VANDERBILT HEALTH

Stimulant use disorder and HIV

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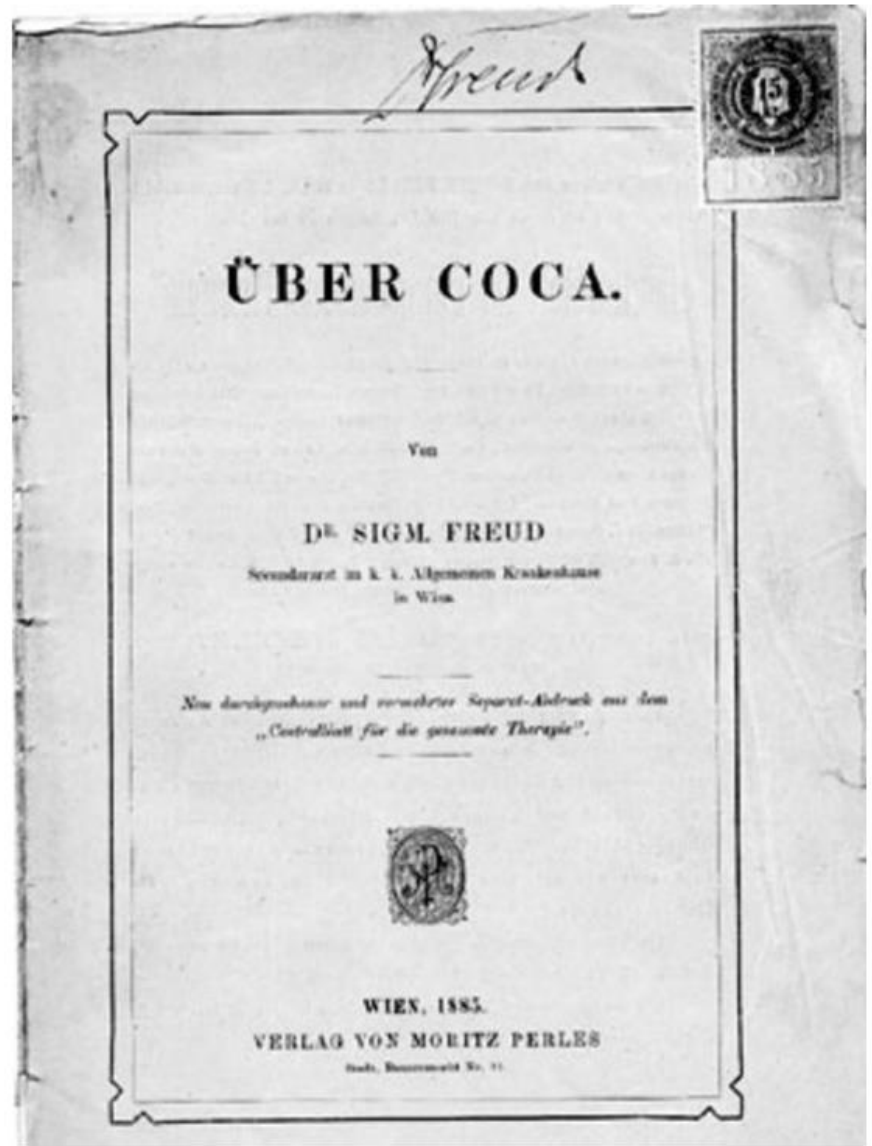
Objectives

- Review the pharmacology, epidemiology, and clinical assessment of stimulant use disorders
- Review the overlap of stimulant use disorder with the opioid epidemic
- Discuss evidence-based treatment options, including harm reduction, psychosocial interventions, and off-label pharmacotherapy
- Review the comorbidity between HIV, injection use, and stimulant use disorder, as well as

No ACCME-defined commercial interest conflicts or disclosures.

stimulant history
before and after Freud

- 5,000 years of ephedra use (China first)
- Andean *coca* buccal use at 0.2-1% purity in S America for 2,000 years
- Freud's *Uber Coca* (1884)
- now extracted to 80-90% purity, then acidified into salt powder or heated at basic pH to "freebase"
  - 60% cut with levamisole
- 1986 Anti-Drug Abuse Act: systemic racism and differential minimum sentencing for powder and "crack"


Freud

ÜBER COCA.

Von

DR. SIGM. FREUD

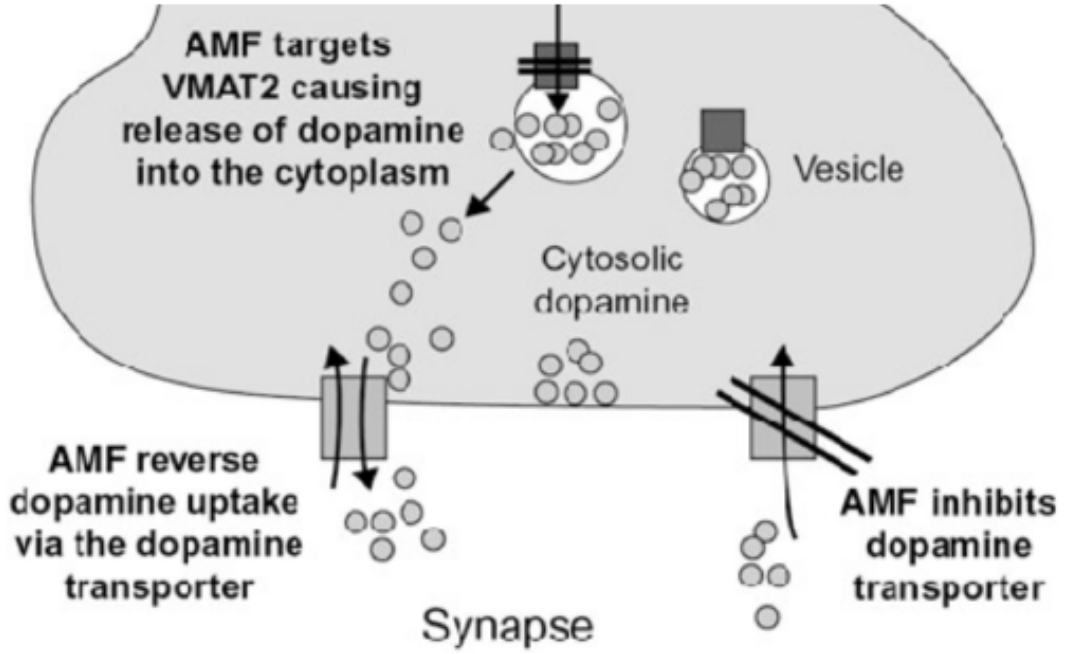
Sekundararzt im k. k. Allgemeinen Krankenhause in Wien.

Neu durchgesehener und vermehrter Separat-Abdruck aus dem „Centralblatt für die gesammte Therapie".

WIEN, 1885.
VERLAG VON MORITZ PERLES

psychostimulant
definition

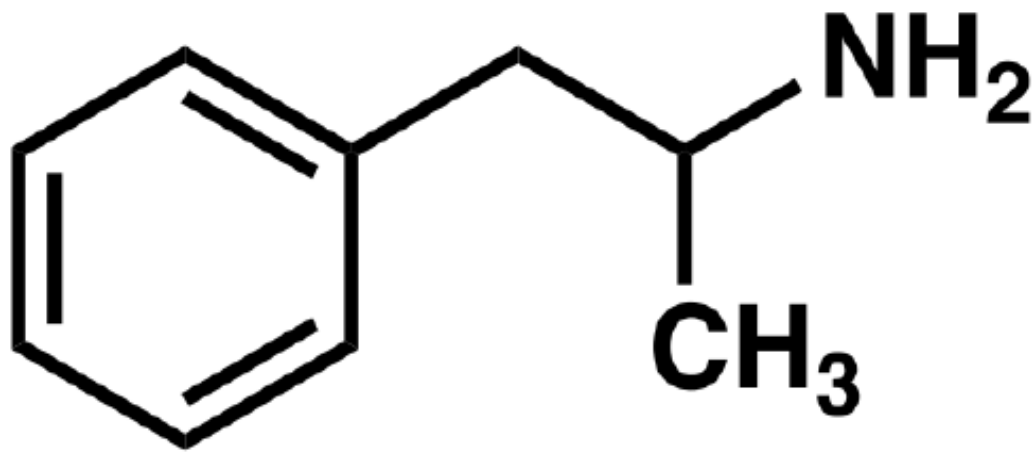
- enhance activity in the central and sympathetic peripheral nervous systems
- augment neurotransmission at norepinephrine and dopamine (ie, catecholaminergic) synapses
- indirect DA/NE/5HT agonists
  - cocaine inhibits reuptake of 5HT, NE, and DA
  - amphetamine also stimulates release into the synapse



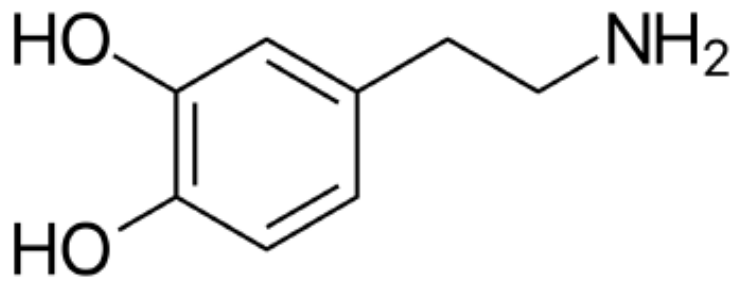
psychostimulant

specific substances

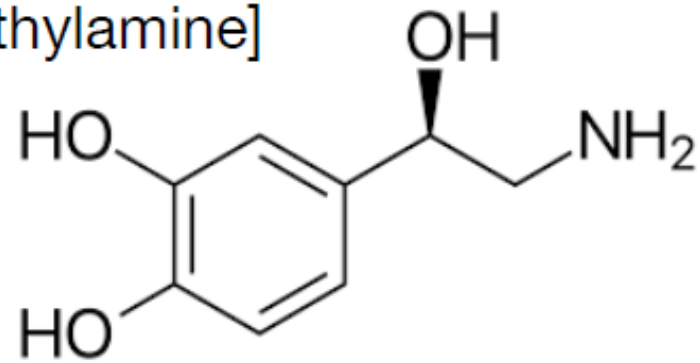
- shared structure: phenethylamine
- plant alkaloids
  - coca, ephedra, khat
  - caffeine*
- synthetic compounds
  - amphetamine, methylphenidate
  - MDMA*, modafinil*



[phenethylamine]



[DA]



[NE]

psychostimulant
shared effects

- ***"desired" effects:***
  - energy/alertness
  - sociability
  - elation or euphoria
  - decreased fatigue, sleep
  - decreased appetite

