Advanced ADHD and prescription stimulants: *challenging the myth of cognitive enhancement*

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Take home message

WHY TREAT ADHD?

- ADHD is an *attention regulation disorder* affecting higher order cognition
- Stimulants have very high effect side in ADHD
- Don't overlook ADHD diagnosis, treatment ameliorates :
  - Outcomes (SUD, obesity, suicidality, car wrecks, accidents, ER visits, unwanted pregnancies, STDs)
  - ADHD underlying condition for a lot of problems:
    - Psychiatric: "treatment resistant"
    - Medical :"poorly controlled diabetes
    - Substance Use Disorders

PRESCRIPTION STIMULANTS ARE NOT STRONG ENHANCERS AND NOT THAT FUN TO GET HIGH WITH:

- In spite of popular opinion *stimulants are not strong cognitive enhancers*
- Alone, stimulants are not particularly euphorigenic drugs of abuse

World Federation of ADHD International Consensus Statement: 208 Evidence-based Conclusions about the Disorder

Summary of Findings

Findings	Items
The syndrome we now call ADHD has been described in the medical literature since 1775.	1 – 13
When made by a licensed clinician, the diagnosis of ADHD is well-defined and valid at all ages, even in the presence of other psychiatric disorders, which is common.	14–19
ADHD is more common in males and occurs in 5.9% of youth and 2.5% of adults. It has been found in studies from Europe, Scandinavia, Australia, Asia, the Middle East, South America, and North America.	20–25
ADHD is rarely caused by a single genetic or environmental risk factor but most cases of ADHD are caused by the combined effects of many genetic and environmental risks each having a very small effect.	26–62
People with ADHD often show impaired performance on psychological tests of brain functioning, but these tests cannot be used to diagnose ADHD.	63–70
Neuroimaging studies find small differences in the structure and functioning of the brain between people with and without ADHD. These differences cannot be used to diagnose ADHD.	71–77
People with ADHD are at increased risk for obesity, asthma, allergies, diabetes mellitus, hypertension, sleep problems, psoriasis, epilepsy, sexually transmitted infections, abnormalities of the eye, immune disorders, and metabolic disorders.	78–100
People with ADHD are at increased risk for low quality of life, substance use disorders, accidental injuries, educational underachievement, unemployment, gambling, teenage pregnancy, difficulties socializing, delinquency, suicide, and premature death.	101–136
Studies of economic burden show that ADHD costs society hundreds of billions of dollars each year, worldwide.	137–147
Regulatory agencies around the world have determined that several medications are safe and effective for reducing the symptoms of ADHD as shown by randomized controlled clinical trials.	148–157
Treatment with ADHD medications reduces accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, educational underachievement, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage pregnancy.	158–177
The adverse effects of medications for ADHD are typically mild and can be addressed by changing the dose or the medication.	178–189
The stimulant medications for ADHD are more effective than non-stimulant medications but are also more likely to be diverted, misused, and abused.	189–194
Non-medication treatments for ADHD are less effective than medication treatments for ADHD symptoms, but are frequently useful to help problems that remain after medication has been optimized.	195–208

Neurosci Biobehav Rev. 2021 Sep; 128: 789–818.
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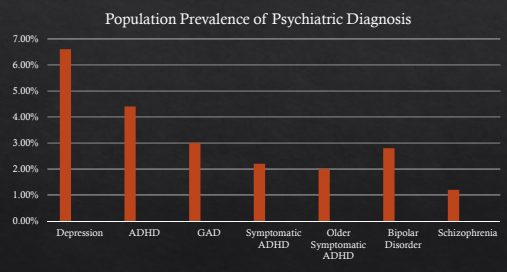
Prevalence of ADHD in Adults

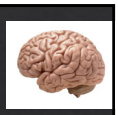
- 3-7% of school age children
- 33-66% have persisting symptoms into adulthood: environment and external supports /coping strategies affect whether many cases become symptomatic and treatment is sought
- 4.4% of general adult population
- ADHD generally still *under* diagnosed (10.9% received treatment in 2006)-though over-diagnosed by rogue telemedicine companies
- 35% not diagnosed until adulthood: *higher IQ linearly associated with a later diagnosis*
- *Lack of structure during pandemic prompted clinic presentation*

DSM-IV-TR 4th ed.
Kessler,R, National Comorbidity Survey, Am J Psychiatry, 2006.

ADHD is the 2nd most common Psychiatric condition



CNS difference in ADHD



Structural MRI: *smaller volumes*

- Prefrontal cortical region
- Basal Ganglia
- Corpus callosum
- Cerebellum

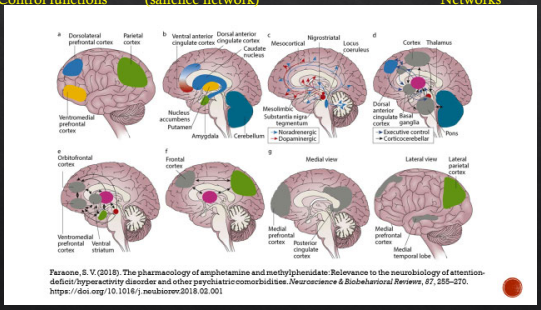
Functional MRI: *hypoactivation*

- Prefrontal cortex
- Caudate nucleus
- Cerebellum
- Parietal Cortex

Faraone , S. The pharmacology of amphetamineas . Relevance to Neurobiology of ADHD . Neuroscience and Beh. Rev. ,2018

