# The Pharmacology of Smart Drugs

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# Financial Disclosure

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# 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


2007 to 2016

# Mainstream media coverage

- Recent publications in Harvard Business Review, The Guardian, Forbes, The New York Times, Science Alert, Scientific American, The Stanford Daily, Intelligence Squared, Huffington Post, Rolling Stone, Motherboard, The Atlantic, Observer, etc
- 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

**Cognitive Enhancers**

- Caffeine
- Nicotine
- Modafinil
- Methylphenidate
- Adderall

**Nootropics**

- Amino acids
- Mushrooms
- Botanicals
- Nutraceuticals
- **Racetams**

All nootropics are cognitive enhancers…
but not all cognitive enhancers
are nootropics.

# 5 characteristics of Nootropics

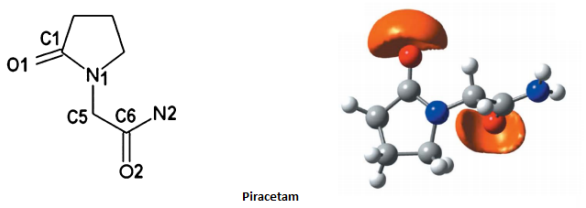
- Enhance learning and memory
- Few side effects & extremely low toxicity.
- Protect the brain from physical or chemical injury like concussions, barbiturates or scopolamine
- Increase the efficacy of neuronal firing
- Help brain function under disruptive conditions such as electroconvulsive shock or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

# Nootropics

# 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




Piracetam

*( Modified from: Tilborg A, et al. Structural study of piracetam polymorphs and cocrystals: crystallography redetermination and quantum mechanics calculations. Acta Crystallogr B. (2011) )*

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

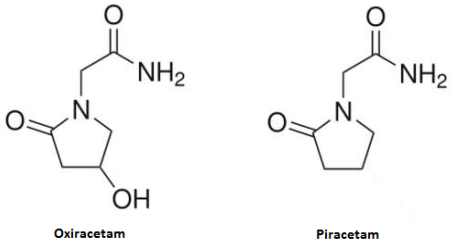
# Piracetam Clinical Research

- Piracetam offers antioxidant protection to brain cells in specific regions[10]
- Increased local blood flow and oxygen and glucose delivery to brain tissue, increased GABA[11]
- Studies show preservation of cognitive decline in organic degenerative diseases. Additional uses include: breath holding spells[12], dyslexia, post-concussive, post cerebral ischemia[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.[9]

# Oxiracetam




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

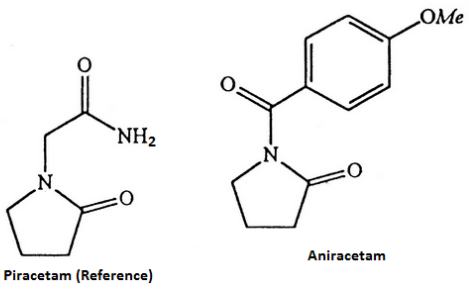
# Oxiracetam Clinical Research

- Increase Long Term Potentiation, slight increase in testosterone, and positive modulation of AMPA receptors.[14, 15, 16]
- Stimulates Protein Kinase C, intracellular intermediate of memory formation.[17]
- Reduce effects of cognitive decline in elder populations with a particular efficacy towards verbal learning.[18]
- Neuroprotective when used in pre-treatment against trimethyltin (organic neurotoxin).[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




Piracetam (Reference)

Aniracetam

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

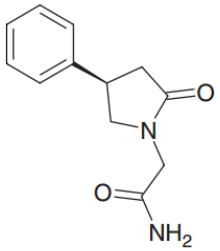
# Aniracetam Clinical Research

- Increases blood flow to the association cortex. Increases release of dopamine and serotonin in prefrontal cortex. Improved judgement and reduces impulsiveness.[21]
- Upregulate and mobilize BDNF-potentially increasing neuroplasticity.[22, 23]
- Anti-depressant effects[24]
- Anxiolytic properties[25]

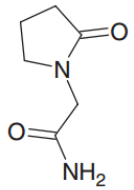
# Properties of Aniracetam

- Classification: AMPAkine, 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[20], mediates interaction between cholinergic, dopaminergic and serotonergic systems.
- Side Effects and adverse reactions similar to parent compound.

