IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nootropics Used As Smart Drugs: A Systematic Review Of Neuroenhancement In Modern Times

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Abstract: Nootropics, commonly referred to as "smart drugs," have gained increasing attention in recent years for their purported ability to enhance cognitive performance. These substances range from synthetic compounds like modafinil and racetams to natural supplements such as ginkgo biloba and bacopa monnieri. This review paper aims to explore the classification, mechanism of action, and efficacy of various nootropics, examining both scientific evidence and ethical implications. While certain nootropics demonstrate promise in improving memory, focus, and executive function, concerns regarding safety, long-term effects, and misuse persist. This review evaluates current research trends and regulatory challenges, highlighting gaps in knowledge and suggesting future directions for responsible nootropic use.

Index Terms - Nootropics, Smart Drugs, Cognitive Enhancement, Modafinil, Memory Boosters, Neuroenhancement, Brain Supplements

Introduction

The pursuit of enhanced cognitive performance has fascinated humanity for centuries, from ancient herbal remedies to modern pharmaceutical innovations. (1)In recent decades, this quest has intensified with the emergence of nootropics—a class of substances designed or believed to improve mental functions such as memory, creativity, attention, and overall intelligence. Coined by Corneliu E. Giurgea in 1972, the term nootropic refers to compounds that enhance learning and memory, protect the brain from injury, and possess low toxicity.

With increasing academic, professional, and personal performance demands, the use of nootropics—both prescription-based and over-the-counter—has seen a notable rise, particularly among students, professionals, and even military personnel. From modafinil, a wakefulness-promoting agent, to caffeine, the most widely used psychoactive compound globally, the spectrum of nootropics is vast and diverse.

This review aims to systematically evaluate the different categories of nootropics, their mechanisms of action, clinical efficacy, safety profiles, and ethical considerations surrounding their use. We also address the gap between public perception and scientific evidence and examine regulatory challenges in monitoring these substances.

Classification of Nootropics

Nootropics can be broadly categorized based on their origin and mechanism of action:

A. Natural Nootropics
- Bacopa monnieri: Known for memory enhancement and neuroprotection.
- Ginkgo biloba: Traditionally used to improve blood flow to the brain and support memory.
- Panax ginseng: Shown to enhance mood and reduce mental fatigue.
- L-theanine (found in green tea): Known for promoting relaxation without sedation, especially when combined with caffeine.

B. Synthetic Nootropics
- Modafinil: Prescribed for narcolepsy and sleep disorders; used off-label for focus and alertness.
- Racetams (e.g., piracetam, aniracetam): Enhance neuronal function and are often used for memory support.
- Noopept: A peptide-derived nootropic claimed to be faster-acting and more potent than racetams.
- Amphetamines (e.g., Adderall): Prescribed for ADHD; their use for cognitive enhancement in healthy individuals is controversial and carries abuse potential.

Mechanism of Action
Nootropics exert their cognitive-enhancing effects through multiple neurobiological pathways:

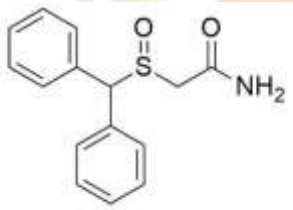
1. Neurotransmitter Modulation: Many nootropics increase levels of acetylcholine (important for memory), dopamine (motivation and reward), or serotonin (mood regulation).

2. Neuroprotection: Some compounds reduce oxidative stress, enhance mitochondrial function, or stimulate neurotrophic factors like BDNF (Brain-Derived Neurotrophic Factor), which promotes neuronal survival and plasticity.

3. Cerebral Blood Flow Enhancement: Substances like ginkgo biloba improve oxygen and nutrient delivery to brain cells by dilating blood vessels.

4. Wakefulness and Arousal: Drugs like modafinil inhibit dopamine reuptake and affect orexin systems, promoting alertness without the jittery effects of stimulants like caffeine.

