work, to maintain levels of attention and performance when sleep-deprived, and to improve task-related motivation. It is uncertain how laboratory measures of drug-related cognitive effects translate to activities of daily living. Prescription stimulants and wakefulness-promoting agents are commonly used off-label by students and others, and such use is associated with a variety of adverse mental health conditions and patterns of substance misuse. Physicians should avoid prescribing these drugs off-label for this purpose. Only a limited amount of information is available on the patterns of use of nonprescription substances used for cognitive enhancement, and their safety and efficacy have not been systematically examined. Evaluation of these issues is complicated by a multitude of proprietary blends that are available for consumption and the behavior of individuals who choose to create their own combinations.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 9-A-16

Subject: Increasing Awareness of Nootropic Use

Presented by: Louis J. Kraus, MD, Chair

Referred to: Reference Committee E
(Theodore Zanker, MD, Chair)

INTRODUCTION

American Medical Association (AMA) Policy D-100.969, "Increasing Awareness of Nootropic Use," holds that nootropic use may be a potential health problem and that our AMA will research the demand, use, and adverse effects of nootropics used individually and in combination.

The term nootropic was introduced in 1972 by a Romanian psychologist and chemist, Corneliu E. Giurgea, from the Greek words νους (nous) or "mind," and τρέπειν (trepein) meaning to "bend or turn."[1] Nootropics (also called "smart drugs") are prescription drugs, supplements, or other substances that are claimed to improve cognitive functions of healthy individuals, particularly executive function, memory, learning, or intelligence.[1,2] The term "smart pill" was first introduced in the 1960s, referring to a drug that increases the cognitive ability of anyone taking it, whether the user is cognitively impaired or normal. In their best-selling book, *Smart Drugs and Nutrients*, Dean and Morgenthaler (1990) reviewed a large number of synthetic and natural substances that have been used by healthy individuals for the intended purpose of increasing cognitive abilities.[3] Other descriptive terms that have been used by both popular media and academicians include "neuroenhancement," "cognitive enhancement," "pharmacological cognitive enhancement," and "cosmetic neurology," each with variations in their definitions, depending on the source.

Nootropic use has invoked increasing media scrutiny in many countries around the world, with special emphasis placed on the nonmedical use of prescription stimulant drugs by college students. Media portrayals have featured a growing trend in the personal use of nootropics, with less attention devoted to safety or adverse events.[4] The movie "Limitless" and television series based on the same theme have encouraged re-examination of the possibility that pharmacologic enhancement of mental acuity and cognitive function may be a near-term reality. Many studies have been conducted on attempts to improve cognitive function in individuals with cognitive decline, and in those who have suffered traumatic brain injuries or who have other mental or neurological disorders. This report addresses the use of putative nootropics by otherwise normal, healthy individuals with the intention of improving memory, learning or other aspects of cognition.

METHODS

English-language articles were selected from a search of the PubMed database through April 30, 2016 using the search terms for various putative nootropics according to the following format (for example): "methylphenidate" AND "cognition," NOT "Alzheimers" NOT "ADHD." In some

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cases, alternate disease exclusions were applied (e.g., "narcolepsy" when searching for modafinil). The Cochrane Controlled Trial register and library of systematic reviews also were searched using specific nootropic candidate names. Additionally, articles were selected from a search of the PubMed and Google Scholar databases using the search terms "nootropic," "smart drug," and "cognitive enhancement." Various internet sites managed by manufacturers and purveyors of nootropic products and formulations also were consulted and the Consumer Healthcare Products Association was contacted in search of market information. Additional articles were culled from the reference lists contained in the pertinent articles and other publications.

HOW ARE NOOTROPICS EVALUATED?

