Cognition refers to the mental processes involved in thinking, knowing, remembering, judging, and problem-solving. Cognitive dysfunctions are integral part of dementia, Parkinson disease and psychiatric disorders like schizophrenia, bipolar disorders and depression. Pharmacological Cognitive Enhancers are molecules that help improve aspects of cognition like memory, intelligence, motivation, attention and concentration and include various nutrients, herbal medicines and pharmaceutical drugs. A few pharmaceutical drugs like donepezil, memantine, rivastigmine, methylphenidate are approved for enhancing cognition by different drug authorities across the world. Many new cognitive enhancers like piracetam, gingko biloba, citicoline etc. have been identified and researched, although satisfactory evidence is lacking. Many of them do not have established efficacy, have out of label use or are under research. This review describes various Pharmacological Cognitive Enhancers, their role in different neuro-psychiatric disorders, and current status of international recommendations.

Key words: Cognitive enhancer, cognitive impairment, neuro-psychiatric disorders

INTRODUCTION

Cognition is a term referring to the mental processes involved in gaining knowledge and comprehension. These processes include thinking, knowing, remembering, judging, and problem-solving. These are higher-level functions of the brain and encompass language, imagination, perception, and planning. Hence, cognitive skills are different from academic skills. Cognitive functions are mainly categorized into memory, attention, creativity and intelligence. They are subjective in nature and may be affected by number of factors that includes ageing, stress, various medical conditions such as hypertension, dementias, Parkinson's disease (PD), cancer, HIV (Human Immunodeficiency Virus) and psychiatric illnesses like schizophrenia, bipolar disorders.

Population aging is a worldwide phenomenon and India has an ever increasing population of the elderly. Census reports indicate that the Indian population has approximately tripled during the last 50 years, but the number of elderly Indians has increased more than fourfold. Considering the trends, the United Nation predicts that the Indian population will again grow by 50 percent in the next 50 years, whereas the elderly population is expected to grow another fourfold. Cerebral abilities have been observed to diminish significantly with advancing age. Thus, memory enhancers are going to be of great importance in the near future.

Poor memory, slow recall and retention problems are common in today's stressful and competitive world. Stress and emotional problems are ever increasing in today's fast life. These problems combined with ageing population, may lead to memory loss, amnesia, anxiety, high blood pressure, depression, to more ominous threat like schizophrenia and dementias like Alzheimer's disease (AD). All these disorders have some components of or predispose to cognitive decline.

Cognitive enhancement may be defined as the amplification or extension of vital capacities of the mind through improvement or augmentation of information processing systems. Cognitive Enhancers (CE), simply put, are molecules that help improve some aspect of brain function or cognition. They are drugs, supplements, nutraceuticals and functional foods that are expected to improve mental functions such as cognition, memory, intelligence, motivation, attention and concentration. CE are thought to work by altering the availability of the brain's supply of neurochemicals (neurotransmitters, enzymes, and hormones) amongst which the central cholinergic function is known to play a prominent role. They may act by improving the brain's oxygen supply, or by stimulating nerve growth.

Pharmacological CE include various nutrients (vitamin-E, acetyl-L carnitine), herbal medicines (asparagus, gingko biloba, ginseng) and pharmaceutical drugs. Only a few pharmaceutical drugs are approved for enhancing cognition. Many of the CE do not have established efficacy, have out of label use or are under research. This is complicated by the difficulty of defining and quantifying cognition and intelligence. This review describes various Pharmacological CE, the role of CE in different neuro-psychiatric disorders, and current status of Cochrane database recommendations. However, Cognitive Enhancement in healthy population, mild cognitive impairment and non pharmacological CE are not considered in this review.
COGNITIVE DYSFUNCTIONS

Cognitive dysfunction is a major health problem in 21st century with increasing burden of ageing population and psychiatric disorders. It is the loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with daily functioning. It is one of the most functionally debilitating aspect of many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, depression, AD dementia, cerebrovascular impairment, seizure disorders, head injury and parkinsonism. Cognitive decline is an established entity in neurodegenerative disorders such as AD and Parkinson's disease and CE are treatments of choice.

