Stimulant treatment for ADHD: Not exactly Opioids 2.0, but close?

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- Andrea Truncali MD, MPH
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- Lauren Moran, MD, MPH
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- Margaret Chaplin, MD, FASAM
  - No disclosures

Goals

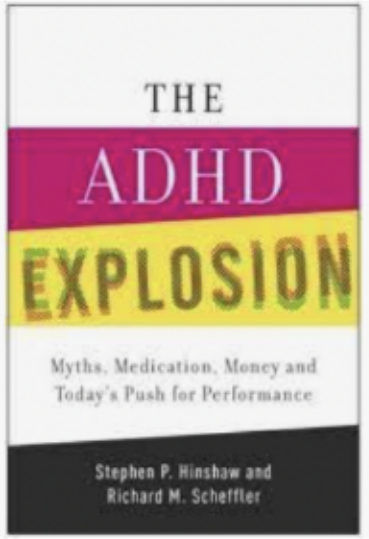
- Raise awareness of the complexity of ADHD* diagnosis
- Understand evidence for treatment of adult ADHD alone and with SUD
- Understand the potential harms of treating adult ADHD with stimulant medication

*ADHD = attention deficit hyperactivity disorder, used interchangeably with ADD =attention deficit disorder

Learning Objectives

- Identify considerations in enhancing specificity of making an ADHD dx in adults
- Describe the evidence for benefit of treatment of adult ADHD, and the limitations of that evidence
- Outline potential harms of stimulant therapy

Why delve into this topic?



- Increasing rates of ADHD treatment nationwide
  - 16% pre to post pandemic[1]

What are the implications for public health practice? MMWR, 3/2023

Growing recognition of ADHD in adults and increases in prescription stimulant fills raise questions about current adult ADHD care. Development of clinical recommendations for diagnosing and managing adult ADHD could help guide safe and

- Providers without expertise increasingly involved in diagnosis and treatment (PCPs prescribe more stimulants than psychiatrists)[2]
- ADHD disproportionately affects people with substance use disorder (SUD) and comes with the tension of increased potential risk of developing, activating, or contributing to a stimulant use disorder
- Pharmaceutical company interest has led the research in this field

1. Advisory Board, May 2022
2. Moran et al., NEJM 2019
3. Olfson et al., J Clin Psychiatry 2013

ADHD Diagnosis

- ADHD is a real illness with morbidity as well substantial cost to society[1]
- 3-7% adults have ADHD [2,3], 10-21% in those with SUD[4-6]
  - Lower rates of dx in Hispanic than white populations
- ADHD is associated with increased
  - Unemployment
  - Car accidents
  - Mortality
  - Impaired relationships
  - SUD
    - originally suggested that treatment of childhood ADHD prevents SUD, but evidence supporting that is mixed[8]

1. Schein et al, J Manag Care Spec Pharm, 2022
2. Song et al, J Glob Health, 2021
3. Kessler et al , Arch Gen Psy,chiatry 2005
4. van Emmerik-van Oortmerssen et al, Drug Alc Dep, 2012
5. Rohner et al, Int J Env Res Pub Hlth, 2023
6. Huntley, et al. BMC Psychiatry 2012
7. Piper, PloS one, 2018
8. Volkow & Swanson, Am J Psychiatry 2008

Why is adult ADHD diagnosis difficult?

- Checklists are usually positive – what is a disorder vs what is normal ?
- Multiple causes of inattention
  - Other psychiatric disorders including active SUD, complex PTSD; Lifestyle (poor sleep, stress); “Multitasking”
- No diagnostic test - requires comprehensive evaluation
- People craving substances may feel convinced of the diagnosis and press hard for treatment
- Popular diagnosis on social media – can create a hypochondriasis effect

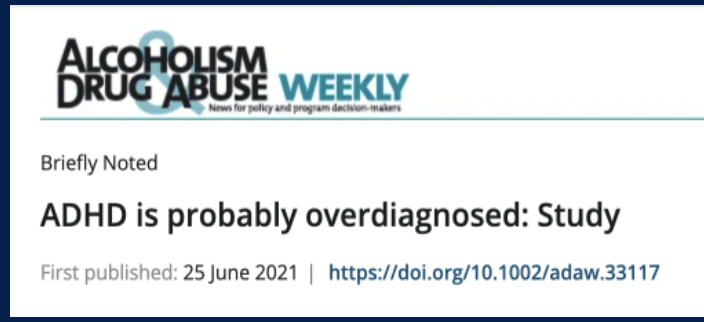
What is Adult ADHD?

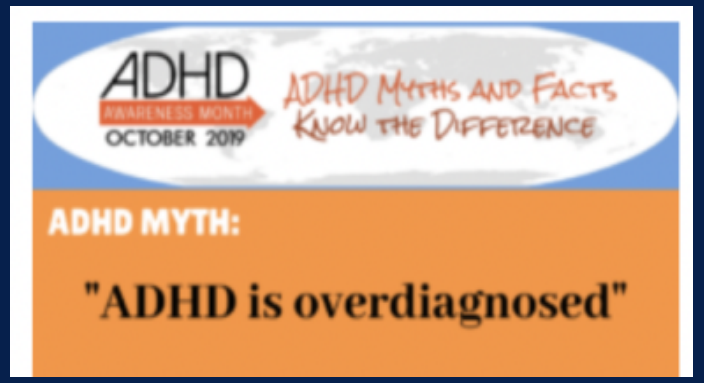
Extension of childhood, distinct entity or undiagnosed comorbidity ?