Testing Protocols

Virtually all of the published research on nootropics has been done in laboratory settings where various aspects of cognitive function have been tested using a wide array of validated psychological paradigms. Executive function is a collection of cognitive processes essential for higher order mental function.[5,6] Two major aspects of executive function are working memory and cognitive control. Executive function is responsible for the maintenance of information in a short-term active state to guide task performance and inhibit irrelevant information or responses, respectively. Related executive abilities (i.e., planning, fluency, and reasoning) also have been the subject of published studies.[5]

Categories of Cognitive Enhancers

Cognition enhancers such as prescription stimulants influence primary psychological states, including arousal and alertness which affect cognitive operations.[6] Some potential enhancers may act directly on cognitive operations (e.g., memory, attention) while others influence neural systems underlying long-term potentiation, which is critical for learning and memory consolidation.[7] Conceptually, a third category affects integrated cognitive operations. Substances that target fast excitatory synaptic transmission mediated by glutamate receptors are of theoretical interest for the latter.[7] Examples include substances activating subtypes of cholinergic nicotinic receptors or those that allosterically modulate glutamate receptors (so-called ampakines).[8,9] Brain imaging in primates has shown that ampakines expand cortical networks activated by a complex task.[10]

PATTERNS OF USE

The nonmedical use of prescription drugs for cognitive enhancement has been extensively investigated (see below). International sales of non-prescription supplements exceed $1 billion annually and are growing.[11] A subset of consumers and Internet-based purveyors appear to be highly engaged, but information on the use of specific products or a systematic analysis of individuals engaged in self-treatment with putative cognition enhancers is not available.

PRIMARY NOOTROPIC DRUGS AND COMPOUNDS OF INTEREST

Prescription Stimulants

Methylphenidate, dexmethylphenidate, and mixed amphetamine salts act in various ways to augment neurotransmission involving dopamine and/or norepinephrine, affecting cortical and subcortical systems that enable people to focus and flexibly deploy attention. They are FDA-approved to treat attention-deficit hyperactivity disorder. Recent systematic reviews have evaluated the putative cognitive effects of these drugs.[12-17] Because of its role in executive function, the

effects of these drugs on working memory have been extensively studied. The evidence concerning the effects of prescription stimulants on working memory is mixed and task-dependent. The preponderance of evidence indicates that effects on "learning" in normal individuals is limited to situations where testing involves delayed recall and recognition, suggesting effects on memory consolidation. Positive effects of prescription stimulants on attention, inhibition, and planning are more evident in subjects with lower than optimal baseline performance. The pattern of evidence also is mixed with respect to the effects of prescription stimulants on overall executive function. Prescription stimulants do not routinely improve more complex cognitive processing in normal individuals, and sometimes their use interferes. Accordingly, the cognitive effects of stimulants appear to be highly variable among individuals, are dose-dependent, and limited or modest at best.

Many adverse events are associated with prescription stimulants including the potential for substance misuse and dependence, exacerbation of other mental health and neurologic disorders including seizures, and elevated cardiovascular risks (i.e., blood pressure, cardiac arrhythmias, peripheral vasculopathies) and rarely sudden death.

Modafinil

Modafinil is a wakefulness promoting agent that is distinct from amphetamine derivatives in terms of its neurochemical effects and behavioral profile; its precise mechanism of action is not well established.[18,19] In addition to its wakefulness-promoting effects, modafinil produces psychoactive and euphoric effects, and some alterations in perception that are typical of central nervous system stimulants in humans. Modafinil is FDA-approved for the treatment of excessive daytime sleepiness in narcolepsy, shift work sleep disorder, and obstructive apnea/hyponea syndrome. Although a substantial portion of the published literature on the effects of modafinil involves sleep-deprived subjects, recent reviews also have evaluated the cognitive effects of modafinil in otherwise healthy subjects.[17-22] The cognitive effects of a related drug, armodafinil (R-modafinil; Neuvigil™), have not been well-studied in healthy individuals. A prodrug of modafinil (adrafinil) was an approved drug in France until 2011 and remains available via Internet-based sites. The cognitive effects of this agent have not been published, but because it is converted to modafinil in the body, its pharmacological profile is reported to resemble that of modafinil.

Modafinil consistently improves attention and vigilance in non-sleep deprived as well as sleep-deprived healthy individuals.[17-20] In particular, experiments have shown improvements in sustained attention and selective attention and motivation in a manner that "may make unappealing tasks more appealing."[23] Such tasks therefore may be undertaken and completed more easily. The effects of modafinil on memory are less clear. Some studies report beneficial effects of modafinil on spatial and numeric working memory.[22] However, a review of 31 randomized controlled studies reported no significant changes in memory.[17] The cognitive effects of modafinil strongly depend on the individual baseline performance. Similar to methylphenidate, modafinil appears to positively affect low-performing individuals to a greater extent than high-performing individuals.

