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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

TREATMENT OF STIMULANT USE DISORDERS

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project ECHO

GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

✓ No conflicts of interest/disclosures

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OBJECTIVES

1. Brief overview of stimulant-related physiology & epidemiology
2. Recognizing & treating stimulant use disorders:
   - Diagnosis & management of acute effects (brief)
   - Psychotherapies (brief)
   - Pharmacotherapies
3. Special populations
   - ADHD in stimulant-abusing pts: to Rx, and how?

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STIMULANTS:

What Substances Are We Talking About?

Cocaine

Amphetamines:

- Prescription Meds
- Methamphetamine
- Multiple other modified amphetamines

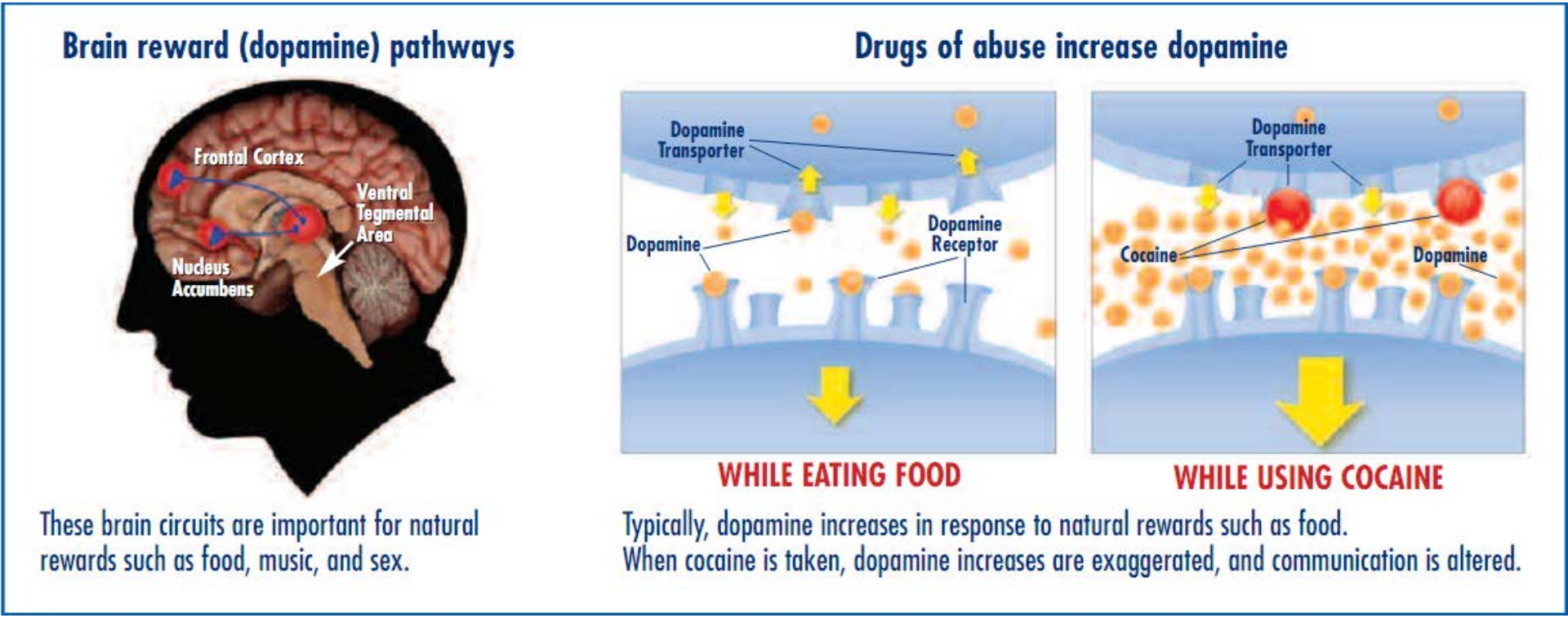
MDMA (*3,4-methylenedioxy-methamphetamine*)

[Note: mixed stimulant-psychodelic properties, w/↑serotonin > dopamine and abuse >> addiction.]

Others:

- Cathinones: Khat & Synthetics (e.g., "Bath Salts")
- Piperazine-like substances (various)
- Phenylaklylpyrrolidines (various)

COMMONALITIES
(WHAT MAKES A STIMULANT A STIMULANT?)



NIDA (2008) Drugs, Brains, & Behavior

-Inhibit dopamine & NE reuptake

-Some also potentiate dopamine-release (e.g., amphetamines, methamphetamines, cathinones)

COMMONALITIES: Clinical Effects

Short-term (Intoxication & Withdrawal):

- Psychiatric: euphoria, ↑energy & activity, alertness, insomnia, restlessness, anxiety/panic, erratic & violent behavior, paranoia, psychosis, poor judgment.
- Cardiovascular: vasoconstriction, arrhythmias, MI, ↑HR, HTN
- Neurologic: headache, enlarged pupils, stroke, seizure, coma
- Other: ↑body temp, dehydration, renal injury, abdominal pain & nausea, ↓ appetite, premature delivery & placental abruption
- Withdrawal: Depression, fatigue, hypersomnolence, sleep disturbances, motoric phenomena, paresthesias.

Long-term:

- End organ damage (CNS, cardiac, renal, hepatic, other) from hypoperfusion, toxic effects, rhabdomyolysis.
- Nutrition: poor nutrition & weight loss.
- Psychiatric: Prolonged confusion, depression, anxiety, inattention, psychosis, aggression, memory, and sleep issues.
- Infection: Risk of HIV, HCV, other infectious diseases.

IDENTIFYING STIMULANT USE DO

Confirm & Characterize Stimulant Use:

- Based on ***pt's report***, SUDs ***screening tools***, ***collateral*** evidence, ***symptoms/signs***, ***toxicology***, etc

DX: Use → impairment/distress:

- Symptoms:
  - Persistent desire or unsuccessful efforts ↓ use.
  - Cravings
- Behaviors:
  - Using ↑ amounts or over longer period than intended.
  - Excessive time obtaining, using, recovering
  - Failure to fulfill major role obligations
  - Use despite consequences
  - Important activities given up/reduced
  - Recurrent use when physically hazardous.
  - Use despite knowledge of physical/psychological problems
- Physiologic Changes:
  - Tolerance, Withdrawal

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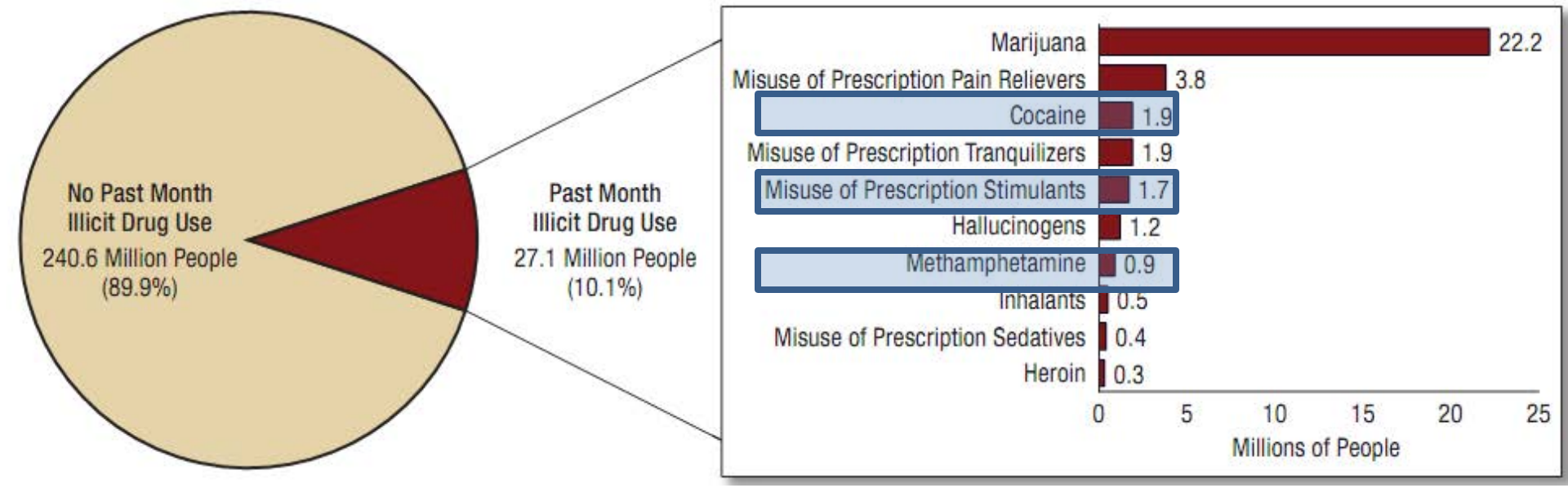
STIMULANTS: HOW BIG A PROBLEM?

Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2015



SAMHSA (2015) Behavioral Health Trends in the United States: Results from the 2015 National Survey on Drug Use and Health

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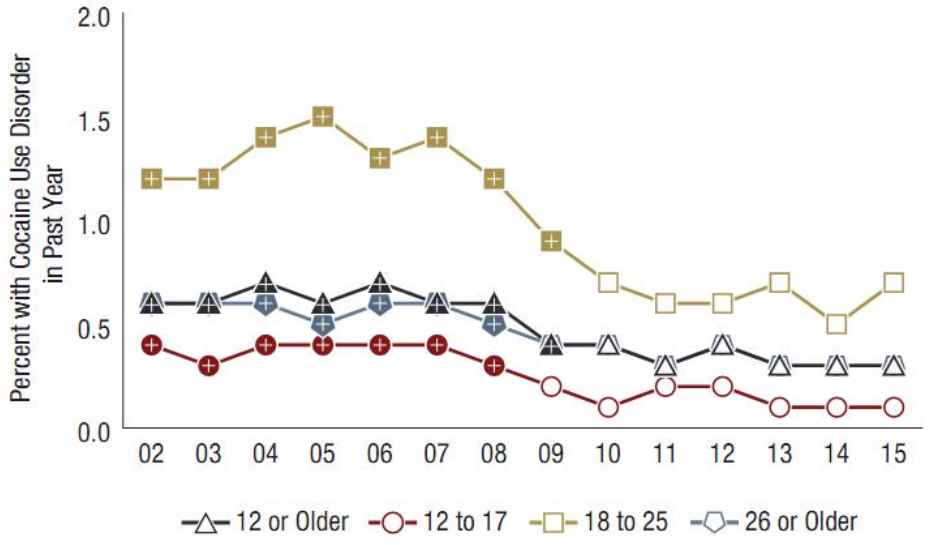
COCAINE USE AND ITS CONSEQUENCES

- 1.9 million (> 12yo) used cocaine (crack ~394K users)
- Young adults ~2.5X those > 25yrs old.
- Men >> women (2X use & death rates)
- 423,000 ED visits (2009)
- >5,000 deaths/yr annually

Figure 33. Cocaine Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2015



SAMHSA (2015) BHTUS; SAMHSA DAWN Study (2010)

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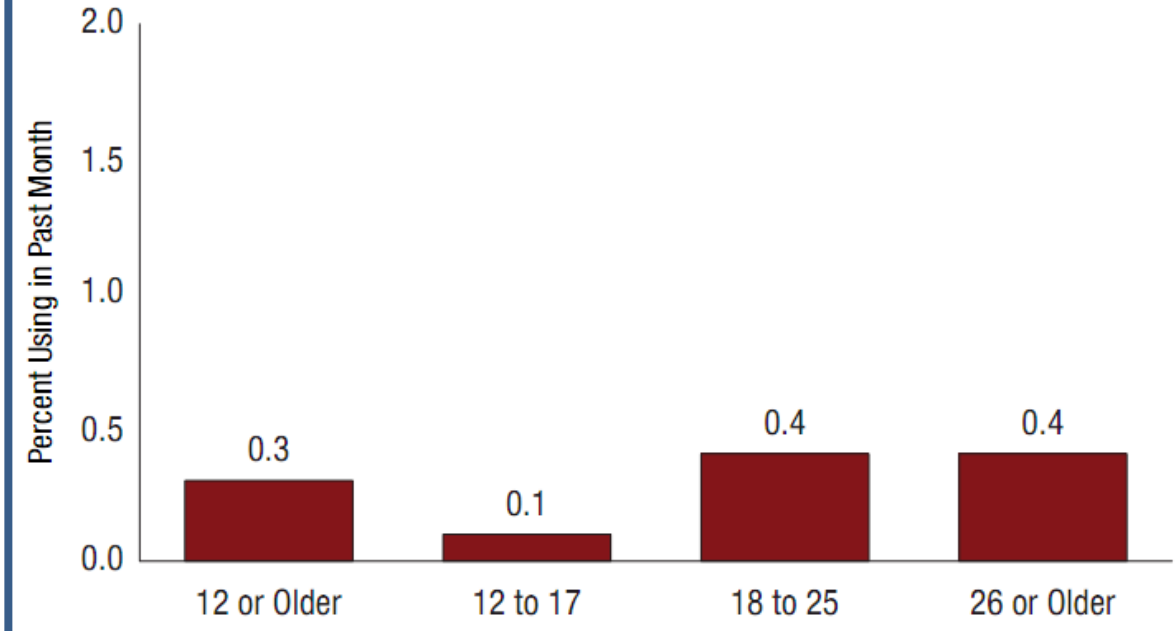
METH/AMPHETAMINE MISUSE & ITS CONSEQUENCES

- ~900,000 used Meth in priormonth
- 1.7 million misused Rx-ed stimulants in prior month
- ED visits due to illicit meth/amphet effects:
  - ~93,000 (2009)
  - >60% involved at least one other substance.

SAMHSA BHTUS (2015);
SAMHSA DAWN Study (2010)

Figure 12. Past Month Methamphetamine Use among People Aged 12 or Older, by Age Group: Percentages, 2015



RX STIMULANT MISUSE & DIVERSION

- **HS students** w/stimulant rxs:
  - 15% shared, 7% sold meds to peers in past year
- **College students** w/stimulant rxs:
  - 61.5% shared or sold meds ≥ 1 in their life
- **Adults** w/methylphenidate rxs:
  - 44% diverted, 29% misused in past month

Darredeau et al (2007); Garnier et al (2010); Webb et al (2013); Wilens et al (2008)

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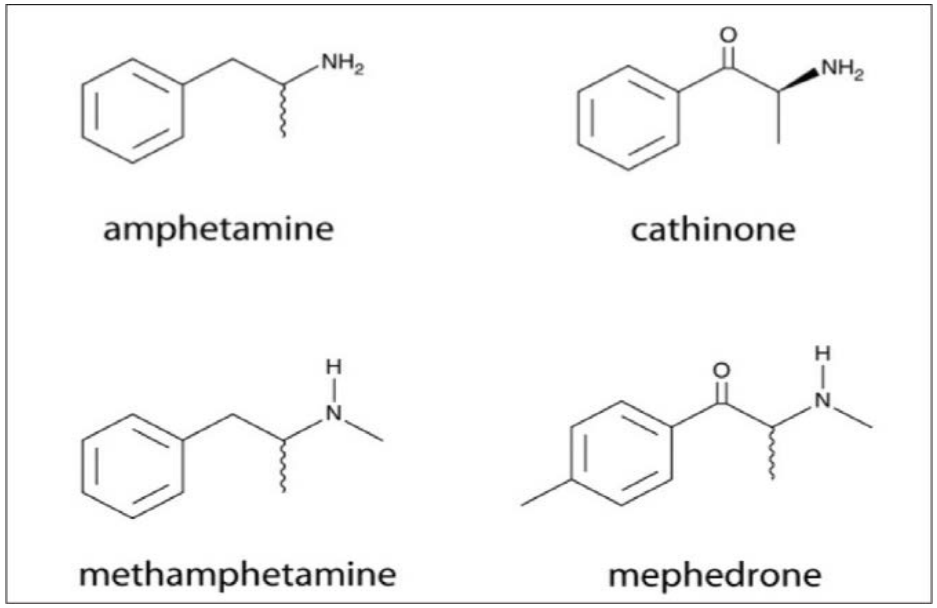
"BATH SALTS": SYNTHETIC CATHINONES

- MOA like Meth (+ ↑5HT like MDMA)
- Easy access (historically): Internet, head shops
- Not detected on standard tox-screens
- Rates of use uncertain



STIMULANT USE DISORDERS:

TREATMENT

2014 NSDUH

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ACUTE INTOXICATION & WITHDRAWAL

Monitor for vitals/lab abnormalities

- Hyperthermia, dehydration, renal function

Supportive

- Cardiac, Renal, Hyponatremia effects may require IVF/electrolytes, HTN control, +/-hospitalization
- Psychiatric symptoms: assess, monitor, +/-ED/hospitalization for safety
  - Agitation: Benzodiazepines
  - Hallucinations: low-dose antipsychotics for hallucinations
    - Avoid aggressive use of antipsychotics due to increased morbidity

