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# Cognitive Enhancers- Truth vs. Hype.

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**ABSTRACT**

Cognition is a term referring to the mental processes involved in gaining knowledge and comprehension. It is a higher-level function of the brain and encompasses language, imagination, perception, and planning. Cognitive enhancers are neuro-active substances that elevate individual's cognitive abilities in a meaningful & sustained way. Many groups of drugs have been used as cognitive enhancers or nootropics- be it racetams like piracetam, cholinergics like citicoline, acetylcholinesterase inhibitors like rivastagmine, AMPAkines like memantine or smart drugs like modafinil and methylphenidate. Glutaminergic input activates AMPA receptors resulting in depolarization that opens NMDA receptors of the NR2A subtype. This promotes calcium ion entry into neurons thereby causing membrane potentiation that helps in learning and cognition. Cognitive enhancement can either happen by increasing blood flow to the brain, enhancing neurotransmission, increased neuronal metabolism by stimulation of hormones and enzymes, increased nerve growth factor and improvement of cerebral functions like memory. However, it is difficult to attribute a specific mechanism of action to a particular drug or neurotransmitter. Nootropics have been used for a wide array of conditions ranging from developmental conditions like Attention Deficit Hyperkinetic Disorder (ADHD) to neurodegenerative conditions like Alzheimer's disease and Parkinson's disease. However, in the recent past there has been a sudden surge in the use of these cognitive enhancers in normal, healthy individuals as well. Cognitive enhancers have proved quite an asset when it comes to slowing down the disease progression. However, in the healthy population there is a dearth of literature regarding their long term safety and efficacy. Ethical issues are also a matter of concern.

**Keywords:** memory, nootropics, Alzheimer's disease, glutamine, smart drugs, ADHD

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**What are cognitive enhancers?**

The word cognition comes from the Latin verb cognosco (con 'with' and gnōscō 'know') which implies 'to conceptualize' or 'to recognize'. In the modern era, cognition is a term referring to the mental processes involved in gaining knowledge and comprehension. [1] Knowledge and comprehension, in turn, include an interplay of thinking, knowing, remembering, judging, and problem-solving. [2] Cognition is thus considered a higher-level function of the brain and encompasses language, imagination, perception, and planning. Cognitive processes use existing knowledge to generate new knowledge.

Cognitive enhancers are neuro-active substances that elevate individual's cognitive abilities in a meaningful & sustained way. [3] There is no dearth of evidence regarding the use of caffeine and nicotine to increase alertness and maintain wakefulness amongst human population.Initially these drugs were used with the intent of treating cognitive decline in cases of schizophrenia, depression, dementia or Alzheimer's disease. However, off late these agents have shown to increase mental performance in healthy minds as well. There has been a sudden surge in research for potential substances in this field and various studieshave been conducted and validated in experimental models recently. Along with the sudden surge in popularity of these drugs in the current era, various synonyms like "smart drugs" or "memory enhancing drugs" or "nootropic drugs" (from the Greek words*noos* for mind and *tropein* for toward) have been ascribed to cognitive enhancers.

According to a global drug survey done in 2015, one in 10 "healthy" (no diagnosis of Attention Deficit Hyperkinetic Disorder {ADHD}) study participants (9.8%) had at least once used prescription or illegal stimulants to improve performance at work or while studying. [4] Participants from New Zealand, the Netherlands, and Hungary were the most experienced with use of nootropics (15.2% to 18.2%), while the rate of participants in USA was only slightly above the average (11.6%). [4] Methylphenidate and dexamphetamine were the substances most commonly used cognitive enhancers in this survey.

**Types of cognitive enhancers**

The pharmacological strategies behind cognitive enhancers are diverse and wide-ranging: drugs that inhibit lipid peroxidation or apoptosis, act as glutamate antagonists or Gamma Amino Butyric Acid (GABA) agonists, sodium and calcium channel blockers, and so on. [5-7] There have been a huge bunch of pharmacological agents available in the market under the umbrella labelled cognitive enhancers or nootropics or neuroprotectants. Albeit the various options available, none of these cognitive enhancers have been approved by the Food and Drug Administration (FDA). The various groups of drugs are as follows:

1. **Racetams-**Piracetam, pramiracetam, oxiracetam, aniracetam, nefiracetam
2. **Cholinergics-** Choline, Citicoline, Lecithin, Phosphatidylcholine
3. **Acetylcholinesterase (AChE) inhibitors-**Tacrine, Galantamine, Rivastigmine, Donepezil
4. **AMPAkines-**Memantine, Sunifiram, Unifiram, Ampalex(CX-516)
5. **Smart drugs-**Adarafinil, Modafinil, Armodafinil, Methylphenidate
6. **Dopaminergics-**Rasagiline, Selagiline
7. **Nootropicvitamins-** Vitamin B1 (Thiamine), Vitamin B3 (Niacin), Vitamin B5 (Pantothenic Acid), Vitamin B6 (Pyridoxine), Inositol, Vitamin B12 (Cobalamin)
8. **Neuro-hormones-**Dehydroepiandrosterone (DHEA), Vasopressin, Desmopressin, Melatonin, Pregnenolone

**How do they act?**

Before getting into the mechanisms of action of various cognitive enhancers it becomes imperative to have a brief overview of memory- its components and the process of formation of each component. Mental performance is a sum total of four components: [8]

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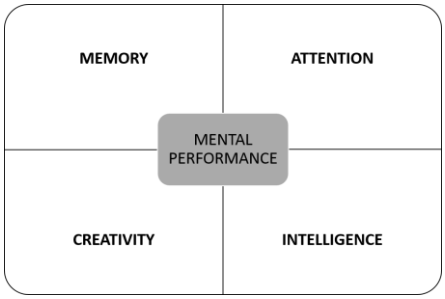


**Figure 1: Factors affecting mental performance of an individual**

Memory formation is one of the key differentiating features between the highly evolved and the lesser evolved organisms. Memory is not a single entity; the acquisition, formation and recall of memories are a set of complex processes involving various neuronal circuits in the brain.[8]Based on the duration, some memories may last for only a few minutes or hours (short term [STM] or working memory) or may last days, months or even a lifetime (long-term memory (LTM)). With respect to the content, memory is classified into implicit memory (also known as procedural or non-declarative memory) and explicit memory. Implicit memory is unconscious and refers to a collection of motor abilities, habits, emotional feelings and sensations. This memory is used in motor skills. Declarative or explicit memory on the other hand deals with facts, ideas and events that have been consciously learnt over a period of time and can be recollected. [8] The process of memory formation seems to proceed through three general stages.

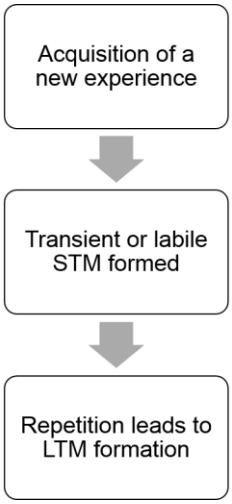


**Figure 2: Process of memory formation**

Another noteworthy point is, there is no single region of brain or no single neurotransmitter implicated in the development of STM OR LTM. Memory formation is mainly attributed to three regions of the brain- hippocampus (responsible for encoding new information), strio- frontal complex (responsible for decision making) and frontal lobe (responsible for archiving and retrieval of memory). *N*-Methyl-d-aspartate (NMDA) glutamate receptor subtype activation,leading to activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor seems to be the central dogma in the formation of STM or LTM. [8] The early phase of LTMlasts only 1–3 h and does not require new protein synthesis in the brain. It involves covalent modifications of pre-existing proteins which strengthens pre-existing connections and converts STM to LTM. [8] The molecular details of the early phase of LTP is as follows: [8]