In placebo-controlled clinical trials, the most common adverse reactions ($\geq$ 5%) associated with the use of modafinil were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.[24] Rarely the drug may cause serious skin rashes including Stevens-Johnson syndrome, psychiatric symptoms, and cardiovascular events.

<u>Patterns of Prescription Stimulant Use Among Students</u>. Many surveys have been conducted on the nonmedical use of prescription stimulants by high school and college age students. Evidence supports the view that American high school and college students (and their European counterparts) have embraced the nonmedical use of prescription stimulants, and some information

exists on the demographics of students most likely to use prescription stimulants for cognitive enhancement. The source of these drugs is most commonly diversion from a peer who has a prescription. Among high school seniors, the lifetime prevalence of both medical and nonmedical use of prescription stimulants is 9.5%.[25] Based on large, self-administered, cross-sectional web-based surveys (N >26,000), the past year diversion and nonmedical use of prescription stimulants in college-age students increased from 5.4% in 2003 to 9.3% in 2013.[26] Most nonmedical users take prescription stimulants sporadically, with higher rates of use among Caucasians, fraternity/sorority members, and males, and at institutions with more competitive admissions criteria.[27] In one survey of medical students, 18% had used prescription stimulants at least once, with the first use usually occurring in college; approximately 11% reported use during medical school training.[28]

Increases in the nonmedical use of prescription stimulants are concerning not only because of their potential for misuse, but also their association with other adverse events and behavioral consequences including depression, sleep deprivation, irritability, and headache.[26] Individuals who engage in patterns of nonmedical stimulant use are more likely to smoke, binge drink, use cocaine, and screen positive for substance use disorders.[29] In one study, nonmedical use of prescription stimulants for studying was associated with alcohol and cannabis use disorders, and academic decline.[30] College students who use stimulants for cognitive enhancement also display higher levels of trait impulsivity and novelty seeking, and lower levels of social reward dependence and cognitive empathy.

Motivations for Prescription Stimulant Use. Less sophisticated information is available on the reasons for use, especially for cognitive enhancement. Key national surveys on drug use (e.g., National Survey on Drug Use and Health; Monitoring the Future) do not seek information on the use of stimulants for cognitive enhancement, just "nonmedical" use. Reported motivations for stimulant use among students include increased wakefulness, alertness, energy, and increased motivation; improved concentration; and a perceived ability to better cope with memorizing and study.[27,29] The peak periods of stimulant use are before tests, during certain high demand academic assignments, and during finals week.

OTHER PUTATIVE NOOTROPIC AGENTS

More than 130 (mostly nonprescription) putative nootropic agents are listed or described on various websites promoting their use.[31-33] In addition to prescription stimulants and wakefulness-promoting agents, other primary categories are "racetams," cholinergic derivatives/acetylcholinesterase inhibitors, botanical products sold as dietary supplements, ampakines, and various substances influencing the neurotransmitters dopamine, serotonin, or gamma-aminobutyric acid, as well as certain hormones, metabolic "enhancers," neuroprotective agents, and nutrients. The most common categories of putative nootropic agents across websites are briefly discussed below.

Piracetam and Derivatives

More than 50 years have passed since the discovery of piracetam.[34] Piracetam and several chemical analogues (phenylpiracetam, pramiracetam, aniracetam, oxiracetam, etiracetam, nefiracetam, rolziracetam) are available in other countries or via the Internet. Many of these products are being marketed as dietary supplements. No generally accepted mechanism of action has emerged, but the "racetams" appear to modulate ion flux (e.g., Na^+, Ca^{2+}, K^+) through various membrane channels or modify ion transport mechanisms; antioxidant and neuroprotective features also have been described.[34] Some racetams, in particular aniracetam, exhibit ampakine-like properties (see below). A newer agent marketed as an antiepileptic drug in the United States (levetiracetam) reduces the

activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells. Levetiracetam also binds to a synaptic vesicle protein, SV2A, thought to be involved in the regulation of neurotransmitter release.