- ***adverse effects:***
  - tachycardia, ACS/MI, dysrhythmia
  - CVA, seizure, pupillary dilation
  - anxiety/irritability
  - impaired cognition
  - dyskinesia/stereotypy
  - psychosis — tactile hallucinations!

psychostimulant

medical complications by organ system

TABLE 54.1 Acute Medical Complications of Stimulant Intoxication

Organ System	Medical Effects
Head, ears, eyes, nose, throat	Pupil dilation; headache; bruxism
Pulmonary[a]	Hyperventilation, dyspnea; cough; chest pain; wheezing; hemoptysis; acute exacerbation of asthma; barotrauma (pneumothorax, pneumomediastinum); pulmonary edema
Cardiovascular	Tachycardia; palpitations; increased blood pressure; arrhythmia; chest pain; myocardial ischemia or infarction; ruptured aneurysm; cardiogenic shock
Neurologic	Headache; agitation; psychosis; tremor, hyperreflexia; small muscle twitching; tics; stereotyped movements; myoclonus; seizures; cerebral hemorrhage or infarct (stroke); cerebral edema
Gastrointestinal	Nausea, vomiting; mesenteric ischemia; bowel infarction or perforation
Renal	Diuresis; myoglobinuria; acute renal failure
Body temperature	Mild fever; malignant hyperthermia
Others	Rhabdomyolysis

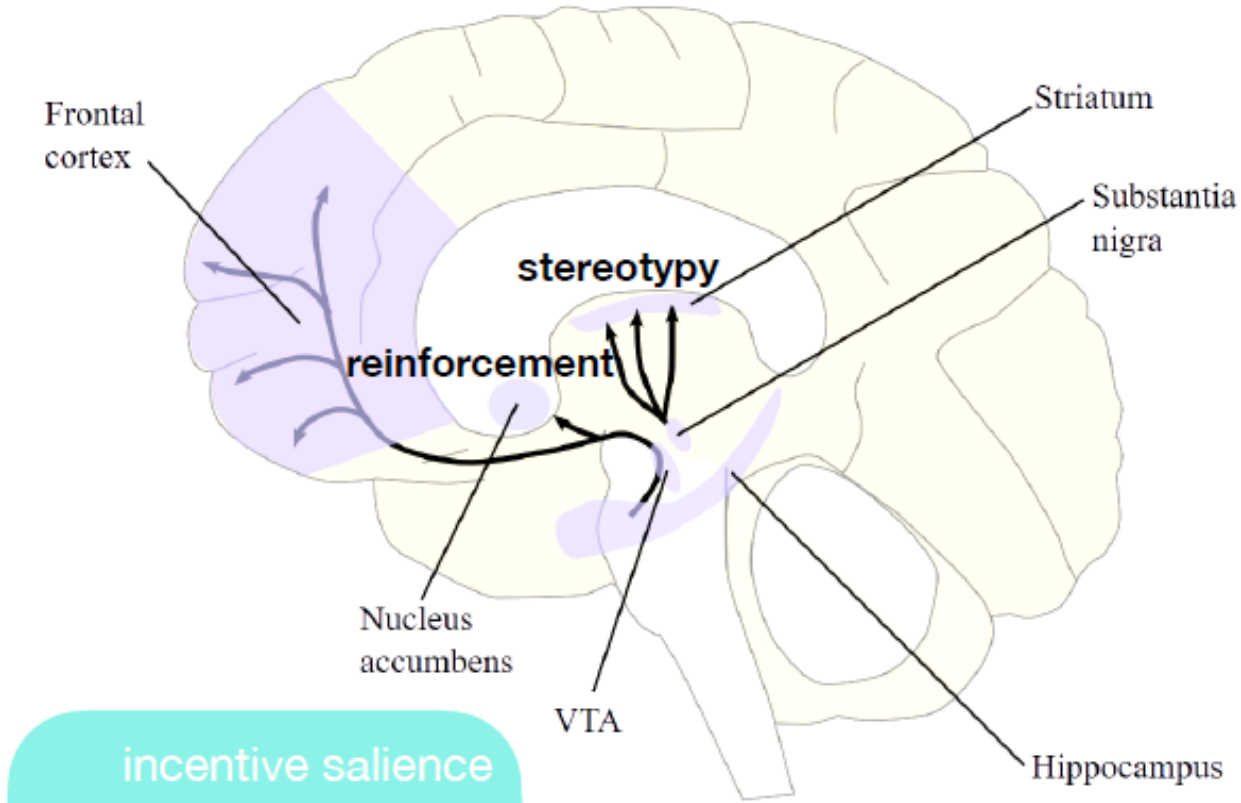
[a]All pulmonary complications except hyperventilation and pulmonary edema come primarily from the smoked route of administration.

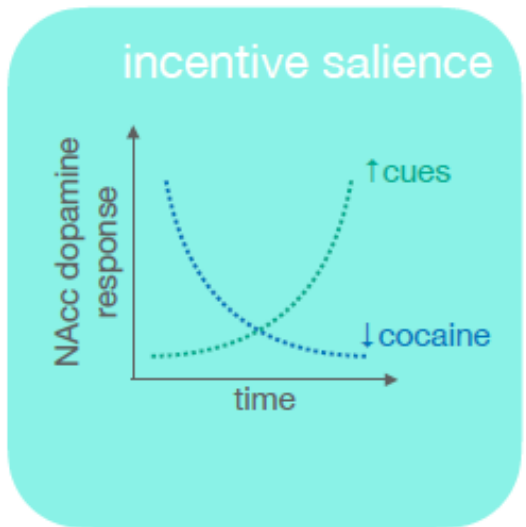
ASAM Principles of Addiction Medicine, 6th Ed., 2019.

reward system

stimulants and the striatum

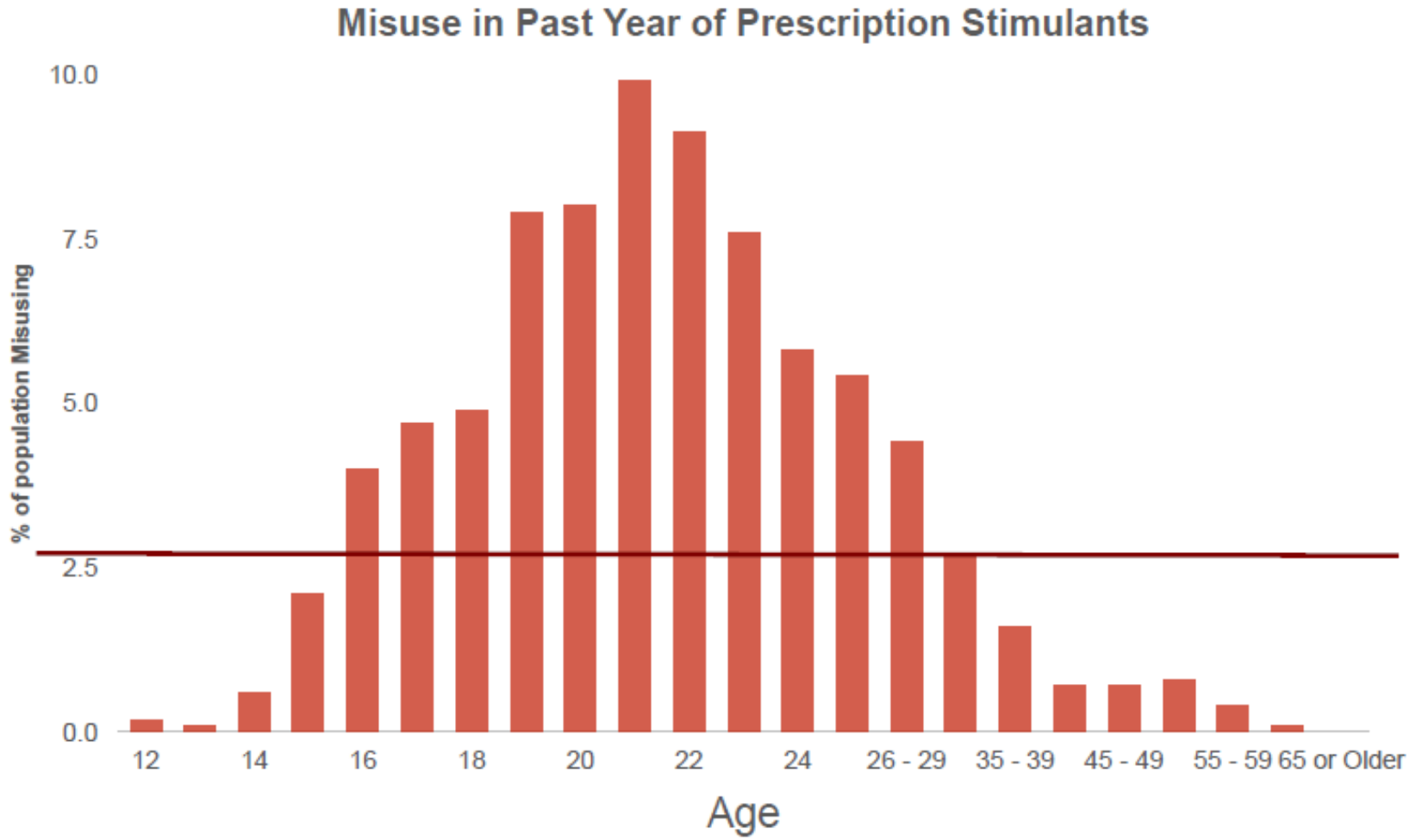
- mesolimbic dopamine system
- ventromedial striatum includes the nucleus accumbens (NAc), which mediates reinforcement
- repeated NAc activation leads to incentive salience for associated cues
- cues then independently induce DA firing in the NAc, resulting in compulsive motivation





