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NEURO STIMULANTS COGNITIVE ENHANCERS AS NOOTROPICS IN MULTI TASK HECTIC SCHEDULE

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ABSTRACT

Cognitive enhancers are a little-known class of supplements and drugs that can actually increase the brain's performance on key intellectual measurements. These cognitive supplements are also known as smart drugs and are referred to in the scientific community as "Nootropics". Cognitive enhancers supply the brain with higher levels of neurotransmitters and stimulate important receptors to improve memory, learning, reasoning, attention and mood. The result is optimization of certain basic mental functions and higher scores of fluid intelligence. While cognitive enhancers are still viewed as science fiction by most of the general public, there is extensive research from neuroscience and clinical trials that backs up their effectiveness.

KEYWORDS: Cognition, Neuro stimulants, Nootropics, Nutraceuticals, Racetams, DHA, AMPA.

INTRODUCTION

Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience and the senses. It encompasses processes such as knowledge, attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving and decision making, comprehension and production of language, etc. Human cognition is conscious and unconscious, concrete or abstract, as well as intuitive (like **knowledge** of a language) and conceptual (like a **model** of a language). Cognitive processes use existing knowledge and generate new knowledge.

The processes are analyzed from different perspectives within different contexts, notably in the fields of linguistics, anesthesia, neuroscience, psychiatry, psychology, education, philosophy, anthropology, biology, systemics, logic and computer science.

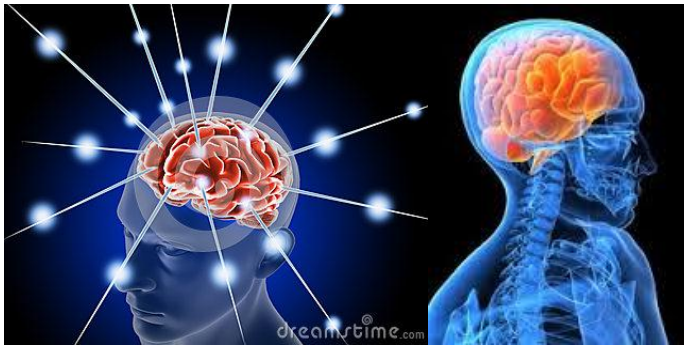


Figure-1: Brain stimulation

These and other different approaches to the analysis of cognition are synthesised in the developing field of cognitive science, a progressively autonomous academic discipline. Within psychology and philosophy, the concept of cognition is closely related to abstract concepts such as mind and intelligence. It encompasses the mental functions, mental processes (thoughts) and states of intelligent entities (humans, collaborative groups, human organizations, highly autonomous machines and artificial intelligences). Thus, the term's usage varies across disciplines; for example, in psychology and cognitive science, "cognition" usually refers to an information processing view of an individual's psychological functions. It is also used in a branch of social psychology called social cognition to explain attitudes, attribution and group dynamics. In cognitive psychology and cognitive engineering, cognition is typically assumed to be information processing in a participant's or operator's mind or brain. Cognition can in some specific and abstract sense also be artificial. The term "cognition" is often incorrectly used to mean "cognitive abilities" or "cognitive skills."[1,2]

Medical school is hard work. There are long hours for weeks on end and we have to keep proving ourselves even after we qualify as doctors. There is a constant pressure to pass exams, engage in extracurricular activities, conduct research projects and publish, to be competitive for future jobs. This is a strain on any student's motivation, concentration and focus. It is perhaps no surprise that many students turn to aids such as coffee, revision courses, tutors, or even special diets. In recent years, some students have been using a number of "cognitive enhancing" drugs off licence. There are claims that these can increase concentration and memory and allow prolonged periods of attention while you are working.

These are the terms for a group of drugs intended for use in medical and psychiatric disorders such as attention deficit hyperactivity disorder, fatigue, shift-work sleep disorder and narcolepsy. Methylphenidate (Ritalin), Adderall (mixed amphetamine salts) and more recently modafinil (Provigil) have gained a reputation among some students as cognitive enhancers.[3,4]

Figure-2: Cognition

But are these drugs effective? Evidence shows that in healthy people they seem to enhance elements of executive function, an umbrella term for high-level cognitive processes including working memory, planning, attention, problem solving and multitasking. Working memory has been shown to be enhanced by methylphenidate, a drug that increases the concentration of dopamine and noradrenaline by preventing their reuptake. Both of these chemicals are involved in a variety of brain functions and are important mediators of concentration. Neuroimaging has shown that methylphenidate reduces the activation of the areas of the brain involved in working memory during novel tasks, implying a reduced working memory load. Interestingly, in this study, the people who did worse on the cognitive task before receiving the drug benefited the most. A similar effect has been observed for the drug bromocriptine. A newer drug, modafinil, has been shown to inhibit inappropriate impulsive responses and improve performance when fatigue sets in. This drug inhibits dopamine and noradrenaline reuptake but also seems to have effects on histamine, orexins and serotonin, which may explain why it promotes wakefulness. The acetylcholinesterase inhibitor donepezil, which is licensed for use in slowing the progression of Alzheimer's disease, has been shown to enhance the performance of pilots after flight simulator training. Acetylcholine might be involved in memory and increasing its concentration seems to benefit patients with Alzheimer's disease and also healthy people. Other drugs are being investigated. Although the benefits of these drugs for treatment of their intended medical conditions are well

documented, we must also consider their side effects. People with attention deficit hyperactivity disorder or narcolepsy may consider it reasonable to endure mild side effects to increase their quality of life overall. But is this justifiable in people who just want to pass their exams?[5,6]