Noocept (N-phenylacetyl-L-prolylglycine ethyl ester) is a dipeptide derivative of piracetam promoted and prescribed in Russia and neighboring countries as a nootropic. It is a prodrug for the endogenous peptide cycloprolylglycine. The registered brand name Noopept™ is trademarked by the manufacturer JSC LEKKO Pharmaceuticals. The compound is patented in both the United States and Russia. It is sold as a dietary supplement in the United States and as a prescription medication in other countries. It is sometime grouped with the "racetams" because it shares some similarities. Much of the published literature is not in English and that literature was not evaluated.

The majority of the published literature on the "racetams" has been on their use in animal models or in patients with various conditions including cognitive or memory disorders, epilepsy and seizures, traumatic brain injury, neurodegenerative diseases, stroke/ischemia, and anxiety disorders.[35,36] A Cochrane Review from 2001 concluded evidence was insufficient to support the view that piracetam improves cognitive impairment or dementia.[37] The cognitive effects of the "racetams' have not been studied in a controlled fashion in normal healthy individuals.

Cholinergic Derivatives

The most popular agents in this category include choline, α-glycerophosphatidyl choline, centrophenoxine (meclofenoxate), 5'-cytidine diphosphate choline (citicholine), and acetyl-L-carnitine. These products are being marketed and sold as dietary supplement products in retail stores and on the Internet. These substances have been studied based on the view that boosting cholinergic function improves memory and cognition because loss of cholinergic pathways is predominant in the early stages of Alzheimer's disease. Citicholine is a precursor in the synthesis of phosphatidylcholine, a cell membrane component that may be degraded during cerebral ischemia/hypoxia. Acetyl-L-carnitine has some activity at cholinergic neurons, stabilizes neuronal membranes, and enhances mitochondrial function. Many studies have evaluated the effects of cholinergic agents in animal models of dementia, and they have been used in various disease states associated with cognitive impairment.[38,39] The potential for acute cognitive enhancing effects in normal individuals also has been examined, but only in a limited manner.[38,40-42]

Botanical Products

Major putative botanical nootropics are *Gingko biloba*, *Panax ginseng*, *Bacopa monnieri* (brahimi), and *Centella asiatica* (gotu kola). One systemic review and one meta-analysis of ginko concluded that it is not a cognition enhancer in normal healthy individauls.[43,44] Similarly, a Cochrane review on ginseng concluded that this substance does not enhance cognition in healthy participants.[45] *Bacopa monnieri* is a traditional Ayurvedic herb used to "sharpen intellect and attenuate mental deficits."[46] An analysis of six randomized controlled trials of 12 weeks duration suggested that daily administration of *Bacopa monnieri* may improve free memory recall but no other aspects of cognitive performance.[47] A meta-analysis of randomized controlled trials indicated that chronic treatment with *Bacopa monnieri* improved speed of attention and decision reaction time, but further large scale studies are required to confirm significant cognitive effects.[48] Recent single dose studies of this botanical indicate some modest cognitive effects based on standard cognitive test batteries and multitasking performance measurements.[49,50] Other botanical compounds of interest include *Huperzia serrata*, which contains a substance (Huperzine A) that inhibits acetylcholinesterase, periwinkle extract (vinpocetine) and "sage oil" (*Salvia lavandulifolia*). All of

these botanical substances are readily available for purchase in retail stores or on the Internet. They can be purchased as single substances or as components of complex blends.

Ampakines

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as the AMPA receptor) is a non-NMDA-type ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system. Its name is derived from its ability to be activated by the artificial glutamate analog AMPA. Glutamate is the most common excitatory neurotransmitter in the mammalian central nervous system. Ampakines are currently being investigated as potential treatments for a range of conditions involving mental disability and pathologies such as Alzheimer's disease, Parkinson's disease, schizophrenia, treatment-resistant depression and ADHD. Many synthetic AMPA receptor agonists are available via chemical supply companies. Interest in these compounds is prompted by the role played by NMDA receptors in synaptic plasticity and long term potentiation, a neurobiological mechanism fundamental to long term memory formation. Aniracetam (N-anisoyl-2-pyrrolidinone) is one of the parent compounds in the ampakine class; it is available for purchase in dietary supplement formulations. Sunifiram (1-benzoyl-4-propanoylpiperazine) is another ampakine-like substance available online. None of these compounds has been formally studied for cognitive effects in otherwise healthy patients.