epidemiology

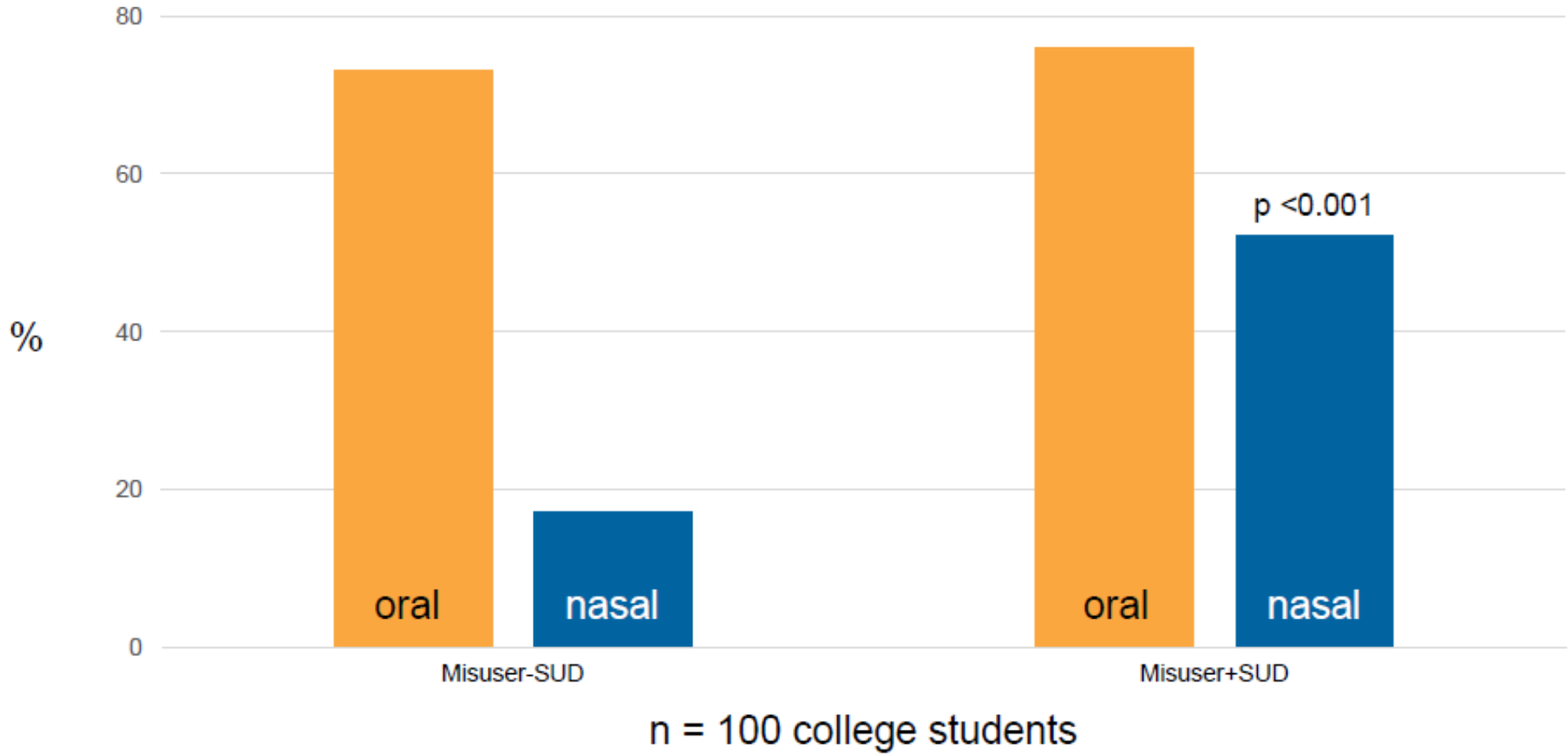
non-medical stimulant use



SAMHSA. National Survey on Drug Use and Health (NSDUH), 2015.

epidemiology

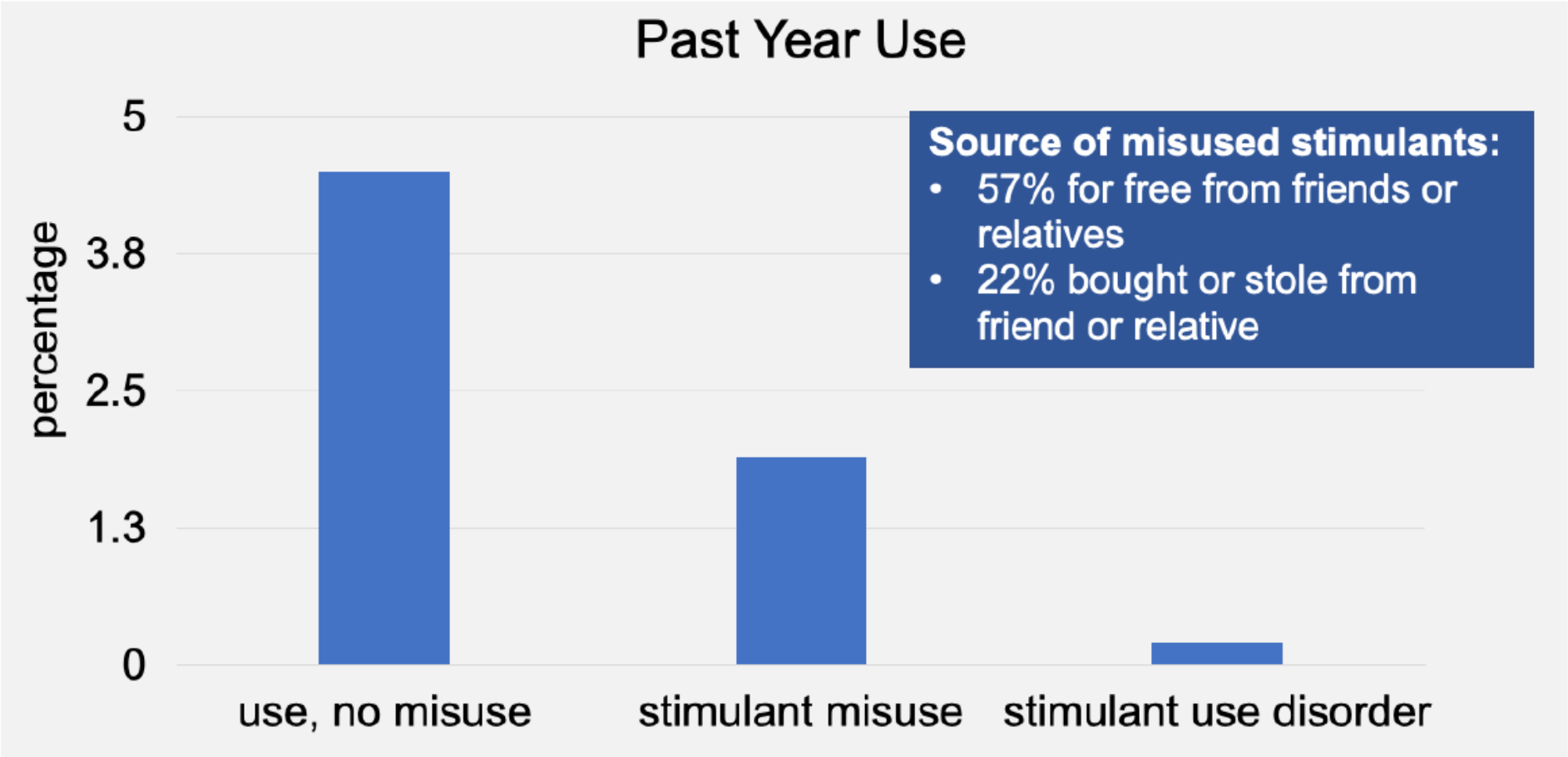
non-medical stimulant use — route matters!



n = 100 college students

Wilens et al. Am J Addiction, 2020.

misuse risk.

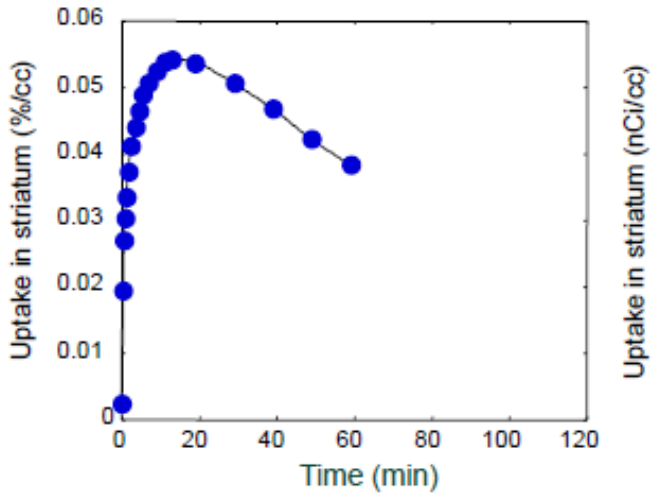


Adapted from A Yule.

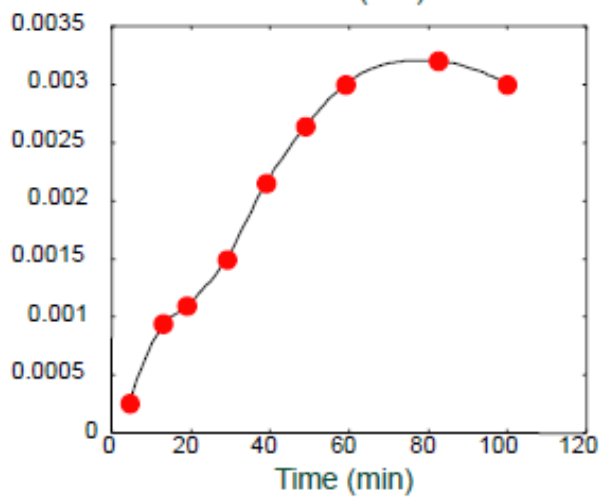
Route matters

IV methylphenidate produces more euphoria than PO — the "rate hypothesis"