Mechanism of action of selected nootropic agents
Modafinil



2-[(Diphenylmethyl)sulfinyl]acetamide

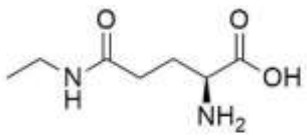
Modafinil is a wakefulness-promoting agent categorised as a eugeroic drug, widely investigated for its nootropic properties. Its mechanism of action is complex and not entirely elucidated, but it involves modulation of multiple neurotransmitter systems.[5]

Modafinil primarily acts by inhibiting the reuptake of dopamine through the dopamine transporter (DAT), thereby increasing extracellular dopamine concentrations in the prefrontal cortex, a region critical for executive function and working memory. Additionally, modafinil influences the levels of norepinephrine, histamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA) in the brain.[3]

It is believed that modafinil's cognitive-enhancing effects arise from the synergistic stimulation of dopaminergic and noradrenergic pathways, particularly the locus coeruleus and hypothalamus, as well as inhibition of GABAergic transmission, which contributes to heightened cortical arousal and vigilance .[3]

Moreover, electrophysiological studies and imaging techniques such as SPECT have demonstrated increased cerebral blood flow and metabolism in the anterior cingulate cortex and thalamus, supporting its role in attention modulation and memory enhancement.[1]

L-Theanine



(2S)-2-amino-4-(ethylcarbamoyl)butanoic acid

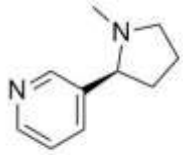
L-Theanine, a naturally occurring amino acid found in green tea (Camellia sinensis), is recognized for its calming yet cognition-supporting properties. Its mechanism involves modulation of neurotransmitter systems, especially glutamate, GABA, dopamine, and serotonin pathways.[6]

L-Theanine acts as a glutamate analog and can bind to AMPA, kainate, and NMDA receptors, albeit with much weaker affinity, leading to a reduction in excitotoxicity and stabilization of synaptic activity [Froestl et al., 2012]. Concurrently, it enhances alpha brain wave activity, promoting a relaxed yet alert mental state, which is crucial for sustained attention, working memory, and reduced mental fatigue.[2]

Additionally, L-Theanine may upregulate GABA synthesis and increase levels of dopamine in the brain, particularly in the striatum and hippocampus, facilitating improved mood, focus, and stress resilience without sedation.[3]

Its neuroprotective effects are further supported by its antioxidant action and modulation of the hypothalamic-pituitary-adrenal (HPA) axis, potentially reducing the cognitive impact of stress and aging-related cognitive decline.

3. Nicotine



3-[(2S)-1-methylpyrrolidin-2-yl]pyridine

Nicotine exerts its nootropic effects primarily through interaction with neuronal nicotinic acetylcholine receptors (nAChRs), which are widely distributed in the central nervous system, especially in areas involved in learning, memory, and attention such as the hippocampus and cortex.[7]

These nAChRs are ligand-gated ion channels that, upon activation by nicotine, allow the influx of sodium (Na^+) and calcium (Ca^{2+}) ions, resulting in neuronal depolarization and increased excitability.[7]

Nicotine enhances synaptic transmission and neurotransmitter release, particularly of dopamine, acetylcholine, norepinephrine, and serotonin, all of which are implicated in cognition and mood regulation.[7]

Stimulation of α4β2 and α7 subtypes of nAChRs has been shown to enhance attention, working memory, and cognitive performance, making nicotine a candidate for addressing cognitive impairments such as in Alzheimer's disease and post-stroke dementia.[7]

In rat cortical neurons, nicotine was shown to modulate the functional state of nAChRs, improving receptor sensitivity and enhancing cholinergic neurotransmission under pathological conditions, such as neurodegeneration.[7]

Additionally, post-stroke dementia models demonstrated that nicotine could potentially counteract memory deficits by improving cholinergic tone and neuronal plasticity through its effect on nAChRs.[7]

These actions suggest nicotine may provide short-term cognitive enhancement by augmenting cortical arousal, promoting attentional filtering, and facilitating long-term potentiation mechanisms in the hippocampus.[7]

However, despite these promising effects, the narrow therapeutic window, addictive potential, and long-term neurochemical alterations caused by nicotine limit its therapeutic use as a nootropic agent.[7]

Pharmacological Properties of Nootropic Drugs

Nootropic drugs, also known as cognitive enhancers, exhibit diverse pharmacological properties that influence brain function by targeting various neurotransmitter systems, cerebral metabolism, and neuroprotection mechanisms.