COMBINATIONS

Even though high quality evidence is lacking to establish persistent nootropic effects for most of the substances discussed above, Internet purveyors and discussion boards commonly discuss the concept of “stacking” nootropics for use, either by purchase of pre-formulated combinations or providing instructions on building your own stacks. Users are commonly instructed to select a racetam, choose a choline supplement, and then add a natural or herbal nootropic to the mix. No controlled data are available on the efficacy or safety of this practice, only testimonials and blogs from satisfied customers. The Appendix lists four such formulations and their ingredients. With few exceptions,[51] none of these formulations has been subjected to randomized controlled studies.

ETHICAL CONCERNS

The ethics of pharmacological cognitive enhancement has been extensively debated in the academic literature and by several national ethics advisory bodies including the U.S. President’s Council on Bioethics.[52-54] Some issues include whether the safety profile of nootropics justifies restricting (or permitting) their elective use, and whether individuals could be coerced into using nootropics by explicit/implicit pressures in order to compete at school or the workplace. Additionally, does unequal access to nootropics have implications for distributive justice, and does their use constitute cheating in competitive contexts? Some colleges have established policies that the nonmedical use of prescription stimulants constitutes cheating in the academic environment. A full discussion of the ethical issues is beyond the scope of this report and the attached policy recommendation is based on lack of evidence of safety and efficacy.

GUIDANCE FOR PHYSICIANS ON PRESCRIBING NOOTROPICS

The American Academy of Neurology has developed guidance for responding to requests from adult patients for “neuroenhancement” medications. The guidance denotes the concept that “the medical principles for prescribing medications (to normal adult patients) for neuroenhancement are identical to those for prescribing medications to treat medical conditions.”[55] The adoption of this guidance has been opposed, with some emphasis placed on the fact that off-label use of prescription stimulants for cognitive enhancement is inadvisable for a number of reasons.[56,57] High-

level concerns include meeting regulatory standards for prescribing controlled substances and the high potential for misuse of these substances.[56,57] Limited analysis of physician prescribing of methylphenidate for cognitive enhancement suggests that physicians place greater weight on safety concerns than on "benefits" when considering whether to offer pharmacological cognitive enhancement.[58]

CONCLUSIONS

Existing evidence suggests that putative nootropics are used by otherwise healthy individuals to pursue a competitive advantage at school or work, to maintain levels of attention and performance when sleep-deprived, and to improve task-related motivation. Experimental studies of cognitive effects are based on laboratory evaluations using standardized psychometric measures. It is uncertain how these findings translate to activities of daily living. Prescription stimulants and wakefulness-promoting agents are commonly used off-label by students and others. Such use is associated with a variety of adverse mental health conditions and patterns of substance misuse. Only a limited amount of information is available on the patterns of use of nonprescription substances used for cognitive enhancement, and their safety and efficacy have not been systematically examined. Evaluation of these issues is complicated by availability of a multitude of proprietary blends and by the fact that individuals create their own combinations. The recommendation to oppose the prescribing of stimulants and modafinil for cognitive enhancement is based on the increase in nonmedical use which has occurred over the last decade, the harms attributable to such use, and a need for physicians to comport with the requirements of the Controlled Substances Act which holds that a "prescription for a controlled substance must be issued for a legitimate medical purpose in the usual course of practice."

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted and the remainder of the report filed.

1. That our American Medical Association (AMA): (a) opposes the prescription of controlled substances, including stimulants and wakefulness-promoting agents, for the purpose of cognitive enhancement in otherwise normal, healthy individuals; and (b) discourages the nonmedical use of prescription drugs, including stimulants and wakefulness-promoting agents for cognitive enhancement at all levels of education and in the workplace. (New HOD Policy)

2. That our AMA encourages continued research into the risks and benefits of drugs and other substances for improving function in patients undergoing cognitive decline or who are experiencing cognitive impairment. (New HOD Policy)

3. That our AMA encourages more research into the patterns of use, as well as risks and benefits, of dietary supplements (including herbal remedies) being promoted for cognitive enhancement. (New HOD Policy)

4. That AMA Policy D-100.969, "Increasing Awareness of Nootropic Use" be rescinded. (Rescind HOD Policy)

5. That our AMA urge the Federal Trade Commission to examine advertisements for dietary supplements and herbal remedies that claim cognitive enhancement to ensure that they are truthful and not misleading, and are substantiated. (Directive to Take Action)

Fiscal Note: Less than $500

REFERENCES

1. Lanni C, Lenzken SC, Pascale A, et al. Cognition enhancers between treating and doping the mind. *Pharmacol Res*. 2008;57(3):196-213.

