The Pharmacology of Smart Drugs

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Financial Disclosure

- Dr. Jessica Brandes, ND has no financial disclosures or affiliations with manufacturers in this presentation.
The Rise of Smart Drugs

1 in 5 have used drugs to stimulate their focus, concentration or memory
- Nature 2008 Survey
Google searches over time

2011 Movie “Limitless”

2007 to 2016

Mainstream media coverage


• Nootrobox raises $2.3M in venture equity (2015), truBrain raises $1.6M (2015).
What We’re Not Talking About Today

- **Adderall** - Stimulant-related emergency hospital visits rose 300% between 2005 and 2011\(^1\). Prescriptions increased 2.5x between 2007-2011.

- **Methylphenidate** - The U.S. produces and consumes 85% of the world’s methylphenidate supply.

- **LSD microdosing** - HuffPost and Forbes reports of its use to increase productivity and mood when taken at 1/10 normal dose. All supplies purchased on “dark web”.

Cognitive Enhancers and Nootropics
Some examples

<table>
<thead>
<tr>
<th>Cognitive Enhancers</th>
<th>Nootropics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Caffeine</td>
<td>• Amino acids</td>
</tr>
<tr>
<td>• Nicotine</td>
<td>• Mushrooms</td>
</tr>
<tr>
<td>• Modafinil</td>
<td>• Botanicals</td>
</tr>
<tr>
<td>• Methylphenidate</td>
<td>• Nutraceuticals</td>
</tr>
<tr>
<td>• Adderall</td>
<td>• Racetams</td>
</tr>
</tbody>
</table>

All nootropics are cognitive enhancers… but not all cognitive enhancers are nootropics.
5 characteristics of Nootropics

• Enhance learning and memory
• Few side effects & extremely low toxicity.
• Protect the brain from physical or chemical injury like concussions, barbiturates or scopolamine
• Increase the efficacy of neuronal firing
• Help brain function under disruptive conditions such as electroconvulsive shock or hypoxia
Racetam Family

- Family of chemicals used in the enhancement of cognition and memory
- Developed by Dr. Corneliu Giurgea in 1964 and originally inspired by the quest of identifying a new sleeping pill.
- Cyclic derivative of GABA.
- Possessed no sedative like effects in trials. Instead, inhibited nystagmus and vertigo.
- Human trials (1966) on post-concussive patients with noted improvement in memory and cognition with long term use.²

Piracetam

Cognitive and memory formation improvement particularly in individuals suffering from age related cognitive decline.
Piracetam Clinical Research

- Piracetam offers antioxidant protection to brain cells in specific regions\textsuperscript{10}

- Increased local blood flow and oxygen and glucose delivery to brain tissue, increased GABA\textsuperscript{11}

- Studies show preservation of cognitive decline in organic degenerative diseases. Additional uses include: breath holding spells\textsuperscript{12}, dyslexia, post-concussive, post cerebral ischemia\textsuperscript{13} and TBI.

Properties of Piracetam

- Classification: Cyclic GABA derivative, water soluble

- Dose: 600mg TID up to 1,600mg TID, potential need for loading dose due to time needed to increase receptors.

- MOA: Acetylcholine receptor stimulant.
  Neuronal: Piracetam modulates neurotransmission in a range of transmitter systems (including cholinergic and glutamatergic), has neuroprotective and anticonvulsant properties, and improves neuroplasticity. Vascular: it demonstrates reduced erythrocyte adhesion to vascular endothelium, hinders vasospasm, and facilitates microcirculation.\textsuperscript{9}
Oxiracetam

Increased focus and memory formation. Anecdotal evidence of visual and auditory sensory enhancement.

Oxiracetam Clinical Research

- Increase Long Term Potentiation, slight increase in testosterone, and positive modulation of AMPA receptors.\textsuperscript{14, 15, 16}

- Stimulates Protein Kinase C, intracellular intermediate of memory formation.\textsuperscript{17}

- Reduce effects of cognitive decline in elder populations with a particular efficacy towards verbal learning.\textsuperscript{18}

- Neuroprotective when used in pre-treatment against trimethyltin (organic neurotoxin).\textsuperscript{19}

- Potential repair from neuronal damage from chronic alcohol use
Properties of Oxiracetam

- Classification: GABA analogue 5x more potent than piracetam
- Dose: 200-800mg BID-TID. Up to 1,600mg daily with no side effects.
- MOA: Oxiracetam serves to support phospholipid metabolism, positively modulate AMPA receptors, and interacts with neurotransmitter release, potentiates acetylcholine release.
- Side effects and adverse effects similar to piracetam.