1. Cognitive Enhancement:

Nootropics improve cognitive functions such as memory, attention, and learning capacity by modulating neurotransmitters like acetylcholine and glutamate.[

2. Cholinergic Modulation:

Many nootropics act as cholinergic agonists or modulators, enhancing acetylcholine synthesis and release in the brain, which is crucial for memory and learning.

3. Neuroprotective Effects:

Nootropic agents exhibit neuroprotective actions by stabilizing neuronal membranes, scavenging free radicals, and inhibiting neurotoxic pathways, thereby protecting neurons from age-related or pathological damage.[6]

4. Cerebral Blood Flow Enhancement:

Some nootropics such as Piracetam and dihydroergocristine enhance regional cerebral blood flow, contributing to improved cognitive performance, particularly in elderly individuals.[1]

5. Glutamatergic and NMDA Receptor Modulation:

Certain nootropics modulate glutamatergic transmission and NMDA receptors, which are important for synaptic plasticity and long-term potentiation, underlying learning and memory.

6. Modulation of Nicotinic Acetylcholine Receptors:

Nootropic compounds such as those studied by Zhao et al. modulate neuronal nicotinic acetylcholine receptors, which are critical in memory formation and attention regulation.[7]

7. Adaptogenic and Stress-Protective Effects:

Herbal nootropics like Rhodiola and Schisandra act as adaptogens, increasing the body's resistance to stress and fatigue, thereby supporting mental performance under stressful conditions.

8. Anti-Aging and Anti-Dementia Potential:

Nootropic agents delay the progression of neurodegenerative diseases such as Alzheimer's by exerting anti-inflammatory and antioxidant effects.

9. Cognitive Restoration in Psychiatric Conditions:

Drugs like Piracetam have shown promise in improving cognitive symptoms in schizophrenia, possibly via modulation of glutamatergic pathways.

10. Mood and Anxiety Regulation:

Some nootropics, such as phenibut, exhibit anxiolytic properties by modulating GABAergic transmission, contributing to emotional stability and cognitive clarity.

11. Metabolic Enhancement in Brain Cells:

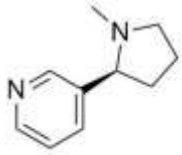
Nootropics often increase mitochondrial efficiency and glucose utilization in neurons, enhancing overall brain energy metabolism.

12. Improvement in Neuroplasticity and Synaptogenesis:

Long-term use of nootropics can facilitate neuroplastic changes and synaptogenesis, which support learning, adaptation, and memory retention.[2]

Pharmacological Properties of Selected Nootropic Agents

1. **Nicotine**



3-[(2S)-1-methylpyrrolidin-2-yl]pyridine

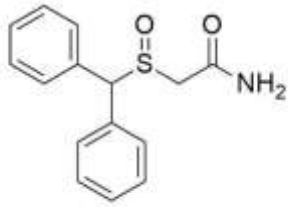
Absorption, Distribution, Metabolism, Excretion (ADME): Nicotine is rapidly absorbed through the lungs, oral mucosa, and skin. It has high bioavailability and is widely distributed in the brain. It is primarily metabolized in the liver by CYP2A6 into cotinine and excreted renally.

Dose Ranges: Typical doses in nootropic use range from 1–2 mg per administration via gums or patches.

Onset and Duration of Action: Onset is within minutes (inhaled), and effects last 1–2 hours depending on the route.

Drug Interactions: Nicotine can interact with antipsychotics, theophylline, and beta-blockers by altering hepatic enzyme activity.

2. Modafinil



2-[(Diphenylmethyl)sulfinyl]acetamide

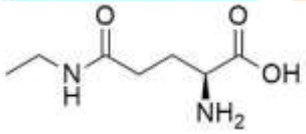
Absorption, Distribution, Metabolism, Excretion(ADME): Modafinil is well absorbed orally (≥80% bioavailability), reaches peak plasma concentrations in 2–4 hours, and is extensively metabolized in the liver via amide hydrolysis and CYP3A4. It is mainly excreted in urine as inactive metabolites.[7]

Dose Ranges: Therapeutic doses range from 100–200 mg/day.