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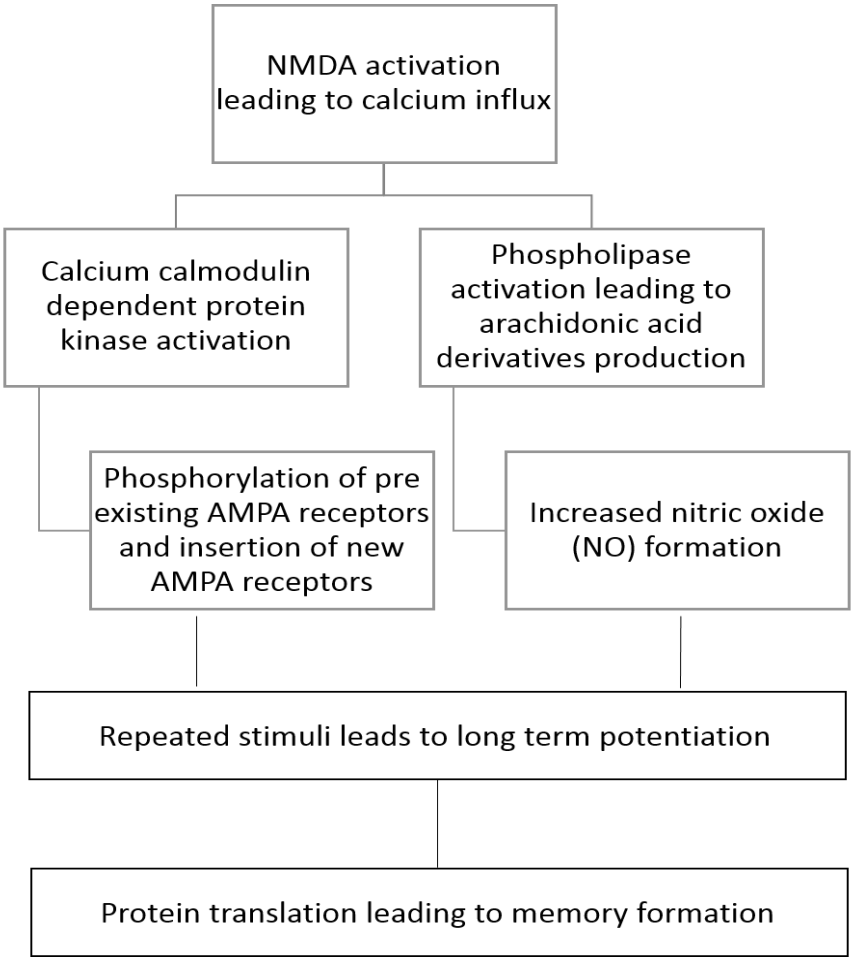


**Figure 3: Process of formation of Long Term Memory**

Many theories have been postulated to explain human cognitive functions, including conscious perception, the most commonly accepted one elucidated by Pereira Jr and Furlan in 2009. [9] The model contributes to explain the physiological bases of cognitive functions according to the following stages: [9]

1. Glutaminergic input activates AMPA receptors resulting in depolarization that opens NMDA receptors of the NR2A subtype. This promotes calcium ion entry into neurons thereby causing membrane potentiation that helps in associative learning (mostly by means of a signalling cascade and gene expression that leads to an increase in AMPA-dependent response)
2. At the same time, the glutaminergic input activates other metabotropic receptors in the neuronal membrane of other astrocytes that wraps almost all such active synapses.
3. Local glutaminergic converging input from various astrocytes are synchronized and the resulting (additive) stimulation crosses a given threshold and elicits coherent calcium waves with the potential of integrating all local information.
4. When global brain synchronisation occurs, calcium waves integrate sensory, cognitive and affective/emotional wave patterns from distinct neuronal populations from all across the brain.

The above cascade of events leads to further binding of the released glutamate to extrasynaptic NMDA receptors of the NR2B subtype, which leads to slow inward driving of calcium currents, thereby leading to delayed depolarization and an increase of CaMKII phosphorylation and AMPA excitability, a process we called “meta-potentiation”. [10] This step is essential for the formation of LTM.

Cognition, in general can be improved by increasing blood flow to the brain, enhancing neurotransmission, increased neuronal metabolism by stimulation of hormones and enzymes, increased nerve growth factor and improvement of cerebral functions like memory. What exactly do cognitive neuromodulators do? It might be

convenient to conceptualize a selective one to one correlation between a specific neurotransmitter and a particular cognitive function. [11] For example, dopamine has been strongly linked with working memory (WM) and attention [12], whereas serotonin has been prominently associated with affective processes. [13, 14] However, serotonergic modulation as well as noradrenaline and acetylcholine can influence WM as well. [15] Conversely, dopamine has been found to influence affective processing. [16, 17] A simple mapping between a specific neurotransmitter and a particular cognitive function therefore seems highly unlikely. To add to the complexity, neurotransmitters act via a wide range of receptor systems. Thus, dopamine acting at D1 receptors can have very different – even opposing – effects to that of its actions at D2 receptors. [18, 19] Similarly, serotonin has 17 different receptor systems. In addition, dopamine can have very different effects at different areas of the brain. [20] Its release can also be modulated in a highly specific regional manner by other neurotransmitters, such as glutamate within the nucleus accumbens. [21] Noradrenaline and dopamine can interact to modulate spatial WM neuronal responses in prefrontal cortex in a synergistic fashion. [18, 22]Thus, this interplay between various neurotransmitters and the various receptors they act on plays a very pivotal role in various elements of cognition formation.