Cognitive dysfunction is a primary symptom of schizophrenia and some affective disorders. Different mental illnesses affect cognition differently. Furthermore, not every person is affected in the same way. Some people with schizophrenia have more cognitive problems than others. Some people with depression or bipolar disorder have problems in one aspect of cognitive functioning but not another. Cognitive deficits are a separable feature from positive (e.g. hallucinations and delusions) and negative (e.g. blunted affect, poverty of speech) symptoms in chronic mental disorders such as schizophrenia. The cognitive problems are evident even when other symptoms are controlled and patients are not psychotic. Furthermore, research has shown that those parts of the brain that are used for specific cognitive skills, often do not function normally in people with schizophrenia and certain affective disorders. Current antipsychotic treatments have little impact on cognitive impairments. A wide range of compounds are therefore being assessed for cognitive enhancement in schizophrenia. Similarly, attempts to ameliorate cognitive deficits following stroke and head injury are being actively explored.

Deficits of attention, learning and memory are established in developmental conditions such as attention deficit hyperactivity disorder (ADHD) and drugs acting to improve these domains such as methylphenidate and atomoxetine, are now in widespread use.

There are different strategies and tests to measure cognition. The most commonly used are the intelligence tests (Raven's Progressive Matrices, Stanford-Binet IQ test, Wechsler Adult Intelligence Scale), M.M.S.E (Mini Mental State Examination), Tests for memory and executive functioning (California Verbal Learning Test, Continuous Performance Task) and Cognitive development tests/Neuropsychological Batteries (Cambridge Neuropsychological Test Automated Battery, Luria-Nebraska Neuropsychological battery, Barcelona Neuropsychological Test). Imaging techniques such as functional magnetic resonance imaging (fMRI) have become prominent tools in cognitive neuroscience to assess individual cognitive functions.

STRATEGIES FOR ENHANCING COGNITION

A range of strategies have been proposed to enhance cognition. Most interventions target either underlying disease pathologies or the processes underlying normal cognition, particularly synaptic plasticity. Many act via more than one pathway or target. These strategies and treatments for enhancing cognition range from environmental stimulation and exercise, nutrients, herbal medicines and pharmaceutical drugs.

Before proceeding further, it is essential not to confuse the term cognitive enhancer with the word "nootropic". A CE is simply a substance that enhances concentration and memory. A nootropic is a substance that enhances memory, intelligence, motivation, attention, and concentration. This definition is quite broad and would include all classes of CE. The natural memory enhancing drugs are thought to control the activity of acetyl cholinesterase (AChE) which modulates acetylcholine (ACh) to proper levels by degradation. Accordingly excessive AChE activity results in ACh deficiency which leads to memory and cognitive impairments. These natural agents inhibit the excessive AChE activity and protect the people suffering with dementia.

NUTRIENTS

Micronutrients can affect cognitive function at all ages. Many such dietary supplements are recommended to improve cognition, including 'nootropical' dietary components that act like drugs. These agents are widely available in market and are usually well tolerated with no reported abuse potential.

It has often been suggested that natural memory boosters are the best sources to enhance your memory and mind, and protect yourself from memory decline. This can be achieved by ensuring consumption of optimal levels of eight nutrients from which body can make key brain chemicals. These natural mind and memory enhancers are:

- Acetylcholine precursors
  - i) Dimethylaminoethanol (DMAE)
  - ii) Choline

- Receptor enhancers
  - iii) Pyroglutamate
  - iv) Phosphatidyl1 Serine
  - v) Docosahexaenoic acid (DHA)

- Fuel for brain cells
  - vi) Glutamine

- Circulation improver
  - vii) Gingko Biloba

- Vitamins
  - viii) Vitamin B

These are becoming widely available and can be found in combination in brain boosting supplements, as well as in certain foods. The list of nutritional supplements includes vitamins, neutrasteroids and fatty acids. Vitamin E seems most important in this role with antioxidant and free radical scavenging property.
Some studies have shown that deficiency of vitamin B_6_, B_12_, and folic acid might contribute to age-associated cognitive impairment. Nutritional supplementation of these vitamins may help prevent cognitive decline. Folic Acid supplementation was shown to improve depression in two double blind RCTs. A few other supplements such as acetyl-l-carnitine, alpha-lipoic acid, lecithin, thiamine have also been tried but there is no significant evidence of their efficacy in clinical trials. Melatonin, a hormone with clock-setting properties that is secreted at night from the pineal gland, needs special mention. The levels of melatonin decrease with ageing. Positive effects of melatonin have been reported on sleep and cognition in elderly people.