Onset and Duration of Action: Onset occurs within 1 hour; duration lasts 10–12 hours.[7]

Drug Interactions: Modafinil induces CYP3A4 and inhibits CYP2C19, affecting drugs like oral contraceptives and diazepam.[7]

3. L-Theanine



(2S)-2-amino-4-(ethylcarbamoyl)butanoic acid

Absorption, Distribution, Metabolism, Excretion(ADME): L-Theanine is absorbed from the small intestine, crosses the blood-brain barrier, and is metabolized in the liver into ethylamine and glutamic acid. It is excreted via urine.[6]

Dose Ranges: Effective nootropic doses range from 100–400 mg per day.

Onset and Duration of Action: Effects typically begin within 30 minutes and last up to 4–6 hours.[6]

Drug Interactions: It may have synergistic effects with caffeine and can interact mildly with antihypertensives and CNS depressants.[6]

4. Natural Nootropics (e.g., Bacopa monnieri, Ginkgo biloba)

Absorption, Distribution, Metabolism, Excretion(ADME): Natural nootropics vary but are generally absorbed via the GI tract and metabolized in the liver. Bacopa monnieri, for example, is absorbed slowly, with peak effects seen after chronic administration.

Dose Ranges: Bacopa monnieri: 300–600 mg/day; Ginkgo biloba: 120–240 mg/day.

Onset and Duration of Action: Natural nootropics like Bacopa often require several weeks (4–12 weeks) of administration for full cognitive effects.

Drug Interactions: Bacopa and Ginkgo may interact with anticoagulants, sedatives, and SSRIs due to serotonergic and antiplatelet activity.

Clinical Applications of Nootropics

Nootropics have gained widespread attention due to their diverse clinical applications in both healthy individuals and patients with neurological disorders.

1. Cognitive Enhancement in Healthy Individuals

Nootropic agents such as modafinil and racetams have been shown to improve attention, working memory, and executive function in healthy users without causing sedation or dependency.

They are increasingly used as "smart drugs" by students, professionals, and entrepreneurs to enhance productivity and mental performance.

Despite ethical concerns, their use among healthy individuals continues to grow, especially for tasks requiring high cognitive demand.[3]

2. Treatment of Neurodegenerative Disorders (Alzheimer's & Parkinson's Disease)

Many nootropics are being explored for their neuroprotective properties in Alzheimer's disease by improving cholinergic transmission and reducing oxidative stress.

Drugs like Piracetam and Bacopa monnieri (Brahmi) have demonstrated improved memory retention and cognitive function in Alzheimer's patients.

Additionally, several nootropic compounds enhance cerebral blood flow, which is often impaired in Parkinson's and other age-related cognitive disorders.

3. Use in ADHD and Narcolepsy

Nootropics such as modafinil are also prescribed off-label for attention-deficit/hyperactivity disorder (ADHD) and narcolepsy due to their wakefulness-promoting and focus-enhancing effects.

These agents improve sustained attention and reduce impulsivity, making them beneficial for cognitive regulation in ADHD patients.

4. Academic Performance and Memory Boosting

Academic use of nootropics, particularly among university students, is driven by their ability to improve memory consolidation and retrieval.

Herbal nootropics like Bacopa, Ginkgo biloba, and Schisandra have shown promise in enhancing recall and academic performance during stressful study periods.

5. Military, Sports, and Productivity Enhancement

In high-stress professions such as the military, nootropics are employed to maintain alertness, decision-making, and reaction times under fatigue and sleep deprivation .