***Racetams:*** "Nootrope" was coined to describe a class of drugs that improve "higher cognitive function." The term was invented by Guirgea, who developed piracetam in 1964, the alleged "memory drug". [3] There have been a number of related compounds introduced in the subsequent years (e.g., pramiracetam, oxiracetam, aniracetam, nefiracetam). Their exact mechanism of action is unknown. They were originally thought to improve "cerebral energy metabolism" and were also referred to as "antihypoxidotics", another synonym for cognitive enhancers.[3]It is also possible that they are mildly cholinergic or anti-GABAergic. Few scientists have also postulated them to have a protective action against excitotoxicity, or having a potential interaction with a "steroid-sensitive memory system". [23-25]

i) Piracetam- Piracetam has been shown toincreaseacetylcholine (ACh) concentration and glutamate activity via AMPA and NMDA receptors. It has been shown to improve membrane permeability of neurons thereby enhancing overall neuronal function. Various studies with piracetam have reported to facilitate learning in animal models, to improve the deficit in human performance associated with cerebral hypoxia, and to improve cognitive performance, alertness and fatigue in aged subjects. [26] Piracetamis said to improve verbal learning in normal [27] as well as dyslexic population. [28] It may ameliorate memory deficits in 10-30% of patients with dementia or slow the progression of the disease. [23, 29, 30] Despite all these observed effects, the evidences in favour of piracetam are not very strong and hence the drug still waits for the FDA nod. [31]

ii) Other racetams- Aniracetam is a derivative of piracetam which is 5 times more potent. Apart from stimulating AMPA receptor, it also activates D2 and D3 dopamine receptors & 5-HT(2a) receptor involved in serotonin processing. Pramiracetam is another "cognition activator," which, in various behavioral models and electroencephalographic studies is found to be "superior" to other drugs marketed for cognitive disorders in the elderly. [32] Pharmacologically, the exact mechanism of action has not been elucidated yet. It may be cholinergic and also an indirect dopamine agonist. Like all the "nootropics," it is well tolerated and apparently successful in improving the affective and behavioral symptoms of dementia: learning/memory, motivation, depression and the ability to perform activities of daily living. Nefiracetam has a noble mechanism of action. It potentiates excitatory neurotransmission by prolonging the opening of calcium channels. It also binds to nicotinic ACh receptors and is highly cytoprotective as well. [34]

Uses: Racetams have been used predominantly as an anxiolytic, treatment of ADHD, for improvement of mental clarity and concentration, in clinical depression, for improving motivation in post stroke patients. Use of racetams in Alzheimer's disease has shown mixed results.

***Cholinergics:*** Drugs that enhance acetylcholine neurotransmission have always had their own share of problems because (a) they may be depressants and (b) they may aggravate Parkinsonian symptoms. [3] Those effects are still to be kept in mind, as cholinergic drugs are used on a large scale basis for the treatment of memory disorders, in people with dementia, with stroke or brain injury, or, more recently ADHD. SinceACh is an important neurotransmitter in the physiology of memory and attention, and because there was convincing proof of the involvement of deficits in acetylcholine systems in amnestic patients and patients with attentional disorders, it was appropriate to explore the potential utility of cholinergic drugs in the above mentioned

conditions. [35] Since increased cholinergic activity is known to improve focus, working memory, alertness, mental clarity and performance, anticholinesterases (AChEIs) like rivastigmine and donepezil,by decreasing degradation of ACh, increase ACh concentration in the brain and have been an important category of drugs for the treatment of dementia. Memory impairment being one of the major elements of Total Brain Injury (TBI), it is quite prudent to use cholinergic drugs for the treatment of TBI, with positive effects seen in at least one study. [36] Choline is a water-soluble essential nutrient which maintains structural integrity and has signaling roles for cell membranes. It also increases cholinergic neurotransmission by increasing Ach synthesis. Citicoline is an intermediary in the conversion of choline into phosphatidylcholine in the liver. It increases the availability of choline in the brain by freeing up quantities of choline. Citicolinealso acts by reducing free radical generation in the brain. It decreases phospholipase stimulation thereby reducing hydroxyl radicals in the brain which have been known to decrease cognition and memory. [37]