Some of the short-term side effects that are known for the amphetamine based drugs include decreased appetite, dry mouth and sleeping problems. These are well tolerated by most people and are significant in less than 10% of people. The main worry, however, is that there may be unknown effects that become evident only after many years of use. It is still not known how cognitive enhancers affect neural plasticity in the long term. The appetite suppressant fenfluramine seemed a wonder drug when it was released, but it was removed years later when it was discovered that it had serious cardiac side effects. We may also not be able to pick up the more subtle side effects these drugs may have. For example, do the effects they have on the neurotransmitter systems alter our personalities, mood, or libido? Although there is an established side effect profile for patients taking these drugs for their licensed use, there is a paucity of data about healthy people using them as cognitive enhancers. The potential of cognitive enhancers has been exploited in the past and is likely to be again. Amphetamines were widely used in the Second World War by German, British, Japanese and American soldiers to keep awake and alert and soldiers were sometimes legally required to take these drugs for the sake of military performance. It is conceivable that in the future this may be a requirement in other fields of work. A neurosurgeon could benefit from his or her concentration being augmented while performing high risk surgery, for example and long haul pilots might need drugs to help stay focused in long flights. A recent randomized controlled trial showed that sleep deprived doctors benefited from pharmacological enhancement in situations requiring flexible thinking and decision making. Cosmetic surgery, sports medicine and fertility treatment have “enhanced” human abilities and shaped desires greatly in the past decade and perhaps cognitive enhancement will do the same.

The use of cognitive enhancing drugs has direct implications for patient care. What if morbidity and mortality rates of patients are shown to decline when doctors’ cognition is enhanced? Will we be obliged to take them in the future? It may be that the public could demand cognitively enhanced doctors. Some scientists believe that cognitive enhancement is already a reality for many people who are willing to enhance their cognition and that others may be falling behind. A plausible scenario in the future is as follows. A student is preparing

for his or her last exam and feels that to finish learning the curriculum he or she needs to "pull an all-nighter." The student has read about an article about a new drug that promotes "wakefulness" in shift workers and thinks it could be useful during revision. So he or she visits the general practitioner and requests modafinil. How should the doctor respond? Some general practitioners we have spoken to said they would recommend sleep hygiene (that is, methods to alter behavioural and environmental factors that interfere with sleep, such as drinking coffee at night or napping in the daytime) during exams and to avoid the cramming that so many students endure. On the other hand, others might give a one-off prescription. It is clear that opinion is divided and there are no studies describing doctors' views on the subject.[7,8]

The role of the doctor is important in cognitive enhancement because doctors will be the gatekeepers for these drugs if their use is accepted in society. Is it ethical for a general practitioner to prescribe a one-off dose of such drugs? What happens if such visits become a regular occurrence? An article published in Nature by a group of eminent neuroscientists asked for a "responsible use of cognitive enhancers in the healthy." They argue that this is possible if these drugs are properly regulated and an initial step would be for physicians, educators and regulators to develop policies for their use. Other steps include building an information base about their effects, developing guidelines for their use, increasing public understanding and creating appropriate legislation so that they can be used safely. One potential way to reconcile the use of cognitive enhancing drugs comes from philosophy. It could be argued that these drugs do to our minds "internally" what external devices such as the internet and smart phones do every day. For example, your mind can be extended to a notebook that stores information about different medical conditions in the same way another person remembers such information. Similarly, it can be argued that cognitive enhancing drugs do internally what another person's notebook or innate memory might do. Should the use of cognitive enhancers be allowed, or do they create an unfair playing field when it comes to exams and job opportunities? The verdict is still unclear. These drugs are not currently licensed for cognitive enhancement, however and their acquisition and use for such purposes is illegal. It is unclear whether this serves as a deterrent. The long-term pharmacological effects and potential for harm are also unknown. Are these risks worth taking to gain the competitive edge?

Nootropics also called **smart drugs**, **memory enhancers**, **neuro enhancers**, **cognitive enhancers** and **intelligence enhancers**—are drugs, supplements, nutraceuticals and functional foods that improve one or more aspects of mental function. Specific effects can include improvements to working memory, motivation, or attention. The word nootropic was coined 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.[9,10]

Here are only a few drugs that are known to improve some aspect of cognition. Many more are in different stages of development. The most commonly used class of drug is stimulants, such as caffeine. These drugs are purportedly used primarily to treat cognitive or motor function difficulties attributable to disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and ADHD. Some researchers, however, report more widespread use despite concern for further research. Nevertheless, intense marketing may not correlate with efficacy. While scientific studies support the beneficial effects of some compounds, manufacturer's marketing claims for dietary supplements are usually not formally tested and verified by independent entities.