The omega-3 fatty acid have recently been promoted for enhancing cognition. Docosohexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) are among the most relevant forms of omega-3 fatty acids involved in intercellular signaling events, synaptic functioning, maintenance of neuronal structure, synaptic membrane fluidity and reducing oxidative stress and inflammation. These fatty acids are usually found in low quantities in food, usually in the modern diet. Many reviews and meta analysis have found efficacy of DHA and EPA in psychiatric disorders like dementia, major depression, bipolar disorders, ADHD and other neuro-developmental disorders in doses of 1-2 gm/day. However, the evidence base is modest with mixed results and needs further research.

Dietary polyphenols, such as curcuminoids and flavonoids are found in plants and have been associated with the reduction of stroke in a 15 year longitudinal study. Dietary supplementation of blueberry extract has shown to reverse cognitive deficits in an AD animal model. Curcumin, a major chemical component of the turmeric plant (Curcuma longa), has shown excellent efficacy in counteracting neuronal dysfunction in several models of neurodegenerative diseases such as AD and focal cerebral ischemia.

**Herbal Products**

There is a growing interest in the use of herbal products in the western as well as in developing countries. Medicinal plants Ginkgo Biloba, Bacopa moniera, Shankhpushpi etc. has been found to increase memory power. Many such products have been used to treat conditions such as anxiety, depression, seizures, poor memory, dementia, insomnia and drug intoxication. Memory herbs act by increasing the levels of neurotransmitters, particularly acetylcholine. They also improve blood flow to the brain, thereby increasing its oxygen and nutrient supply, which will aid brain function and memory. Promising benefits have been seen from researches using herbal treatments for Alzheimer's and Dementia. In addition, these herbs are inexpensive and can be easily obtained. Therefore, natural products may provide a new source of beneficial nootropic drugs provided they are adequately tested. Pharmaceutical companies have realized a source of potentially beneficial agents, namely phytochemicals and are investing huge resources in identifying agents that could be used to improve cognition and slow mental deterioration afflicting numerous people around the world. These herbs have significant benefits that have yet to be fully exploited. A list of potential herbal plants that possess memory enhancing properties has been shown in table 1.

**PHARMACEUTICAL DRUGS**

<table>
<thead>
<tr>
<th>S.no</th>
<th>Common name/ Hindi Name</th>
<th>Botanical Name</th>
<th>Active constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Garli/ Lasun</td>
<td>Allium sativum Linn.</td>
<td>Salylycysteine</td>
</tr>
<tr>
<td>2.</td>
<td>Brahmi</td>
<td>Bacopa monneri Wetst</td>
<td>Bacassides A and B</td>
</tr>
<tr>
<td>3.</td>
<td>Green tea</td>
<td>Camellina sinensis Linn.</td>
<td>Flavonoids epigalochatechin-3-gallate (EGCG), Isoflavone-diadzein</td>
</tr>
<tr>
<td>4.</td>
<td>Saffron</td>
<td>Crocus sativus Linn.</td>
<td>Crocin, Crocetin</td>
</tr>
<tr>
<td>5.</td>
<td>Turmeric</td>
<td>Curcuma longa Linn.</td>
<td>Curcuminoids- Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin and Calebin-A</td>
</tr>
<tr>
<td>6.</td>
<td>Indian gooseberry /amla</td>
<td>Emblica officinalis</td>
<td>Vit-C, Phlyemblin, Phlylinathin and Hypophyllanthin</td>
</tr>
<tr>
<td>7.</td>
<td>Shankhpushpi</td>
<td>Evolvulus alsmoides Linn.</td>
<td>Flavonoids</td>
</tr>
<tr>
<td>8.</td>
<td>Ginkgo</td>
<td>Ginkgo biloba Linn.</td>
<td>Flavonoids, Terpenoids, Kaempferol, Quercetin and Terpene lactones- Ginkgolides and Bilabolide</td>
</tr>
<tr>
<td>9.</td>
<td>Mulethi</td>
<td>Glycyrrhiza glabra Linn.</td>
<td>Glycyrrhizin</td>
</tr>
<tr>
<td>10.</td>
<td>Firmoss</td>
<td>Huperzia serrata (Thunb.ex Murray) Trevis.</td>
<td>Huperizine A</td>
</tr>
<tr>
<td>12.</td>
<td>Tobacco</td>
<td>Nicotiana tabacum Linn.</td>
<td>Nicotine</td>
</tr>
<tr>
<td>13.</td>
<td>Ginseng</td>
<td>Panax ginseng Meyer.</td>
<td>Saponins- protopanaxdixiol, protopanatriol and oleanolic acid Ginsenosides Rg1,Rg2 &amp; Rg3</td>
</tr>
<tr>
<td>14.</td>
<td>Paan-patta</td>
<td>Piper betel Linn.</td>
<td>Arecoline</td>
</tr>
<tr>
<td>15.</td>
<td>Kava</td>
<td>Piper methysticu m Frost.</td>
<td>Kavalectones</td>
</tr>
<tr>
<td>16.</td>
<td>Sage</td>
<td>Salvia officinalis Linn.</td>
<td>Monoferpenoid, Carnosic acid and Rosmarinic acid</td>
</tr>
<tr>
<td>17.</td>
<td>Giloy</td>
<td>Tinospora Cordifolia</td>
<td>Tinosporine, Tinosporide</td>
</tr>
<tr>
<td>18.</td>
<td>Ashwagandha</td>
<td>Withania sommifera Linn.</td>
<td>Withanolides, Sitoindosides VII-X and Withaferin</td>
</tr>
</tbody>
</table>

