Nootropic Medications

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Disclosure

I have received research grants from and/or served as an advisor to several pharmaceutical and health companies. I own stock in Adverse Events Inc, Maxwell Health and Muses Labs whose products are not discussed here.

I will discuss investigational and off-label uses.

Objectives

- What is a nootropic?
- Who is doping?
- What is the evidence
- Where are we headed?

What is a Nootropic?

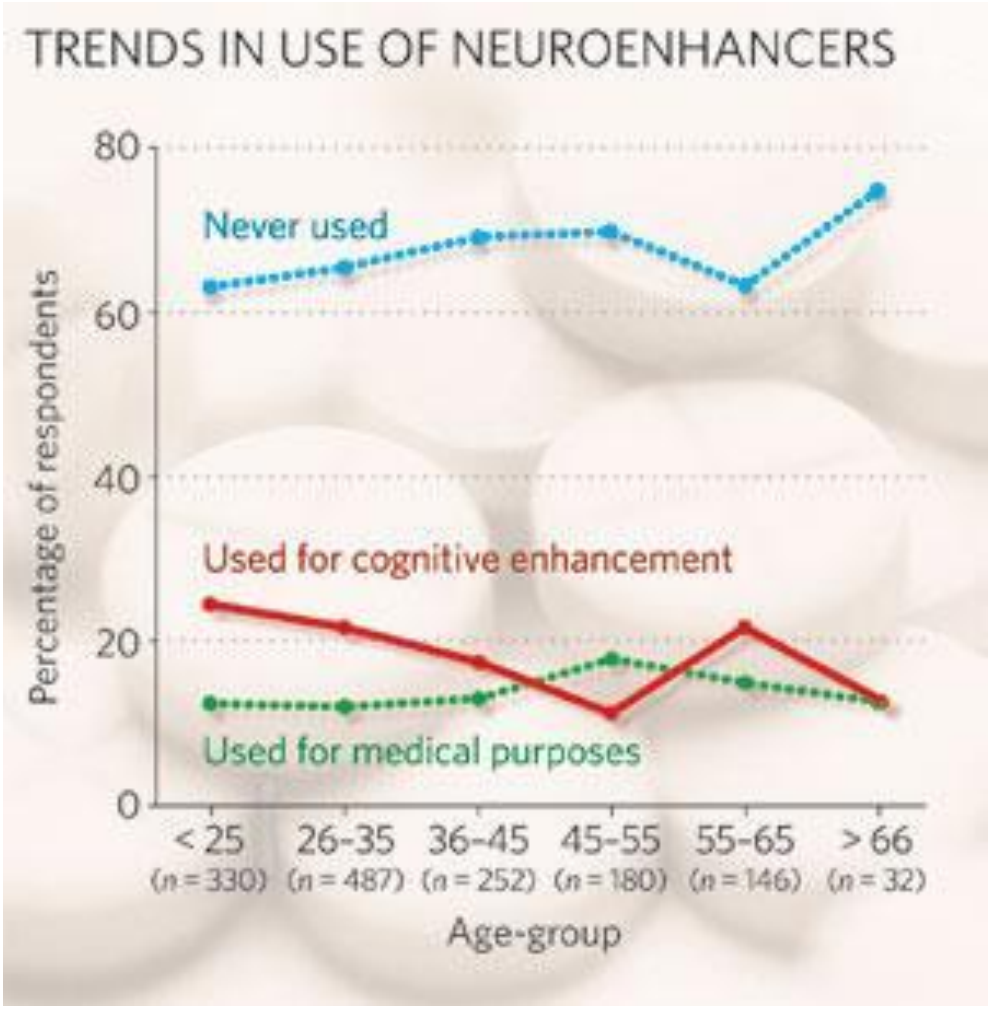
- Nootropic – coined in 1964 by Corneliu Giurgea – “to bend the mind”
  - ↑Learning, ↑executive function and ↑coupling; nontoxic
- Today - Prescription drugs, OTC nutraceuticals, bulk lab chemicals
- No widely accepted definition (“smart drugs”) – “does it matter?”
  - Drugs that enhance “cold” cognition (e.g. attention, speed, memory, spatial)
  - Drugs that enhance neuronal health (e.g. blood flow, NGF) or cognitive reserve
  - Drugs that optimize “hot” cognition, social cognition, decision making, IQ

Yerkes-Dodson Law, 1908

Classes of Nootropics

- Racetams (e.g. piracetam)
- Cholinesterase Inhibitors (e.g. donepezil)
- Phenylethylamines (e.g. methylphenidate)
- Eugeroics (e.g. modafanil)
- Nicotine (e.g. smoking)
- Xanthines (e.g. coffee, Red Bull)
- MAO-B inhibitors (e.g. selegiline)
- Phosphatidylserine (2003 FDA qualified health status)
- Monoaminergic agents (e.g. atomoxetine, bupropion)
- Ampakines (e.g.
- Others

Who is using “smart drugs”?



Poll of 1,600 adults - 60 countries

- 80% said healthy adults should be able to take it if they wanted to
- 69% said they would risk mild side effects

Source: Nature 2008

Cholinesterase Inhibitors: RCTs in Normals

- 1978 – Physostigmine enhances memory acutely in normal individuals
  (Davis KL et al. Science 1978)
- Current view: expectations outweigh actual benefits
  - 20 RCTs in all ages, only 4 in elderly
  - N=18, flight performance of middle aged pilots “maintained” by 5 mg DON
  - N=20, delayed recall improved by 5 mg DON after 6 weeks (elderly)
  - N=26, memory and speed worsened by DON 10 mg after 2 weeks (elderly)
- Side effects: GI, cardiac, syncope

Repantis D et al. Pharmacol Res 61, 473, 2010

Beglinger LJ et al. J Clin Psychoph 25(2), 2005

Phenethylamines: RCTs in Normals

- 1920-1950: Amphetamine noted to enhance arousal, speed, working memory (and make boring tasks fun)
  - Banned in sport competitions but "Go-to" drug for military missions
- 46 RCTs (*Repantis D et al. Pharmacol Res 62, 2010)*
  - Only 3 small RCTs in normal elderly
  - N=53, 5-30 mg MPH, 6-weeks, no benefits
  - N=60, 20-40 mg MPH, no memory benefits, 40 mg increased alertness
  - Post-training MPH improves memory retention *(PNAS 2008)*
  - N=60, RCT of MPH 20 mg in AD showed small benefit on attention *(Lanctot KL et al. Int Psychogeriatr 2014)*
- Side effects: cardiac, dependence, etc.

Eugeroics: RCTs in Normals

- 1998-2003: Modafanil approved for narcolepsy, shift work sleep disorder; rejected by FDA for ADHD.
- Promotes vigilance and enhances working memory in shift workers
  - Banned in sport competitions but “Go-to” drug for military missions
- 45 RCTs (*Repantis D et al. Pharmacol Res 62, 2010)*
  - Two small elderly studies (N=10, N=45) of 100 mg dose – no consistent benefits
  - Wakefulness and attention improves in sleep-deprived people
  - Greater benefit in those performing at lower levels ?
- Side effects: skin reactions, abuse

Conclusions

- Sizable demand for both episodic and continuous use
- Perceptions of efficacy exceed evidence
    - No large well controlled studies in normal elderly
    - Real world benefits not established (except in those impaired)
    - Risks (e.g. cardiac) in elderly likely greater than in young
- DOD has been main funder, mostly nonpublic
- Development of further evidence is recommended
    - Combinations of nootropics
    - Variability based on age, genotype, metabolism
    - Dosing