- Three cohorts address this question
  - Dunedin, New Zealand Cohort, 2015
  - Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA), 2018
  - Berkeley Girls ADHD Cohort, 2019
- ADHD persists into adulthood at rates of 5-20%
- In cases that develop symptoms de novo, after age 12
  - NZ cohort ruled out anxiety and depression, found 55% had SUD
  - Other two cohorts explained symptoms as due to other causes in all but 1-2% of these new onset cases
- Clinically, if you don't have childhood onset you are likely treating something other than ADHD

ADHD: Over or Under Diagnosed?

- It is likely both over and underdiagnosed
- High degree of symptom overlap with SUD and other psychiatric conditions is major cause of misdiagnosis
- There is clear evidence of overdiagnosis
  - Broadening of criteria → higher prevalence and stimulant treatment for milder symptoms
    - Evidence of less efficacy for individuals with milder symptoms [1]
  - Children born earlier in the school year are diagnosed and treated with greater frequency than those born later in the year [2]
  - US vs international





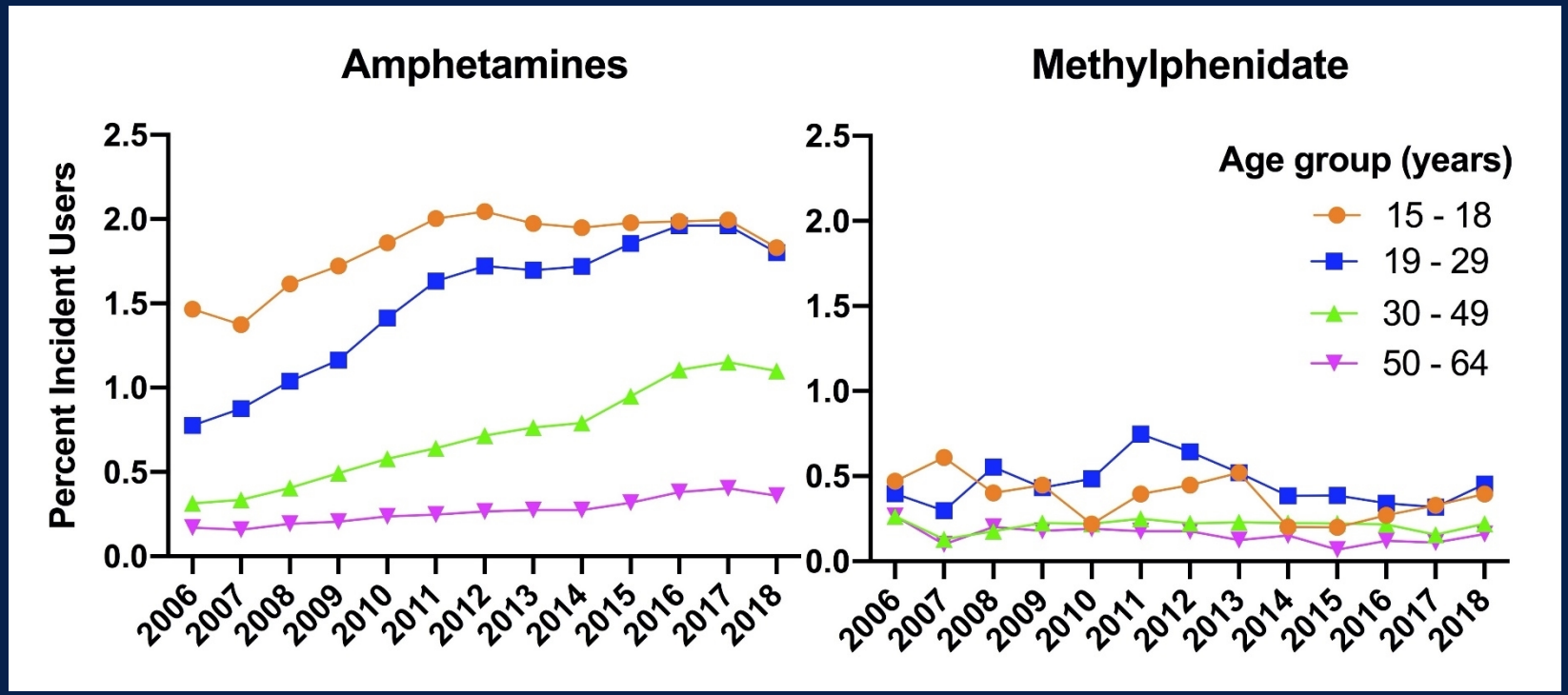
1. Kazda, JAMA Network Open, 2021
2. Layton, et al, NEJM, 2018

Malingering and ADHD

- High prevalence of individuals exaggerating symptoms (22% adults) [1]
- Evidence that some individuals "fake" ADHD symptoms in order to obtain stimulant prescription[2]
- Undergraduates coached about ADHD via Internet compared to students with ADHD [3]
  - Those coached to fake ADHD met diagnostic criteria for ADHD via symptom checklists
  - Self-rating scales (ie, Conner's Adult ADHD Rating Scale, ADHD Rating Scale) - particularly susceptible to faking and now easily accessed by patients
- Multiple other studies corroborate findings using symptom checklists alone, unable to distinguish between those fabricating and those with true ADHD[4,5]