IV MPH



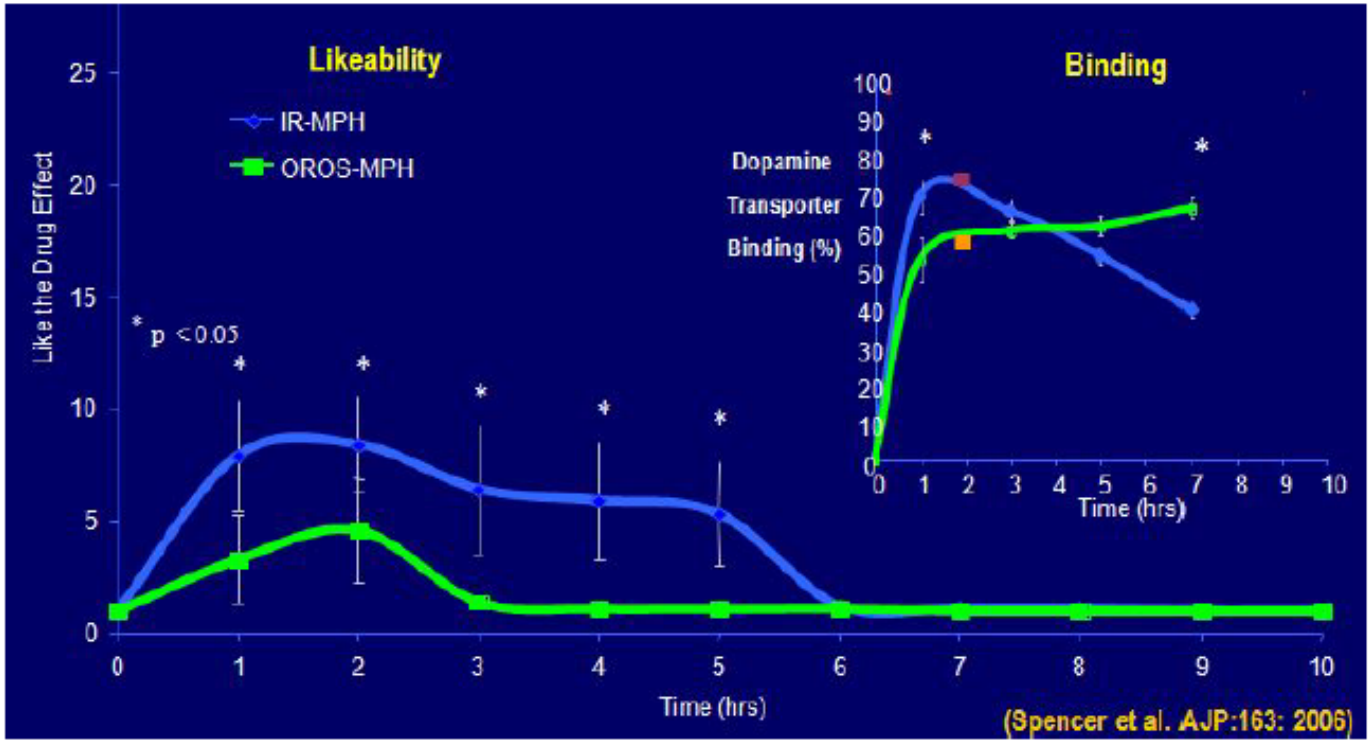
PO MPH



Volkow et al., Arch Gen Psych 52:1995, J Neurosci 2001.

ER vs IR matters

relative duration of action and "likability"



Spencer et al. *Am J Psychiatry*. 2006;163(3):387-395.

Nicotine co-use effects

Preclinical animal model demonstrates <u>nicotine-mediated priming effect on cocaine</u> via increased striatal histone acetylation and altered long-term synaptic plasticity in the NAcc.

Cocaine does *not* cause the same effect for subsequent nicotine!

Concerning for early exposure to nicotine vaping devices.

Supports a “gateway” hypothesis.

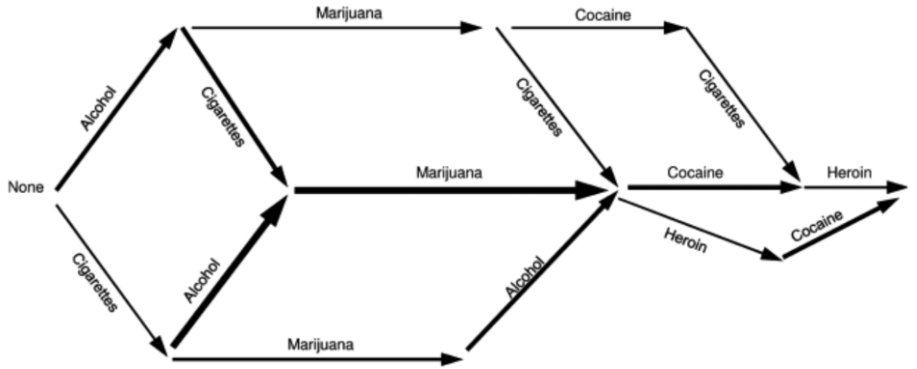


Figure 2 Pathways of drug involvement.

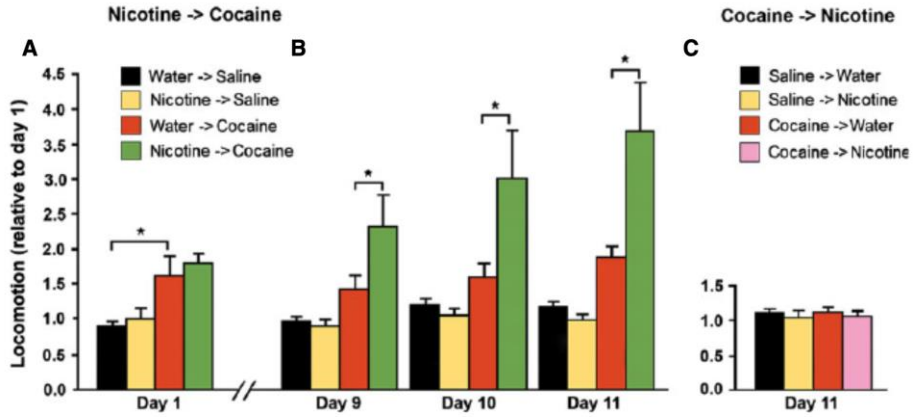


Figure 3 24-hour nicotine treatment has no effect on cocaine-induced locomotion (Panel A), whereas 7 days of nicotine treatment increases the locomotor effects of cocaine on days 9 through 11 (Panel B). By contrast, cocaine does not change the baseline activity of nicotine (Panel C). *p<0.05.

Kandel and Kandel. *Acta Paediatrica* 2015

defining StUD:

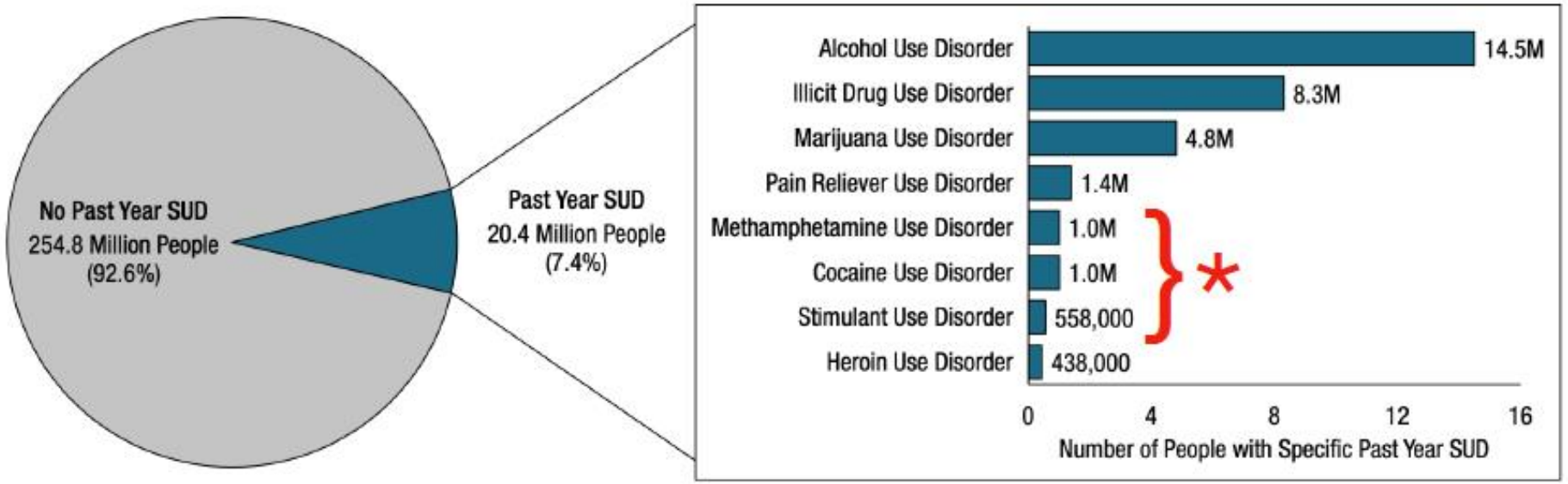
impaired function due to changes in physiology, control, and consequences

DSM 5: SUD.	significant distress or impairment and 2+:
physiology	tolerance *(and sensitization)*
	withdrawal: *~1 wk anhedonia, fatigue, inattention*
	craving
control	continued use despite recognized consequences
	lost control of how much or how long used
	time spent obtaining, using, recovering
	attempts/desire to cut down
consequences	activities given up
	interpersonal problems
	failed role obligations
	hazardous use
severity	mild: 2-3; moderate: 4-5; severe: 6+

DSM5, 2013.

epidemiology
stimulant use disorders

Figure 46. People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2019

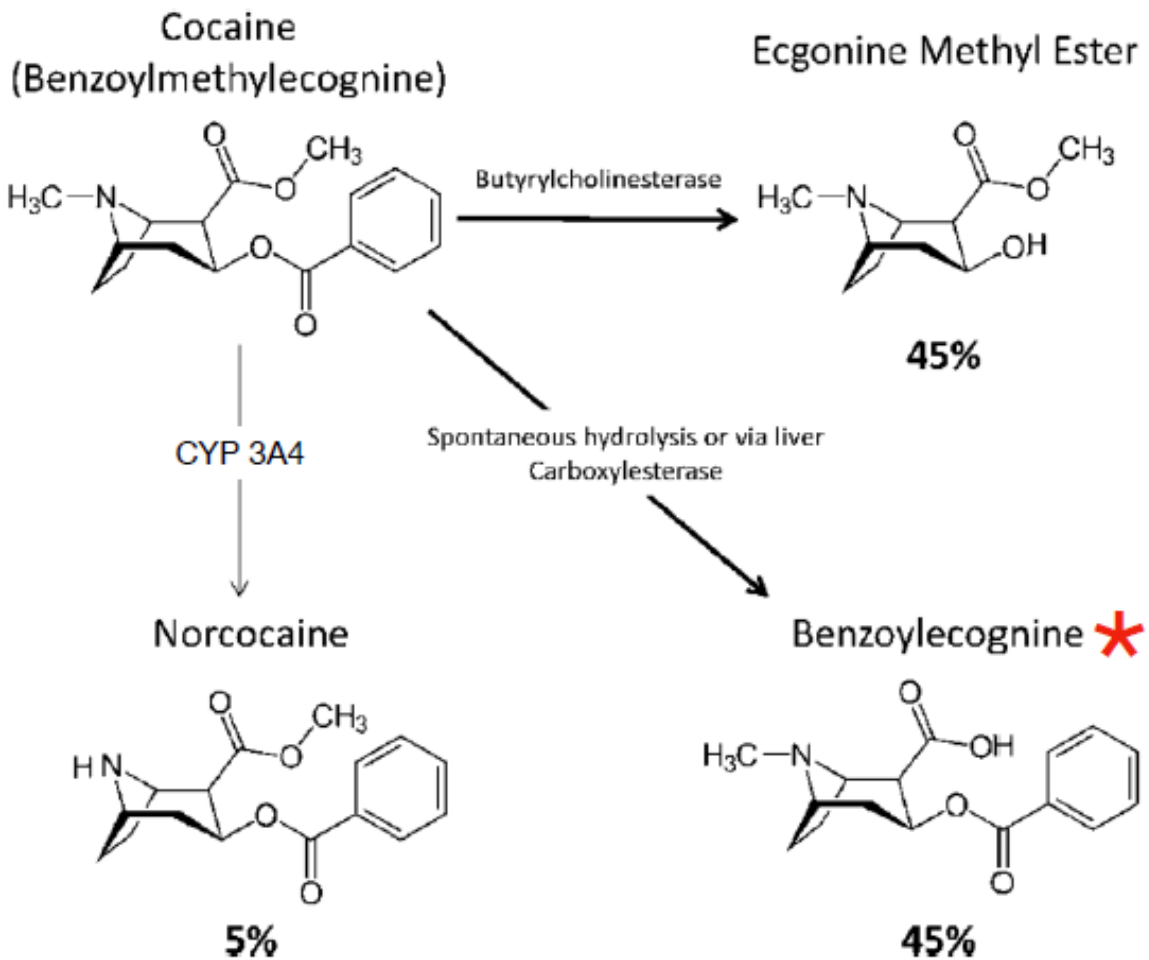


Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.