Academic use

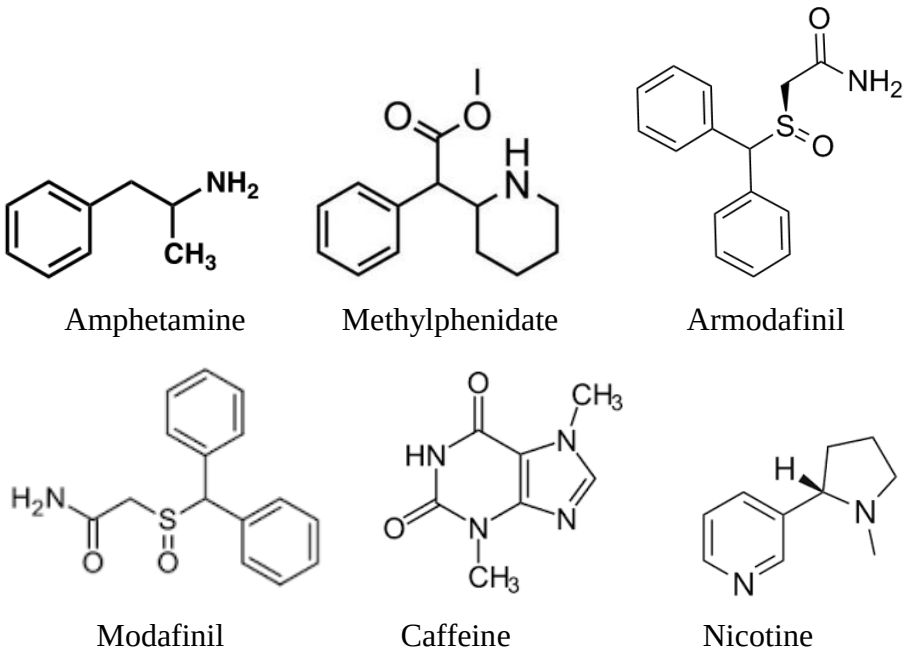
In academia, nootropics have been used to increase productivity, despite their long-term effects lacking conclusive research in healthy individuals. The use of prescription stimulants is especially prevalent among students attending academically competitive colleges. Surveys suggest that 0.7–4.5% of German students have used cognitive enhancers in their lifetime. Stimulants such as dimethylamylamine and methylphenidate are used on college campuses and by younger groups. Based upon studies of self-reported illicit stimulant use, 5–35% of college students use diverted ADHD stimulants, which are primarily used for performance enhancement rather than as recreational drugs.

Several factors positively and negatively influence the use of drugs to increase cognitive performance. Among them are personal characteristics, drug characteristics and characteristics of the social context. The main concern with pharmaceutical drugs is adverse effects and these concerns apply to cognitive-enhancing drugs as well. Long-term safety data is typically unavailable for some types of nootropics (e.g., many non-pharmaceutical cognitive enhancers, newly developed pharmaceuticals and pharmaceuticals with short-term therapeutic use). Racetams—compounds that are structurally related to piracetam—have few serious adverse effects and low toxicity, but there is little evidence that they enhance

cognition in individuals without cognitive impairments. While addiction to stimulants is sometimes identified as a cause for concern, a very large body of research on the therapeutic use of the "more addictive" psychostimulants indicates that addiction is fairly rare in therapeutic doses. On their safety profile, a systematic review from June 2015 asserted, "Evidence indicates that at low, clinically relevant doses, psychostimulants are devoid of the behavioral and neurochemical actions that define this class of drugs and instead act largely as cognitive enhancers."[11,12]

Stimulants

In 2015, systematic medical reviews and meta-analyses of clinical research in humans established consensus that certain stimulants, only when used at low (therapeutic) concentrations, unambiguously enhance cognition in the general population; in particular, the classes of stimulants that demonstrate cognition-enhancing effects in humans act as direct agonists or indirect agonists of dopamine receptor D_1, α-2 adrenoceptor or both receptors in the prefrontal cortex. Relatively high doses of stimulants cause cognitive deficits.[13,14]



Amphetamine Methylphenidate Armodafinil

Modafinil Caffeine Nicotine

Figure-3: Nerve stimulants

Amphetamine (Adderall, dextroamphetamine, and lisdexamfetamine [an inactive prodrug]) – systematic reviews and meta-analyses report that amphetamine benefits a range of aspects of cognitive control (e.g., attentional control, inhibitory control, episodic memory and working memory, among others) in the general population and these effects are especially notable in individuals with ADHD. A 2015 meta-analysis of high quality evidence

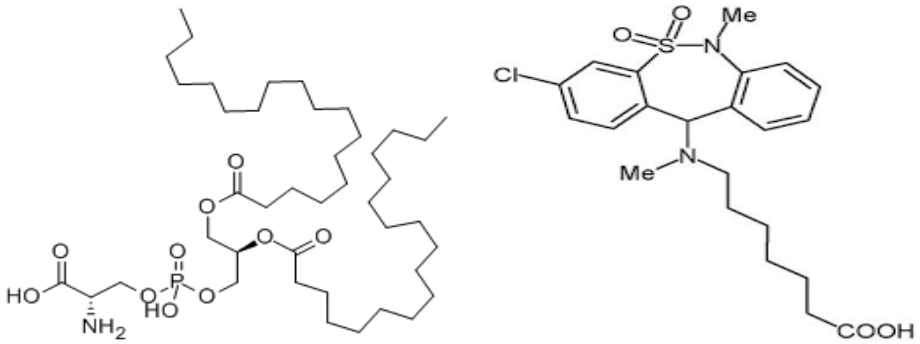
found that therapeutic doses of amphetamine and methylphenidate improve performance on working memory, episodic memory and inhibitory control tests in normal healthy adults. It also improves task saliency (motivation to perform a task) and performance on tedious tasks that require a high degree of effort.