These agents are also explored in sports and corporate sectors to boost endurance, reduce anxiety, and enhance strategic thinking and focus. [3]

Comparative Analysis of Key Nootropic Drugs

Piracetam is considered the prototype nootropic. It works mainly by modulating neuronal membrane fluidity and enhancing neuroplasticity, which improves learning and memory. However, its clinical efficacy is still debated in large-scale trials.[8]

Modafinil is officially approved for narcolepsy and other sleep-related disorders. It also shows off-label benefits in improving attention and executive functioning in healthy individuals. Despite this, long-term safety data are still limited.[9]

Herbal nootropics such as Bacopa monnieri and Ginkgo biloba act through antioxidant, neuroprotective, and cholinergic mechanisms. Evidence supports their role in mild cognitive enhancement, but variability in dosage standardization and delayed onset reduce their reliability.[11]

Psychostimulants like methylphenidate and amphetamines provide rapid improvements in working memory and attention, especially in ADHD patients. However, they carry risks of dependence, tolerance, and ethical controversy when misused for non-medical cognitive.[18]

Ethical debates highlight that natural nootropics are safer but slower in effect. In contrast, synthetic drugs like modafinil or methylphenidate raise issues of fairness, coercion, and long-term neurobiological risks.[12]

Therefore, no single nootropic is universally suitable for all cognitive demands. The choice of agent must consider efficacy, safety, accessibility, and ethical [15]

Safety, Side Effects, and Ethical Considerations

The safety profile of nootropic drugs varies greatly depending on their pharmacological class, dosage, and duration of use. Piracetam and related racetams are generally considered safe with mild adverse effects such as headaches, gastrointestinal discomfort, and insomnia.[8]

Modafinil is regarded as relatively well tolerated, but it can cause insomnia, anxiety, headaches, and in rare cases, cardiovascular complications, raising concerns over long-term use in healthy individuals.[9]

Herbal nootropics such as Bacopa monnieri and Ginkgo biloba are associated with fewer side effects. However, they may interact with other medications and produce mild gastrointestinal upset or nausea when taken in higher doses.[11]

Psychostimulants like methylphenidate and amphetamines carry higher risks including dependence, tolerance, appetite suppression, insomnia, and cardiovascular strain, which restricts their use in non-clinical populations.[18][19]

From an ethical standpoint, the non-medical use of nootropics for cognitive enhancement raises debates about fairness, coercion, and social inequality. Critics argue that their use may create competitive pressure in academic and professional settings, giving unfair advantage to some individuals.[12][13]

Additionally, concerns have been raised about the long-term effects of cognitive enhancers on brain development, especially in younger users, where safety data remain insufficient .[16]

Therefore, while nootropics offer potential cognitive benefits, responsible regulation, patient education, and ethical guidelines are essential to balance their risks and benefits in both therapeutic and non-medical contexts.[17][21]

Conclusion

Nootropic drugs represent a rapidly expanding area of pharmacological and clinical interest, offering the potential to enhance memory, attention, learning, and overall cognitive performance. Evidence from both synthetic agents such as piracetam, modafinil, and methylphenidate, and natural compounds such as Bacopa monnieri and Ginkgo biloba, highlights their diverse mechanisms of action and therapeutic applications. While these agents show promising results in managing neurological and psychiatric disorders, their non-medical use for cognitive enhancement in healthy individuals continues to generate debate regarding safety, long-term outcomes, and ethical acceptability. Current findings suggest that although most nootropics demonstrate relatively favorable safety profiles, adverse effects such as insomnia, gastrointestinal disturbances, cardiovascular risks, and potential for dependence cannot be overlooked. Moreover, ethical concerns surrounding fairness, social inequality, and the pressure to enhance cognition underscore the importance of regulatory and societal oversight. Future research should focus on well-controlled clinical trials to clarify efficacy, establish standardized safety profiles, and evaluate the neurobiological consequences of prolonged use. In conclusion, nootropics hold significant promise as therapeutic and cognitive-enhancing agents, but their responsible development, regulation, and ethical application are essential to ensure that the benefits outweigh the risks for both patients and healthy users.

ACKNOWLEDGEMENT

I would like to thank all the authors who came together for the fulfilment of this project. All my capable fellows have dedicated their hard work, knowledge and skillset for this result.

I would also like to thank our mentor, who guided, encouraged and led us throughout this review paper.

Lastly, I would like to thank all the authors, and publications using whose knowledge we came up with this project.

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