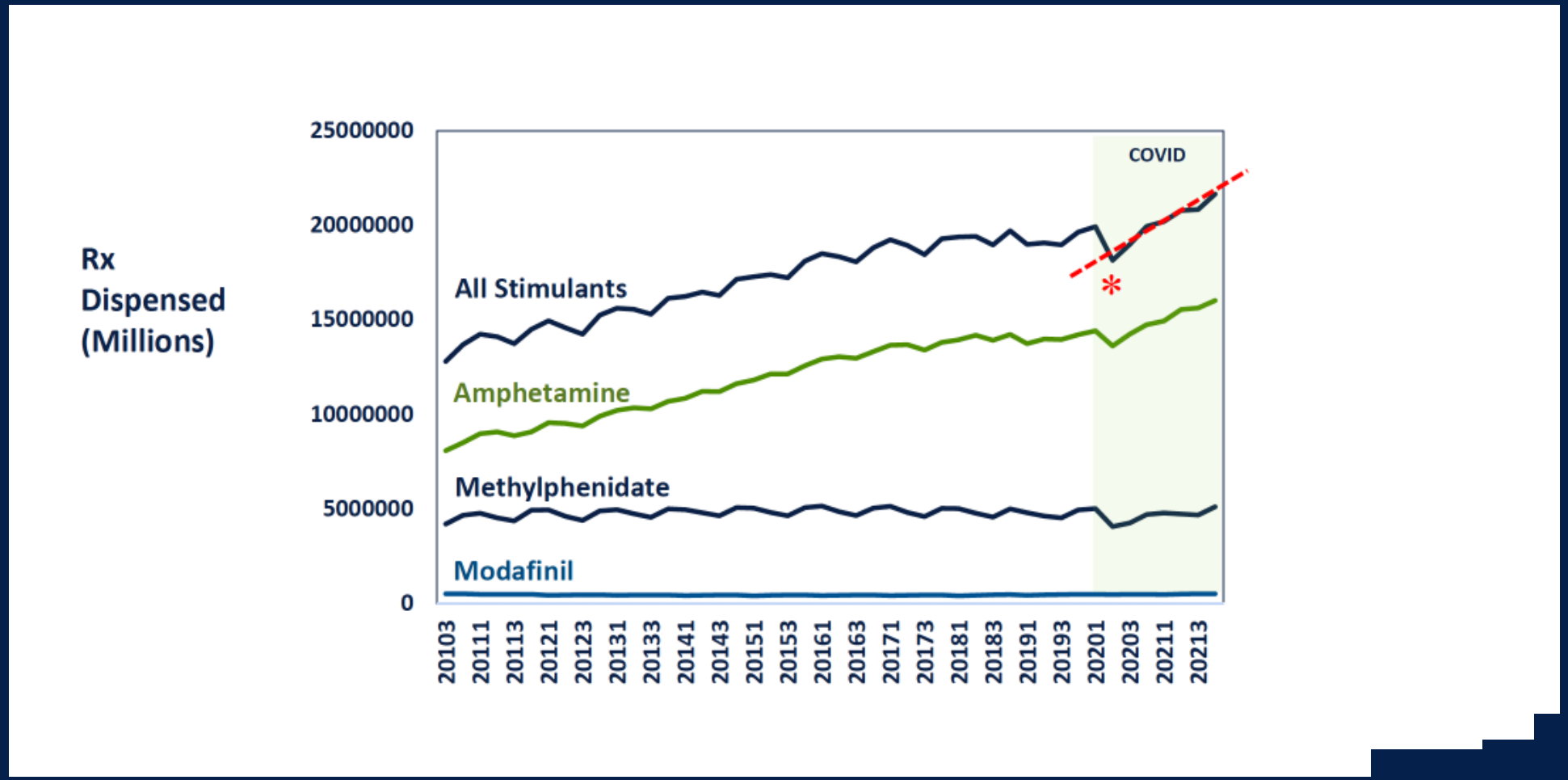
1. Marshall et al., Clinical Neuropsychologist, 2010
2. Fuermaier et al., J Neural Transmission, 2021
3. Sollman et al., Psychological Assessment, 2010
4. Quinn CA, Arch Clin Neuropsychol, 2003
5. Booksh et al., J Atten Disorders, 2010

New Stimulant Prescriptions 15-64 years old



Data source: Optum Clinformatics, United Health data

Quarterly Prescriptions



Data from IQVIA, presented at RADARS System 16th Annual Meeting, 2022

Disparities

- Black and Latino children less likely than white children (36% and 56%) to have diagnosis of ADHD[1]
- Stimulant prescriptions for individuals living in areas with highest proportion white population 3.86 times higher than areas with lowest proportion white population
- In adults, white adults more likely to have ADHD diagnosis or Rx, but growth rates for Blacks 3x higher (2008-2013)[3]

1. Glasofer, J Racial Ethn Health Disparities, 2022
2. Tseregounis, et al., J Atten Disord 2020
3. Fairman et al., J Atten Disord 2020

Disparities in Stimulant Prescribing

- Data from Mass General Brigham (MGB), point prevalence of stimulant use 16 – 35 years of age receiving outpatient care 2005 – 2019 (n=5,496):
  - Amphetamines
    - White: 6.0%
    - Asian 1.3%, Black 1.6% and Hispanic 1.1%
  - Methylphenidate
    - White 3.6%,
    - Asian 1.5%, Black 1.1%%, Hispanic 1.3%

DSM-5 Broadened Diagnostic Criteria:

5 Symptoms of Inattention

5 Symptoms of Hyperactivity

Symptoms Present before age 12

Symptoms Present in 2 Domains

Reduces Quality of Social or Vocational Life

Not due to any other Mental Disorder

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013

Choose Your Own Adventure!