**Acetylcholinesterase inhibitors**- Cholinergic drugs or AChEIs have been successfully used in AD patients resulting in significantly better cognitive performance when compared with placebo. [38] However, there is not much information about the effects of these drugs on cognition in healthy adults. The results have not been very promising in patients with mild cognitive impairment (MCI) as well. [39] However, some results about the potential effects on healthy subjects have been published. For example, one study reports on rivastigmine-modified memory and learning performance in healthy elderly subjects. [40] Donepezil has also been shown to improve cognitive performance in healthy young subjects. [41] It is important to stress that in animal experiments the effect of cognition enhancers in general and of AChEIs present a bell shaped curve, i.e. increasing the dose beyond a certain point reduces the performance. [42] Thus, in a nutshell, it would be apt to point out that although there is mounting evidence in favour of use of cholinergic group of drugs as cognitive enhancers, further studies still need to be carried out to chart out their use in the healthy brain.

***AMPAkines:*** Memantine has been in use in Germany for almost 25 years for treatment of cognitive impairment in elderly and more recently has also been initiated for severe AD. [43] The drug is a reversible glutamate NMDA receptor antagonist that may modulate physiological or pathological excessive activity of glutamate receptor. Modulators of AMPA receptors have also been developed on the basis of the expectation that they might facilitate NMDA receptor-dependent induction of LTM and, thereby, the acquisition of new memories. [8] AMPA-kines like sunifiram activate glutamatergic AMPA receptor thereby promoting alertness, increasing attention span and memory. They have also been shown to promote growth of neurons and the formation of long term memories. They are been studied as potential treatment option in Alzheimer's disease, Parkinson's disease, schizophrenia, treatment-resistant depression, neurological disorders such as ADHD.

***Smart drugs:*** Drugs like modafinil, methylphenidate interact with constitutive neurochemicals, such as hormones, enzymes and neurotransmitters in the body, thereby exhibiting benefits in cognitive disorders like ADHD, anxiety, Alzheimer's and Parkinson's disease. In healthy individuals they have been shown to provide substantial boost to normal thinking, learning, memory, and focus albeit the results are still debatable. Modafinilis aneugeroic i.e. wakefulness promoting agent. This is achieved by the release of histamine in brain which promotes wakefulness. [44] Modafinil has been shown to increase certain cognitive functions, such as sustained attentionand working memory. Methylphenidate on the other hand has a different modus operandi. It prevents re-uptake of dopamine & norepinephrine in the brain, thus enhancing the function of neurons in the prefrontal cortex responsible for impulse control, motivation, and mental clarity. [45] It also acts as a 5HT1A receptor agonist. Modafinil and its analogues (adrafinil and armodafinil) have been approved for use in treatment of sleep associated disorders like narcolepsy, shift work sleep disorder, obstructive sleep apnea and jet lag as well as for treatment of ADHD. They have been found to be potentially useful in depression, bipolar, opiate and cocaine dependence, Parkinson's and schizophrenia. Methylphenidate has been approved for use only in ADHD and has been used for off-label indications like treatment-resistant lethargy, bipolar affective disorder (BPAD), major depressive disorder.

***Dopaminergic drugs:*** Rasagiline and selegilineare irreversible inhibitors of monoamine oxidase thereby increasing dopamine concentration in the brain. They are believed to possess neuro-protective property which is due to their effect on the mitochondria leading to blockade of apoptosis of neuronal cells, the primary pathology in neurodegenerative disorders. These dopaminergics are primarily used as monotherapy in early Parkinsonism and as adjunctive therapy in advanced Parkinsonism. These drugs have also been tried for treatment of restless leg syndrome and AD.