# Phenylpiracetam



Phenylpiracetam



Piracetam (Reference)

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

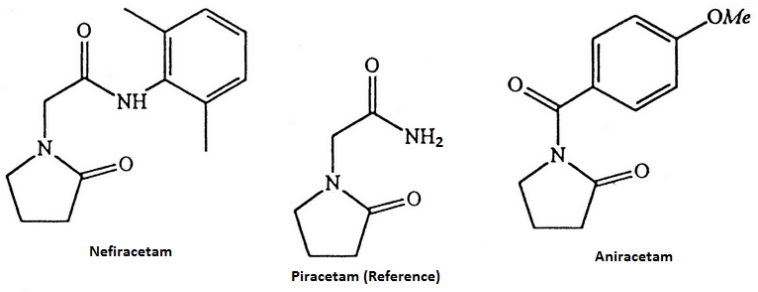
# Properties of Phenylpiracetam

- 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.[27]
- Some antidepressant qualities at 100mg BID.[28]
- Study suggests there may be immunosupportive qualities as identified by reducing anxiety and fear response.[29]

# Nefiracetam

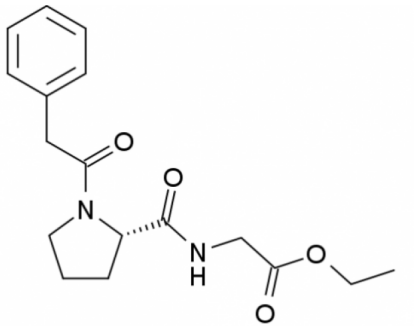



Promotes memory formation with daily supplementation, does not work acutely.

# Properties of Nefiracetam

- Dose: 150-450 per day max. Demonstrates increased ability to form memories when taken long term (7 day min).[30] 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.[31]

# Noopept

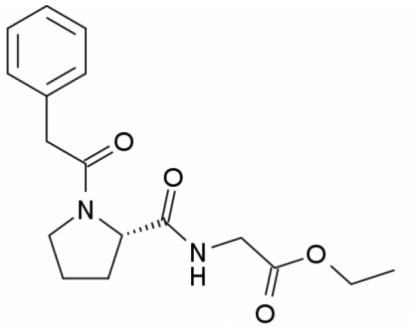



Mild cognitive boost and physcostimulatory effect while promoting cognitive health and memory.

# 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]

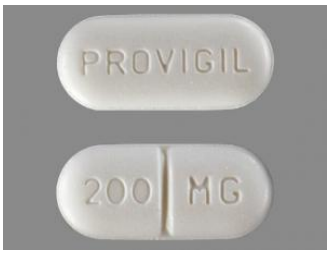
# Nicotine Clinical Research

- 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.[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.[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.[42]
- Armodafinil improves alertness, overall clinical condition, and long term memory.[43]
- Improves learning and memory by enhancing glutamatergic excitatory synaptic transmission and inhibiting GABAergic inhibitory synaptic transmission.[44]
- Resting-state imaging studies have shown modafinil intake increases regional blood flow.[45]
- Improved verbal short-term memory[46], improved learning rates and accuracy due to better orientation of sustained attention.[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.
- MOA: sympathomimetic-like agent. Not identical to sympathomimetic amines. Selective, relatively weak, atypical dopamine reuptake inhibitor.
- 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


[1] http://www.samhsa.gov/newsroom/press-announcements/201308080100

[2]Giurgea, Corneliu. "The Nootropic Concept and Its Prospective Implications." Drug Development Research. (1982): 441-446.

[3]Verma DK, Joshi N, Raju KS, Wahajuddin M, Singh RK, Singh S.
Metabolic enhancer piracetam attenuates rotenone induced oxidative stress: a study in different rat brain regions. Acta Neurobiol Exp (Wars). 2015;75(4):399-411.

[4]Akopian VP, Balian LS. [Mechanism of action of piracetam on cerebral circulation]. Farmakol Toksikol. 1987 Jan-Feb;50(1):38-41.

[5]Sawires H, Botrous O. Double-blind, placebo-controlled trial on the effect of piracetam on breath-holding spells . Eur J Pediatr. (2012)13.

[6]Güngör L, Terzi M, Onar MK. Does long term use of piracetam improve speech disturbances due to ischemic cerebrovascular diseases . Brain Lang. (2011).