Methylphenidate – a substituted phenethylamine that improves cognitive control (e.g., working memory, episodic memory and inhibitory control) in the general population. It also improves performance on tedious tasks that require a high degree of effort. At above optimal doses, methylphenidate has off target effects that can decrease learning by activating neurons not involved in the task at hand. It has the ability to inhibit processing of irrelevant tasks in the prefrontal cortex and basal ganglia, enhancing task saliency.[15,16]

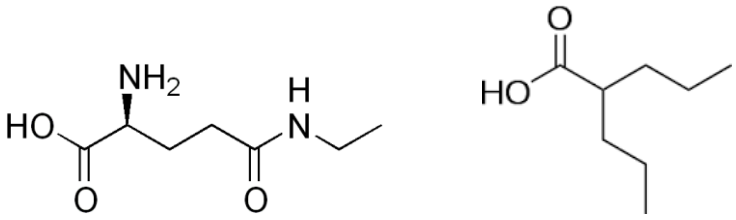
Eugeroics (armodafinil and modafinil) – wakefulness promoting agents; modafinil increases alertness, particularly in sleep deprived individuals and was noted to facilitate reasoning and problem solving in a systematic review. They are clinically prescribed for narcolepsy, shift work sleep disorder and daytime sleepiness remaining after sleep apnea treatments.

Xanthines (caffeine) – shown to increase alertness, performance and, in some studies, memory. Children and adults who consume low doses of caffeine showed increased alertness, yet a higher dose was needed to improve performance. A 2014 systematic review and meta-analysis found that concurrent caffeine and L-theanine use has synergistic psychoactive effects that promote alertness, attention and task switching; these effects are most pronounced during the first hour post-dose.

Nicotine – A meta-analysis of 41 double-blind, placebo-controlled studies concluded that nicotine or smoking had significant positive effects on aspects of fine motor abilities, alerting and orienting attention and episodic and working memory. A 2015 review noted that stimulation of the α4β2 nicotinic receptor is responsible for certain improvements in attentional performance; among the nicotinic receptor subtypes, nicotine has the highest binding affinity at the α4β2 receptor (k_i=1 nM), which is also the biological target that mediates nicotine's addictive properties.[17,18]



Phosphatidylserine Tianeptine



L-theanine Valproic acid

Figure-4: Nootropics

Miscellaneous

Phosphatidylserine (a phospholipid) with DHA and EPA (ω-3 fatty acids) – two Cochrane Collaboration reviews on the use of supplemental ω-3 fatty acids alone (without phosphatidylserine) for ADHD and learning disorders conclude that there is limited evidence of treatment benefits for either disorder.

Tianeptine – enhances several metrics of cognition in animal models. It has also been shown to prevent stress-induced dendritic remodeling in various brain structures and antagonizes alcohol's neurodegenerative effects.

L-theanine – the amino acid L-Theanine, which is able to cross the blood-brain barrier. L-Theanine increases the activity of the inhibitory neurotransmitter GABA, which has anti-anxiety effects. It also increases dopamine and the production of alpha waves in the brain. Studies show that caffeine and L-Theanine can have synergistic effects. The combination of the two is particularly potent at improving brain function. Because of the L-Theanine and the smaller dose of caffeine, green tea can give you a much milder and different kind of "buzz" than coffee. Many people report having more stable energy and being much more productive when they drink green tea, compared to coffee.

Valproic acid – a study has suggested that valproic acid may be able to enhance the cognitive ability of absolute pitch.

Nutraceuticals

Bacopa monnieri ***Panax ginseng***

Salvia officinalis ***Ginkgo biloba***

Figure-5: Nutraceuticals

Bacopa monnieri – A nutraceutical herb. Two review articles concluded that there is some evidence for memory-enhancing effects, but further research is needed.

Panax ginseng – A review by the Cochrane Collaboration concluded that "there is a lack of convincing evidence to show a cognitive enhancing effect of *Panax ginseng* in healthy participants and no high quality evidence about its efficacy in patients with dementia." According to the National Center for Complementary and Integrative Health "Although Asian ginseng has been widely studied for a variety of uses, research results to date do not conclusively support health claims associated with the herb." According

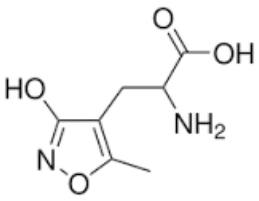
to a review published in the journal "Advances in Nutrition", multiple RCTs in healthy volunteers have indicated increases in accuracy of memory, speed in performing attention tasks and improvement in performing difficult mental arithmetic tasks, as well as reduction in fatigue and improvement in mood.[19]

Salvia officinalis – Although some evidence is suggestive of cognition benefits, the study quality is so poor that no conclusions can be drawn from it.