The Case of the Fidgety Fellow

Jeff is a 29 yo M with OUD, initially presenting to your outpatient addiction clinic 2 weeks ago, and appears to be stabilizing on 16 mg of bup/nal. Staff in the IOP are reporting that he frequently interrupts and can't sit still during sessions. He reports a diagnosis of ADHD made at age 14, "but my parents didn't believe in meds". He also report a successful trial of lisdexamphetamine 70 mg with another doctor last year, "but she won't prescribe it anymore 'cause I was using". He is unemployed, lives with his girlfriend who works as a nurse, and their 3 year old daughter.

What else do you want to know?

Diagnostic Assessment

- Slow it down, set expectation that you won't Rx at initial visit
- Limitations and utility of assessment tools
- Obtain Collateral: parents, partners, co-workers, clinicians
- Inheriting patients: do your own homework!
- Look closely at co-morbidities

What Would You Do?

1. To do a quick screening tool on Jeff in which he endorses all symptoms of ADHD, put him back on Lisdexamphetamine 70 mg qAM, and return in a month… Go to slide # 37

2. To conduct a thorough assessment for ADHD as well as other psychiatric co-morbidities, get a UDS, check the PDMP, obtain collateral from his girlfriend and past prescriber, suggest some behavioral modifications and consider starting him on Guanfacine 1 mg BID…. Go to the next slide

Jeff: The Fidgety Fellow

- After a thorough assessment….

Jeff returns 2 weeks later reporting that guanfacine has helped him sit still and feel calmer, though inattention continues to interfere with IOP and his life at home.

He stabilizes nicely in early recovery as supported by good engagement in IOP, attendance at local 12 step meetings, improved relations with his partner and several negative UDS's. Records from his prior stimulant prescriber are consistent with Jeff's report, indicating lisdexamfetamine being stopped after opioids were detected on a UDS. You spoke with his partner who reports frequent discord when Jeff fails to complete household chores, has poor follow-through on commitments, and is frequently distracted during conversations.

After a thorough discussion of the risks and benefits of stimulant treatment for ADHD in the context of SUD, you decide together to restart lisdexamfetamine 30 mg.

MORE ADVENTURES AHEAD

What is the evidence base for pharmacologic treatment ?

Conflicts of Interest (COIs)

- Many prominent researchers in ADHD receive funding by pharmaceutical companies that market prescription stimulants[1]
  - Cochrane review on methylphenidate in adults, 2016, retracted for COIs
  - Senate Investigation, 2008
- Patient/family advocacy groups receive funding from pharmaceutical companies[1]
- Panels responsible for widening definition of ADHD & allowing adult ADHD diagnosis[2]
  - Majority of members have ties to industry
- Substantial marketing dollars devoted to practicing physicians
  - 25% of all industry payment to pediatricians in 2014 were for 3 stimulant medications [3]
  - 1 in 18 physicians received marketing from stimulant pharmaceutical companies, most funds ($7B) for lisdexamfetamine, (2014-2018)[4]

1. Schwarz, ADHD Nation, 2016 (book)
2. Moynihan et al., PLOS Medicine, 2013
3. Parikh et al., Pediatrics, 2016
4. Hadland et al., JAMA Pediatrics, 2020

Why do we treat adult ADHD?

- Subjectively feel better/reported reduction in MH symptoms
- Employment
- Accidents/Injuries
- Relationships
- ?Reduce SUD/support recovery

What outcomes would you look for to support treatment?

- Symptom scales
- Psychiatric assessment
- Retention in care
- Employment history
- Traffic safety data
- Hospitalizations/ER visits
- Social history data
- Substance use
- **How long would it take to see these outcomes?**

Evidence Review: Cochrane review on amphetamines for adults, 2018

- 19 RCTs using dextroamphetamine, lisdexamfetamine or mixed amphetamine salts
- 18 US studies, 10 were multisite
- Mean study length 5.3 weeks, range 1-20wks
- All placebo-controlled, three also included an active comparator: guanfacine, modafinil, or paroxetine.
- 16/19 studies definitely pharma funded, 1 publicly funded (Levin 2015 SUD and ADHD), 2 did not disclose funding source