Table 1 showing some commonly used herbal plants with their active constituents.

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Pharmaceutical market is full of a number of compounds used for their cognition enhancing property. These drugs improve memory by altering the balance of neurotransmitters in the brain that are involved in the initial learning of a memory or its subsequent reinforcement. Some of the agents also modulate the process at transcriptional and translational level.

I. ESTABLISHED COGNITIVE ENHANCERS

Certain group of drugs are established CE with proven efficacy and benefits in enhancing cognition in disorders like dementias, parkinsonism, depression, ADHD and chronic psychiatric illnesses. They are either approved or are in process of approval by established drug controlling authorities across the world.

Cholinesterase Inhibitors

Abnormalities in cholinergic neurons are prominent among the pathological changes in the brains of patients with cognitive decline. The impact of these abnormalities can be reduced by inhibiting the enzymatic breakdown of acetylcholine. Cholinesterase inhibitors inhibit the excessive AChE activity and protect the people suffering with dementia. Donepezil, rivastigmine, galantamine are the frequently used cholinesterase inhibitors.

Donepezil

A significant body of evidence suggests that donepezil is effective in people with mild to moderate Alzheimer's disease. There is evidence to suggest that its efficacy may extend to the treatment of people with more severe forms of AD. A systematic review of the use of donepezil in people with vascular dementia over a six month period demonstrated some benefit to patients with mild to moderate cognitive impairment.

Donepezil was also found effective in improving mental function, full scale IQ, and clinician ratings in adult TBI (Traumatic Brain Injury). Donepezil has been used “off-label” therapeutically in the pediatric population, particularly those diagnosed with ADHD. In 2003, a study explored the use of donepezil in 43 children diagnosed with autism with favorable results. Donepezil has also been studied in patients with mild cognitive impairment, schizophrenia, cognitive impairment associated with multiple sclerosis, CADASIL (Cerebral Autosomal-Dominant Arteriopathy with Sub cortical Infarcts and Leukoencephalopathy) syndrome, and Down syndrome.

Donepezil should be used with caution in patients with cardiac disease, cardiac conduction disturbances, chronic obstructive pulmonary disease, asthma, severe cardiac arrhythmias and sick sinus syndrome. Patients with gastrointestinal disorders should use caution because nausea or vomiting may occur.

Galantamine

Galantamine can be used to manage cognitive impairments in people with mild to moderate Alzheimer's disease, vascular dementias and people with mixed dementias. Greatest benefit is achieved in patients with moderate dementia with an MMSE score of less than 18. Evidence from two large RCTs showed that galantamine has a significant positive impact on functional ability and behavior for people with AD.

Rivastigmine

Rivastigmine can be used to manage people with mild to moderate AD, people with dementia with Lewy Bodies and Parkinson's Disease Dementia. Rivastigmine treatment showed significant benefits in cognitive and global function. There is evidence from one study that the cognitive benefits of rivastigmine treatment were more robust in patients with moderately severe dementia. In people with dementia with Lewy bodies, rivastigmine may be effective in reducing apathy, anxiety and hallucinations.