Connecting hypoactivation to ADHD symptomatology

Cortical Cognitive Control functions | Fronto-striatal circuits (salience network) | DA+NE Circuits | Executive Control Networks



Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255–270. https://doi.org/10.1016/j.neubiorev.2018.02.001

Reward Network | Alerting Network | Default Mode Network

Stimulants Mechanism of Action

Methylphenidate

- Inhibit DA transporter
- Inhibit NE transporter
- Agonist at 5HT1A receptor
- Binds Alpha 2 adrenergic receptor to simulate cortical excitability(precognitive effect)

Amphetamine

- DAT blocker
- NET blocker
- Increase DA vesicular release (effect at vesicular monoamine transporter) VMAT
- Inhibits MAO activity
- Downstream effects on:
  - Ach
  - 5HT
  - Opioid receptors
  - Glutamate receptors

Stimulants affect networks differently in ADHD and controls

In healthy men, increases activation in

- Dorsal attention network (DAN)
- Deactivates the default mode network (DMN)
- Frontostriatal pathways

(Faraone, et.al, 2020

In subjects with ADHD, enhances activity in

- Fronto-parietal networks
- Salience and memory networks
- dACC
- Dorsolateral PFC
- Anterior insula
- Parietal cortex
- Hippocampus
- Striatum

Neuropsychiatric correlates in ADHD

Enhance under-activated functional connectivity and executive control

- Improve strategic planning, working memory
- Improve attention orientation, shifting, maintenance
- Increase sense of reward in boring tasks, reduce irrepressible need for immediate reward
- Facilitate activation and task completion
- Reduce distraction by inappropriate shifting into DMN

DSM-5 ADHD diagnosis



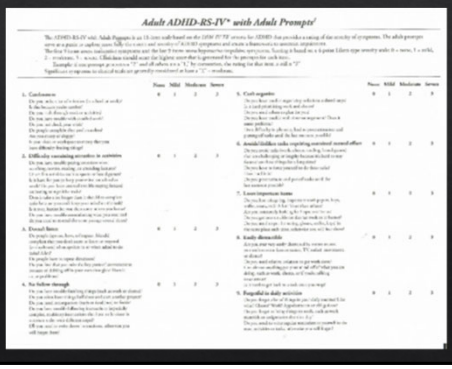
- 5 or more:
  - Inattentive symptoms(predominately inattentive type)
  - Hyperactive/ impulsive symptoms(predominantly Hyperactive/impulsive type)
  - Both(combined type).
- **Lifelong disorder** (DSM-5 symptoms before age 12)
- Constant
- Persistent across 2 or more settings
- **Impair functioning**
- **Diagnosis of exclusion: does not occur during active psychosis, mood disorder, anxiety disorder PD, SUD intoxication /withdrawal , sleep disorder, neurologic disorder, drug reaction)**
- **Attention is a complex entity: includes sustained attention, shifting attention, salient attention, hyperfocus, and filtering attention**

*Pictures from Bing

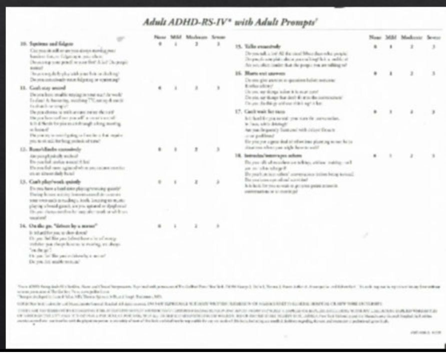
Diagnosis

- Scales:
  - To diagnose: ADHD-RS for adults 5/12 in often to very often range
  - To follow: ASRS Adult self report scale: Look for 50% reduction in symptoms
- Neuropsych testing—Cost is $2400
  - Standard of Care: Diagnosis by clinical interview
  - False negatives on testing
  - Testing useful for LD, IQ, Executive function, head trauma
  - *EF Behavioral rating scales most correlate with function*

DSM-5 Inattentive Symptoms


Adult ADHD-RS-IV with Adult Prompts†*

DSM-V Hyperactive /impulsive symptoms



Adult ADHD-RS-IV with Adult Prompts†*

None Mild Moderate Severe

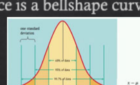
Differential Diagnosis for ADHD

1. **Medication Effects**
   Decongestants
   Psychostimulants (prescribed, illicit)
   Theophylline
   Caffeine
   CNS sedatives, sleep agents
   Pain meds, psychopharmacologic agents
2. **Alcohol/Substance Abuse**
   Intoxication
   Withdrawal
3. **Medical**
   Sleep apnea (loud snoring, apneic periods, morning confusion)
   Narcolepsy (sleep attacks, sleep paralysis, hypnogogic, hallucinations, cataplexy)
   Head trauma
   Meningitis, Encephalitis
   Neurological events (signaled by focal neurologic signs)
   AIDS related cognitive problems
   Dementia (new onset cognitive changes)
   Seizure Disorder
   Thyroid Disease
   Hearing loss
   Metabolic imbalance
   Anoxia
   Low Testosterone
4. **Psychiatric**
   Depression (depressed mood, lack of pleasure and interest, sleep and weight changes, low energy, thoughts of death)
   Antisocial Personality Disorder (sociopathy)
   Thought Disorder (delusions, hallucinations, mind control)
   Bipolar Disorder
   Anxiety Disorder
5. **Congenital Disorders**
   Learning Disability
   Autism, P.D.D.
   Tic or Tourette's
   Genetic disorders (Turners)
   Neonatal events (anoxia)