Ginkgo biloba – Different reviews come to different conclusions. A 2009 Cochrane review found not enough evidence to make conclusions in those with dementia. Another review stated "there is consistent evidence that chronic administration improves selective attention, some executive processes and long-term memory for verbal and non-verbal material."

Racetams

Racetams are a class of drugs that share a pyrrolidone nucleus. Some, such as piracetam, are considered nootropics. Some such as oxiracetam and phenylpiracetam are also stimulants. Others such as levetiracetam and seletracetam are anticonvulsants. Racetams generally show negligible affinity for common central nervous system receptors, but modulation of central neurotransmitters, including acetylcholine and glutamate, has been reported. Although aniracetam and nebracetam show affinity for muscarinic receptors, only nefiracetam demonstrates nanomolar interactions. Modification of membrane-located mechanisms of central signal transduction is another hypothesis. Like some ampakines, some racetams such as piracetam and aniracetam are positive allosteric modulators of the AMPA receptor.



AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Racetams are understood to work by activating glutamate receptors that are co-localized with cholinergic receptors, thus increasing the frequency of activation of the latter. Racetams are posited to enhance memory through interaction with cholinergic and glutamate receptors in the central nervous system. Methylphenylpiracetam is a positive allosteric modulator of the sigma-1 receptor. The racetams are structurally similar compounds, such as pramiracetam, oxiracetam, coluracetam and aniracetam, which are often marketed as

cognitive enhancers and sold over-the-counter. Racetams are often referred to as nootropics, but this property of the drug class is not well established. The racetams have poorly understood mechanisms of action; however, piracetam and aniracetam are known to act as positive allosteric modulators of AMPA receptors and appear to modulate cholinergic systems.[20]

Pramiracetam is a central nervous system stimulant and nootropic agent belonging to the racetam family of drugs. It is marketed by Menarini under the brand name **Pramistar** as a treatment for memory and attention deficits in aging people with neurodegenerative and vascular dementias in Italy and some Eastern European countries. Pramiracetam was discovered by scientists at Parke-Davis, at that time a division of Warner-Lambert, in the late 1970s; patents expired in 1996. Warner-Lambert conducted clinical trials in Alzheimer's Disease and abandoned that indication after Phase II trials showed mixed results; it then began to develop it as an orphan drug as an adjunct to electroconvulsive therapy for major depressive disorder, in part to take advantage of the administrative exclusivity provided by the orphan status. It licensed European rights to Menarini which continued developing it for dementias, and in 1991 it licensed US and other non-European rights to Cambridge Neuroscience, Inc, (CNI) which pursued the ECT indication, as well as a use in restoring cognitive function after stroke or traumatic brain injury. CNI obtained the orphan designation for the ECT use from the FDA in 1991, which was later withdrawn when CNI abandoned the drug. CNI conducted a clinical trial in 4 people who had cognitive problems following a head injury. Trials conducted by or on behalf of Menarini and Warner-Lambert included two small trials conducted in the Ukraine, one in people with cerebrovascular disease and another in people with concussion. Another small trial was performed on Italy, on healthy people in whom amnesia was induced with scopolamine.

Oxiracetam (ISF 2522) is a nootropic drug of the racetam family and very mild stimulant. Several studies suggest that the substance is safe even when high doses are consumed for a long period of time. However, the mechanism of action of the racetam drug family is still a matter of research. Oxiracetam is not approved by Food and Drug Administration for any medical use in the United States. There has been effort put into investigating the possible use of oxiracetam as a medication to attenuate the symptoms of dementia. However, no convincing results were obtained from studies where patients suffering from Alzheimer's dementia or organic solvent abuse were given 800 mg of the drug

orally twice daily. The proven effects of the drug are limited to beneficial effects that lead to higher scores in tests for logical performance, attention, concentration, memory and spatial orientation. These tests were performed on patients with mild to moderate dementia and ADHD and the doses were 800–2400 mg orally twice a day for one to six months. Improvement has also been seen in patients with exogenic post-concussion syndrome, organic brain syndromes and other dementias. According to V. Gallai et al, oxiracetam is more effective than piracetam for this purpose.

Research shows oxiracetam improves hippocampally-mediated learning performance by increasing membrane-bound protein kinase C (PKC). When compared to control mice, oxiracetam-treated DBA mice demonstrated a significant increase in spatial learning performance as determined by the Morris water navigation task. This increase in performance was correlated to an increase in membrane-bound PKC.[21]

Oxiracetam acts also as a positive allosteric modulator of the AMPA receptors. The major metabolites of Oxiracetam include: β-hydroxy-2-pyrrolidone, N-aminoacetyl-GABOB, GABOB (β-hydroxy-GABA) and glycine. Thus its metabolic route is exactly parallel to that of piracetam, aniracetam, phenylpiracetam and all other members of the racetam family, and also pyroglutamic acid.