One meta-analysis comparing the tolerability and the effect on cognition of donepezil, galantamine and rivastigmine in people with dementia concluded that the efficacy of the three drugs is similar. Donepezil was associated with fewer study drop outs than either rivastigmine or galantamine, suggesting that donepezil may be better tolerated at therapeutic doses.

Glutamate NMDA Receptor Antagonist (Memantine)

Memantine is a reversible glutamate NMDA receptor antagonist which prevents excitatory amino acid neurotoxicity without interfering with the actions of glutamate that are necessary for learning and memory. The efficacy of memantine has been examined in people with moderate to severe AD and mild to moderate vascular dementia. In patients with moderate to severe AD there was a non-clinically significant positive effect from use of memantine on activities of daily living at six months. Memantine can be used to manage moderate AD for people who cannot take acetyl cholinesterase inhibitors and as an option for managing severe AD. A review by Sani and colleagues concluded that the use of the drug in OCD and post-traumatic stress disorder holds promise, while findings relating to generalized anxiety disorder are rather disappointing. Results in eating disorders, catatonia, impulse control disorders (pathological gambling), substance and alcohol abuse/dependence, and attention-deficit hyperactivity disorder were inconclusive. Memantine also appears to possess neuroprotective properties similar to those of lithium, hence useful in bipolar disorders, schizophrenia, depression and OCD.

Nicotine

Nicotine stimulates nicotinic cholinergic receptors and have been proposed to be act through modulation of signaling pathways, i.e. increased extracellular-signal regulated kinase and cAMP response element binding protein (CREB) phosphorylation. Both alpha7 and alpha4beta2 nicotinic receptors in the hippocampus are involved in cognitive functions. Nicotine, as well as other nicotinic drugs, may provide useful therapeutic treatment for a variety of cognitive impairments including those found in AD, schizophrenia, parkinson's disease and ADHD. Nicotine skin patches significantly improve attentional performance in people with these disease states as well as normal non smoking adults. Further work has investigated the relationship of nicotine systems with dopaminergic and glutaminergic systems in the basis of cognitive function.

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Stimulant Drugs/Mono-Amines Modulators

Methylphenidate, amphetamines and atomoxetine are the major drugs that act as stimulants or act through stimulation / modulation of mono-amine pathways. Monoamine neurotransmitters such as dopamine, serotonin, and noradrenaline have proven effects on cognition. The interaction of dopamine and glutamate can promote Long Term Potentiation and Long Term Depression in various brain regions. Modafinil, another stimulant, has a role in improving cognition in adult ADHD patients. Its mechanism is still poorly understood but it is postulated to exhibit effects on catecholamine, serotonin, glutamate, gamma amino-butyric acid (GABA) and histamine systems in the brain. All these drugs have been found to improve working memory, episodic memory, attention and learning.

There have been several reviews of psycho-stimulants as monotherapy for unipolar depression. Most studies in nonelderly adults (under 65 years of age) were negative and, in the positive studies, stimulants were only modestly beneficial to certain subgroups compared with placebo. There are several positive open trials, audits and case reports regarding the use of psycho-stimulants to augment standard antidepressant treatment. The two negative RCTs using methylphenidate as an augmentation agent compared with placebo in adults with major depression showed no statistically significant improvement or accelerated response. A number of case reports have noted the successful use of methylphenidate, dexamphetamine and modafinil for treating apathy in a range of neurological conditions. Other off label uses include depression in medical and neurological illnesses, cocaine dependence, treating sedation caused by psychotropic drugs, improving cognition in schizophrenia and as "Wakefulness Enhancers".

Caffeine

Caffeine is used on daily basis for its effects as a mild stimulant in the form of coffee, tea and soft drinks. Caffeine is unique in that few regard it as a "drug" due to its relatively mild effects when compared with other more potent stimulants. However, caffeine has significant cognitive enhancing properties, with the ability to enhance focus, alertness and improving information processing, memory, and complex cognitive functioning. Experimental trends indicate that caffeine seems to be most effective at enhancing delayed recall, recognition memory, and verbal memory. Caffeine intake (< 6 cups/day) has been associated with less depressive symptoms, fewer cognitive failures, and lower risk of suicide. However, its putative therapeutic effects on depression and ADHD have been insufficiently studied. Patients with panic disorder and performance social anxiety disorder seem to be particularly sensitive to the anxiogenic effects of caffeine, whereas preliminary data suggests that it may be effective for some patients with obsessive compulsive disorder (OCD).