Medical Problems Presenting Relative Contraindications to Stimulants
Hypertension
Cardiac conduction abnormalities
Ischemic heart disease
IHHS
Narrow angle glaucoma
Pregnancy
Tourette's, Tics
Severe anxiety, psychosis
Preadolescent, short stature

Miscellaneous facts about diagnosis

- Intelligence is a bellshape curve, the diagnosis exists across IQ spectrum



- DSM principle: are symptoms affecting *functioning* in social, occupational, academic areas
- Average attention span is ~50 minutes; 18 min for full retention
- Distractibility is most common symptom, best screener
- Encourage adaptive compensatory obsessive behaviors; true OCD symptoms serve no function

Malingering ADHD

- 65-85% of stimulants acquired by diversion from friends, black market, not scamming physicians
- *Weigh risk and benefits of false negative diagnosis* (with PDMP and watching patterns problems show themselves quickly)
- UDS can be part of your treatment policy or PRN
- Look for red flag patterns of use and have low threshold to switch to non-stimulant

Wilens, 2008. J Am Acad Child and Adolesc Psychiatry

Lifetime Comorbidity of Psychiatric Conditions with ADHD

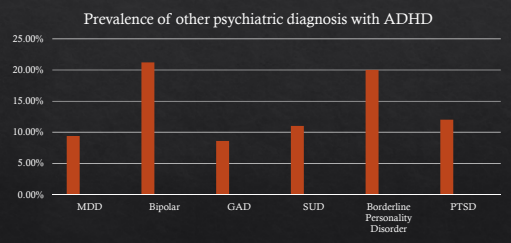
- 75% All adult ADHD cases have a comorbid psychiatric condition, some 2-4
- Mood Disorders 25%
- Anxiety Disorder 25-50%
- Alcohol Abuse 32-53%
- Substance Abuse 8-32%

(SUD risk approaches 16% lifetime risk with treated ADHD)

- Personality Disorder 15%
- Antisocial PD 25%
- Learning Disabilities 20-50%

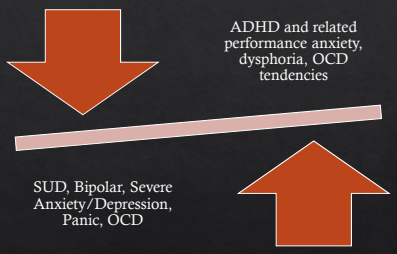
Shekim,W.O. *Compr Psychiatry*, 1990

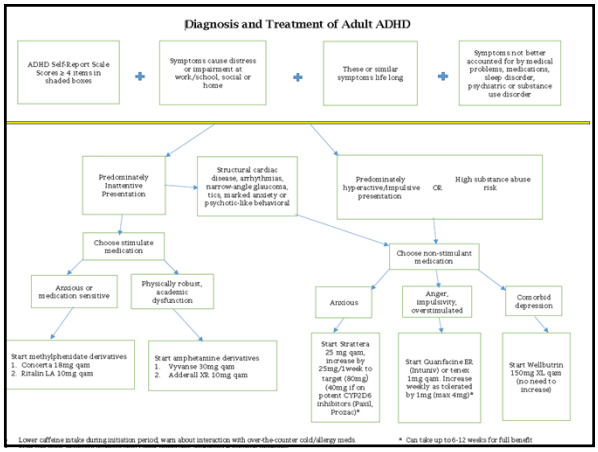
Point prevalence Comorbidity of ADHD with common psychiatric conditions



Kessler Am J Psych 2006
Spencer, AE. J Clinical Psych. 2016
Schiweck C, Arteaga-Henriquez G, Aichholzer M, et al. Comorbidity of ADHD and adult bipolar disorder: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2021

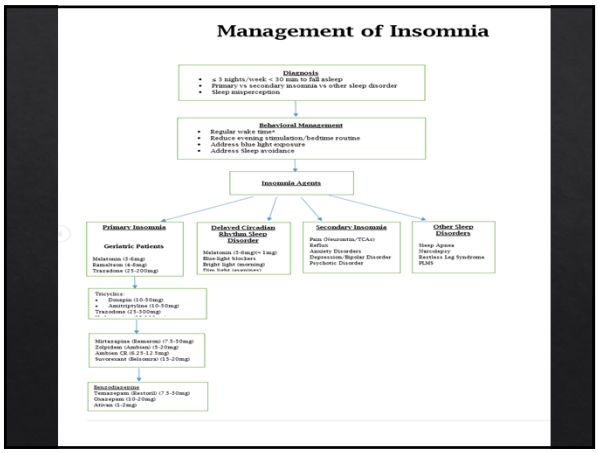
Order of treatment of psychiatric treatment when comorbities present