Aniracetam

Enhances holistic thinking like brainstorming and problem solving. Improved judgment, reduced impulsiveness, decreased anxiety or social failure, and possesses anti-depressant properties.
Aniracetam Clinical Research

- Increases blood flow to the association cortex. Increases release of dopamine and serotonin in prefrontal cortex. Improved judgement and reduces impulsiveness.\textsuperscript{21}

- Upregulate and mobilize BDNF-potentially increasing neuroplasticity.\textsuperscript{22, 23}

- Anti-depressant effects\textsuperscript{24}

- Anxiolytic properties\textsuperscript{25}

Properties of Aniracetam

- Classification: AMPA kinase, fat soluble, very short half life subject to first pass metabolism.

- Dose: 400mg common start, 500-750mg BID max.

- MOA: positive modulator of AMPA receptors\textsuperscript{20}, mediates interaction between cholinergic, dopaminergic and serotonergic systems.

- Side Effects and adverse reactions similar to parent compound.
Phenylpiracetam

Cognitive (R-isomer) and physical enhancement: increases cold and extreme stress tolerance. CNS stimulant, most neuroprotective.

Properties of Phenylpiracetam

• Classification: Psychostimulatory phenyl-derivative of piracetam. More potent (60x), more neuroprotective, physical enhancement.

• Dose: 200-300mg BID, half-life 2.5-3 hours, R-isomer > racemic mixture. No loading period.

• MOA: increases the density of nicotinic acetylcholine, GABA, dopamine and N-methyl-D-aspartate receptors.

• Banned by the World Anti-Doping Agency for improving tolerance to cold and extreme stress.26
Phenylpiracetam Clinical Research

- Improvement in function (physical and cognitive) in persons who suffered from strokes.\textsuperscript{27}
- Some antidepressant qualities at 100mg BID.\textsuperscript{28}
- Study suggests there may be immunosupportive qualities as identified by reducing anxiety and fear response.\textsuperscript{29}

Nefiracetam

Promotes memory formation with daily supplementation, does not work acutely.
Properties of Nefiracetam

• Dose: 150-450 per day max. Demonstrates increased ability to form memories when taken long term (7 day min). Fat soluble.

• MOA:
  Nefiracetam appears to modulate signalling via the glycine binding site of the NMDA receptor, and it is thought to be a partial agonist (rather than allosteric modulator) since it does not work nicely with other ligands such as glycine. Very weak effect on AMPA receptors. PKC activation.

• Extremely toxic to dogs (renal necrosis), but not rats or monkeys.

Noopept

Mild cognitive boost and physcostimulatory effect while promoting cognitive health and memory.
Noopept Clinical Research

- Improves MMSE scores and was effective in persons with post-traumatic cerebral insufficiency (Piracetam was only effective in those with vascular disease and not trauma patients).\(^{33}\)

- Classification: di-peptide conjugate. 1,000x potency. A Cycloprolylglycine pro-drug.\(^{32}\)

- Dose: 10-30mg daily. Safe for up to 56 days. 2 weeks use for eval. Mega dosing leads to brain fog.

- Not technically a racetam.

Acetylcholine

- Acetylcholine in the brain alters neuronal excitability, influences synaptic transmission, induces synaptic plasticity, and coordinates firing of groups of neurons.
Acetylcholine

- Potentiates behaviors that are adaptive to environmental stimuli.
- Decreases responses to ongoing stimuli that do not require immediate action.
- Promote burst firing, suppress tonic firing.
- Contributes to synaptic plasticity.\(^3\)

Properties of Acetylcholine

- Alpha-GPC and phosphatidylcholine are comparable in bioavailability. Alpha-GPC also increases growth hormone for 2 hours following ingestion.\(^4\)
- Dosage: 400-550mg TID up to 1,200mg-1,650mg daily
- Adverse effects begin around 3,500mg daily and include: dizziness, high blood pressure, sweating, and impaired liver function
Acetylcholine Clinical Research

• Enhanced MMSE and cerebrovascular flow from 1,000mg/day citicoline.⁵

• Citicoline improved processing speed, working memory, verbal learning, verbal memory, and executive function in low baseline performers.⁶

• Acute dosage of CDP-Choline enhanced cognitive function as identified by monitoring resting state brain oscillations in healthy volunteers.⁷

• Supplementation including Alpha-GPC maintains reaction time, and subjective feelings of focus and alertness to both visual and auditory stimuli in healthy college students.⁸

Nootropic Stacks

• Take two or more nootropics and combine them to achieve synergistic effects that achieve a desired effect

• Choline is one of the most common ingredients in a stack due to the mechanism of action
Types of Choline