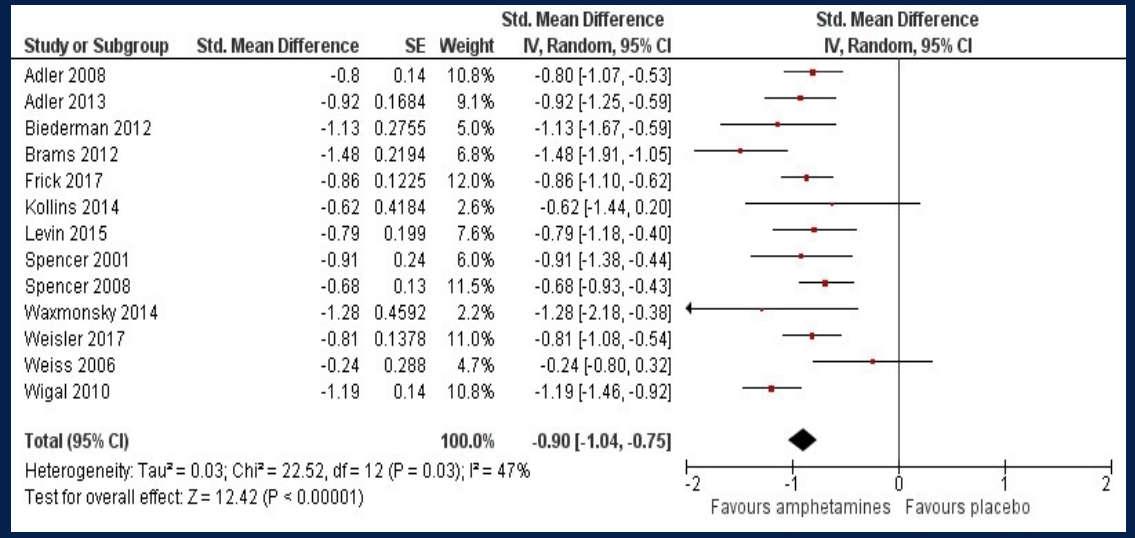
Cochrane, 2018, Outcomes

- Participants: avg age 35, 57% male, mostly Caucasian, few studies SUD+
- Outcomes reviewed:
  - Severity of ADHD symptoms
  - Retention in treatment
  - Adverse events
- Results
  - **Low to very low quality data** (lack of blinding, attrition, selective reporting without *a priori* outline of outcomes, crossover without washout phase, short duration, baseline wellness -ext validity problem)

Cochrane, 2018: Results

Severity of Sxs:

- Clinician rating, n=2028, SMD −0.90 (−1.04 to −0.75)
- Patient rating, n=120, SMD −0.51, (−0.75 to −0.28)



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Adler 2008	-0.8	0.14	10.8%	-0.80 [-1.07, -0.53]
Adler 2013	-0.92	0.1684	9.1%	-0.92 [-1.25, -0.59]
Biederman 2012	-1.13	0.2755	5.0%	-1.13 [-1.67, -0.59]
Brams 2012	-1.48	0.2194	6.8%	-1.48 [-1.91, -1.05]
Frick 2017	-0.86	0.1225	12.0%	-0.86 [-1.10, -0.62]
Kollins 2014	-0.62	0.4184	2.6%	-0.62 [-1.44, 0.20]
Levin 2015	-0.79	0.199	7.6%	-0.79 [-1.18, -0.40]
Spencer 2001	-0.91	0.24	6.0%	-0.91 [-1.38, -0.44]
Spencer 2008	-0.68	0.13	11.5%	-0.68 [-0.93, -0.43]
Waxmonsky 2014	-1.28	0.4592	2.2%	-1.28 [-2.18, -0.38]
Weisler 2017	-0.81	0.1378	11.0%	-0.81 [-1.08, -0.54]
Weiss 2006	-0.24	0.288	4.7%	-0.24 [-0.80, 0.32]
Wigal 2010	-1.19	0.14	10.8%	-1.19 [-1.46, -0.92]
Total (95% CI)			**100.0%**	**-0.90 [-1.04, -0.75]**

Heterogeneity: Tau² = 0.03; Chi² = 22.52, df = 12 (P = 0.03); I² = 47%
Test for overall effect: Z = 12.42 (P < 0.00001)

- Clinical significance? Varies.
- Clinician ratings: change of 1-2/7 points on Clinical Global Impression Scale (a one question scale); some found 30% ADHD-symptom reduction for patient rating
- No differences for amphetamine vs guanfacine, modafinil (low power?)
- **Retention:** No effect, **RR=1.06** (95%CI 0.99-1.13); 17 studies, n=2323
- **Adverse events:** Increased AE-related withdrawals (**RR 2.69,** 95% CI 1.63 to 4.45; 17 studies, 2409 participants)

Evidence reviews: Cochrane, 2022 Methylphenidate IR and OROS

- Similar limitations to prior: heavy industry influence, duration 2-3months, high risk bias
- For OROS, no effect on missed days of work at 13wks (very low certainty evidence) and small-mod effect on self rated adhd sxs
- For IR, included one direct comparison with Lithium
  - No diff in MPH vs Li
  - Very low certainty evidence for a difference compared with placebo on pt and provider rating scales

Head to head comparisons?

- Scant direct comparisons: standard teachings about relative effects are based on informal and indirect comparisons of effect sizes
- Network metanalysis of pharmacologic therapy in adults[1]
  - 81 unique RCTs, most at high or unclear risk bias, 5 RCTs low risk of bias
  - 57/81 industry funded, authors conflicts not included in that value
  - No clinically significant differences between medications
  - Positive effect of pharmacotherapy (stimulant and non-stimulant)
    - Effect lost when the analyses were restricted to studies at low risk of bias (probably underpowered)
  - Certainty of the evidence deemed low to very low
- Another network MA, showed amphetamine > atomoxetine and methylphenidate (MPH) but atomoxetine similar to MPH [2]

1. Elliot et al. PLoS One, 2020
2. Cortese, et al Lancet Psychiatry, 2018

Head to Head Comparisons

Population	Intervention	Primary Outcome	Notes
N=98 , recruited from outpt psychiatry, excluded SUD [1]	Paroxetine vs dex-amp (both up to 40mg/day) x20wks	**NS difference in ADHD rating scale IV:** DEX approx 4pt (out of 56) lower, but p=0.06	35% lost to fup (estimated 20% loss of power), industry funded
N=52, recruited from flyers at psychiatry clinic in Taiwan, open label[2]	MPH 10-20 TID vs atomox (0.5–1.2 mg/kg/day) x8-10wks	**NS difference** in Intraindividual variability in reaction time (reduced in both groups)	Mean daily dosages approx. 30mg MPH, 80 mg atomox
N=63, ?how recruited (same group as above), open label [3]	MPH 10-20 TID vs atomox (0.5–1.2 mg/kg/day) x8-10wks	**NS differences** in ADHD scales, QOL and Weiss functional impairment scale	Adhd scales - Self report scales for inattention, hyperactivity and clinician CGI
N=60 Korean pts on SSRI for MDD with only partial response, rater blinded [4]	OROS Methylphenidate vs atomoxetine, titrated to clinical response, 12wks	**NS differences** in ADHD self report scale and CGI	Atomox (59mg male/80mg female), MPH (56mg F, 59mg M), Adults adhd self report scale and CGI