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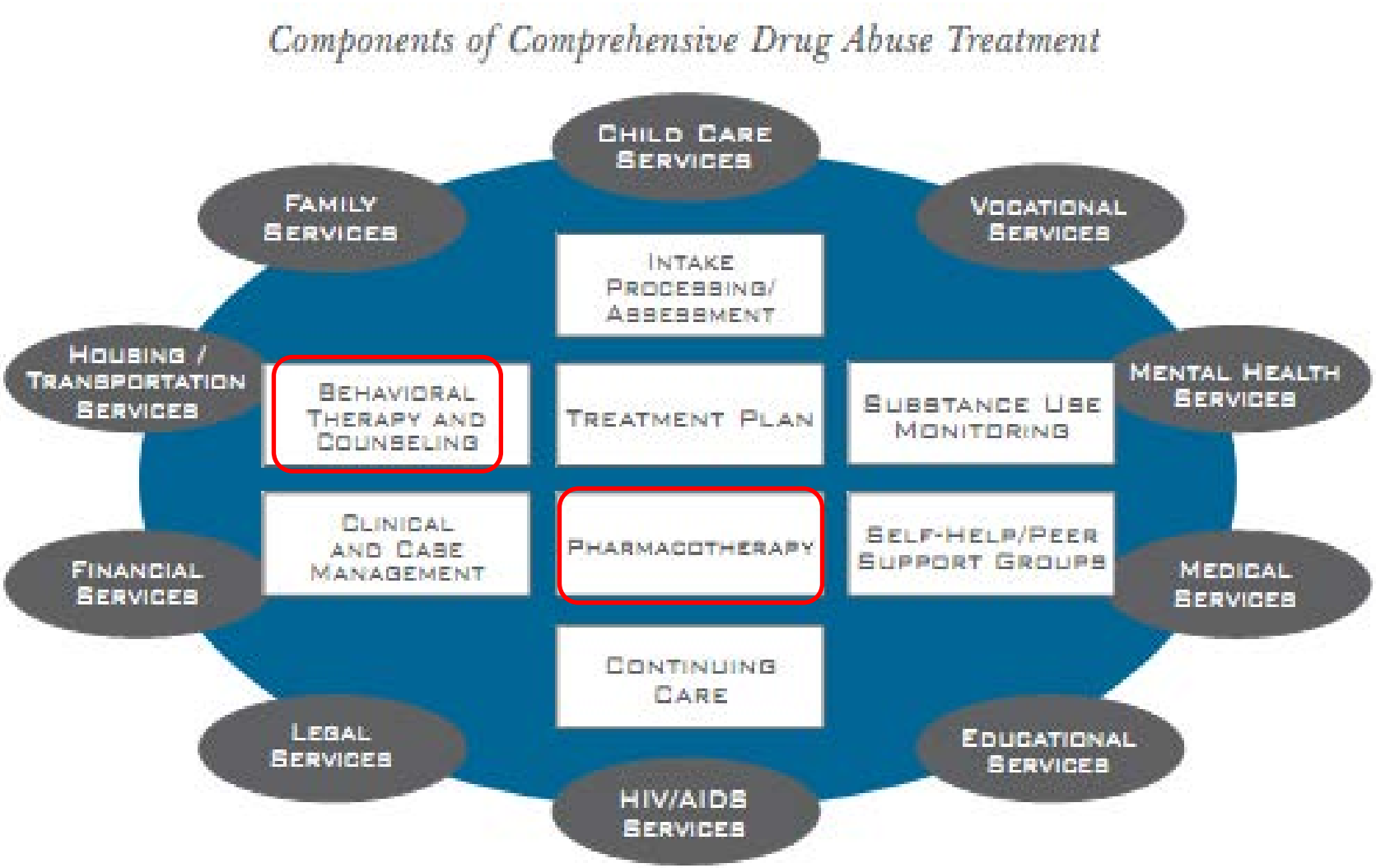
TREATING STIMULANT USE DISORDERS



PSYCHOTHERAPIES: A GENERAL APPROACH

↑ intensity for↑ severity or inadequate response

- Outpatient addictions counseling/groups
  - Intensive outpatient tx (largely group-based)
    - Individual therapies (plus groups): CM, CBT
      - Intensive residential, pharmacotherapy

–Note: assess & treat co-morbid psychiatric and other SUDs

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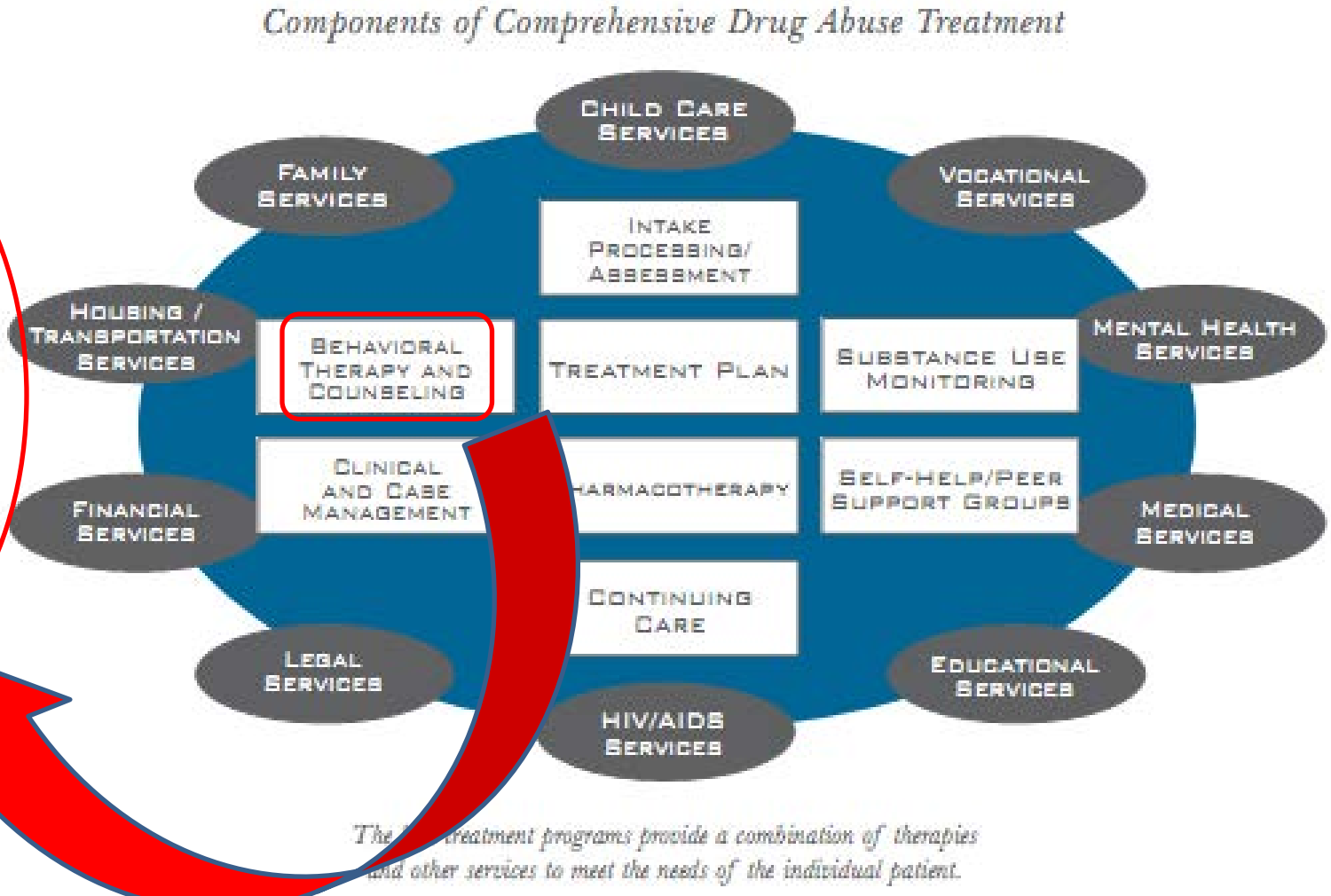
TREATING STIMULANT USE DISORDERS

What Works?



PSYCHOTHERAPIES FOR STIMULANT USE

Therapy Modalities:

- Contingency Management (CM)
- Cognitive Behav. Therapy (CBT)
- Motivational Enhancement Therapy (MET)
- 12-Step Facilitation
- Family Therapy (esp. for youth)

Pros:

- Evidence-based
- Skill-building (often)
- ↑ internal motivation
- Bridge to additional tx
- Can use in multiple settings

Cons:

- Time, resource-intensive
- Limited workforce
- Modest effect sizes
- Not suitable for all pts (e.g., cognitive requirements)
- Unclear sustained benefit