***Neuro- hormones:*** Few decades ago, owing to the "trophic" influence on cells by enhancing the metabolic activity and the viability, there was intense interest in the therapeutic potential of various neuroactive peptides like adrenocorticotropin (ACTH) and melanocyle-stimulating hormone (MSH). [3] These effects include increased blood flow in the target region and stimulation of RNA/protein synthesis. [46] The above mentioned effects were thought to result from peptide effects on neurons and/or glial cells, similar to the peptide-target cell interactions that occur in peripheral tissues.Some neuropeptides, notably ACTH, MSH, oxytocin and vasopressin, were shown to affect the learning process, particularly in animals. [47] Subsequent work demonstrated that the heptapeptide ACTH 4-10, a peptide fragment common to both the ACTH and the MSH molecular structures, was responsible for the learning effects of these compounds. [48, 49] There were also studies of vasopressin and other posterior pituitary hormones,the rationale being, vasopressin which has structural similarity to ACTH 4-10, might modulate some aspect of the learning/memory process. [50] However, it was not possible to extrapolate the preclinical results to the clinical arena. The tripeptide thyrotropin-releasing hormone (TRH) has been shown to improve long-term neurological outcome following experimental spinal cord injury in cats. [51] TRH has also been successful in improving recovery from experimental brain injury in animals. [52] It has inhibitory and excitatory effects when applied to individual neurons; it interacts with a number of neurotransmitters, including NE, DA, 5HT, Ach, GABA and glutamate. [53] In Japan, TRH and its analogs in infusion form, have also been used in patients with Alzheimer's disease, vascular dementia, in cognitively impaired alcoholics, in epilepsy and in the post-ECT state. [54-57]

Nerve growth factor (NGF) is a protein that acts as a neurotrophic factor for central cholinergic neurons. In animal studies NGF has been shown to "preserve" cholinergic neurons from lesion-induced degeneration, and improve learning in rats with cholinergic septohippocampal lesions. [58] The effects of NGF on the human brain is hard to test in patients with brain disorders associated with cholinergic deficits, such as Alzheimer's disease, because the protein cannot cross the blood-brain barrier, but intraventricular infusions have been done with potentially beneficial effects. [58] However, the results are still pretty preliminary to provide any concrete proof.

**Clinical uses of cognitive enhancers**

In the last decade, pharmacological treatments aimed at improving cognitive functions in pathological states of the brainhave been widely explored and have even become established in clinical practice. [60] In developmental conditions such as ADHD, drugs acting on the noradrenergic and dopaminergic systems, such as methylphenidate, are the drugs of choice. [61-63] For neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, AChEIs and memantine are now standard treatments. [64-66] In psychiatric disorders such as schizophrenia, cognitive deficits are a separable feature from positive and negative spectrum of symptoms, with current antipsychotic drugs having negligible impact on cognitive impairments. Nootropes are therefore being assessed for cognitive enhancement in this disorder. [67] Similarly, attempts to ameliorate cognitive deficits following stroke and TBI are being actively explored, although none have been established. [68, 69]

However, the last few years has seen a major surge in the attempt to use nootropes in the healthy individuals as well. Most of the above discussed drugs have been prescribed "off- label" for improving memory retention, alertness, creativity, concentration and overall cognition in stressful jobs like military personnel, pilots, doctors and students. Widespread use of these medications can be attributed to the nemesis of stress and competitive environment in the 21$^{st}$ century and the easy availability of these drugs over the internet without a prescription.

**Measurement of cognitive enhancement**

One of the major area of contention with the use of cognitive enhancers is to find out an effective way to measure their efficacy. There is no consensus among treating physicians to show the effectiveness of nootropics. In clinical studies of neurodegenerative conditions – such as Alzheimer's disease, Parkinson's disease with dementia (PDD), dementia with Lewy bodies (DLB) and vascular dementia – the gold standard outcome measure has become the ADASCog (Alzheimer's Disease Assessment Scale). [70] This is a relatively short battery of cognitive tests covering memory, orientation, language, visual construction and limb praxis skills measured on a 70-point scale. Many trials have also revealed changes in CIBICplus (Clinician's InterviewBased Impression of Change), ADASCGIC (Alzheimer's Disease Assessment ScaleClinical Global

Impression of Change) or Neuropsychiatric Inventory (NPI) scores. [71, 72] However, the major pitfall of the above mentioned scales is that they seem to capture psychiatric effects of drug interventions more effectively than the cognitive effects. [11] For example, the CIBICplus is a semistructured instrument that attempts to evaluate four areas: general, cognitive and behavioural functions and activities of daily living, based on the clinician's observations of the patient at interview, together with information supplied by a caregiver. By contrast, the NPI evaluates delusions, hallucinations, dysphoria, anxiety, agitation or aggression, euphoria, disinhibition, irritability or lability, apathy, aberrant motor activity, and nighttime behaviour disturbances. It also relies on a structured interview with a caregiver who is familiar with the patient. [11] Another problem encountered with such scales is that they are relatively crude and highly subjective. Many of them were developed specifically for Alzheimer's disease and might not be very sensitive for other neurodegenerative conditions. Similar issues also persist with rating scales used in treatment studies of developmental disorders such as ADHD.