1. Weiss and Hechtman, J Clin Psychiatry, 2006
2. Ni, et al. Journal of Psychopharmacology, 2016
3. Ni et al. J Atten Disord 2017
4. Shim et al, Clin Psychopharmacol Neurosci.

Functional Outcomes

- In observational studies in adults, prescription stimulants <u>associated with:</u>
  - Decreased car accidents[1]
  - Decreased unemployment among women, not men [2]
- Meta-analysis of RCT data shows modest effect on short-term abstinence from cocaine use, mostly attributed to higher dose amphetamines[3]

1. Chang et al., JAMA Psychiatry, 2017
2. Li et al., JAMA Network Open, 2022
3. Tardelli et al., Psychopharmacology, 2020

Functional Outcomes: What stimulants do not do

- Improve learning of material:
  - Children randomized to methylphenidate had markedly improved classroom behavior, but no improvement in learning [1]
- Substantially improve performance on neuropsych tests: [2]
  - College students: RCT crossover Mixed amphetamine salts vs Placebo
  - Inconsistent results performance on tests of attention, working memory, processing speed
  - Substantial effects of stimulants on subjective drug liking [2]
- Substantially improve GPA [3]
  - Adherence → 0.11 improvement in GPA

1. Pelham et al., Journal of Consulting and Clinical Psychology, 2022
2. Weyandt et al., Pharmacy, 2018
3. Marcus et al., J Am Acad Child Adolesc Psychiatry, 2011

Functional Outcomes: In the clinic

In what ways are you not functioning well now that we can track together?

- Job
  - Do you have one?
  - Feedback from supervisors
  - Punctuality, completing tasks, errors
- Home Life
  - Managing responsibilities, housework, projects, appts
  - Parenting
- Social
  - Feedback from loved ones
  - Listening, interrupting, emotional regulation

Choose Your Own Adventure #2

The Co-Morbidity Conundrum

- Edie is a 39 yo woman with OUD on bup/nal. Prior to treatment for OUD she also used cocaine regularly “which actually helped me”, but has been avoiding cocaine because she’s on probation. She now presents asking about medication for ADHD. She has a history of childhood trauma, and for a period of time in childhood was treated with stimulants. She is working full time at a local grocery distributor and feels unfocused. Her sleep is impaired by nightmares that relate to past trauma. She uses marijuana “dabs” to help with sleep and anxiety.

What else do you want to know?

Approaching Treatment

- Set realistic expectations
  - "This isn't going to turn you into a person without ADHD"
  - Goal isn't "to feel something"
- You can validate and not medicate
- Foundation of Recovery: which part of the brain is in the driver's seat?
- Co-morbidities
- Consider a non-stimulant trial first
- Cannabis considerations[1,2]
- Behavioral Strategies
- ROI's

1. Volkow et al, NEJM 2013
2. Curran et al, Nature Reviews, 2016

What would you do?

1. To advise Edie that marijuana and PTSD are likely to be significantly contributing to her symptoms and prioritize those issues to target, Go to slide #36

1. To advise Edie that because of prior cocaine use you are concerned about increased risk with potentially addictive medication and would not prescribe stimulants to her, go to the next slide…

Edie: The Co-Morbidity Conundrum

- You advise Edie that because of prior cocaine use you will not prescribe stimulants to her….

Edie becomes angry, accusing you of “not wanting to help me because of my past” and storms out of the evaluation. She later apologizes, and insightfully reports her reaction was reminiscent of emotions he experienced during past traumatic experiences with authority figures. She continues on in treatment, maintaining abstinence from opioids over the next year, though her cannabis use increases, and at several points tests positive for illicit amphetamines and cocaine.

GAME OVER ☹

Edie: Comorbidity Conundrum

You advise Edie that marijuana and PTSD are likely to be significantly contributing to her symptoms …..

- Edie stops using cannabis and starts individual therapy. You titrate up prazosin to 5 mg qhs and her sleep improves. She does feel that she gets distracted at work but continues to hold her job and her supervisor reports she is a ‘great worker’. She still thinks a stimulant may help her, but understands that this may also be a form of craving. As time goes on and her feet are more firmly rooted in her recovery, she notes improvement in her functioning and clarity of mind without cannabis, and concludes that a stimulant trial isn’t worth the risk.

CONGRATULATIONS!

Jeff

- Restart Lisdexamphetamine 70 mg, and return in a month…

- Jeff reports the med is working “great!”, and you begin seeing him monthly. A few months later he calls a week after his meds were refilled, stating that when he was opening the bottle the rest of his capsules washed down the drain. You ask him to come in for a urine drug test that day, but can’t get him in for another week. At his appt he initially appears guarded and withdrawn, though by the end of the visit he shows you images on an infrared camera that he believes is proof that people have been hiding in the walls of his house, and perseverates on the FBI monitoring him.

GAME OVER

Harms

What are the risks of concern with stimulants?