SAMHSA. National Survey on Drug Use and Health (NSDUH), 2019.

toxicology:

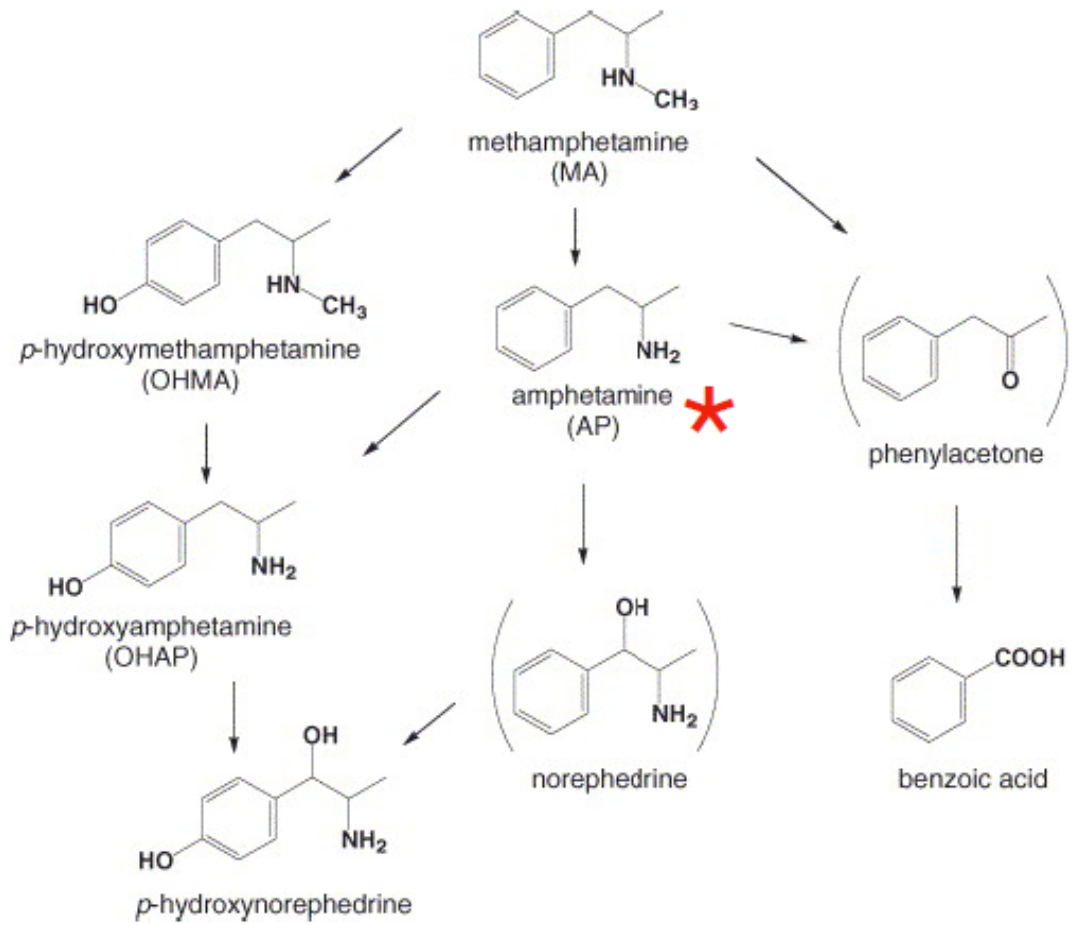
cocaine metabolism — don't forget *cocaethylene* from ethanol co-use!



Connors *et al. J Pharm Exp Thera.* 2013.

toxicology:

amphetamine metabolism



Kanamori *et al. Foren Sci Internat.* 2015.

No FDA-approved medications...

for stimulant use disorder, though there is RCT-level evidence for some pharmacotherapy.

treatment

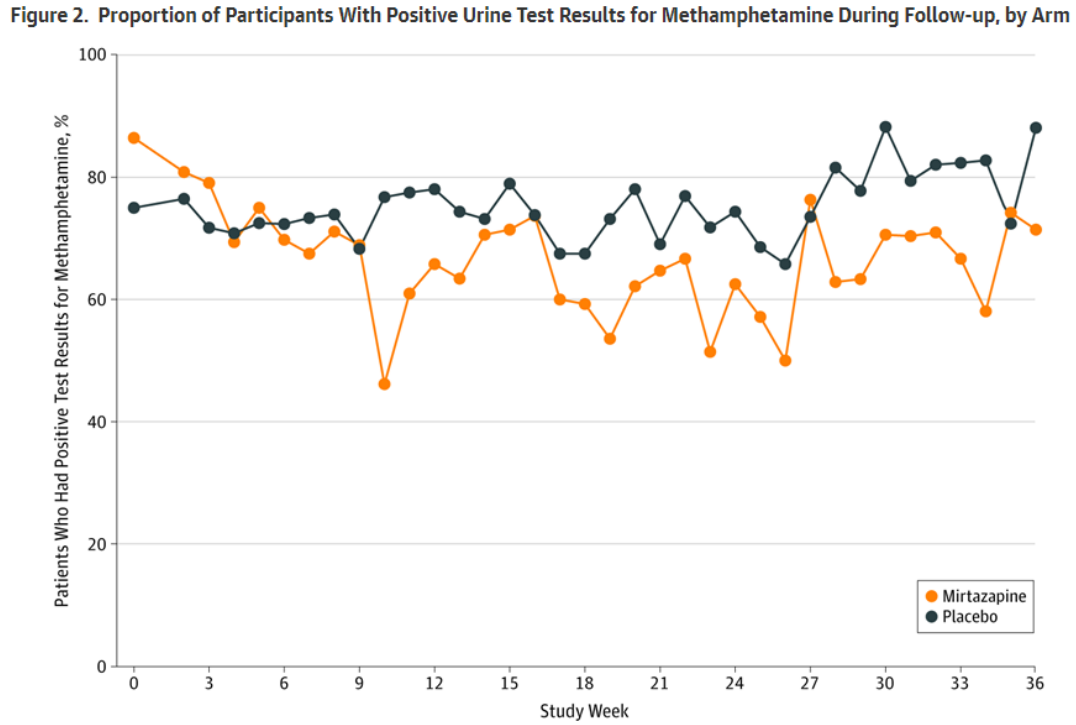
off-label options

- no FDA-approved agents
- aripiprazole may worsen cocaine cravings, though may have delayed efficacy
- newer studies with galantamine and single-dose ketamine have some positive findings

medication class	use	notes
benzodiazepines	intoxication management	few studies; favored over anticholinergic antipsychotics
antidepressants	relapse prevention	best evidence for mirtazapine, bupropion; older desipramine data
anticonvulsants	relapse prevention	some evidence for topiramate in cocaine
adrenergic agents	relapse prevention	doxazosin and a1R/DbH phenotype
opioid antagonists	relapse prevention	naltrexone with some mixed results
disulfiram	relapse prevention	inhibits DA-b-hydroxylase
stimulant (agonist therapy)	relapse prevention	higher doses, amphetamines better

Mirtazapine in HIV-risk population

- 2 double-blind placebo-controlled trials in methamphetamine use disorder
- 30 mg daily x24 weeks
- N = 180 across 2 studies
- Response at week 12
- Reduced sexual risk behaviors
- Improved sleep and depression



Coffin et al. JAMA Psych 2020.

Doxazosin in cocaine use disorder

- 2 randomized placebo-controlled trials
- 8 mg daily x12-13 weeks
- N = 111 across 2 trials
- Response at week 5-6
- Role for a1 adrenoreceptor polymorphism in responders

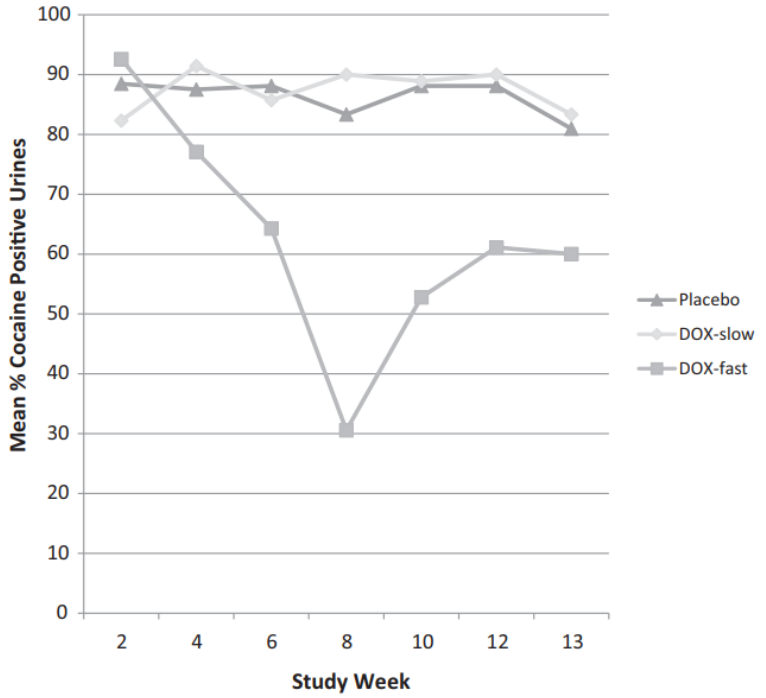


Fig. 2. Percentage of cocaine-positive urine toxicology per two-week time block across the 13-week trial for the placebo (green line) versus doxazosin (blue – DOX-slow; red – DOX-fast) treatment groups. This graph includes participants only during their enrollment in the study; once the participant discontinued involvement in the trial (i.e., missing three consecutive clinic visits), their urine data was no longer included in this graphical representation.