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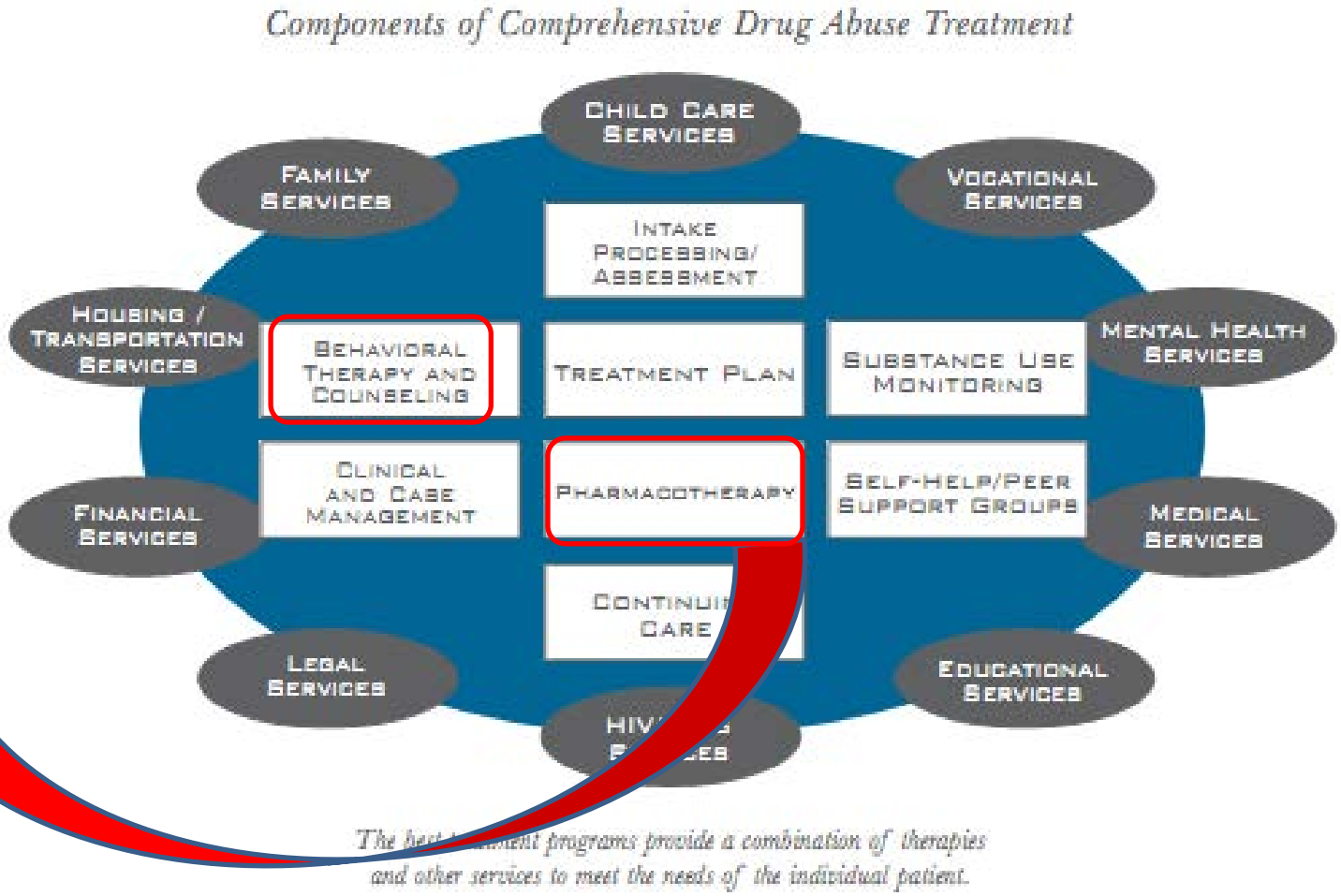
PHARMACOTHERAPY FOR STIMULANT USE DISORDERS

????



POP QUIZ!

Question: ***Which medications are FDA-approved for treatment of a stimulant use disorder?***

Answer: ***None*** ☹

POP QUIZ!

Question: ***Which medication(s) have shown potential benefit for sustaining remission from cocaine use?***

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POSSIBLE MEDICATION(S) FOR COCAINE USE DISORDER?

Evidence suggestive of likely use-reduction w/Rx:

- Disulfiram, topiramate, methylphenidate

Equivocal, to date:

- Modafinil, amantadine, varenicline, naltrexone, doxazosin, NAC, TA-DC Vaccine

Ineffective (based on available data):

- Lithium, Carbamazepine, TCAs, SSRIs, bupropion, Nefazodone, Selegiline, antipsychotics

DISULFIRAM FOR COCAINE USE DISORDER

Mechanism(s) of Action:

- Inhibits dopamine β-hydroxylase, ↓dopamine → norepinephrine
  - Disrupts neurotransmitter balance in reward system?
- ↑ cocaine plasma levels (MOA unknown) → cocaine more aversive?
- FDA approved for ETOH use disorder
  - ~80% of pts w/cocaine use disorder have comorbid ETOH use disorder. Can ↓ in ETOH use promote ↓ cocaine use?

Pani et al., 2010

Disulfiram & CBT for Cocaine in Outpatients

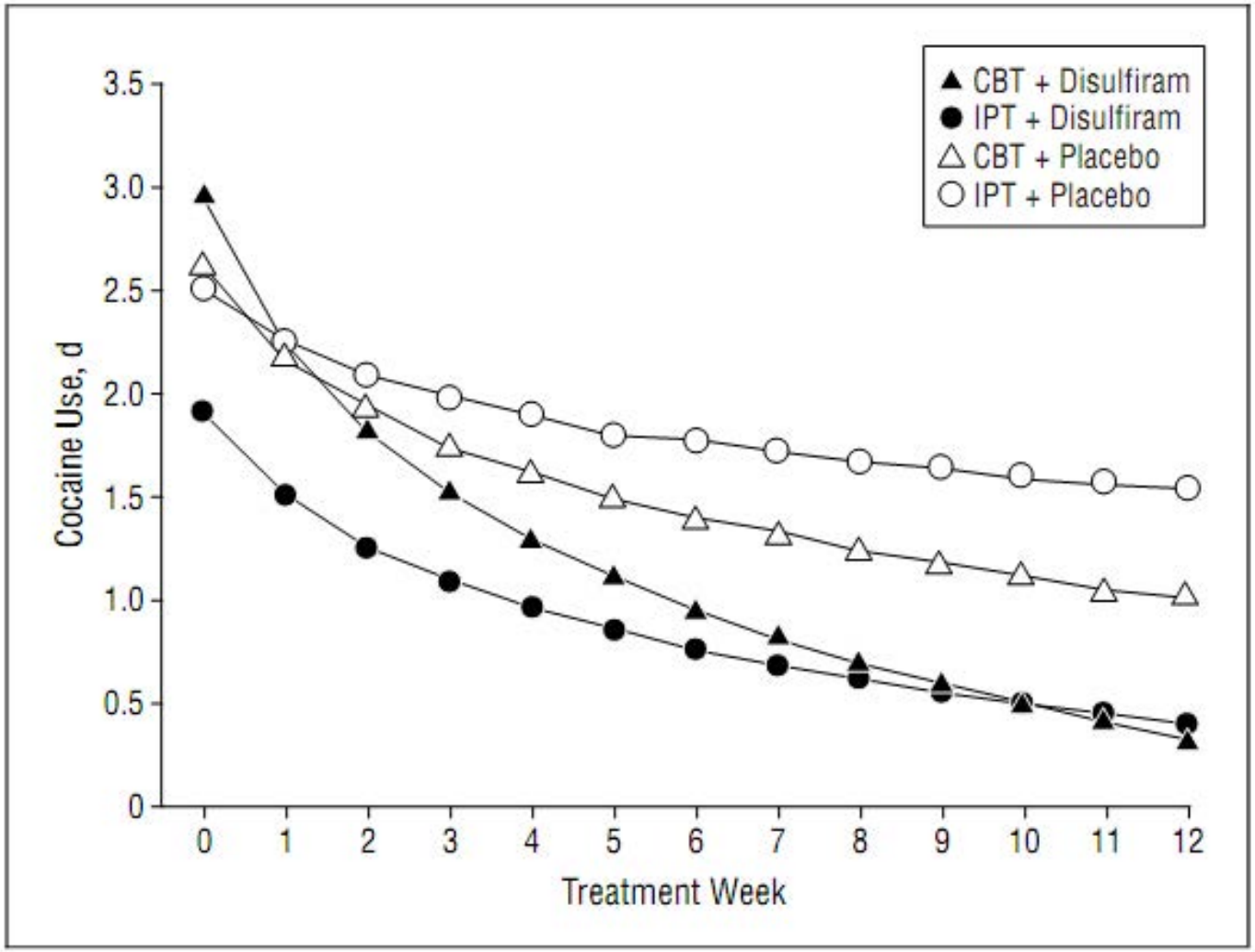


Figure 2. Frequency of cocaine use by treatment week. Effects are estimates from random regression analyses. CBT indicates cognitive behavior therapy; IPT, interpersonal psychotherapy.