II. CLINICALLY USED BUT NOT ESTABLISHED COGNITIVE ENHANCERS

A lot of pharmaceutical drugs are being marketed, promoted and clinically used as nootropics/cognition enhancers in various neuro-psychiatric disorders. Most of these drugs do not have proved efficacy but enjoy trust of medical practitioners across the world as CE.

Piracetam

Many pyrrolidone derivatives are available worldwide, including piracetam, oxiracetam, aniracetam, nefiracetam and levetiracetam. Piracetam is a derivative of the neurotransmitter GABA. Piracetam was the first successful nootropic drug marketed. Actions of piracetam include enhancement of brain metabolism (by increasing glucose utilization, blood & oxygen flow), increasing cerebral phospholipids & cellular membrane fluidity, amplifying the density of the muscarinic cholinergic, NMDA & AMPA (Alpha-amino-3-hydroxy-5-Methyl-4-isoxazole-Propionic Acid) Cerebral Cortex Receptors.

A meta-analysis on piracetam assessing 19 double-blind trials noted a significant benefit associated with piracetam in patients with some type of cognitive ailments. Piracetam seems to be an effective adjunct therapy to valproate in models of myoclonus epilepsy. At least one study noted benefit to tardive dyskinesia symptoms, but the benefits were only seen as long as treatment was maintained. The evidence for improving cognition in AD and senile dementia patients, is now seen as too inconsistent to support the use of piracetam for these conditions. Piracetam's overall effect on lowering depression and anxiety is higher than improving memory. Piracetam also appears to be effective in treating cognitive impairment in alcoholism.

Alpha glycerylphosphorylcholine (alpha-GPC)

Alpha L-GlycerylPhosphorylCholine is a precursor for the neurotransmitter Acetylcholine. It is the active form of choline that rapidly penetrates the blood brain barrier, naturally found in small amounts in milk and soybeans. One study using Alpha-GPC alongside both caffeine and phosphatidylserine has found increased attention and reaction time in persons undergoing acute stress. Alpha-GPC is associated with improved learning, memory and cognition in animal studies. Alpha-GPC had beneficial effects in AD, vascular dementia as well as transitory ischemic attack or stroke.

Gingko Biloba

Clinical trials have assessed use of Gingko Biloba for the treatment of cerebral dysfunction, age related cognitive decline and for slowing the progress of neurodegenerative disorders such as dementia. A systematic review of data derived from the Cochrane Collaboration meta-analyses of the efficacies of Ginkgo biloba and cholinesterase inhibitors suggests that Ginkgo is less potent in establishing cognitive improvement than the cholinesterase inhibitors, though Ginkgo is tolerated as well as placebo. A number of studies demonstrate that using Ginkgo to treat dementia has a positive benefit on cognition and function. The differences between Ginkgo and placebo are more pronounced in patients with advanced AD. Almost all studies
show that Ginkgo is safe with few side effects, although two studies failed to demonstrate a clinical benefit \(^{96,97}\). Further trials are required before a statement can be made about the effective dose of Ginkgo for the treatment of patients with dementia. Ginkgo has been studied as a potential treatment for sexual dysfunction related to SSRI use, but failed to show any effectiveness in placebo-controlled trials \(^{96,99}\). Preliminary studies failed to show any effect of ginkgo on cognitive function in patients with multiple sclerosis \(^{100}\).

**Citocline**

CDP-choline (Cytidine Diphosphocholine or Citocline) is a molecule which confers choline to the body and is able to convert into uridine, therefore conferring benefits associated with both molecules to a degree and being claimed to support acetylcholine and phospholipid metabolism. Studies suggest that CDP-choline supplements help prevent memory impairment resulting from poor environmental conditions \(^{101}\). Citocline supplementation also improves memory retention \(^{102}\). Preliminary research has found that citocline supplements help improve focus and mental energy and may possibly be useful in the treatment of attention deficit disorder \(^{103}\). Citocline is associated with improved recovery after stroke \(^{104}\) and benefits cocaine addiction \(^{105}\).