Although, there has been an immense amount of research work regarding finding out the various possible mechanisms of action of cognitive enhancers at a cellular level, there has been no significant breakthrough in this aspect.Instead, more insight might be obtained from an understanding of the modulatory effects of drugs on large scale brain networks underlying cognitive skills at the systems level. [11] Early studies have demonstrated how drugs such as AChEIs and methylphenidate might modulate visual attention and WM via effects on parietal, frontal and extrastriate occipital regions. [73-75] More recent investigations have focused on the effects of drugs on functional connectivity across a brain network. For example, reboxetine, a noradrenergic reuptake inhibitor, improved performance on a visuomotor task, an effect that was associated with enhanced effective connectivity between right hemisphere parietal and frontal regions, as well as their influences on left hemisphere regions. [76] A different and novel approach which has been applied to clinical populations is to examine metabolic deficiencies associated with neurodegenerative conditions, such as motor and cognitive deficits in PD, using fluorodeoxyglucose PET. [77] Researchers have also started to use this methodology to investigate the effects of treatment at the cellular level, raising the possibility of producing a basic account of how a drug might modulate function in a particular brain disorder. The result of these network studies seems to be the characteristically different effects on the neuronal restingstate functional connectivity across brain network nodes in various neurodegenerative disorders, as indexed by fMRI. [78]

**Promises and pitfalls**

The use of cognitive enhancers in disease conditions like Alzheimer’s disease and other dementias has shown good results although the disease process per se has not been halted. These diseases are neuro degenerative conditions which progress irrespective of the fact whether cognitive enhancers are administered or not.Similar is the case with use of nootropics in psychiatric conditions like schizophrenia. They do not form the first line drug in these conditions. They are just supplemented along with antipsychotics and antidepressants to tide over the cognitive symptoms.

A major issue in assessing cognitive enhancement studies for the purpose of measuring the efficacy of these cognitive enhancers is the problem of effect size. [11] First, in studies of healthy subjects, there is no universal, standard battery of tests that has been agreed on, so comparisons across studies and populations are not easy. It is not possible to compare effect sizes for different drugs if the tests used measure different aspects of cognition. Overall, however, the effects of cognitive enhancers such as methylphenidate, modafinil and AChEIs in healthy individuals seems to be quite modest according to recent systematic reviews. [79, 80] Secondly, many experimental investigations in healthy subjects have used single dose assessments which mainly cater to assess the mechanism rather than establishing optimal cognitive enhancement in the long run. [11] Very few studies have examined the effects of repeated doses or long term effects, which might represent the actual picture with respect to overall costs and benefits of taking cognitive enhancers on a regular basis. Third, as we have seen, although clinical trials in patients often use standardized bedside tests, they might be hampered by their insensitivity and limited range of measurement. [11]

Another area of great concern is the long term safety of nootropics. These drugs could be accompanied by deleterious side effects ranging from toxicity to physical or psychological dependence. This becomes all the more important considering the widespread off label prescription of these drugs. The FDA does not require companies to produce safety and efficacy data for off label use of drugs. [81] Moreover the uncontrolled availability of this genre of drugs as dietary supplements on the internet makes it all the more

susceptible for various side effects and toxicities that go unreported and unmonitored. Individuals who are ready to trade health risks in return for cognitive benefits are especially vulnerable to unscrupulous entrepreneurs who misrepresent the effectiveness of their cognitive enhancement products for monetary benefits. [81]

One of the most debatable concerns regarding the use of cognitive enhancers is how ethically correct it is to use these substances in various facilities be it sports or any competitive examinations. Those against the concept of use of nootropics argue that accomplishments achieved through the use of these agents are unearned and therefore not worthy of reward. [81] However there has been an increase in the rally in favour of cognitive enhancers in the recent past. Since the manufacturing and marketing control of these "supplements" becomes increasingly difficult, it would be easier to accept these drugs if they do provide some societal benefits. If these drugs can, for instance, increase concentration and vigilance among soldiers or increase the productivity of researchers, then it would indeed be a bad policy to restrain these compounds. The key question, thus is, how to maximize the benefits and minimize the harms and where to draw the line.