[7]Winblad, B. Piracetam: A Reviewof Pharmacological Properties and Clinical Uses. CNS Drug Reviews. 2005;11(2):169-182.

[8]Marchi M, Besana E, Raiteri M. Oxiracetam increases the release of endogenous glutamate from depolarized rat hippocampal slices . Eur J Pharmacol. (1990).

[9]Satoh M, et al Aniracetam augments, and midazolam inhibits, the long-term potentiation in guinea-pig hippocampal slices . Neurosci Lett. (1986).

[10]Raiteri M, Costa R, Marchi M. Effects of oxiracetam on neurotransmitter release from rat hippocampus slices and synaptosomes . Neurosci Lett. (1992).

[11]Alkon D, Olds J. Protein kinase C: a nexus in the biochemical events that underlie associative learning. Acta Neurobiol. Exp. 1995, 53: 197-207.

[12]Dysken MW, et al. Oxiracetam in the treatment of multi-infarct dementia and primary degenerative dementia . J Neuropsychiatry Clin Neurosci. (1989)

[13]Hlinák Z, Krejcí I. Oxiracetam pre- but not post-treatment prevented social recognition deficits produced with trimethyltin in rats . Behav Brain Res. (2005).

[14]Nakamura K, Kurasawa M, Shirane M. Impulsivity and AMPA receptors: aniracetam ameliorates impulsive behavior induced by a blockade of AMPA receptors in rats.
Brain Res. 2000 Apr 17;862(1-2):266-9.

[15]Arai AC1, Kessler M. Pharmacology of ampakine modulators: from AMPA receptors to synapses and behavior. Curr Drug Targets. 2007 May;8(5):583-602.

[16]Wu X1, Zhu D, Jiang X, Okagaki P, Mearow K, Zhu G, McCall S, Banaudha K, Lipsky RH, Marini AM. AMPA protects cultured neurons against glutamate excitotoxicity through a phosphatidylinositol 3-kinase-dependent activation in extracellular signal-regulated kinase to upregulate BDNF gene expression. J Neurochem. 2004 Aug;90(4):807-18.

[17]Nakamura K, Tanaka Y. Antidepressant-like effects of aniracetam in aged rats and its mode of action. Psychopharmacology (Berl). 2001 Nov;158(2):205-12.

[18]Nakamura K, Kurasawa M. Anxiolytic effects of aniracetam in three different mouse models of anxiety and the underlying mechanism. Eur J Pharmacol. 2001 May 18;420(1): 33-43.

[19]Lawrence JJ, Brenowitz S, Trussell LO. The mechanism of action of aniracetam at synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors: indirect and direct effects on desensitization. Mol Pharmacol. 2003 Aug;64(2):269-78.

[20]Kalinskiĭ PP, Nazarov VV. Use of phenotropil in the treatment of asthenic syndrome and autonomic disturbances in the acute period of mild cranial brain trauma. Zh Nevrol Psikhiatr Im S S Korsakova. (2007)

[21]Koval'chuk VV, et al. Efficacy of phenotropil in the rehabilitation of stroke patients. Zh Nevrol Psikhiatr Im S S Korsakova. 2010;110(12 Pt 2):38-40

[22]Zvejniece L, et al. Investigation into stereoselective pharmacological activity of phenotropil. Basic Clin Pharmacol Toxicol. 2011 Nov;109(5):407-12.

[23]Samotrueva MA, Tyurenkov IN, Teplyi DL, Serezhnikova TK, Khlebtsova EB. Psychoimmunomodulatory effect of phenotropil in animals with immune stress. Bull Exp Biol Med. 2011 May;151(1):51-4.

[24]Woodruff-Pak DS, et al. The long-term effects of nefiracetam on learning in older rabbits. Behav Brain Res. (2002).

[25]Sugawara T, et al. Thirteen-week oral toxicity study of the new cognition-enhancing agent nefiracetam in dogs. Arzneimittelforschung. (1994).

[26]Amelin AV, et al. Noopept in the treatment of mild cognitive impairment in patients with stroke. Zh Nevrol Psikhiatr Im S S Korsakova. 2011;111(10 Pt 1):44-6.

[27]Gudasheva TA, et al. The major metabolite of dipeptide piracetam analogue GVS-111 in rat brain and its similarity to endogenous neuropeptide cyclo-L-prolylglycine. Eur J Drug Metab Pharmacokinet. 1997.