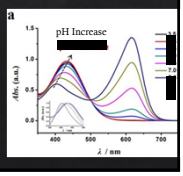
Choosing and combining ADHD Medications

- **Consider primary target symptom and comorbid conditions**
  - *Attention issues or PRN use*: stimulant is first line : 1.2 EFFECT SIZE
  - *Hyperactive/Impulsivity/need all day coverage*: Guanfacine ER (Intuniv) or Tenex), Atomoxetine
  - *Anxiety/Depression*: Bupropion, atomoxetine, TCA, Viloxazine(Qelbree)
  - *Hyperaroused, comorbid PTSD, over-stimulated, excess autonomic activity, hypertension*- alpha-agonists(guanfacine, clonidine), B-blockers
  - *Narcolepsy, Hypersomnia* NOS: modafanil, armodafanil
  - *History of Substance Abuse*—consider Strattera, Guanfacine Wellbutrin, TCAs, Clonidine, B-blockers or safer long-acting stimulants
  - Comorbid Binge eating disorder: Vyvanse is FDA approved
- Interactions: Stimulants safe with all of above 2nd line agents. Watch for:
  - Over activation when stimulant added to bupropion(also Bupropion is 2D6 inhibitor and stimulants 2D6 substrate.
  - TCAs may increase brain levels of amphetamine
  - Watch for hypotension, bradycardia, psychosis or hypomania when bipolar or cyclothymia present
- Medication side effects of 2nd agent can be used to address ADHD and secondary problems:
  - clonidine , intuniv. propranolol for insomnia, tachycardia, mild hypertension
  - Bupropion, stimulants, modafanil as adjunct antidepressant , wakefulness

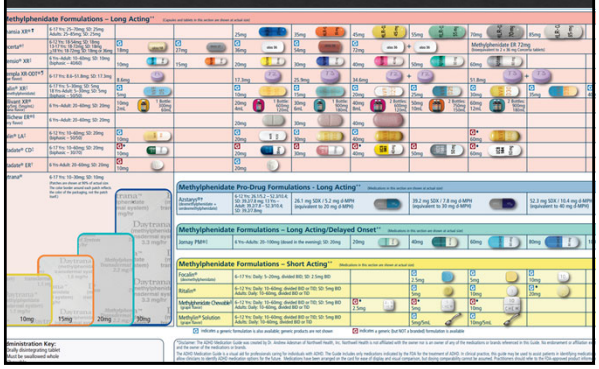


Principles in using stimulants

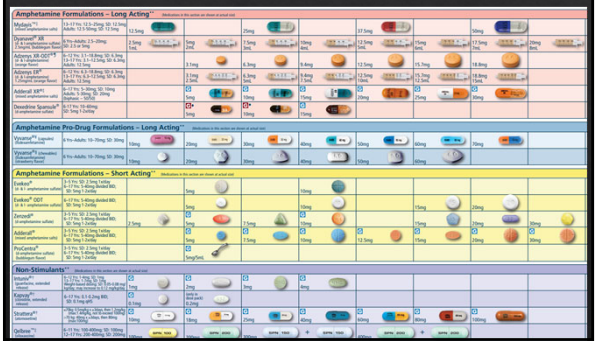
- Treat over the whole work or school day
- Use Long-acting stimulants in under age 25, SUD history
- Family benefits useful info
- Amphetamines safer in pregnancy than methylphenidate agents, all enter the placenta and breast milk
- Lower seizure threshold
- Gastric pH sensitive; antacids increases absorption while high fat intake slows
- Interact with MAOIs
- Some serotonergic activity

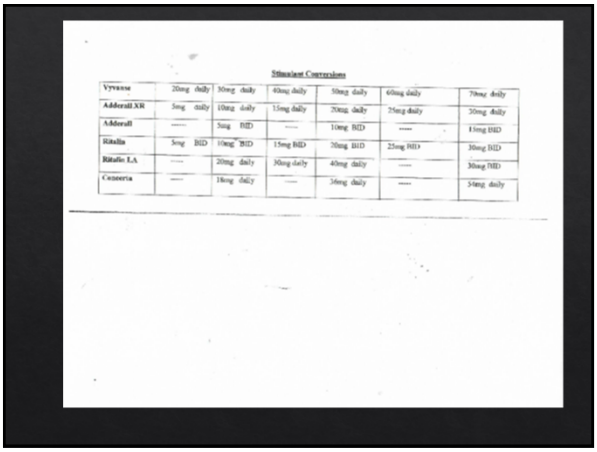


Methylphenidate agents



Amphetamine agents



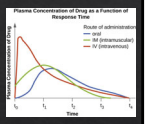


Getting started prescribing stimulants

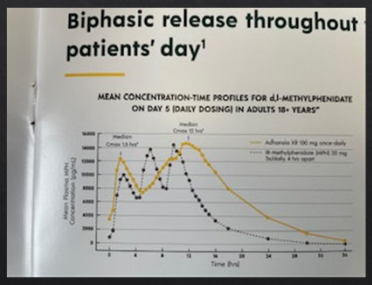
- Assess sleep issues before starting
- Get baseline BP , pulse and weight and follow regularly
- *If side effects occur assess if rebound or medication effect
- *Expect autoinduction/ hepatic up-regulation at 3 week mark
- See patient frequently at first q 3-4 weeks
- Give written instructions