**Newer targets as nootropes**

Oxidative stress, as an implicating factor for the development of neurodegenerative disorders, opened up the possibility of use of antioxidants for treatment of neurodegenerative disorders and cognitive enhancement. Oxidative stress is a response to the overwhelmed antioxidant defenses. The chain reactions that develop an oxidative stress stop when two free radicals react with each other or when they are rendered harmless by reacting with an antioxidant. Naturally, therapeutic attention has been directed to pharmacologic agents that also seem to function as "free radical scavengers", integral to the function of antioxidant enzymes. [3] These include Vitamins C and E, retinoic acid (Vitamin A, beta-carotene), deprenyl or selegiline, an MAO-B inihibitor, gingko biloba extract, selenium, zinc and riboflavin. [82]

***Omega 3 fatty acids:*** Docosahexaenoic acid (DHA) and Eicosapentanoic acid (EPA) are together referred to as omega 3 fatty acids. Omega-3 fatty acids are necessary for the normal growth and development of brain, and are also required for maintenance of normal brain function in adults.[3]Deficiencies of DHA are associated with learning deficits in infants and children, while inclusion of plentiful DHA in the diet improves learning ability. Low serum DHA is said to be a "significant" risk factor for Alzheimer's disease. There are lower levels of omega-3 fatty acids in the parahippocampal cortex of patients with AD. [83] Low levels of serotonin and dopamine metabolites are found to be inversely related to plasma DHA in violent patients. Animal studies have indicated a therapeutic role for DHA in rats that were subjected to transient forebrain ischemia. [84] Omega-3 supplements have also shown reduction in stress-induced aggression in young adults.

***NSAIDs:*** Anti-inflammatory drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors could play a pivotal role to inhibit the course of AD. Various studies have shown lower rates of dementia in patients who have been taking NSAIDs for their usual indications. [85] The major mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX) activity and thus the synthesis of prostaglandins,major inflammatory mediators in the body. The idea that inflammatory responses may be a component of the development of AD began in 1987, when plaques in brains from AD patients were found to be filled with reactive microglial cellsthat are known to secrete complement proteins and COX-2. [3] Drugs that inhibit the activity of COX-2 enzyme are thus expected to interrupt, or at least ameliorate the inflammatory processes that are potentially neurotoxic.This effect is however not shared by aspirin. [85] However these theories are still at a preliminary stage and a lot of further research would be needed to substantiate the above proposed neuroprotective actions.

***Gingko biloba:*** Extracts from the leaves of the Gingko tree (maidenhair tree) have been used for hundreds of years in Chinese medicine for various proposed medicinal properties. [3] In the USA, it has not been given the status of a "drug," but rather a "dietary supplement," and it is one of the most popular dietary supplements available. In Europe it is being used for "cerebral insufficiency," a blanket term for symptoms like absent-mindedness, difficulties with concentration and memory, confusion, lack of energy, fatigue, impaired physical performance, depression and anxiety, usually associated with aging. [86] *Gingko biloba* is now the most commonly prescribed drug in France and Germany. There have been a number of studies that have supported the use of gingko extract for a number of neuropsychiatric problems, like neurasthenia (fatigue and tiredness); age-associated memory impairment; cerebral insufficiency; and dementia. [87-89] Preclinical studies have also

demonstrated a positive recovery effect with gingko in brain trauma and spinal cord injury. Gingko extract is a potent antioxidant and a reversible inhibitor of monoamine oxidase as well. It tends to reduce glucocorticoid synthesis, which may account for its proposed "anti-stress" effect. [91-92] There is no apparent toxicity from gingko biloba, but there are no long-term safety/efficacy studies, either. [93]

## CONCLUSION

It would be probably apt to say that we have only taken amateur steps to examine the potential for cognitive enhancement in humans. In both healthy individuals and many patient groups, the overall effects of drugs generally seem to be modest. However, there is evidence that the benefits of these drugs might be a little more significant in certain subgroups having a specific genetic defect or suffering from certain specific neurodegenerative disorders like AD. Moreover, newer drugs aimed at enhancing the response of neurotransmitter systems directed on to a specific region of the brain, might prove to have greater effects than existing modulators that globally increase levels of a neurotransmitter. However, research done in this aspect is just the tip of the iceberg. Moreover, this is one area where clarity is not just needed about how the drug acts or how safe the drug is but the ethical debate also needs to be resolved. Once these points of contentions are clarified, cognitive enhancers might prove an immensely useful tool towards the betterment of human race in future.

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