- Soy lecithin-2.5-9.5% choline by weight
- CDP-Choline (citicoline)-18% choline by weight, but it also a uridine precursor
- Phosphatidylcholine-13% choline by weight, most common food source
- Alpha-GlycerophosphoCholine-40% by weight, reliably crosses blood brain barrier
- Choline Bitartrate-40% by weight, but ineffective conversion

Non-Nootropic Cognitive Enhancers
Common Cognitive Enhancers

• Caffeine
• Nicotine
• Modafinil
• Methylphenidate
• Adderall

Making the most of caffeine

• World’s most popular drug
  (92-98% of people in North America consume caffeine)

• Antagonizes adenosine receptors. Its effects also induce changes in acetylcholine and dopamine systems, and interact with the serotonergic system

• L-theanine (80-200mg) is synergistic with caffeine in regards to attention switching and alertness and reduces susceptibility to distractions. 1:1 or 2:1 ratio is common
Nicotine as cognitive enhancer

• Meta-analysis repeatedly demonstrated improvements in memory (working and episodic), alerting attention (accuracy, response, and orienting), and motor abilities.\(^{38}\)

Nicotine Clinical Research

• Reliable improvements in attention are seen with various doses of nicotine in a somewhat dose-dependent manner. Improvements in directing and keeping attention on stimuli are seen with improved accuracy.\(^{38}\)

• Improvements in memory, specifically short-term episodic memory, have been found to be significant in a meta-analysis on nicotine.\(^{38}\)

• Improvement in cognition, reduced anxiety when associated with cognitive decline.\(^{39}\)

• Enhance the reward response to non-drug stimuli and has been shown to reduce neural fatigue.\(^{40, 41}\)
Properties of Nicotine

- Sources: patch < gum < inhaler
- Classification: parasympathomimetic alkaloid from the solanaceae family.
- Dose: 1mg-21mg, average cigarette contains 10-14mg, but only 1-1.5mg makes it into circulation. Detection in brain tissue within 10-20 seconds of inhalation.
- MOA: activation of nicotinic acetylcholine receptors (nAChRs) and dopimanergic receptors.\textsuperscript{34, 35}
- Side Effects: increased HR, BP, LH, Prl, possible addiction, though risk is directly proportional to quantity and speed at which it crosses the BBB.\textsuperscript{36, 37}

Modafinil

Sustained attention, cognitive control, and working memory. Used by the Air Force for fighter pilot alertness.
Modafinil Clinical Research

- Modafinil administration facilitated sustained attention, cognitive control, and working memory.\textsuperscript{42}
- Armodafinil improves alertness, overall clinical condition, and long term memory.\textsuperscript{43}
- Improves learning and memory by enhancing glutamatergic excitatory synaptic transmission and inhibiting GABAergic inhibitory synaptic transmission.\textsuperscript{44}
- Resting-state imaging studies have shown modafinil intake increases regional blood flow.\textsuperscript{45}
- Improved verbal short-term memory\textsuperscript{46}, improved learning rates and accuracy due to better orientation of sustained attention.\textsuperscript{47}

Forms of Modafinil

- Armodafinil>Modafinil>Adrafinil
- Armodafinil is R-isomer and has a reduced dose: 50-250mg daily.
- Modafinil is racemic mixture 100-400mg daily. 15 hour half-life.
- Interacts with triazolam and ethinylestradiol, reduces effectiveness of OCPs and methadone.
Further Considerations on Modafinil

- SNP evaluation to determine efficacy. COMT V158M rsID: rs4680. Homozygous Val (G/G) genotypes maintain executive function and vigilant attention better than homozygous Met (A/A) genotypes, who may have little to no response.\(^{48, 49}\)

- Neural plasticity suffers with modulating use in developing brains. Not to be utilized safely until completion of development of the prefrontal cortex, ages 25+.\(^{50}\)

Properties of Modafinil

- Classification: Eugeroic. Wakefulness-promoting agent.

- Dose: 100-200mg tablets. Up to 400mg in extreme cases, though no evidence it confers clinical benefit.

- FDA-approved for Obstructive Sleep Apnea (OSA), Narcolepsy and Shift Work Disorder (SWD).

- Reduced dose with hepatic impairment, warnings for SJS, TEN. Agiodema warnings with armodafinil.

- C/I in individuals with hypersensitivity to modafinil, not recommended with LVH, or MVP
Conclusion

• Smart drug usage is broad and increasing quickly
• Strong research on many compounds suggesting good efficacy and safety profiles
• Smart drugs in need of broader research in healthy adult subjects
• Risk:Reward ratio needs to be considered on an individual basis

References