**Vitamins/Minerals**

Evidence on whether multivitamin/multimineral tablets improve cognitive function in people of various age groups is conflicting \(^{106-108}\). Multivitamin/multimineral supplements may be helpful for people with marked vitamin or mineral malnutrition. Vitamin B\(_1\) has some evidence from preliminary double-blind trials \(^{109}\). Mild vitamin B\(_12\) deficiency is relatively common in the elderly, so it has been suggested that vitamin B\(_12\) supplements may be appropriate in this age group. However, two studies failed to show any benefits \(^{110,111}\). A review of the literature failed to find any evidence of benefit with Vitamin B\(_12\) \(^{112}\). Folate was not found helpful in one study \(^{113}\), however, in another study, folate supplementation in seniors with high levels of homocysteine improved mental function \(^{114}\). Combinations of B-vitamins, including B\(_1\), B\(_6\), and folate, have proved in-effective \(^{115}\). Weak evidence from a large double-blind, placebo-controlled study hints that use of beta-carotene over many years might enhance mental function \(^{116}\). Vitamin E was not found helpful in maintenance of healthy mental function in women over 65 in a large study \(^{117}\).

One study failed to find any benefit with zinc \(^{118}\). Preliminary trials suggest that the amino acid tyrosine may improve memory and mental function under conditions of sleep deprivation or other forms of stress \(^{119}\). Iron is often found deficient in women who marginally experience improvement in mental function when they correct this deficiency \(^{120}\). Carnitine has shown some benefit for reducing mental fatigue and enhancing cognitive functions \(^{121}\). DHEA (Dehydroepiandrosterone), promoted as a brain-boosting supplement, failed to show any significant improvement in mental functions, and there is no direct evidence that DHEA supplements provide any benefit in seniors \(^{122}\). One study did find potential benefits in younger people \(^{123}\).

**Anti-Inflammatory Drugs**

Cytokines are implicated in the pathophysiology of psychiatric disorders such as depression, schizophrenia or anorexia nervosa as well as in neurological, respectively neurodegenerative diseases like Parkinson's or Alzheimer's. This connection between the immune system and the pathogenesis of psychiatric disorders leads to the concept that immuno-modulatory drugs which are already in use for various diseases related to the immune system may also be efficient in the treatment of psychiatric and neurological disorders.

One systematic review showed that anti-inflammatory drugs do not slow progression in cognitive decline and have significant side effects such as gastric ulceration \(^{124}\). Evidence from one study into associated symptoms related to memory, disruptive behavior and depressive behavior in people with AD revealed a clinical effect after treatment with hydroxy-chloroquine. However, there was an insignificant decline in the progression of early/mild AD \(^{125}\). The glucocorticoid prednisolone was found ineffective for the treatment of associated symptoms in people with AD \(^{126}\). One small study showed that the antidepressants exhibit a more rapid onset of action if augmented with aspirin \(^{127}\). Non-steroidal anti-inflammatory drug use was not significantly associated with either dementia incidence or cognitive decline in both sexes \(^{128}\). In a meta analysis, the authors conclude that most of the reported beneficial effects of NSAIDs may result from various forms of bias: recall bias, prescription bias, and publication bias \(^{129}\). A Cochrane systematic review identified no randomized controlled evidence that aspirin benefits patients with vascular dementia \(^{130}\).

**Estrogens**

AD is particularly seen more commonly in postmenopausal women than any other population subgroup. Involvement of estrogen and treatment with estrogen has been proposed as a possible therapeutic target. Estrogen has proved ineffective for the prevention of cognitive decline in women with dementia \(^{131}\). One small RCT (16 participants) showed a favorable effect of estrogen on associated problems in people with dementia \(^{132}\), two further studies point to ineffectiveness of the estrogen treatment \(^{133,134}\).

**Vinpocetine**

Vinpocetine, sold primarily as a dietary supplement, is reported to have cerebral blood-flow enhancing and neuroprotective effects. It is used as an off label drug for the treatment of cerebrovascular disorders and age-related memory impairment. Vinpocetine has been identified as a potent anti-inflammatory agent that might have a potential role in the treatment of parkinson's disease and AD \(^{135,136}\). Vinpocetine appears to be protective against toxin-induced amnesia, suggesting an interaction between the neuroprotective effects and memory formation. However, a 2003 Cochrane review determined that
the results were inconclusive. The results in animal studies favor use of vinpocetine in cognitive decline and drug induced memory impairments.