2. Kennedy D. Just treat, or enhance? *Science*. 2004;304:17.

3. Dean W, Morganthaler J. *Smart Drugs & Nutrients: How to Improve Your Memory and Increase Your Intelligence Using the Latest Discoveries in Neuroscience*. January 1, 1991.

4. Aprtiridge BJ, Bell SK, Lucke JC, Yeates S, Hall WD. Smart drugs "as common as coffee": Media hype about neuroenhancement. 2011. *PLoS ONE* 6(11):e28416. doi:101371/journal.pone.0028416.

5. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? *Psychol Bull*. 2011;137(5):717-741. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3591814/pdf/nihms442605.pdf. Accessed April 26, 2016.

6. Logue SF, Gould TJ. The neural and genetic basis of executive function: attention, cognitive flexibility, and response inhibition. *Pharmacol Biochem Behav*. 2014;August:45-54. doi:10.1016/j.pbb.2013.08.007.

7. Lynch G, Palmer LC, Gall CM. The likelihood of cognitive enhancement. *Pharmacol Biochem Behav*. 2011;99(2):116-129.

8. Wezenberg E, Verkes RJ, Ruigt GS, Hulstijn W, Sabbe BG. Acute effects of an ampakine faramator on memory and information processing in healthy elderly subjects. *Neuropsychopharmacology*. 2007;32:1272-83.

9. Loughhead J, Ray R, Wiley E, et al. Effects of the alpha^{4}beta^2 partial agonist varenicline on brain activity and working memory in abstinent smokers. *Biol Psychiatry*. 2010;67:7115-21.

10. Facilitation of task performance and removal of the effects of sleep deprivation by an ampakine (CX717) in nonhuman primates. Porrino LJ, Daunais JB, Rogers GA, Hampson RE, Deadwyler SA. *PLoS Biol*. 2005 Sep;3(9):e299.

11. Chinthapalli K. The billion dollar business of being smart. *BMJ*. 2015;351:4829.

12. Wood S, Sage JR, Shuman T. Psychostimulants and cognition: A continuum of behavioral and cognitive activation. *Pharmacol Rev*. 2013;66:193-221.

13. Ilieva IP, Hook CJ, Farah MJ. Prescription stimulants' effects on health inhibitory control, working memory, and episodic memory: A meta-analysis. *J Cognitiv Neurosci*. 2015;27(6):1069-89.

14. Bagot KS, Kaminery. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. *Addiction*. 2014;109(4):547-57.

15. Linssen AM, Sambeth A, Vuurman EF, Riedel WJ. Cognitive effects of methylphenidate in healthy volunteers: a review of single dose studies. *Int J Neuropsychopharmacol*. 2014;17(6):961-77.

16. Sahakian BJ, Bruhl AB, Cook J, et al. The impact of neuroscience on society: cognitive enhancement in neuropsychiatric disorders and in healthy people. *Phil Trans R Soc B.* 370:20140214. http://dx.doi.org/10.1098/rstb.2014.0214. Accessed April 16, 2016.

17. Repantis D, Schlattmann P, Laaisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. *Pharmacol Res*. 2010 Sep;62(3):187-206.

18. Minzenberg MJ, Carter CS. Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharm*. 2008;33:1477-1502.

19. Rasetti R, Mattay VS, Stankevich B, et al. Modulatory effects of modafinil on neural circuits regulating emotion and cognition. *Neuropsychopharm*. 2010;35:2101-09.

20. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. *Psychopharmacol*. 2013;229(3):415-34.

21. Battleday RM, Brem AK. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. *Eur Neuropsychopharmacol*. 2015;25(11):1865-81.