Coluracetam (INN) (code name **BCI-540**; formerly **MKC-231**) is a nootropic agent of the racetam family. It was initially developed and tested by the Mitsubishi Tanabe Pharma Corporation for Alzheimer's disease. After the drug failed to reach endpoints in its clinical trials it was in-licensed by Brain Cells Inc for investigations into major depressive disorder (MDD), which was preceded by being awarded a "Qualifying Therapeutic Discovery Program Grant" by the state of California. Findings from Phase-IIa clinical trials have suggested that it would be a potential medication for comorbid MDD with generalized anxiety disorder (GAD). Brain Cells Inc is currently out-licensing the drug for this purpose. It may also have potential use in prevention and treatment of ischemic retinopathy and retinal and optic nerve injury. Coluracetam has been shown to reverse the loss of choline acetyl transferase production in the medial septal nucleus of rats exposed to phencyclidine (PCP) and is considered a potential therapeutic drug for schizophrenia. Coluracetam enhances high-affinity choline uptake (HACU), which is the rate-limiting step of acetylcholine (ACh) synthesis. Studies have shown coluracetam to improve learning impairment on a single oral dose given to rats which have been exposed to

cholinergic neurotoxins. Subsequent studies have shown that it may induce long-lasting pro-cognitive effects in cholinergic neurotoxin-treated rats by changing the choline transporter regulation system.[22]

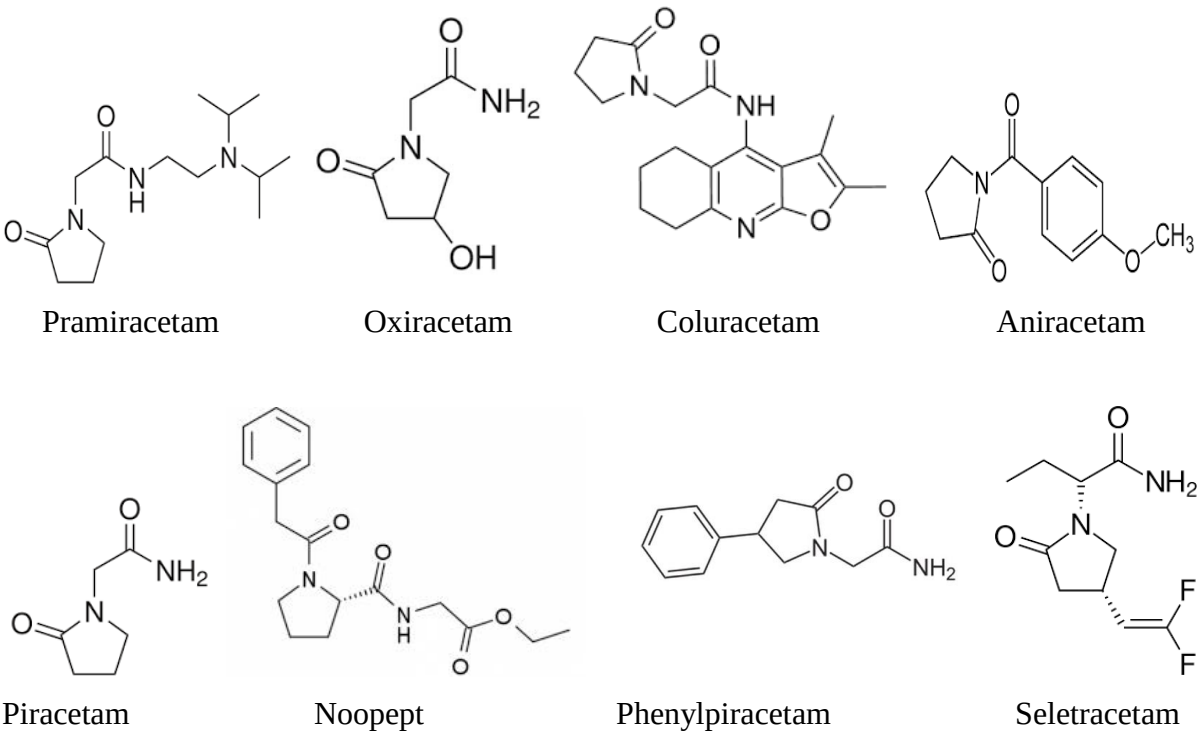


Figure-6: Racetams

Aniracetam (**Draganon**, **Sarpul**, **Ampamet**, **Memodrin**, **Referan**), also known as **N-anisoyl-2-pyrrolidinone**, is an ampakine nootropic of the racetam chemical class purported to be considerably more potent than piracetam. It is lipid-soluble and has possible cognition-enhancing effects. It has been tested in animals extensively, Alzheimer's patients and temporarily impaired healthy subjects. It has shown potential as an anxiolytic in three clinical animal models. It is sold in Europe as a prescription drug, but it is not approved by the Food and Drug Administration for use in the United States. Aniracetam has also been shown to positively modulate the AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as AMPA receptor) and was used as the parent compound to derive a class of drugs known as the ampakines that are being investigated as nootropics and neuroprotective drugs for the treatment of Alzheimer's disease and other neurodegenerative conditions.[23]