Shorter et al. Drug Alc Dep 2013.

Psychopharmacology (2020) 237:2233–2255
https://doi.org/10.1007/s00213-020-05563-3

REVIEW

Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis

Vitor S. Tardelli[1] · Adam Bisaga[2] · Felipe B. Arcadepani[1] · Gilberto Gerra[3] · Frances R. Levin[2] · Thiago M. Fidalgo[1]

Received: 8 February 2020 / Accepted: 18 May 2020 / Published online: 29 June 2020

- meta-analysis of RCTs using agonist treatment for cocaine/amphetamine UD
  - MOD or MPD or AMP
- n = 2,889 (38 trials) from 8-26 weeks
- outcomes: retention and abstinence

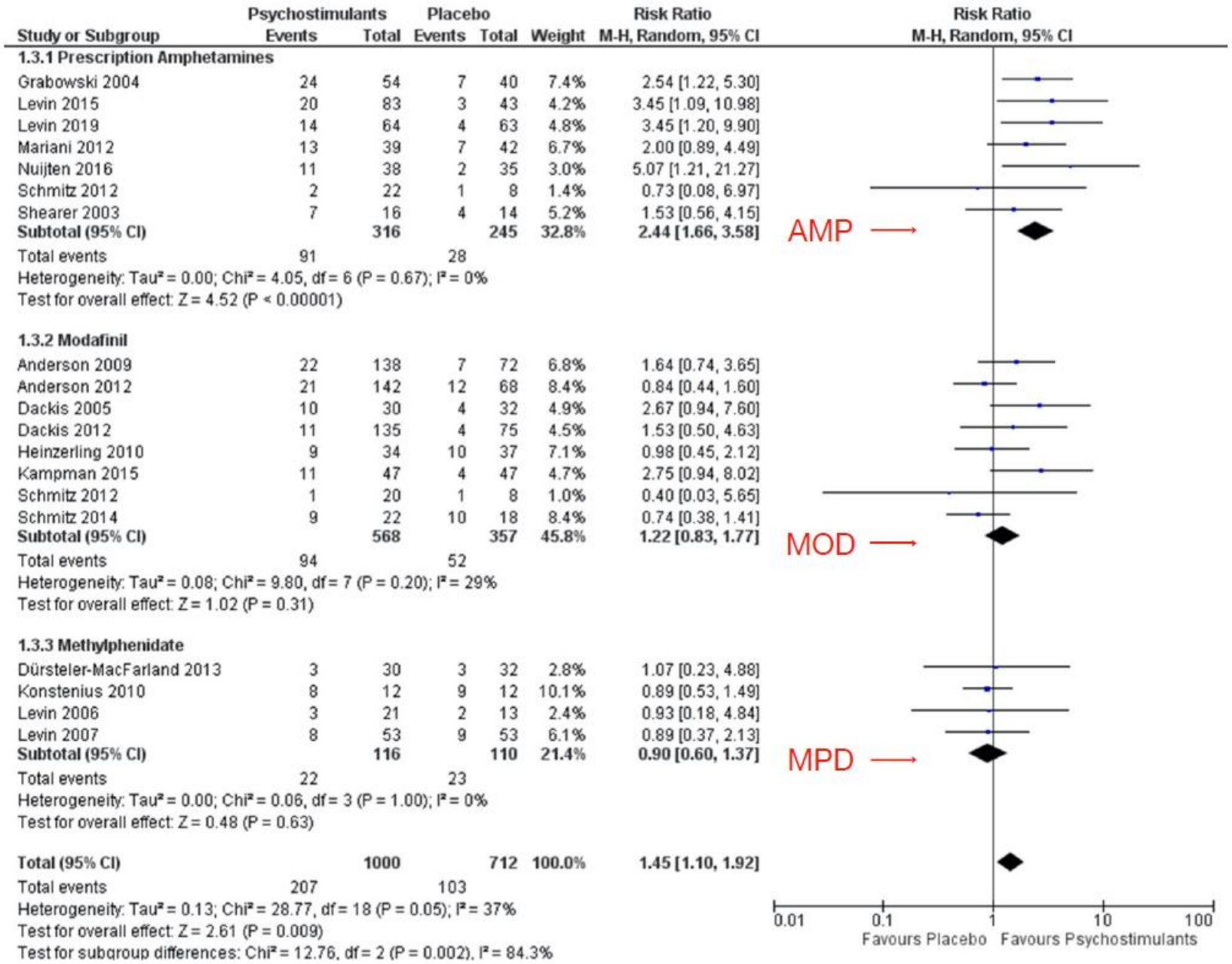


Fig. 3. Overall and by treatment drug effect of prescription psychostimulants compared to placebo for outcome sustained abstinence

- sustained abstinence: AMP

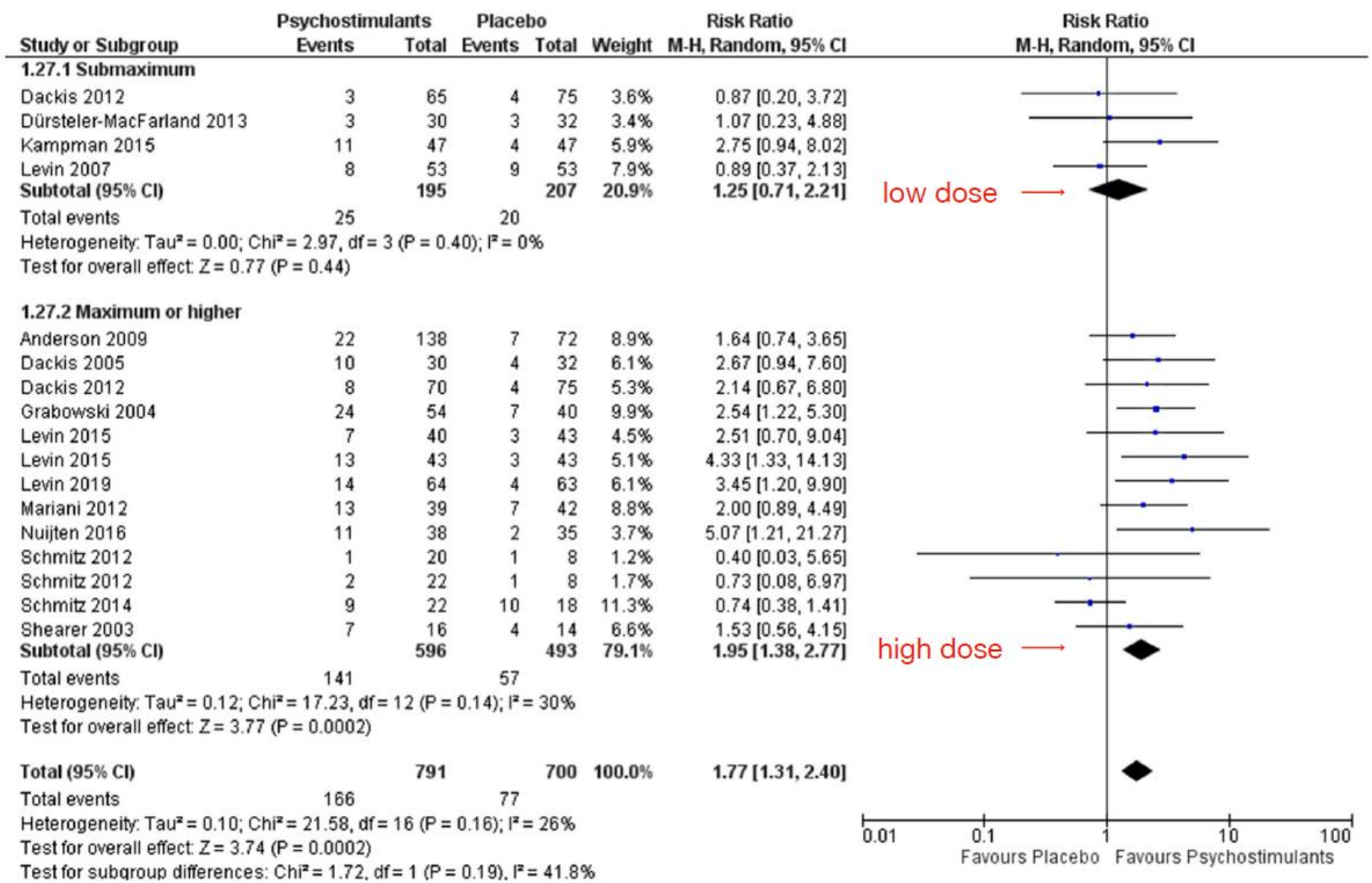


Fig. 7. Overall and by dose effect of prescription psychostimulants compared to placebo on outcome sustained abstinence—CUD only

- sustained abstinence: higher dose

stimulant therapy.