22. Caviola L, Faber NS. Pills or push-up? Effectiveness and public perception of pharmacological and non-pharmacological cognitive enhancement. *Frontiers in Psychology*. 2015;6:1852. doi: 10.3389/fpsyg.2015.01852.

23. Package insert. Modafinil. https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=modafinil. Accessed May 2, 2016.

24. Muller U, Rowe JB, Rittman T, et al. Effects of modafinil on non-verbal recognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology*. 2013;64:4990-5.

25. McCabe SE, West BT. Medical and nonmedical use of prescription stimulants: results from a national multicohort study. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1272-80.

26. McCabe SE, West BT, Teter CJ, Boyd CJ. Trends in medical use, diversion, and nonmedical use of prescription medication among college student from 2003 to 2013: Connecting the dots. *Addict Behav*. 2014;39(7):1176-82.

27. Weyandt LL, Marraccini ME, Gyda B, et al. Misuse of prescription stimulants among college students: a review of the literature and implications for morphological and cognitive effects on brain functioning. *Exp Clin Pharmacol*. 2013;21(5):385-407.

28. Emanual RM, Frellsen SL, Kashima KJ, et al. Cognitive enhancement drug use among future physicians: Findings from a multi-institutional census of medical students. *J Gen Intern Med*. 2012;28(8):1028-34.

29. Sepulveda DR, Thomas LM, Mccabe SE, Cranford JA, Boyd CJ, Teter CJ. Misuse of prescribed stimulant medication for ADHD and associated patterns of substance use: preliminary analysis among college students. *J Pharm Pract*. 2011;24(6):551-60.

30. Arria AM, Wilcox HC, Caldeiraa KM, et al. Dispelling the myth of "smart drugs": Cannabis and alcohol use problems predict nonmedical use of prescription stimulants for studying. *Addictive Behaviors*. 2013;38(3):1643-50.

31. Mental Health Daily. Mental Health Blog. http://mentalhealthdaily.com/2014/11/26/extensive-list-of-nootropics-130-smart-drugs/. Accessed May 3, 2016.

32. pureNootropic. http://purenootropic.com. Accessed May 3, 2016.

33. Nootriment. http://nootriment.com/samrt-drugs/. Accessed May 3, 2016.

34. Gouliaev AH, Senning A. Piracetam and other structurally related nootropics. *Brain Res Brain Res Rev*. 1994;19:180-222.

35. Winblad B. Piracetam: A review of pharmacological properties and clinical uses. *CNS Drug Reviews*. 2005;11(2):169-82.

36. Malykh AG, Sadaie MR. *Drugs*. 2010;70(3):287-312.

37. Flicker L, Grimley Evans G. Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev*. 2001;(2)CD001011.

38. Leermakers ET, Moreira EM, Kiefte-de Jong JC. Effects of choline on health across the life course: a systematic review. *Nutr Rev*. 2015;73(8):500-22.

39. Gareri P, Castagna A, Cotreneo AM, Putignano S, DeSarro G, Bruni AC. The role of citicoline in cognitive impairment: pharmacological characteristics, possible advantages, and doubts for an old drug with new perspectives. *Clin Intervention Aging*. 2015;10:1421-1429.

40. Bruce SE, Werner KB, Preston BF, Baker LM. Improvements in concentration, working memory and sustained attention following consumption of a natural citicoline-caffeine beverage. *Int J Food Sci Nutr*. 2014;65(8):1003-7.

41. Knott V, Smith D, de la Salle S, et al. CDP-choline: effects of the procholine supplement on sensory gating and executive function in healthy volunteers stratified for low, medium and high P50 suppression. *J Psychopharmacol*. 2014;28(12):1095-108.

42. [No author]. Citicholine. Alternative Medicine Review. 2008;13(1):50-57. http://www.anaturalhealingcenter.com/documents/Thorne/monos/CiticolineMono13-1.pdf. Accessed May 4, 2016.

43. Caner PH, Ernst E. Ginkgo biloba is not a smart drug: an updated systematic review of randomised clinical trials testing the nootropic effects of G. biloba extracts in healthy people. *Hum Psychopharmacol*. 2007;22(5):265-78.