After a confirmed test of the anxiolytic efficacy in a mouse model, haloperidol, mecamylamine and ketanserin were applied to determine the pathways aniracetam depends

on to exert its anti-anxiety effects. Haloperidol completely reversed the anxiolytic effects and mecamylamine and ketanserin nearly completely reversed the effects. This shows that aniracetam's anxiolytic mechanism is possibly mediated through D_2, nACh, or 5-HT_{2A} receptor activity. The main metabolite of aniracetam (70-80%), N-anisoyl-GABA, reproduces many of the effects of aniracetam. 2-Pyrrolidinone and p-anisilic acid are additional metabolites of the drug (20-30%), both of which are also active. When ingested orally aniracetam is quickly broken down via first pass hepatic metabolism. The primary metabolites of aniracetam are N-anisoyl-GABA, 2-pyrrolidone and anisic acid. Plasma concentrations are generally in the 5–15μg/L range for aniracetam and 5–15mg/L range for N-anisoyl-GABA, a pharmacologically-active metabolite, during the first few hours after recreational usage of the drug. These two plasma species may be measured by liquid chromatography-mass spectrometry.[24]

Noopept, or N-Phenylacetyl-L-prolylglycine ethyl ester, is a peptide derivative of Piracetam with some exceptional benefits for cognition, memory, mental energy and concentration. This nootropic supplement has really exploded in popularity since 2011 on the strength of peer-review published study results that show Noopept to be 1000 times more potent than Piracetam. Piracetam (sold under many brand names) is a nootropic drug in the racetams group, with chemical name 2-oxo-1-pyrrolidine acetamide. It shares the same 2-oxo-pyrrolidone base structure with pyroglutamic acid. **Piracetam** is a cyclic derivative of GABA. In the United States, it is not approved by the US Food and Drug Administration for any medical use and it is not permitted to be sold as a dietary supplement. In the UK, piracetam is prescribed mainly for myoclonus, but is used off-label for other conditions. Evidence to support its use for many conditions is unclear. The choice of which cognitive enhancer to use is best left to personal preference as there is no such thing as a single best supplement for brainpower. Different individuals will see different effects from the same supplements. One person may find that Noopept is the best for helping them get motivated while another may prefer Pramiracetam. Someone might see the best mood-enhancement effects from Aniracetam while someone else might achieve better results with Piracetam. Which one you use is also dependent on your particular goals and needs. To pick the very best cognitive enhancer for yourself, experience is the most valuable guide. Consider trying Piracetam or one of the weaker Racetams to start with and once you have some familiarity you can consider upgrading to Noopept or Phenylpiracetam. Research into the Racetam category of supplements continues to this day and there are some promising new nootropics

which may soon enter the mainstream. One of the most recently commercialized cognitive enhancers is **Phenylpiracetam** (Phenotropil) – a slightly modified version of Piracetam. This nutraceutical was actually discovered in the 1980's, but only in the past year or two has it been made available through mainstream nootropic providers. It is so exciting to nootropic users because it is said to be 60 times stronger than Piracetam and provides a greater range of benefits. It can give you unprecedented levels of focus and mental drive with great clarity of thought. It is even useful for improving athletic performance, specifically in the areas of stamina and reflex time. Using Phenylpiracetam can promote faster cognition, increase communication between the two hemispheres of your brain and help you experience more creative thought. A dosage of 200 mg is sufficient to experience the benefits of this compound. While Phenylpiracetam is more expensive than the other cognitive enhancement powders listed here, its high potency level is worth it for more experienced nootropic users.[25]

Pramiracetam-One of the downsides of Aniracetam is that it has very low bioavailability and a short half-life. This means you end up taking a larger dosage than you would if it had better absorption into the blood. Pramiracetam corrects some of these problems associated with Aniracetam while offering similar benefits. It is also a fat-soluble analog of Piracetam, but one that is believed to be 30 times more potent and it lasts much longer in the brain. Pramiracetam powder is a memory, learning, mood and energy booster like the other Racetams, but it is highlighted among all of these supplements for its effects on focus and concentration. It may not be the best cognitive enhancement product for everyday use but, it is a well-regarded study drug for those times when you need to be especially productive. Pramiracetam supplements are highly effective at a dosage of around 500 mg taken two or three times a day. The half-life of this smart drug is 5 hours so you may find that two administrations per day is plenty. Remember that as a fat soluble Racetam, it works best on a full stomach or with some lipid source like a fish oil pill. It is considered to be very safe with few known mild side effects and no known dangerous side effects. If you are looking for the best cognitive enhancer for motivation, then Pramiracetam is the perfect choice.

Aniracetam: cognitive enhancers a natural follow-up to Piracetam is Aniracetam – a fat-soluble derivative of this original Racetam which is cited as being 5 times more powerful. The effects of Aniracetam are similar to Piracetam, but with heightened dopamine and serotonin influence. Aniracetam also has greater modulation on the glutamate receptors

which may result in better effects on concentration, motivation and energy. Aniracetam is also considered one of the best nootropics for anxiety relief and treating symptoms of depression. Aniracetam specifically works on the systems of the brain that regulate neuroplasticity and the formation of new memories. This supplement may be able to reduce the rate of receptor desensitization in the hippocampus meaning that it could cause you to be able to remember more details even after a long day of work or studying. Some reviewers say that when taking Aniracetam they are able to recall even the most specific facts after reading a highly technical article. The recommended dosage of Aniracetam is 1,000 to 2,000 mg taken with milk or on a full stomach. Effects will be noticeable very quickly – within 15-20 minutes – but they do not last as long as some other nootropic cognitive enhancers.[26]