[28]Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron. 2012 Oct 4;76(1):116-29.

[29]Kawamura T, Okubo T, Sato K, Fujita S, Goto K, Hamaoka T, Iemitsu M. Glycerophosphocholine enhances growth hormone secretion and fat oxidation in young adults. Nutrition. 2012 Nov-Dec; 28(11-12):1122-6.

[30]Caamaño J, Gómez MJ, Franco A, Cacabelos R. Effects of CDPcholine on cognition and cerebral hemodynamics in patients with Alzheimer's disease. Methods Find Exp Clin Pharmacol. 1994 Apr;16(3):211-8.

[31]Knott V, de la Salle S, Choueiry J, Impey D, Smith D, Smith M, Beaudry E, Saghir S, Ilivitsky V, Labelle A. Neurocognitive effects of acute choline supplementation in low, medium and high performer healthy volunteers. Pharmacol Biochem Behav. 2015 Apr;131:119-29.

[32]Knott V, de la Salle S, Smith D, Choueiry J, Impey D, Smith M, Beaudry E Saghir S, Ilivitsky V, Labelle A. Effects of acute CDP-choline treatment on resting state brain oscillations in healthy volunteers. Neurosci Lett. 2015 Mar 30;591:121-5.

[33]Hoffman JR, et al. The effects of acute and prolonged CRAM supplementation on reaction time and subjective measures of focus and alertness in healthy college students . J Int Soc Sports Nutr. (2010)

[34]Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology (Berl). (2010)

[35]Newhouse P, et al. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. Neurology. (2012)

[36]Barr RS, et al. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence . Biol Psychiatry. (2008)

[37]Potter AS, Bucci DJ, Newhouse PA. Manipulation of nicotinic acetylcholine receptors differentially affects behavioral inhibition in human subjects with and without disordered baseline impulsivity. Psychopharmacology (Berl). (2012).

[38]Kenny PJ, Markou A. Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. Neuropsychopharmacology. (2006).

[39]Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction . Eur J Pharmacol. (2000).

[40]Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. J Consult Clin Psychol. (1993).

[41]Benowitz, N, et al. Nicotine Chemistry, Metabolism, Kinetics and Biomarkers. Handb Exp Pharmacol. 2009; (192): 29–60.

[42]Gill, M., Haerich, P., Westcott, K., Godenick, K. L. and Tucker, J. A. (2006), Cognitive Performance Following Modafinil versus Placebo in Sleep-deprived Emergency Physicians: A Double-blind Randomized Crossover Study. Academic Emergency Medicine, 13: 158–165.

[43]Hirshkowitz M, Black JE, Wesnes K, Niebler G, Arora S, Roth T. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med. 2007 Mar;101(3):616-27.

[44]Yan WW, Yao LH, Chen C, Wang HX, Li CH, Huang JN, Xiao P, Liu CY. Effects of Modafinil on Behavioral Learning and Hippocampal Synaptic Transmission in Rats. Int Neurourol J. 2015 Dec;19(4):220-7.

[45]Joo et al., 2008Joo, E.Y., Seo, D.W., Tae, W.S., and Hong, S.B. Effect of modafinil on cerebral blood flow in narcolepsy patients. Sleep. 2008; 31: 868–873.

[46]Makris, A.P., Rush, C.R., Frederich, R.C., Taylor, A.C., and Kelly, T.H. Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. Exp. Clin. Psychopharmacol. 2007; 15: 123–133

[47]Pringle, A., Browning, M., Parsons, E., Cowen, P.J., and Harmer, C.J. Early markers of cognitive enhancement: developing an implicit measure of cognitive performan ce. Psychopharmacology (Berl). 2013; 230: 631–638.

[48]Bodenmann S, et al. Pharmacogenetics of Modafinil After Sleep Loss: Catechol-O-Methyltransferase Genotype Modulates Waking Functions But Not Recovery Sleep. Clinical pharmacology & Therapeutics. 2009 Mar: 85(3);296-304.

[49]Dauvilliers Y, Tafti M, Landolt HP. Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. Sleep Med Rev. 2015 Aug;22:47-53.

[50]Urban KR, Gao WJ. Performance enhancement at the cost of potential brain plasticity: neural ramifications of nootropic drugs in the healthy developing brain. Front Syst Neurosci. 2014 May 13;8:38.