Principles of treatment continued

- Watch intervals: Maximal therapeutic effect occurs during the absorption phase of the kinetic curve
- Start low go slow
- Bring In Significant others for history when possible
- Educate on diversion, document
- Use meds religiously at first and on weekends
- Check PDMP
- Expect lost scripts, but watch patterns
- PDR doses newer meds are too low, some patients require higher doses
- Consider interactions with other stimulants(caffeine, pseudofed, Claritin-D)
- D-methamphetamine/Desoyxa- still available in 5 mg short acting
- Mixed amphetamine salts: Adderall; Contains three parts salts of D-amphetamine; (dextroamphetamine saccerate, dextroamphetamate aspartate, dextroampetamine sulfate) and one part of l-amphetamine sulfate, inactive.
- Amphetamine is metabolized by oxidation and glucoronization but one step involves CY2D6
- Amphetamine is substrate of and mild inhibitor of CYP2D6/ Wellbutrin is a CYP2D6 inhibitor
- MPH is deesterified to ritalinic acid in the liver
- **Acidification increases renal excretion of amphetamine some unaltered, alkalization decreases



Pharmacodynamics of LA vs. SA Formulations of medication



Lisdexamfetamine dimesylate

Lisdexamfetamine → Hydrolysis → **l-lysine + d-amphetamine**

- pharmacologically inactive prodrug
- D-amphetamine is bonded to l-lysine amino acid
- 20, 30 (=10mg Adderall XR),40, 50(=20 mg Adderall XR),60,70(=30mg of Adderall XR) mg capsule
- Dissolvable in water
- Increased therapeutic life, tolerability, smoother pharmacologic effect
- Rate-limited hydrolysis on red blood cell releases pharmacologically active substance (inactive if snorted or injected)
- Likability half that of oral dexedrine when given IV to cocaine addicts

Maximum Daily Doses
(assuming tolerability and positive effects at lower dosing)

- **PDR doses:**
  - Amphetamine 60 mg
  - Methylphenidate 60 mg
- **Clinical dosing:**
  - Methylphenidate 120 mg (40mg per dose)
  - Amphetamine 100 mg (30mg per dose)
- Genetic assessments appropriate in atypical cases rapid metabolizers

Cardiovascular Safety

- Safety review of data from 1992-2004(www.fda.gov/briefing/2006) reveal no causality between stimulants and unexplained cardiac death. Death rate in patients on atomoxetine and stimulants was half the rate in the general population(1 per 100,000)
- Recent review: Stimulant medications, atomoxetine, Guanfacine and clonidine safe in all ages with healthy heart. Recent review: No increased risk of QTc prolongation, Torsade's de pointes or Sudden Cardiac Death
- Average alterations in cardiac parameters not clinically significant(increase in stimulants and atomoxetine, decreases in alpha agonists. Common changes NCS:
  - heart rate 3-5 bpm
  - BP 1-2 mm Hg
  - No change in QT intervals
- Contraindications or reason for cardiology clearance:
  - Uncontrolled hypertension
  - Known history or family history of structural cardiac abnormalities
  - Known history or family history of electrical abnormality
  - Sudden cardiac death in a family member <age 30.
  - Watch for outliers, monitor BP and pulse
- High rates of ADHD (Amer. Heart Assoc. 35-55%)in children with congenital CV anomalies -WPW syndrome, hypertrophic cardiomyopathy, long QT syndrome
- Adults with sinus tachycardia

Martinez-Raga J et al. Risk of serious cardiovascular problems with medication for ADHD CNS drugs, 2013

Signs and Symptoms of Amphetamine Toxicity

Marked:
- Mydriasis
- Grandiosity, euphoria
- Excitement, agitation

Moderate:
- Anger
- Insomnia
- Restlessness, hyperactivity
- New obsessive thinking
- Muscle tension, jaw clenching
- Tremor, Hyperreflexia
- Confusion
- Paranoia
- Hypertension, tachycardia
- Diaphoresis, palpitations, chest pain

Prescription Stimulant Abuse

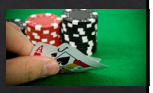
- Non compliance far more common than misuse
- Treatment of ADHD may be "protective"(untreated ADHD 40% have SUD, treated 16%)
- Minority use both *appropriately* and *inappropriately*
- Rapid and eventually intolerable dose escalation required to achieve high
- Prescription stimulants rarely used alone by regular substance users

Fast facts about treating ADHD

- Insomnia in 70% of patients at baseline; treat insomnia aggressively. If due to stimulant try to get last dose in before noon
- Stress comes out as ADHD symptoms: when meds optimized, work comorbid issues including psychological issues
- Consider harm reduction risk when diagnosing ADHD in context of SUD
- Always have option of having significant others dispense or writing 4 one week scripts with different start dates
- Tolerance to stimulants in appropriate medical use occurs in ~1/100 patients. Drug holidays , flipping stimulants and base non stimulants to reduce dose are all helpful approaches

Stimulant medications in special populations

- Stimulant intolerance or sensitivity; try plain dextroamphetamine
- Caution using stimulants in patients with *gambling issues* or porn/video game/streaming addictions
- MCI is not a contraindication for treating true ADHD
- ADHD may be primary or underlie treatment resistant depression/anxiety
- Narcolepsy patients routinely develop tolerance to stimulant medications. ADHD does not
- Primary Hypertension and idiopathic sinus tachycardia once controlled do **not** contraindicate stimulant use if treated. New onset cardiac disease **can** in established patients.
- Bipolar disorder, epilepsy: okay to treat ADHD in well controlled patients