Carroll et al., 2004

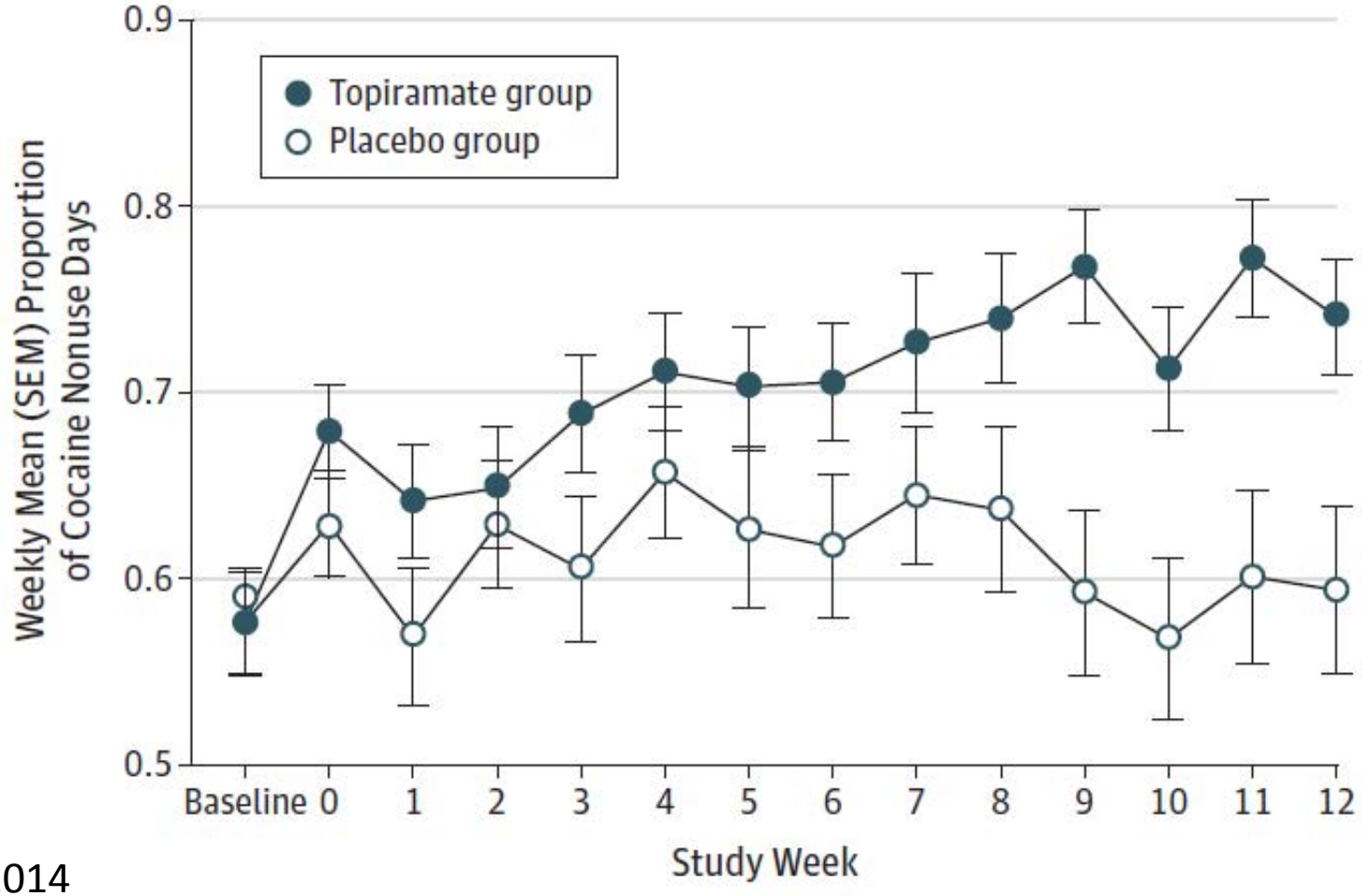
RX OF COCAINE USE DO:
OTHER (PROMISING) RX OPTIONS

- **Topiramate**
  - An antiepileptic, increases GABA activation
  - May be especially effective with CBT

- **Amphetamine salts**
  - Increases dopamine & norepinephrine availability
  - A stimulant "substition therapy" (like buprenorphine-naloxone)?
  - Mixed results (efficacy improves w/retention?)

Topiramate for Cocaine Use Disorder

- 12 wk trial w/142 Cocaine-dependent pts
- Randomized to CBT +: Placebo vs. Topiramate
  - -Target dose, weeks 6-12: 150 mg bid



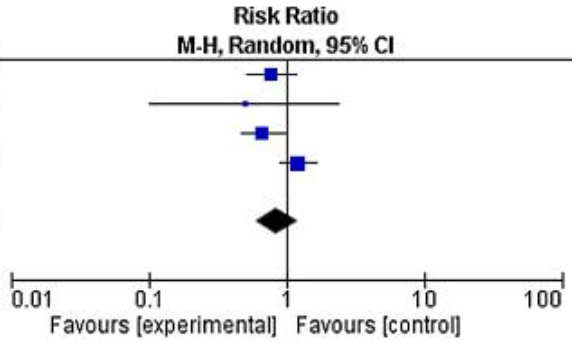
Johnson et al., 2014

Topiramate for Cocaine Use Disorder:

a) Treatment Retention

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Johnson et al. 2013	25	71	32	71	29.3%	0.78 [0.52, 1.17]
Kampman et al. 2004	2	20	4	20	4.6%	0.50 [0.10, 2.43]
Kampman et al. 2013	29	87	41	83	31.4%	0.67 [0.47, 0.98]
Umbricht et al. 2014	33	47	26	45	34.7%	1.22 [0.89, 1.66]
Total (95% CI)		**225**		**219**	**100.0%**	**0.85 [0.60, 1.22]**
Total events	89		103			

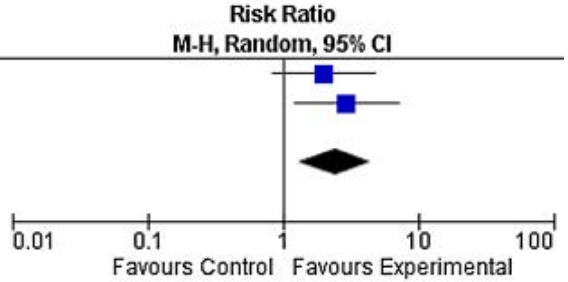
Heterogeneity: Tau² = 0.07; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.88 (P = 0.38)



b) Continuous Abstinence

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kampman et al. 2004	10	20	5	20	50.2%	2.00 [0.83, 4.81]
Kampman et al. 2013	17	83	6	87	49.8%	2.97 [1.23, 7.17]
Total (95% CI)		**103**		**107**	**100.0%**	**2.43 [1.31, 4.53]**
Total events	27		11			

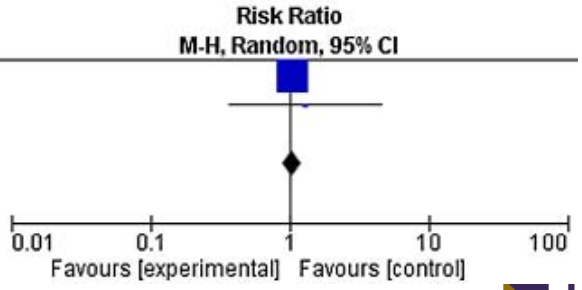
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)



c) Adverse Effects

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Johnson et al. 2013	60	71	57	71	98.5%	1.05 [0.90, 1.23]
Umbricht et al. 2014	5	45	4	47	1.5%	1.31 [0.37, 4.56]
Total (95% CI)		**116**		**118**	**100.0%**	**1.06 [0.91, 1.23]**
Total events	65		61			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)



Singh et al., 2015

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RX OF COCAINE USE DO: STIMULANTS?

- 12wk, multi-center, double blinded, placebo-controlled
- 73 pts w/cocaine & heroin SUDs on methadone
- Randomized to placebo vs dextroamphetamine SR 60mg/day
- Days of cocaine-use ↓ 26% on Rx stimulant

	Sustained-release dexamfetamine group (n=38)	Placebo group (n=35)	Exp(B) (95% CI)	Wald χ^2 (df=1)	p value	Effect size
Primary outcome						
Days of cocaine use during 12-week study	44·9 (29·4)	60·6 (24·3)	1·67 (1·05–2·67)	4·66	0·031	d=0·58
Secondary cocaine use-related outcomes						
Longest period of consecutive cocaine abstinence (days)	17·9 (24·9)	6·7 (11·7)	2·69 (1·66–4·36)	16·17	<0·0001	d=0·58
Consecutive cocaine abstinence for ≥21 days	11 (29%)	2 (6%)	6·72 (1·37–32·97)	5·52	0·019	NNT=4·3
Days of cocaine abstinence in final 4 weeks	15·2 (10·8)	7·5 (9·1)	2·04 (1·26–3·31)	8·45	0·004	d=0·77
Proportion cocaine-negative urine samples in final 4 weeks	10·6 (25·1)	3·9 (17·9)	2·60 (1·14–5·94)	5·11	0·024	d=0·31

Data are mean (SD) or n (%), unless otherwise specified. Exp(B)=exponentiated value of regression coefficient B; odds ratio. df=degrees of freedom. d=Cohen's d, which is a standardised effect size. NNT=number needed to treat.

Table 2: **Primary and secondary cocaine use-related outcomes**

Nuijten et al., 2016

POP QUIZ!

Question: ***What medication has good evidence of promoting abstinence from methamphetamine among chronic users?***