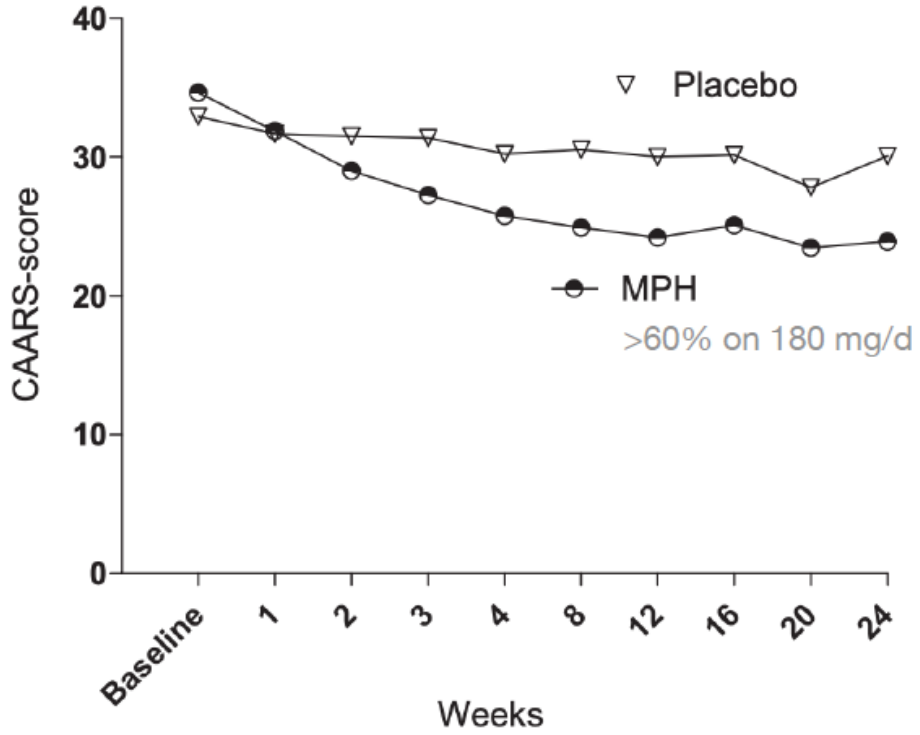


Figure 2 Change in self-rated attention deficit hyperactivity disorder (ADHD) symptoms (95% confidence interval = −13.78 to −1.91, $P = 0.011$)

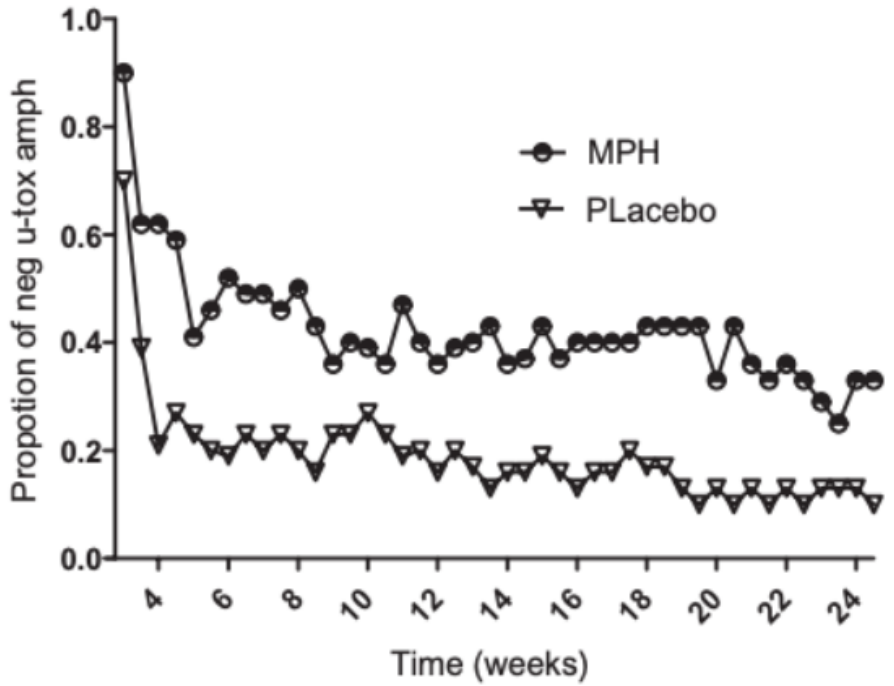


Figure 3 Proportion of negative urine-toxicology after release from prison (weeks 3–24) for the two treatment groups; methylphenidate (MPH) and placebo over 24 weeks of treatment: (a) any drugs amphetamine + other drugs, mean difference 95% confidence interval (CI) = 0.05–0.32; (b) amphetamines only, mean difference

Konstenius et al. *Addiction*. 2014.

stimulant therapy.

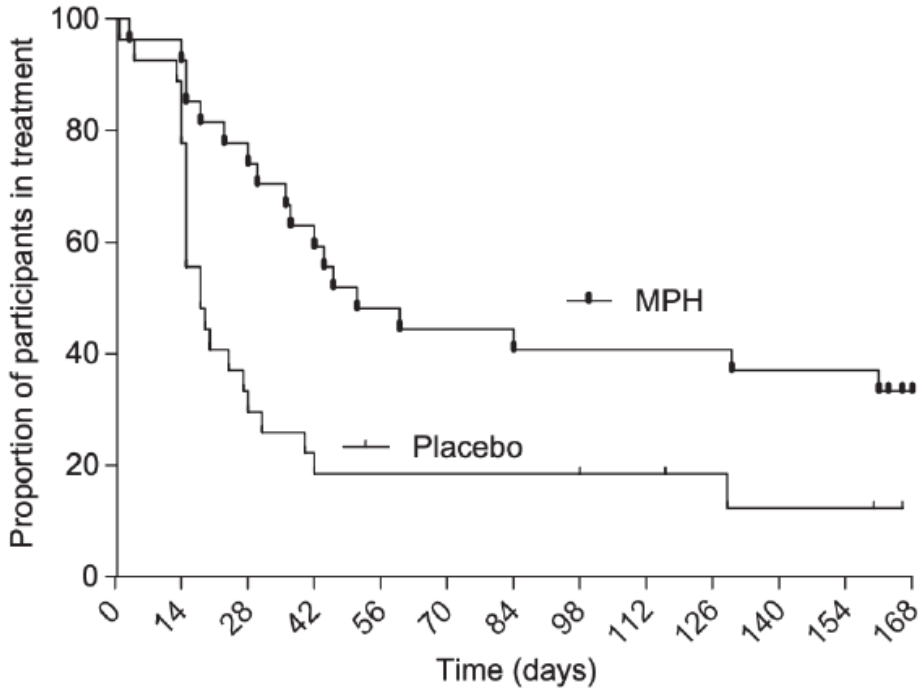
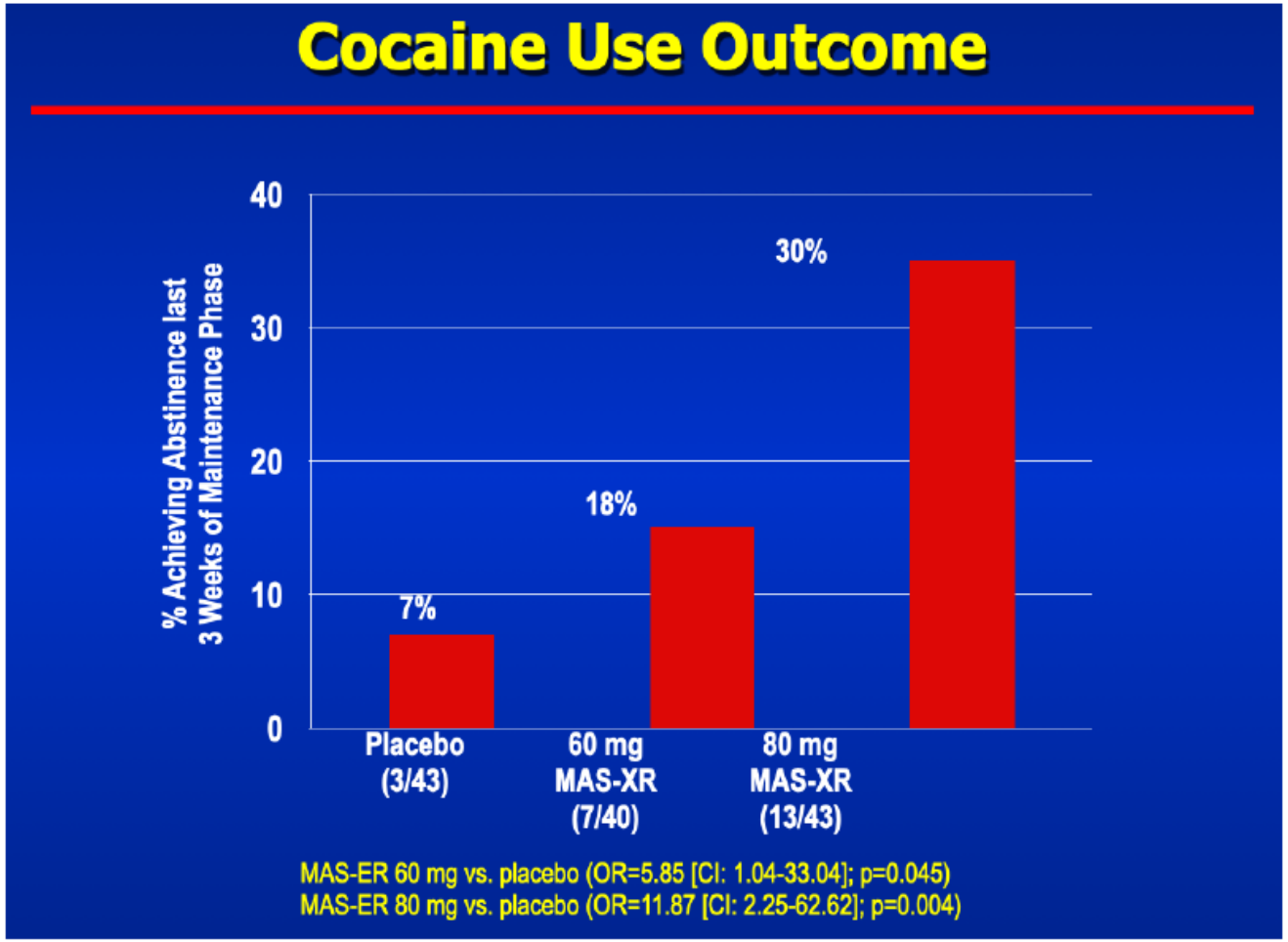


Figure 4 Kaplan–Meier curve for retention in treatment through to last visit at the clinic [methylphenidate (MPH): Md = 51, placebo: Md = 18; hazard ratio 0.38, 95% confidence interval = 0.174–0.647]