44. Laws KR, Sweetnam H, Kondei TK. Is Ginkgo biloba a cognitive enhancer in healthy individuals? A meta-analysis. *Hum Psychopharmacol*. 2012;27(6):527-33.

45. Geng J, Dong J, Ni H et al. Ginseng for cognition. *Cochrane Database Syst Rev*. 2010;dec 8;(120:CD007769. Doi: 10.1002/14651858.CD007769.pub2

46. Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb *Bacopa monnieri*. *Rejuvenation Res*. 2013;16:313-26.

47. Pase MP, Kean K, Sarris J, Neale C, Scholey AB, Stough C. The cognitive-enhancing effects of *Bacopa monnieri.* A systematic review of randomized controlled human clinical trials. *J Alternative Complem Med.* 2012;18(7)1-6.

48. Kongkeaw C, Dilokthornsakul, Thanarangsarit, Limpeanchob N, Scholfield CN. Meta-analysis of randomized controlled trial on cognitive effects of *Bacopa monnieri* extract. *J Ethnopharmacol*. 2014;151:528-35.

49. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled cross-over study to 320 mg and 640 mg doses of *Bacopa monnieri* (CDRI-08) on multitasking stress reactivity and mood. *Phytother Res*. 2014;28(4):551-9.

50. Downey LA, Kean J, Nemeh F, et al. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of *Bacopa monnieri* (CDRI 08) on sustained cognitive performance. *Phytother Res.* 2013;27(9):1407-13.

51. Solomon TM, Leech J, deBros GB, et al. A randomized, double-blind, placebo controlled, parallel group, efficacy study of alpha BRAIN® administered orally. *Hum Psychopharmacol*. 2016;31(2):135-43.

52. President's Council on Bioethics. *Beyond Therapy*. 2003. Washington D.C: U.S. Government Printing Office.

53. Shaw D. Neuroenhancing public health. *J Med Ethics*. 2014;40(6):389-91.

54. Cakic V. Smart drugs for cognitive enhancement: ethical and pragmatic consideration in the year of cosmetic neurology. *J Med Ethics*. 2009;35(12)738.

55. Larriviere D, Williams MA, Rizzo M, Bonnie RJ on behalf of the AAN Ethics, Law and Humanities Committee. Responding to requests from adult patients for neuroenhancements. Guidance of the Ethics, Law and Humanities Committee. *Neurology*. 2009;73:1406-12.

56. Boot BP, Partridge B, Hall W. Better evidence for safety and efficacy is needed before neurologists prescribe drugs for neuroenhancement to healthy people. *Neurocase.* 2012;18(3):181-4.

57. Drabiak-Syed K. Reining in the pharmacological enhancement train: We should remain vigilant about regulatory standards for prescribing controlled substances. *J Law Med Ethics*. 2011;Summer:272-78.

58. Ponnet K, Wouters E, Van Hal G, Heinman W, Walrave M. Determinants of physicians' prescribing behavior of methylphenidate for cognitive enhancement. *Psychol Health Med*. 2014;19(3):286-95.

APPENDIX

Ingredient list for selected nootropic formulation stacks

Alpha Brain®
Vitamin B6
L-tyrosine
L-theanine
L-leucine
Phosphatidyoline serine
L-alpha glycerylphosphorylcholine,
Bacopa monniera extract
Uncaria tomentosa extract
Avena sativa extract
Huperzia serrata extract
Vinpocetine
Pterostilbene

Neurofuse®
Vitamin D3
Vitamin B6
Vitamin B12
Caffeine anhydrous
L-theanine
Choline bitartrate
Phosphatidyl serine
Alpha-lipoic acid
DMAE bitartrate
Rhodiola rosea extract
Vinpocetine
Huperzine A

OptiMind®
Tyrosine
Caffeine
Phosphatidylserine
Vinpocetine (from periwinkle)
Huperzine A (from *Huperzia*)
Bacoside A (from *Bacopa*)

NeuroEnhance™
Ginko biloba extract
Gingoxine
St. John's Wort extract
L-glutamine hydrochloride
Phosphatidylserine
Bacopa monnieri extract
Dimethylaminoethanol bitartrate
L-acetyl carnitine
Vinpocetine