- SUD
- Diversion
- Psychosis/mania
- CV outcomes
- Impact on sleep
- Growth suppression (kids)
- Appetite suppression*
- Tics

What outcomes data would allow us to gauge risk?

- Toxicology testing
- Med diversion monitoring outcomes (PDMP, counts, tox testing)
- ER visits and psychiatric hospitalizations
- CV surrogates and events
- Weight
- **How long would it take to see these?**

* In children followed from MTA study, found growth suppression and INCREASED weight in adulthood

Quality of data on harms, meta-analysis

- Cortese[1], large metanalysis, likely to affect policy
  - Excluded studies with high doses (e.g., 40 mg of mixed amphetamine salts)
  - Tolerability measured by study withdrawal due to side effects, common in this literature
  - Authors acknowledged lack of long-term safety data
  - Criticized in editorials [2-4] "important AEs, i.e., sleep disturbance, headache, loss of appetite" not included
  - Did not highlight the exclusion of people with psychosis, hypertension or tics
  - SUD ignored, both in editorials and authors' plan for dedicated analysis of safety [5]
  - Lack of attention to SUD risk is reminiscent of opioids in the era of marketing about opioid and chronic pain[6]

1. Cortese, et al. Lancet Psychiatry, 2018
2. Editorial, Warren, Nov 2018
3. Editorial, Wang and Zheng, Nov 2018
4. Editorial, Faltinesen et al, Nov 2018
5. Authors Reply , Cipriani, Nov 2018
6. Katz, Clin J Pain, 2007

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER
HERSHEL JICK, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154 Boston University Medical Center

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

Porter J, Jick H. Addiction rare in patients treated with narcotics. NEJM. 1980 Jan 10;302(2):123.

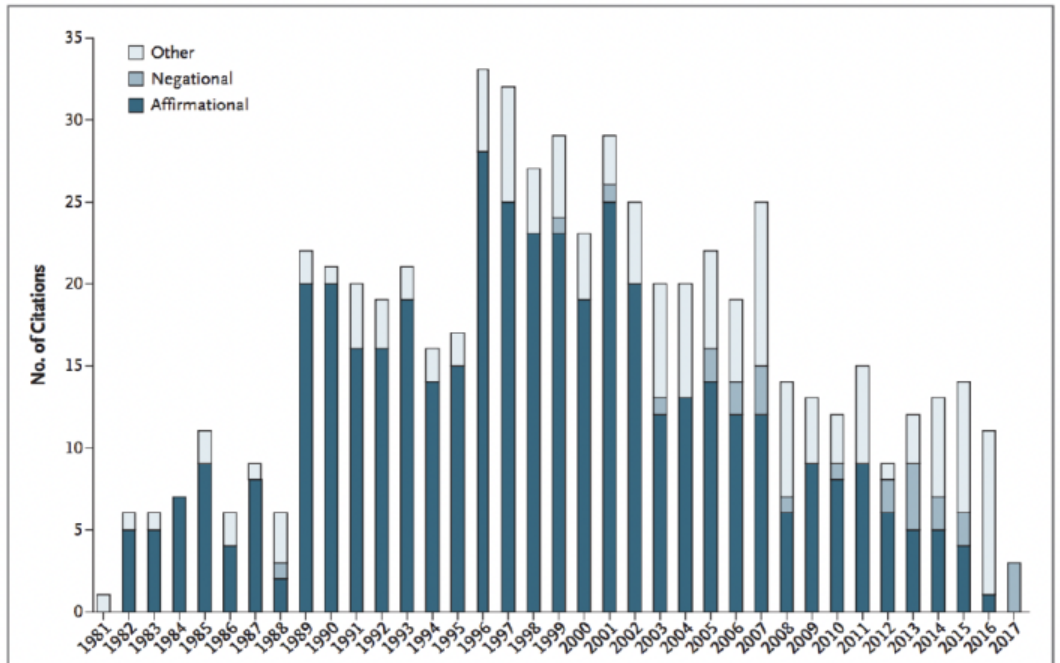


Figure 1. Number and Type of Citations of the 1980 Letter, According to Year.
Shown are number of citations of a 1980 letter to the *Journal* in which the correspondents claimed that opioid therapy rarely resulted in addiction. The citations are categorized according to whether the authors of the articles affirmed or negated the correspondents' conclusion about opioids. Details about "other" citation categories are provided in Section 2 in the Supplementary Appendix.