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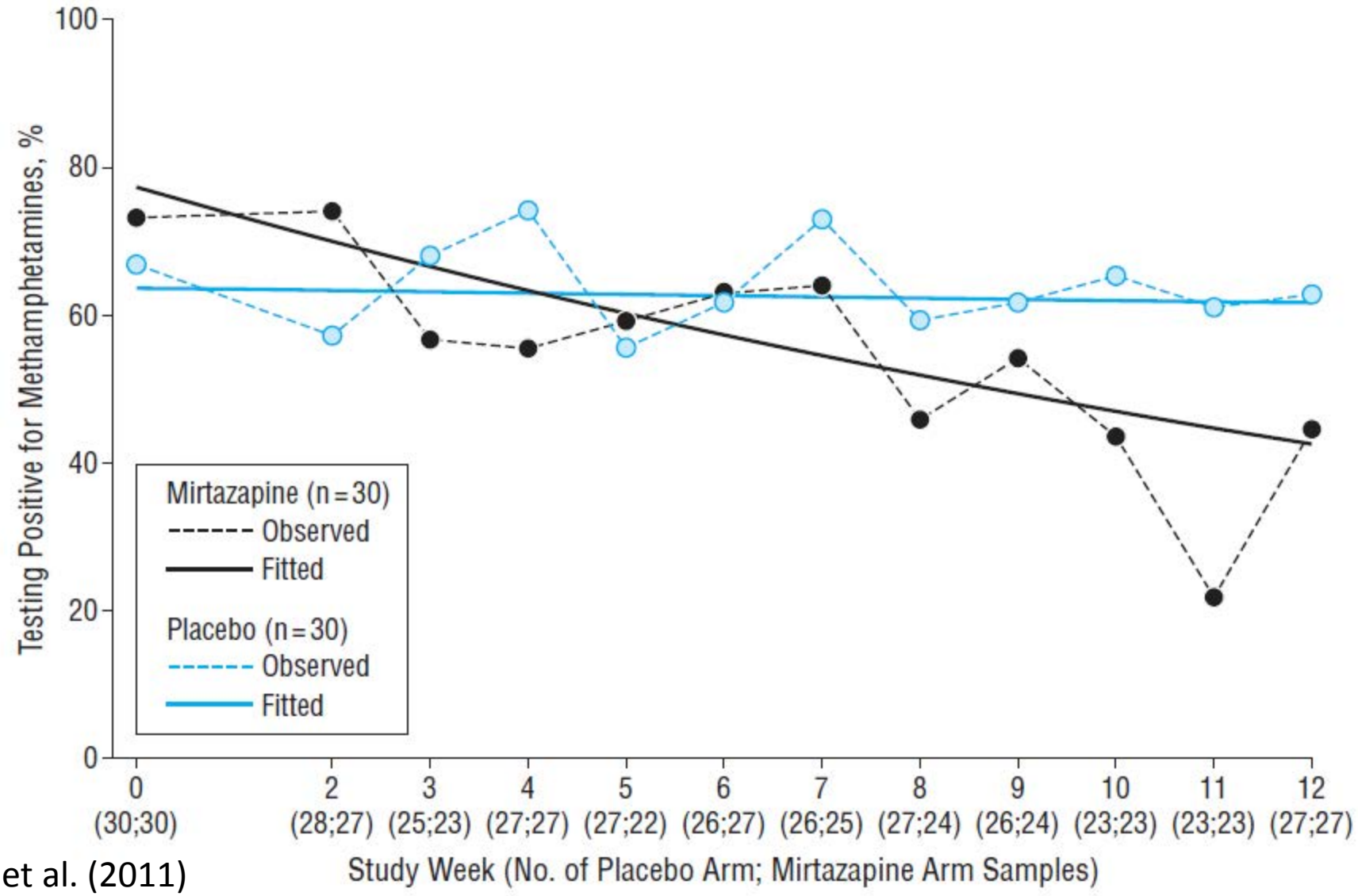
PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER:

- No accepted treatments ☹
- There have been small studies suggesting potential benefit from mirtazapine, bupropion
- Equivocal or negative results for naltrexone, atamoxetine, buprenorphine-naloxone, stimulants

PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER: MIRTAZAPINE (30MG)



Colfax et al. (2011)

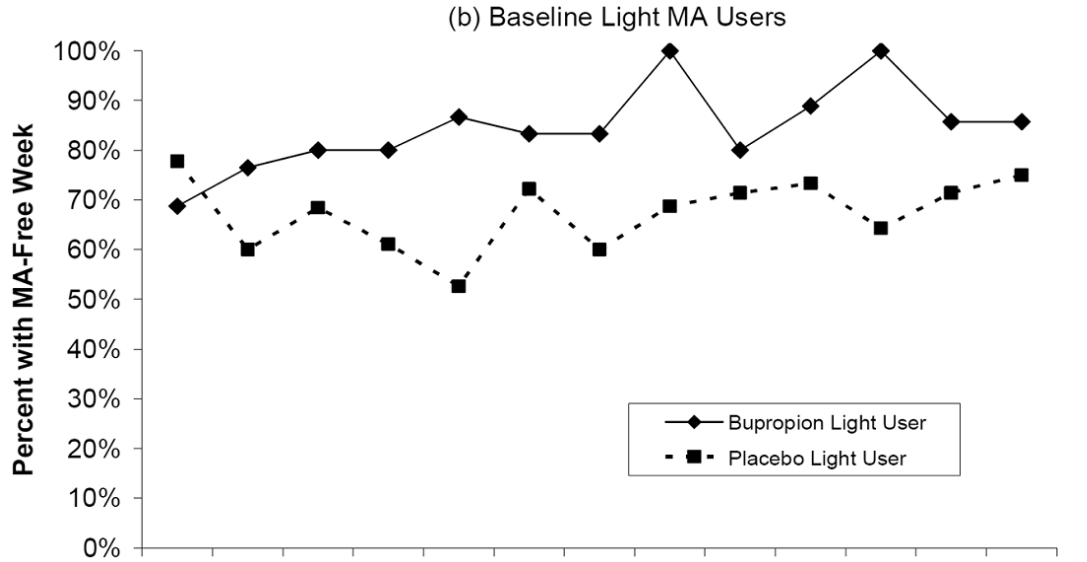
PHARMACOTHERAPY FOR METHAMPHETAMINE USE DISORDER: BUPROPION (300MG)

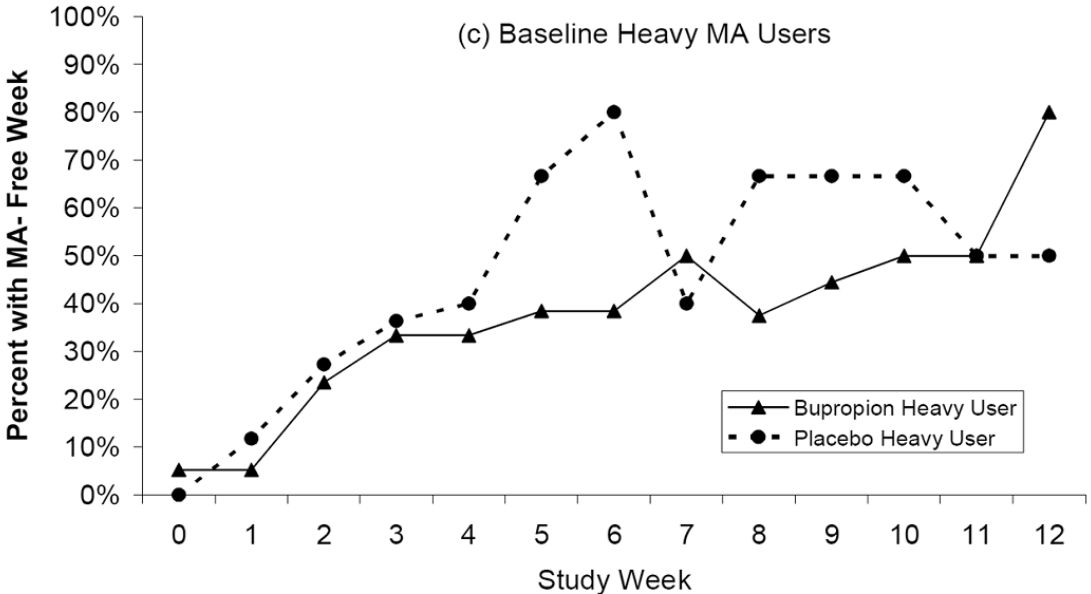
Design:

- 12wk, 151 Meth-dep pts
- Randomized to CBT +:
  - Placebo
  - Bupropion 300mg Qday

Results:

- No diff in abstinence in total sample
- Improvement w/bupropion among light-users





Shoptaw et al. (2008)

A SPECIAL CASE?

PRESCRIBING STIMULANTS FOR CO-MORBID ADHD & STIMULANT USE DISORDERS?