Strattera (atomoxetine HCL):
Non-controlled non-stimulant drug

- NE- reuptake inhibitor
- May help more with executive dysfunction
- Acts selectively in prefrontal cortex: increases NE and DA levels
- Does not increase DA in nucleus accumbens
- Affects cognition and behavior: lacks abuse potential
- Not a scheduled drug, can write refills
- Not perceived as a crutch

Strattera: Efficacy

- Efficacy on core symptoms of ADHD in approximately 60% of adults(.6 compared to 1.1)
- Improvement often less robust (esp. for attention problems) than with stimulants
- Can be equal or better with HA/impulsive symptoms and self management issues (sleep-wake cycle)
- Begins to work at 1 week may take 6 weeks for strong effect, 10-20 weeks for full benefit
- Used safely as adjunct to stimulants
- Weak antidepressant, anti-anxiety properties

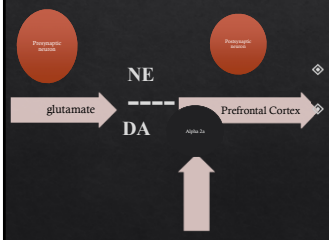
Dosing

- dosage 10 to 120 mg day
- comes in 10, 18, 25, 40, 60,80 and 100 mg capsules
- begin low, go slow
- Start at 25mg qam
- increase by 25 mg increments in divided doses (am and noon) as tolerated up to 75 -80 mg/ day;
- aim for half this dose if patient on a strong CYP2D6 inhibitor such as Prozac, Paxil
- may notice some immediate benefits, usually takes 3-4 weeks for full effect
- t 1/2 = 5 hours: therapeutic effect longer (24 hours?)
- Push dose gradually to highest tolerated or remission

Common side effects

- GI : dry mouth, constipation, appetite suppression, nausea
- Neuro: headache, dizziness, insomnia, somnolence, irritability
- GU: urinary hesitancy/retention, erectile disturbance, anorgasmia
- CVS: increase in BP, pulse, (usually not clinically significant), palpitations
- Gen: flu-like syndrome, fatigue, myalgia
- Liver toxicity/ hepatic necrosis: 2 in 2 million , hepatic enzymes markedly elevated, both patients recovered

Alpha-2A receptor activity in Striatal-frontal Pathways



- Guanfacine ER directly binds to alpha-2a postsynaptic receptor and modulates reception to signal
- Increased signal to noise ratio
- Guanfacine is at least 15 times more selective at alpha-2a receptor than clonidine(2-b thalamus causing sedation; 2-c cortex and locus coeruleus causing sedative and hypotensive effects).

Alternative agents for ADHD in adults

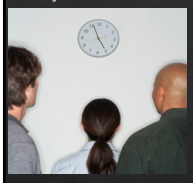
- Bupropion (Wellbutrin)
- SNRIs
- Tricyclics
  - desiprimine
  - imipramine
  - nortriptyline
- MAOI's
- SSRIs-impulsivity only
- Alpha-2 agonists:
  - Clonidine(Catapress, Kapvay)
  - guanfacine (Tenex, Intuniv))
  - Modafanil (Provigil)
- B-blocker
  - naldolol
  - propanolol

Herbal Treatments

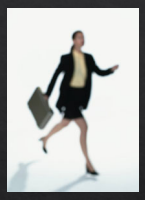
- Modest efficacy in Children
  - DHA/EHA (174mg or 558 mg 6 capsules q d)(fish oil)
  - 500-1500mg bid acetyl-L-carnitine (inattentive type only)
  - Fe supplementation in children with low ferritin levels
  - Zinc supplementation (60-150 mg/day)
- Not shown in clinical trials to be effective:
  - Megavitamin therapy
  - Antiyeast medication
  - Sensory Integration Training
  - Ginkgo
  - Essential fatty acids such as alpha-linoleic acid

Time Blindness

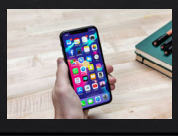
Healthy controls



ADHD: lack internal clock



Externalize brain functions

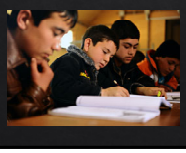


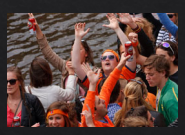
Stimulants in healthy subjects: Dopamine pathways are cue dependent

- Executive control pathways: (striatal pre-frontal, ACC)
  - Enhanced attention
  - Prolonged arousal during sleep deprivation~= coffee and modafanil
  - Inhibition

  *NOT reinforcing
- Reward *pathway: (mesolimbic pathways-ventral tegmentum to nucleus accumbens*)
  - Euphoria
  - Enhanced well-being

  *Reinforcing





Prevalence of nonmedical use for academic enhancement: Misconceptions over benefit