Leung PT et al. A 1980 Letter on the Risk of Opioid Addiction. NEJM. 2017

Quality of data on harms for FDA approval

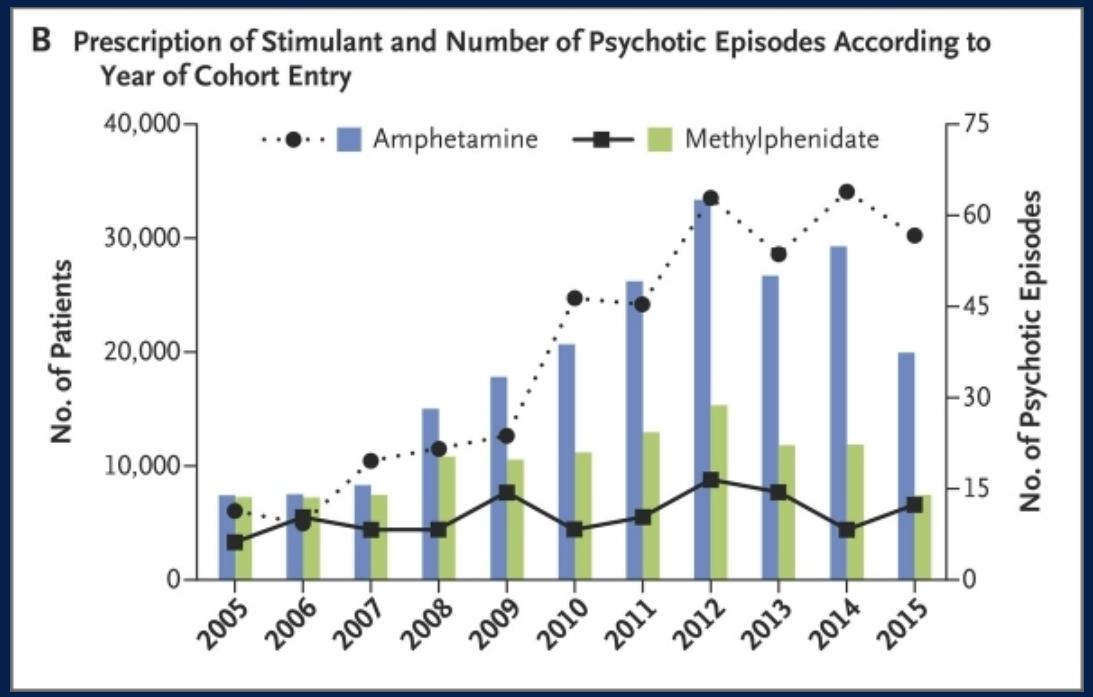
	General Recommendations[3]	Flovent (fluticasone)[2]	Stimulants[1]
Short term studies	300-600 pts ≥ 6 months	1,090 patients total 12-16wks	20 stimulant drugs: 70 pts (median), 4weeks (median). - 11 stimulant drugs approved with total of < 100 patients and 5 drugs approved with < 4 weeks of data
Long term/post marketing	100 patients ≥ 1 year	507 patients in 12-month safety study	FDA required post-marketing studies for 6 drugs but only 2 of the 6 were performed

- Conclusion: Pre-marketing data grossly insufficient to determine safety

1. Bourgeois et al., PLOS One, 2014
2. https://www.accessdata.fda.gov/
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Guidelines.

Psychosis

Risk of new onset of psychosis:
Amphetamines > methylphenidate [1]



Dose dependent increase in first episode psychosis/mania[2]

	Controls	Cases	Adjusted OR ± 95% CI
Dextroamphetamine Equivalents			
None	2,538 (92.9%)	1,170 (87.7%)	Reference
Low: ≤ 15 mg	96 (3.5%)	54 (4.1%)	**1.74** (1.13, 2.72)
Medium: > 15 & ≤ 30 mg	65 (2.4%)	61 (4.6%)	**3.54** (2.21, 5.66)
High: > 30 mg	34 (1.2%)	50 (3.8%)	**5.58** (3.21, 9.68)

1. Moran et al., NEJM, 2019
2. Moran et al., under review

Dextro >30, roughly equivalent to 40mg mixed amphetamine salts

Cardiovascular risks

- Stimulants increase blood pressure and heart rate
- Observational studies (where individuals with pre-existing cardiovascular disease are likely excluded):
  - Non-elderly adults 25 – 64 years [1]
    - No increased risk of serious cardiovascular events (stroke, MI, sudden cardiac death)
  - Elderly adults > 65 years[2]
    - Increased risk of serious cardiovascular events
    - Ventricular arrhythmias, stroke, risk higher shortly after initiating (30 days)

1. Habel et al., JAMA 2011
2. Tadrous et al., JAMA Network Open, 2021

Mortality/Overdose

- Off-label prescribing in adults is rising and is associated with increased all-cause mortality compared to on-label prescribing.[1]
  - Unclear reasons for off-label prescribing
    - But co-morbid psychiatric disorders common
  - Lisdexamfetamine FDA-approved for binge eating disorder
- One observational study from database shows among people on buprenorphine for OUD, prescribed stimulant therapy [2]
  - Associated with
    - 19% increased chance of non-fatal overdose
    - 36% increase in treatment retention
  - Selection bias: only included patients with high adherence to stimulants

1. Westover, at al, Addiction, 2018
2. Mintz et al, JAMA Network Open, 2022

Parallels with the Opioid Crisis

Start with a likeable medication…

- Expansion of Target Population
- Evidence for treatment
  - heavily influenced by pharma
  - based on subjective outcomes
  - ignores important safety outcomes, including SUD

- Rapid Rise in Prescribing[1,2,3]
- "Non-addictive" Formulations[3]
- Higher Acceptable Doses[3]

Increase in Stimulant Related OD Deaths

23% increase from 2020 to 2021[4]

1. MMWR, 2023
2. Piper, 2018, *PloS one*
3. Carpentier & Levin, Har Rev Psy, 2017
4. CDC, June 2022

Key Takeaways

- Adult ADHD carries significant morbidity, with higher prevalence among people with SUD
- Diagnosing ADHD is complex and time consuming
- The evidence base for benefits of treatment with stimulants consists of numerous low-quality studies without functional outcomes
  - the risk of nonstimulants are fewer and could be comparable to stimulants in terms of functional impact
- Risks of stimulants include misuse, SUD, psychosis and CV events however the degree of risk has not been adequately assessed
  - Risk can potentially be mitigated with careful diagnosis and monitoring

Q+A: Audience

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