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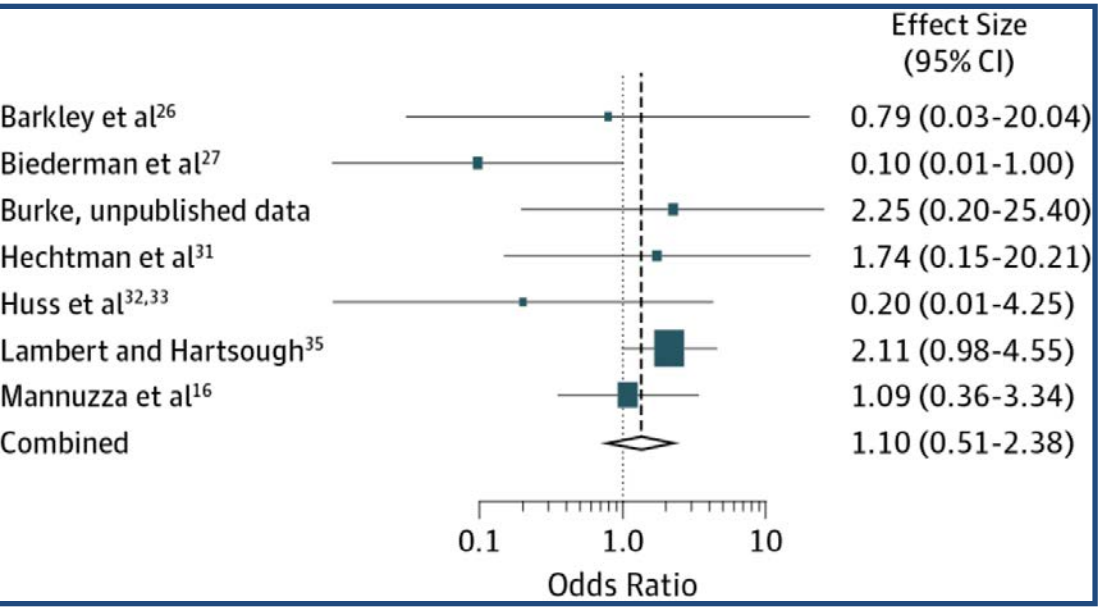
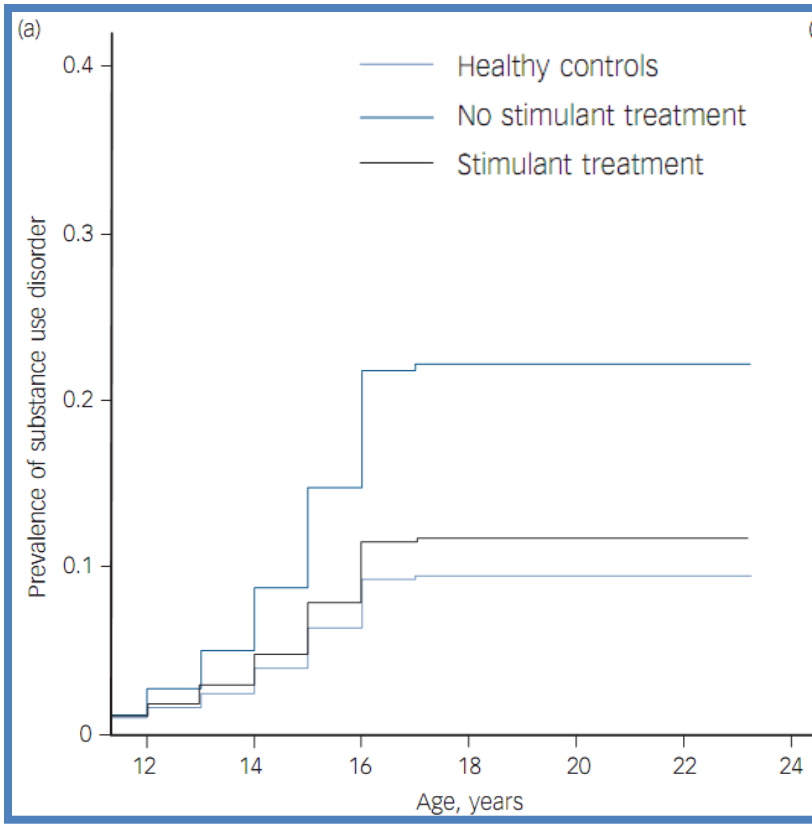
DOES RX OF ADHD WITH STIMULANTS IMPACT DEVELOPMENT OF SUDS?

Risk of Developing Cocaine Abuse or Dependence



Humphreys et al (2013)



Groenman et al (2013)

Conclusions:

- Neutral > protective effects; not harmful

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PSYCHOSTIMULANTS FOR RX OF COMORBID ADHD & STIMULANT ABUSE?

Comorbid ADHD & amphetamine use disorders:

- Very little research
- Rx w/stimulants → no difference in ADHD or SUD (Konstenius et al 2010.)

Comorbid ADHD & Cocaine use disorder:

- More research
- Results suggesting…

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STIMULANTS FOR RX OF COMORBID ADHD & STIMULANT ABUSE…MAYBE

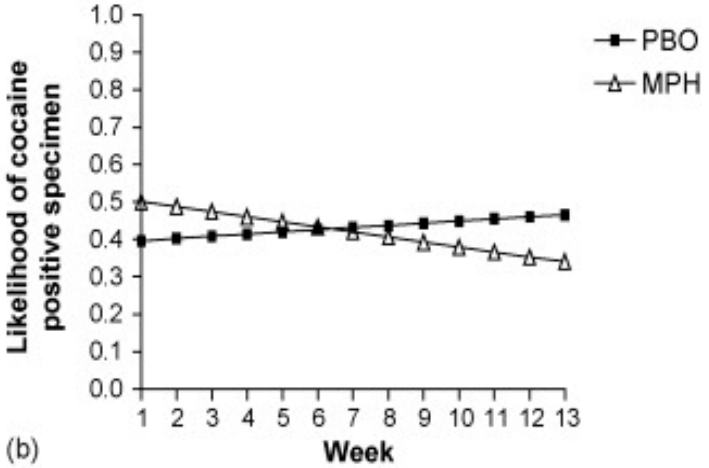
Levin et al 2007:

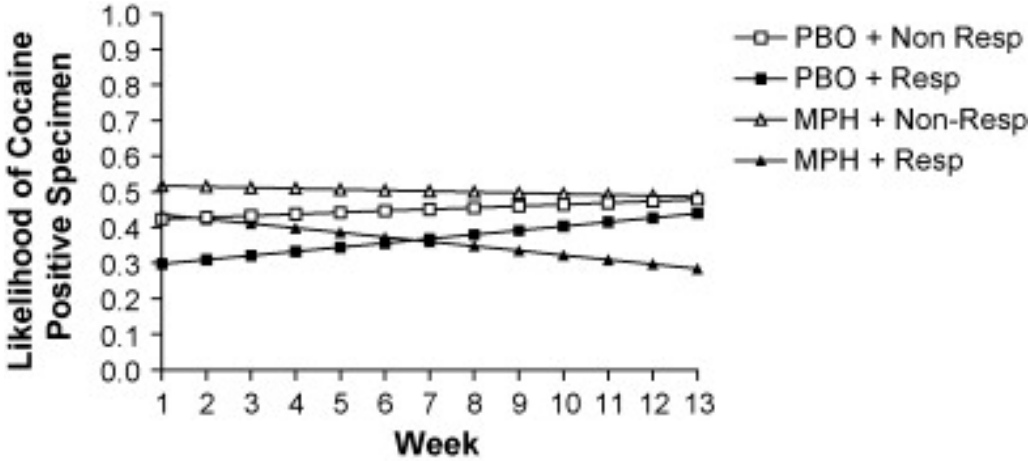
Design:

- 14 week double-blinded, placebo-controlled trial
- 106 adult w/ADHD + Cocaine UD
- CBT + SR-MPH (60mg) vs CBT + placebo

Results:

- Decreased probability of cocaine+ UDAS w/MPH
- No difference in ADHD symptoms





STIMULANTS FOR RX OF COMORBID ADHD & STIMULANT ABUSE…MAYBE NOT

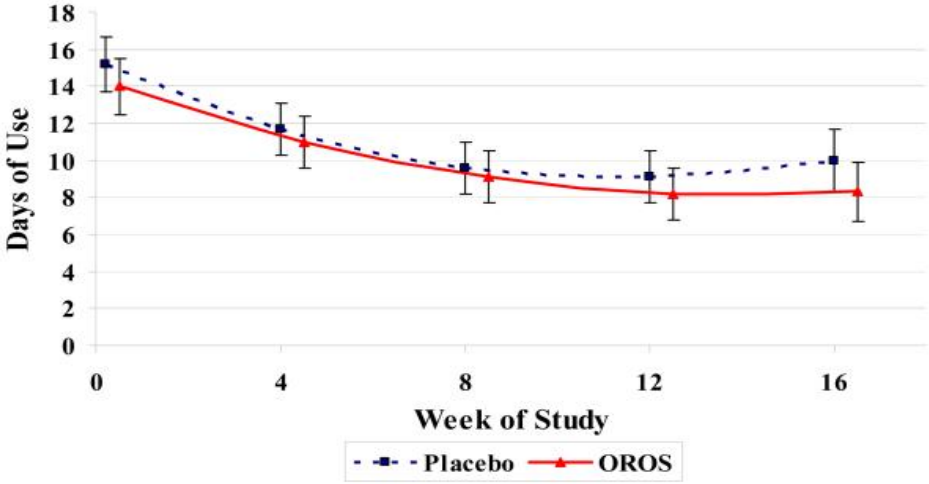
Riggs et al (2011)

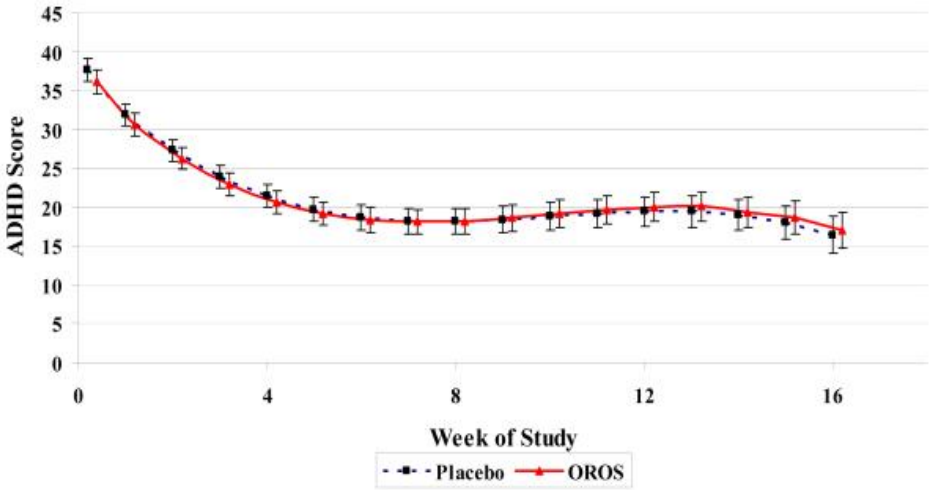
Design:

- 16 wk, double-blinded placebo controlled
- 303 teens w/ADHD + active SUD
- Methylphenidate (Concerta) 72mg/day + CBT vs placebo + CBT

Results:

- No diff in ADHD or substance use
- Drugs of abuse: Cannabis > Alcohol > other drugs





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STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE…MAYBE YES!