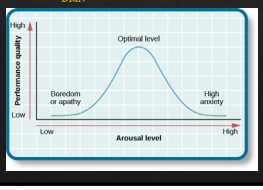
- 17% of students report taking stimulants not prescribed (metaanlaysis ages 9+)
- 11.6% of pharmacy students, 15-47% of medical students, 28.1% of residents physicians report last year NMU
- Increased odds among white male fraternity participants
- Youth and young adults overestimate:
  - prevalence of use of others
  - benefits both they and others receive
- Studies of stimulants in healthy controls show *subjective sense of enhancement consistently high*
- *Actual enhancement* was consistently minimal or very circumscribed

"Cognitive enhancement by nonmedical stimulant use may be a myth based on powerful peer-to-peer testimonies of students who are struggling academically or who have undiagnosed ADHD" Pliska

-Benson, K Flory K, Misuse of Stimulant medication among college students: A comprehensive review and metaanalysis Clin Child Fam Psychol Rev 2015 18 50-76
-Tuan, Brenda Evaluation of nonmedical use of prescription stimulants by college students at three northeastern pharmacy schools J Am Coll Clin Pharm 2019
-Rabin-Kahana, Dafna, Maya Kuperberg Cognitive enhancement drug use among resident physicians: Journal of Addictive Diseases, 2020

Prescription stimulants at therapeutic doses in non-ADHD: does not improve academic functioning

- ADHD
  - Wake up under-activated functional connectivity
  - Enhance executive control
  - Improve strategic planning, working memory
  - Improve attention orientation, shifting, maintenence
  - Increase sense of reward in boring tasks, reduce irrepressible need for immediate reward
  - Facilitate activation and task completion
  - Reduce distraction by inappropriate shifting into DMN



- Non-ADHD healthy controls
  - Non specific increase motivation, energy/wakefulness
  - Small improvements in isolated cognitive task

Current literature:

- Low performing students report the highest use of cognitive enhancing medications (Caviola and Faber, 2015; Repantis et al., 2011);
- Stimulant use has an inverse correlation with grade point average and correlates with poorer academic performance
- Prescription stimulant use can even impair cognitive performance among high-performers with adequate dopamine levels(Bavarian N Illicit use of prescription stimulants in a college student sample Drug Alcohol Depend 2013 132

(Yuan, 2019). McCabe SE. Prevalence and correlates of illicit methylphenidate use among 8th, 10th 12th grade student in the US, JI Adolescent Health, 2004

Non-ADHD : literature on stimulants and cognitive enhancement on actual performance

Stimulants minimally enhance academic performance

- Comprehensive reviews of controlled trials ***exploring objective assessment of cognitive enhancement*** in healthy subjects dosed with methylphenidate or amphetamine salts found an ***equivalent degree of null findings and limited improvement on select measures*** (Ilieva et al., 2015; Repantis et al.,2011; Smiet and Farah et al., 2011; Franke et al., 2014).
- Specific cognitive enhancement studies have shown ***limited benefits on simple attention tasks, but no consistent benefit for complex learning tasks*** (Ilieva et al., 2015; Repantis et al., 2011; Linssen et al., 2014; Ilieva et al., 2013).
- Stimulant medications aggravated performance among individuals with adequate dopamine levels (Swanson et al.,2007; Pliszka 2005; Wilens, 2006).
- On a SAT-style test, participants subjectively reported significant benefit from 20 mg amphetamine salts, but showed limited benefit on 13 objective measures of cognitive ability (Ilieava, et al)

(Psuedo)benefits in Normals are Percieved

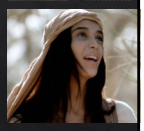
- Strong subjective sense of improvement::
  - A supra-therapeutic initial dose 20 mg of mixed-amphetamine salts showed no statistical benefit on 13 measures of cognitive ability on a SAT academic test, yet participants reported significant benefit (Ilieva et al., 2013).
  - Looby and colleagues found enhancement of mood but no changes in cognitive performance in participants who were told they ingested a stimulant (Looby and Earleywine, 2011)
- Attention Deficit Hyperactivity Disorder (ADHD) symptoms were present in many of the early surveys of use for "enhancement". Also not carefully screened out in many of these studies Subjects receiving
- 30 mg of amphetamine salts also reported enhanced mood and cognitive performance, despite small improvements mingled with worsening performance on several cognitive measures
- Mood enhancement but no improvement in cognitive performance was found in participants who were (falsely) informed they ingested a stimulant.

"The strong attraction for stimulants by healthy student controls is driven largely by positive affect and belief in the medication Effects rather than actual benefit." Ilieva

(Ilieva et al., 2015), (Mezzo et al., 2017; van Rooij et al., 2015; Nagy et al., 2004; Kethavarti et al., 2014; Reh et al., 2014; Rommelse et al., 2007) responding to accepted treatments (Overmeyer et al., 2000; Swanson et al., 2007; Pliszka, 2005; Wilens, 2006)

Expectancy: expectation of benefit alters neurobiologic response

- Placebo effect: beliefs and expectancies shape the neurobehavioral response to a wide range of drugs including stimulants.
  - Both healthy individuals and patient populations show similar expectancy-related neurophysiologic and neurochemical effects within the striatum, insula, parietal cortex, and cingulate cortex when placebo, believed to be a stimulant, is administered
  - Neuroimaging studies of placebo stimulant medication used in healthy individuals
    - Methylphenidate-induced reduction in striatal activity was greater when subjects expected to receive methylphenidate than when they did not
    - When subjects expected to receive methylphenidate but received placebo, notable increases occurred in the ventral cingulate gyrus (emotional reactivity) and nucleus accumbens (reward). This effect was most prominent in stimulant naive subjects



Volkow, et al

Pharmacologic vs expectancy effects of mixed amphetamine salts on objective cognitive performance college aged students

Drug and Alcohol Dependence

Mixed-amphetamine salts expectancies among college students: Is stimulant induced cognitive enhancement a placebo effect?