**Nicergoline**

Nicergoline is an ergot derivative used to treat senile dementia and other disorders with vascular origins. It has been found to increase mental agility and enhance clarity and perception. It decreases vascular resistance and increases arterial blood flow in the brain, improving the utilization of oxygen and glucose by brain cells. Nicergoline has therapeutic potential in number disease conditions including mild to moderate dementia, Alzheimer type dementia and vascular dementia. Overall, data strongly supports nicergoline as a well tolerated and effective treatment that improves cognitive and global functions in patients with mild to moderate dementia. Still, the drug is yet to be explored to its full potential and FDA approval is required.

**Acetyl-L-Carnitine**

Acetyl-L-Carnitine (ALCAR) is an amino acid-like compound related to choline, found in high levels in brain cells. It increases acetylation of Co-enzyme A (a precursor to Acetylcholine), thereby helping in memory enhancement. It also enhances transport of fatty acids into the mitochondria for the generation of metabolic energy. It is widely available as a nutritional supplement. ALCAR has the ability to cross the bloodbrain barrier and enter the brain, where it acts as a powerful antioxidant. Its supplementation has been shown to be neuroprotective in animal studies of cerebral ischemia. It has been shown to be of benefit to Alzheimer's patients. It may have some neuroprotective benefit in the treatment of Parkinson's disease, but further research is required.

**CONCLUSION**

Cognition, as a process, is of a paramount significance in carrying out day to day activities. Cognitive dysfunctions are integral part of dementia, Parkinson disease and psychiatric disorders like schizophrenia, bipolar disorders, depression etc. and are primarily responsible for the socio-occupational decline seen in these disorders. Despite of several years of scientific efforts, still there is no satisfactory therapeutic strategy to cure cognitive impairment. Use of pharmacological CE can be seen as an important step in this context.

CE have been found most effective is in the treatment of degenerative disorders such as Alzheimer's or Parkinson's disease, ADHD and cognitive dysfunctions due to organic diseases. There is no satisfactory evidence of these enhancers in psychiatric disorders though many new CE have been identified and researched. It is still difficult to identify and comment on long-term effects of the use of many CE that are relatively new to the scene, such as attention deficit drugs and various nootropics. It seems logical that, for the time being, an appropriate balance is important in the use of CE. Especially in the case of neurodegenerative diseases, the risk of using new and relatively unknown CE can be outweighed by their potential to improve the health of the patient. The over use of CE often results in under use of non pharmacological interventions like exercise and lifestyle modification. An important but often ignored discussion pertains to the cost of these CE. Most of these CE are costly which limits their use, especially in developing countries like India. A summary of Cochrane recommendations is presented in table 2.

### Table 2 : Highlighting the Cochrane database recommendations for use of Cognitive Enhancers

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<thead>
<tr>
<th>Drug</th>
<th>Sufficient Evidence</th>
<th>Insufficient Evidence</th>
<th>No Evidence</th>
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<tr>
<td>Donepezil</td>
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<tr>
<td>Galantamine</td>
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<tr>
<td>Rivastigmine</td>
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<tr>
<td>Memantine</td>
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<tr>
<td>Piracetam</td>
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<tr>
<td>Citicoline</td>
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<tr>
<td>Nicotinamide</td>
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<td>Nicergoline</td>
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<td>Acetyl-l-carnitine</td>
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<td>Vitamin B12</td>
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<td>Thiamine</td>
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FUTURE DIRECTIONS

A recent breakthrough in scientific and technical field has allowed researchers to understand the basic pathophysiology of the progression of diseases such as Parkinson's disease, AD, Schizophrenia and ADHD. Researchers have unveiled many of the new key players of the pathological cascades which lead to cognitive impairment. However, evidence on indications, use, safety profile and long term effects of most of the CE is lacking. The role of herbal products, multivitamins and dietary supplements needs detailed assessment as they are likely to be safe, indigenous and cost effective. The role of CE in psychiatric disorders is grossly under studied and needs extensive controlled trials. At present, many compounds that alter the function of various neurotransmitters are being developed with AD as a target indication. Of these, the 5-HT6 receptor antagonists appear to hold much potential as new therapies, because in preclinical studies they have shown promising results by modulating multiple neurotransmitter systems. Signal transduction processes involved in the cognition can be targeted for the development of better cognitive enhancing drugs.

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