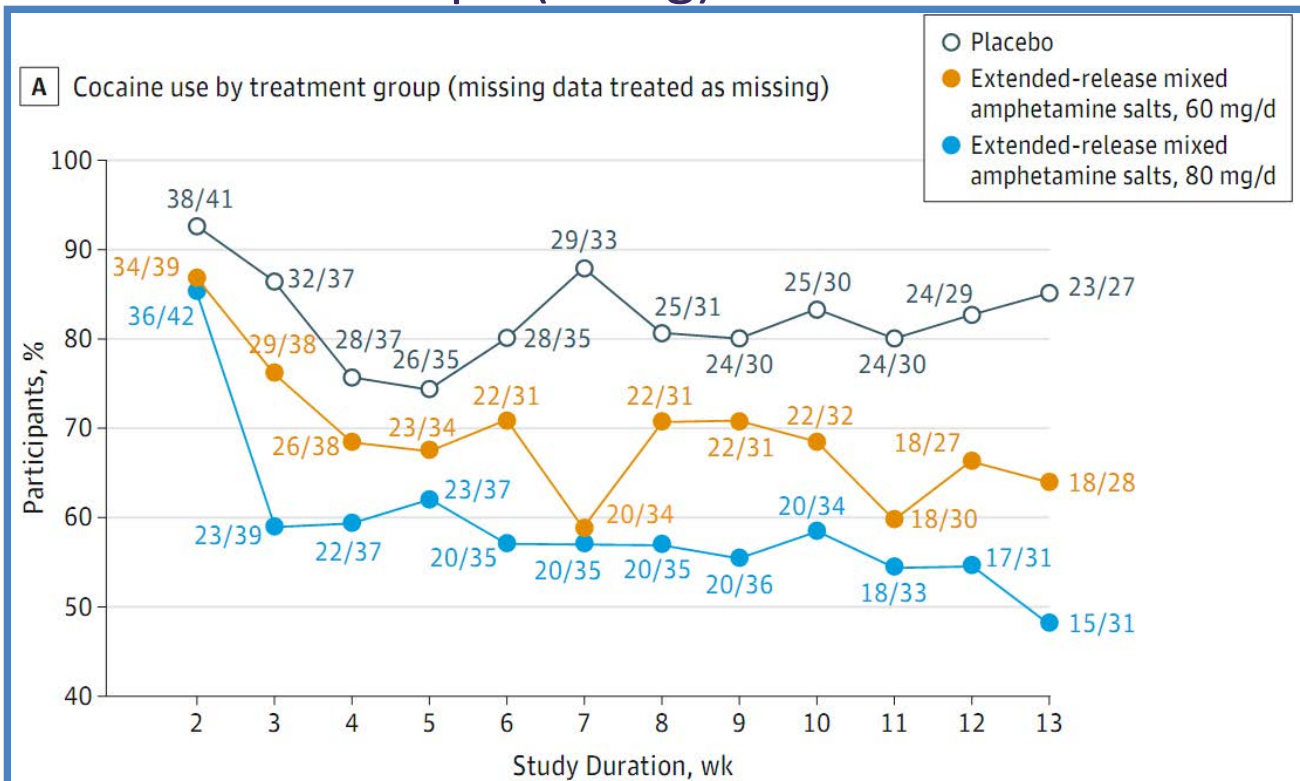
Levin et al 2015:

Design:

- 13 wk double-blinded, placebo-controlled 3-arm trial
- 126 adult w/ADHD + Cocaine UD
- CBT plus: Placebo vs. SR-mixed Amph (60mg) vs. SR-mixed Amph (80mg)

Results:

- Rx w/Stimulant ↓ prob. cocaine-use (UDAS or self-report)
- Rx w/Stimulant ↓ ADHD symptoms



STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE – SUMMARY

Studies suggest:

- No worsening of substance of use disorders
- Unclear utility in amphetamine use disorder
- Accumulating evidence for role in cocaine use disorder
  - May ↓ cocaine use
  - May ↓ ADHD symptoms

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STIMULANTS FOR COMORBID ADHD & STIMULANT ABUSE – TREATMENT APPROACH

Tailor to individual pt:

- Actual AD/HD & of what severity?
- Has SUDs treatment been +/- optimized?
- Hx/risk of mis-use or diversion?

Would non-abusable Txs work for pt?:

- e.g., atomoxetine, bupropion, CBT

Consider long acting stimulant, as appropriate:

- ↑outcomes w/pre-rx abstinence
- Coordinate w/other providers
- Treatment agreement/contract
- Monitor (tox screens, call-backs PRN)
- Use adequate/higher doses

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PRESENTATION SUMMARY:

- Stimulant misuse:
  - Modestly prevalent; often severe individual & social costs
- Acute symptom management: supportive
- Psychosocial Txs are 1st Line:
  - Conting. Management, CBT have most evidence
- Pharmacotherapies:
  - Cocaine:
    - Disulfiram; some evidence for topiramate, stimulants, others
  - Methamphetamine:
    - Small studies ~ potential benefit from mirtazapine, bupropion
  - Consider co-morbid psychiatric DOs in Rx decision /selection
- Tx of AD/HD in stimulant-abusing pts:
  - Case by case, prescribed stimulant can be helpful

QUESTIONS & DISCUSSION

MANY THANKS!

-The PACC community
-Andy Saxon, MD
-Jonathan Buchholz, MD
-Mark Duncan, MD

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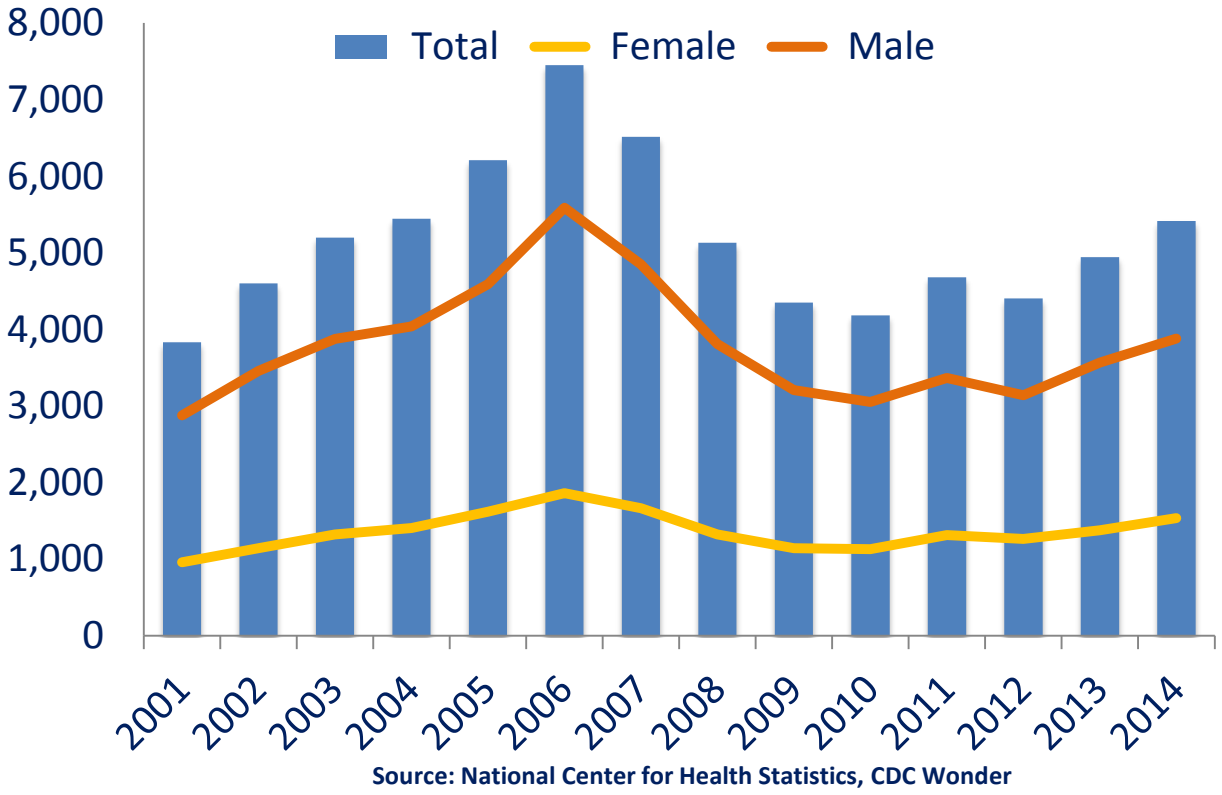
COCAINE USE AND ITS CONSEQUENCES

- Men (0.8%) vs. women (0.4%)
- >5,000 deaths/yr annually (2014)



SAMHSA (2015) BHTUS: Results from the 2015 National Survey on Drug Use and Health

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