- Carefully screened normal controls aged 19-30
- Ruled out ADHD, SUD
- 4 sets of 4 hour Neurocognitive battery with and without MAS(Adderall)
- 31 neuropsych assessments of attention , memory, executive skills

Balanced 4 X 4 design with altered instruction set

- Deception study; IRB approved
  - N=32 put all subject through 4 states. Stimulant/placebo and Told stimulant/Told placebo(deception compt.)
  - 59% women
  - 47%white/non-Hispanic, 46% AA, Hispanic 3/1%, Asian/Pacific Islander 3.1%

Expectancy/placebo state	
10mg MAS(Adderall)/told stimulant	10 mg MAS/ told placebo
Placebo MAS/ told stimulant	Placebo MAS/ told placebo

Results

Subjective assessments

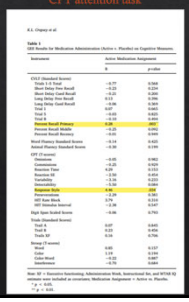
1) Medication assignment: *Agreement between stimulant assignment and perception of assignment 47%* agreement: k=0.047, p=0.590)

2) Global assessment of improvement measure

- Believed on stimulant—report significant improvement(p<0.001)
- True med assignment not affected (p=0.33)

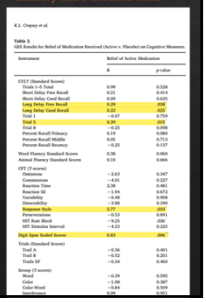
True medication state

Improved on 2/31 subtests: primacy learning task, one CPT attention task



Expectancy state(with and without stimulant)

Improved on 5/31 subtests, 3 memory and 2 attention tasks

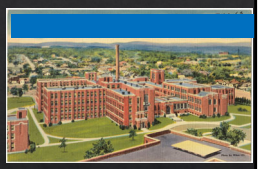


Study Conclusions

- Subjects couldn't distinguish real medicine from placebo medication
- Active stimulant state does not improve cognitive abilities over placebo state
- Areas of improvement are limited 2/31 subtests not reflective of complex learning
- Expectancy/placebo
  - subjectively rate self as performing better
  - possibly more robust improvements 5/31 items
- *Expectation effects if anything supersede actual drug state*

Stimulants as cognitive enhancers or active placebo for college students without ADHD

- Pilot Study 1: (Unpublished data). Survey of large Southern medical school to determine the use and attitudes toward the nonmedical use of prescription stimulants.
- 781 enrolled medical were sent a link to the 58-item confidential survey;
- 467 (59.8%) completed the survey:
- ~15% used in last year.
- *Students predicted 70- 80% classmates regularly engaged in nonmedical stimulant use and academic advantage*
- 92% of regular users in last year in lowest quartile of class
- About a quarter (27%) had been offered stimulant medication by a classmate.
- About half (52%) of PS students reported using prescription stimulants for the first time in medical school



This study demonstrates the power of myth distorting facts and relatively high nonmedical use of prescription stimulants by medical students

Pilot 2: Neuroimaging during Expectancy and Medication states with altered instruction sets

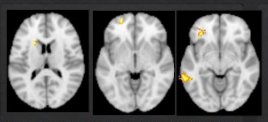
N= 4 underwent neuroimaging by fMRI and testing during 4 states.

10mg MAS(Adderall)/told stimulant	10 mg MAS/ told placebo
Placebo MAS/ told stimulant	Placebo MAS/ told placebo

Does neuroimaging support enhancement comes from placebo effect? Pilot data

BOLD activity during PASAT attention test:

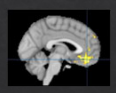
Expectant placebo state *



Increased activity : the left caudate and left *lateral* orbitofrontal cortex

Decreased task related activity compared to baseline state in salience and frontoparietal networks compared to baseline state.

True stimulant state



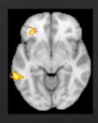
10 mg MAS(Adderall) led to large activation in ***medial*** orbitoforontal cortex

Task-related effects of expectancy and true psychostimulants do not involve the same neurological channels

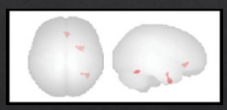
*Expectancy state: believe they receiving a stimulant, but actually received placebo.

Effects of psychostimulant expectancy on functional connectivity on PASAT

Placebo stimulant: Decreased task-related activity despite small overall increase of performance



Expectant state: Stronger functional connectivity of temporal, frontal, and parietal brain



- **Functional connectivity analysis:** temporal, frontal, and inferior parietal signals was stronger when participants were told they received stimulant versus placebo, even though placebo was administered in both conditions

……*Improved cognitive efficiency from stronger functional connectivity?*

Parting message

Challenging incorrect assumptions by the health care community and youth about prescriptions stimulants can reduce harm for non-ADHD healthy young adults and reduce stigma for patients who do have ADHD and deserve evidence- based care.

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