Piracetam: Without a doubt, Piracetam is the most popular cognitive enhancement supplement available. It was first discovered in the 1960's by a European pharmaceutical company and it has been examined in thousands of academic studies and trials since then. While there are more powerful compounds on this list of cognitive enhancers, this is the supplement that most people start with and it does offer proven results for improving brainpower. The main effect of Piracetam is on the acetylcholine neurotransmitter and the cholinergic system. Acetylcholine receptors are closely involved with the formation of new memories and the process by which your brain makes new connections. The best dosage for Piracetam is between 1-4grams taken two or three times every day. You can purchase it either in pill format or as a bulk powder, but you will be substantially less if you buy it in powdered format. It is then easy to take this Racetam by mixing it in water or by dosing it sublingually. You will notice that it has a bitter taste so you may want to mix it with juice to mask some of the flavor. For best absorption, Piracetam should be taken on an empty stomach. The results of this cognitive supplement are noticeable within 30-45 minutes and it will last up to three hours after ingestion. It can take some time for it to build up in your system to reach full effectiveness, so you should wait at least two weeks before increasing your dosage.

Seletracetam (UCB 44212) is a pyrrolidone-derived drug of the racetam family that is structurally related to levetiracetam (trade name Keppra). It was under development by UCB Pharmaceuticals as a more potent and effective anticonvulsant drug to replace levetiracetam but its production has been halted. There are two main mechanisms of action for seletracetam. The first is its high-affinity stereospecific binding to synaptic vesicle glycoprotein 2A (SV2A). Seletracetam has shown potent seizure suppression in models of

acquired and genetic epilepsy, and has been well tolerated by various animal models. The second is it's binding to N-type calcium channels and preventing influx of Ca^{2+} during high-voltage activation that is typical of epilepsy. While similar in structure to nootropic drugs, it is not expected to have cognitive enhancing properties. Seletracetam was in Phase II clinical trials under the supervision of the U.S. Food and Drug Administration (FDA) but its production is on hold.[27]

CONCLUSION

What a fun-looking word: nootropics. It refers to any type of compound or food that has the ability to improve your mental abilities, including your memory, ability to focus, motivation or even mood. While the general category most definitely includes smart drugs, neuro-enhancing supplements fit the bill as well. Daily, neuroscientists are acquiring a more nuanced understanding of the brain, the result being many new pharmaceutical drugs which target exact regions of the brain are in the works. The very same knowledge, though, might reveal how particular supplements might do an equally good job of improving brain function over the long haul. Why go for prescription-strength when you can get the same by shopping the vitamin aisle? In that spirit, here's a list of dietary supplements you could investigate for their potential use as a nootropic. Remember: Do your research and ask a doctor's advice before popping any pill, natural or not. More importantly, not all dietary supplements are created equal, with some brands including additives you may not want (or are allergic to), so it's important to vet any unfamiliar manufacturers. Creatine is an old favorite among gym rats, who use it to enhance their sports performance, but over the past decade or so, the supplement's neuro-enhancing abilities have been demonstrated as well. In one placebo-controlled study, researchers tested the hypothesis that 5grams a day for a six-week period would enhance intelligence test scores while also improving memory. They enlisted the help of 45 young adult, vegetarian subjects and found the supplement had a significant positive effect on both working memory and intelligence, particularly with regard to tasks that require speed of processing. Though they tested vegetarians, the researchers would "expect to see a beneficial effect of creatine supplementation on brain performance in most omnivores apart from those who consume very high amounts of meat." Theanine (or more commonly L-theanine) is found in green tea and mushrooms and also sold as a dietary supplement in the United States. In fact, the Food and Drug Administration has granted it GRAS status (generally recognized as safe). According to various scientific studies, theanine has been found to affect the levels of some neurotransmitters, to prevent beta-amyloid-induced brain

dysfunction, and to protect against stroke. L-theanine is even said to improve sleep quality in boys with attention deficit hyperactivity disorder. In terms of potential nootropic uses, several small studies indicate a combination of L-theanine and caffeine can improve cognitive performance, particular in the areas of focus and alertness. Apparently, though, the effects may not be long-lasting. Passionflower is derived from the above ground parts of the plant. Primarily, people take it for its anti-anxiety effects, which have been proven in smaller scientific studies though not yet confirmed in large scale studies. Some other people use it to treat insomnia as well as neuralgia and withdrawal symptoms while coming off opiates or benzodiazepines. In patients undergoing surgery as well as those about to be treated by a dentist, passionflower has been effectively used to reduce apprehension. DHA and ω-3 fatty acid found in fish and seaweed, can improve your memory while protecting against certain psychiatric disorders. Various surveys of people with major depression indicate they have depleted levels of ω-3 fatty acids and one large study found depressive symptoms were significantly higher among infrequent fish consumers. However, no study has ever proven ω-3 fatty acid supplementation effective in relieving major, moderate or even mild depression. That said, some data suggest it is a safe preventive measure and may reduce the risk of progression of certain psychiatric disorders. While one review of scientific studies found that DHA supplements significantly improves cognitive development in infants — though does not improve cognitive performance in children, adults, or the elderly — another review shows it can protect against mild cognitive impairment, dementia, and the risk and progression of Alzheimer's disease in the elderly.

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