- improved retention on high-dose OROS-MPH

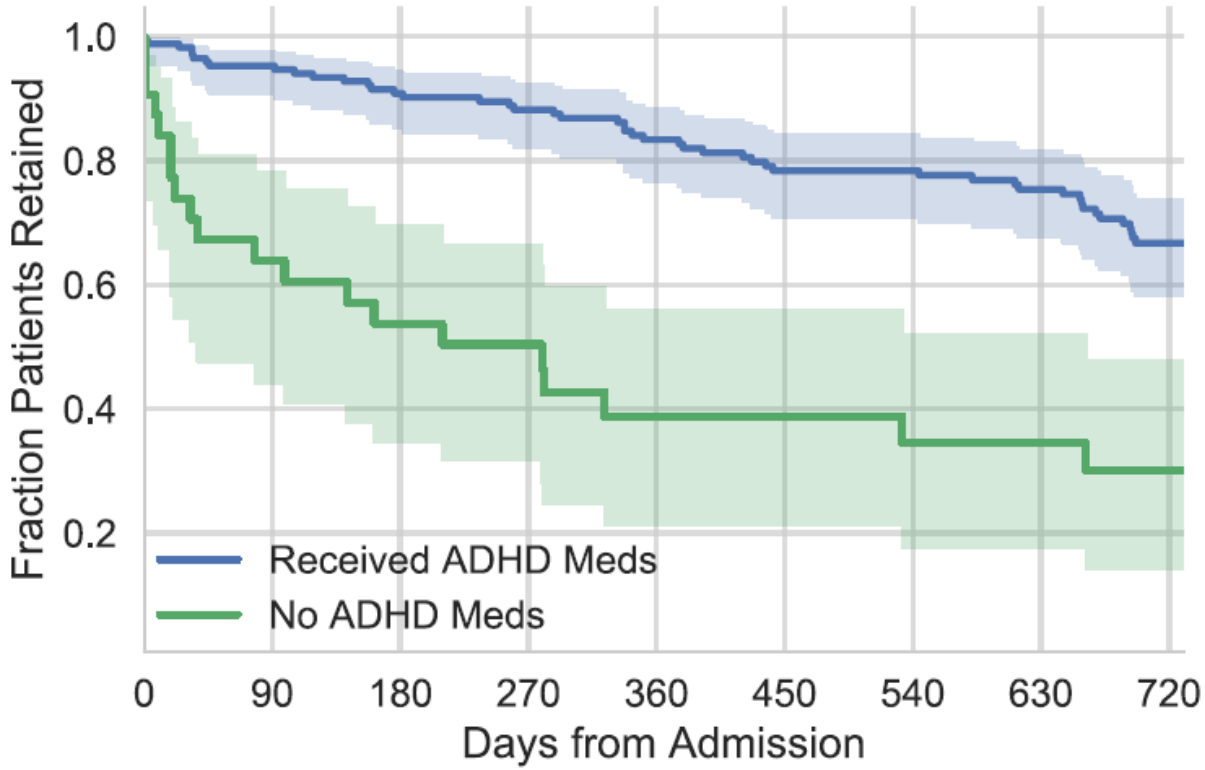
Konstenius et al. *Addiction*. 2014.

stimulant therapy.



Levin et al. *JAMA Psychiatry*. 2015.

stimulant therapy.



- improved short- and long-term retention in naturalistic setting

Kast et al. *J Clin Psychiatry*. In-press.

safety.

- 2016 Cochrane Review of stimulants for adult ADHD
  - no difference in drop-out due to any AE; n = 1,601; CI -0.01 to 0.01
  - no difference in drop-out due to CV event; n = 688; CI -0.02 to 0.01
  - no difference in serious AE; n = 444; CI -0.06 to 0.01
- does not address risk of relapse, overdose, or related SUD outcomes

Castells et al. *Cochrane Review.* 2016.

clinical application.

risk mitigation strategies	risks			
	misuse	diversion	toxicity	SUD stability
q1wk visit	x	x	x	x
toxicology screens		x		x
1-week supply	x	x	x	
PDMP monitoring		x		x
long-acting formulation	x	x	x	
shared decision-making	x		x	x
outcome measures + limits	x	x	x	x
involve support network	x	x	x	x

agent	dose range	outcome	population	studies	notes
D-amphetamine; MAS-ER*	up to 60 mg/day; up to 80 mg/day	~12 wks; better retention, less cocaine-pos urine vs PBO	median n = 33; CUD, with some comorbidities (ADHD, OUD)	6 from 2001 to 2016; summary in Brandt et al. Addiction 2021	corroborated by recent meta-analysis, Tardelli et al. 2020
modafinil	up to 400 mg/day	8-12 wks; only for non-AUD (3-wk abst, less cocaine-pos urine)	median n = 59; CUD	5 from 2009 to 2015; summary in Brandt et al. (id)	poor adherence; one study showed discordant effects in men and women
bupropion-naltrexone	450 mg/day ER + 380 mg ER q3wks	12 wks; 13.6% had "response" (3 neg meth-pos urines out of 4)	n = 403 (stage 1); n = 225 (stage 2)	Trivedi et al. NEJM 2021	very high retention, unclear PO adherence
mirtazapine	up to 30 mg/day	36 wks; RR ~0.7 for meth-pos urine at 12+ wks follow-up	n = 120; MUD in MSM and TGW	Coffin et al. JAMA Psych 2020	finding despite ~25% adherence; less risky sexual behavior, better sleep/dep
topiramate*	200-300 mg/day (over 8 wks)	~12 wks; more abst and less cocaine-pos urine	median n = 58; CUD often with AUD/OUD	5 from 2004-2014; summary in Brandt et al. (id)	low adherence in later trials
doxazosin	8 mg/day (over 4 wks)	12 wks; 35% reduction in cocaine-pos urine vs PBO	n = 76, CUD with ADRa1d AT and DbH TT phenotypes; n = 35, CUD	Shorter et al. AJDAA 2020; Shorter et al. DAD 2013	promising pharmacogenetics
disulfiram	250 mg/day	~12 wks; meta-analysis with worse retention; less reported use	median n = 58; CUD often with OUD	4 from 2004 to 2014; summary in Brandt et al.	may be affected by low DbH phenotype; possible sex-based discordant responses

Brandt et al. Addiction, 2021; *ASAM Principles of Addiction Medicine, 6th Ed.*, 2019.

cocaine vaccine

response dependent on IgG titers and (possibly) recovery stage

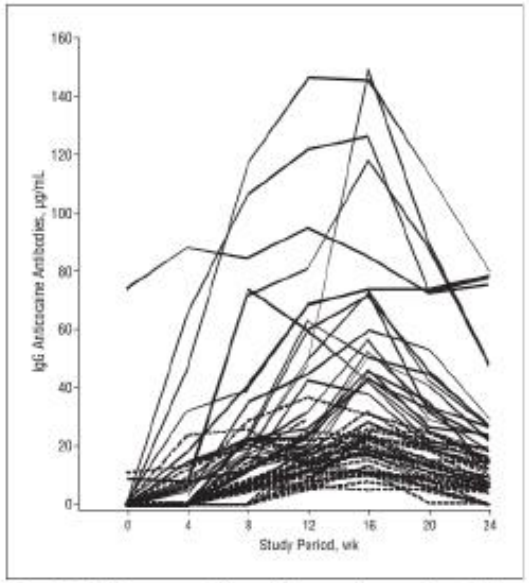


Figure 2. The IgG responses to the succinylnorcocaine–recombinant cholera toxin B-subunit protein vaccine were highly variable. Among the 55 subjects immunized with the cocaine vaccine (at weeks 0, 2, 4, 8, and 12), 21 (38%) attained levels of 43 µg/mL or greater (solid lines). Of those, 3 were highly responsive subjects, with 1 having greater than 60 µg/mL of IgG anticocaine antibodies even before immunization. Two made a vigorous response after the second injection (week 4 samples). Eight subjects made more than 43 µg/mL after 3 injections, and 8 required 4 or more injections of antigen to make a response that exceeded 43 µg/mL of IgG anticocaine antibodies. Antibody responses for the remaining 34 subjects are shown with dotted lines. The respective numbers of subjects at weeks 2, 4, 8, 12, 16, 20, and 24 were 55, 55, 55, 55, 54, 51, and 51.

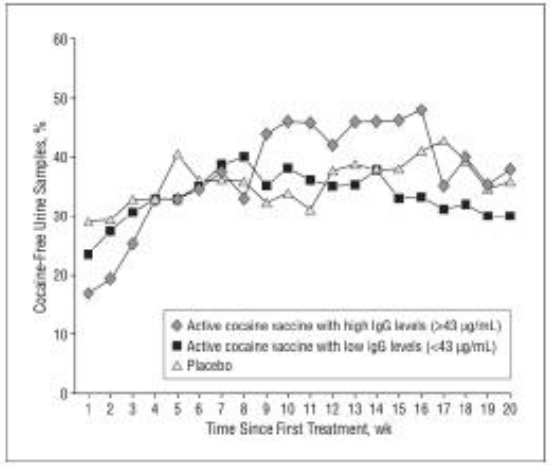


Figure 3. Mean weekly cocaine-free urine samples by medication condition for weeks 1 to 20. The y-axis represents 100 times the weekly mean proportion of cocaine-free urine samples for the 3 treatment groups. Standard errors are not shown for clarity but range from ±3% at any time. The group with high IgG levels had significantly more cocaine-free urine samples than the other 2 groups during weeks 9 to 16 (t=2.26; P=.03) and a significantly greater increase in cocaine-free urine samples than the other 2 groups from weeks 1 to 16 on hierarchical linear modeling analysis (Z=4.8; P<.001). The 3 groups did not differ in cocaine-free urine samples during weeks 17 to 20.

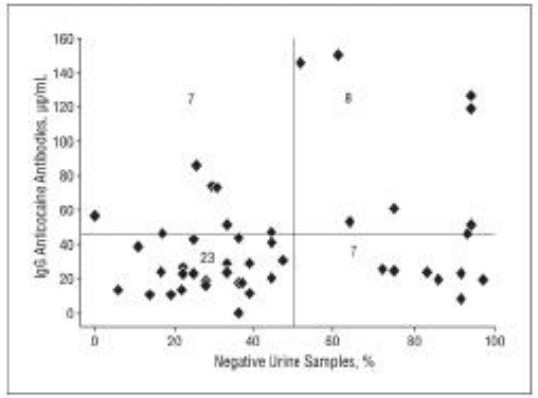
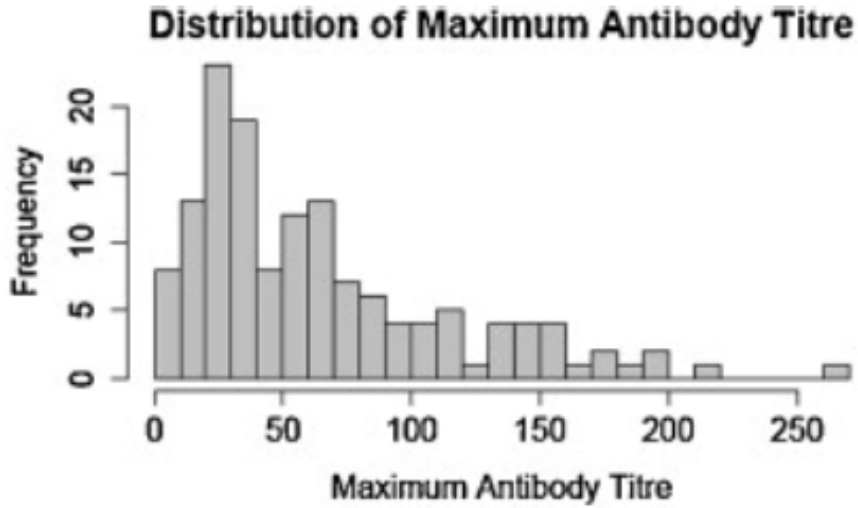


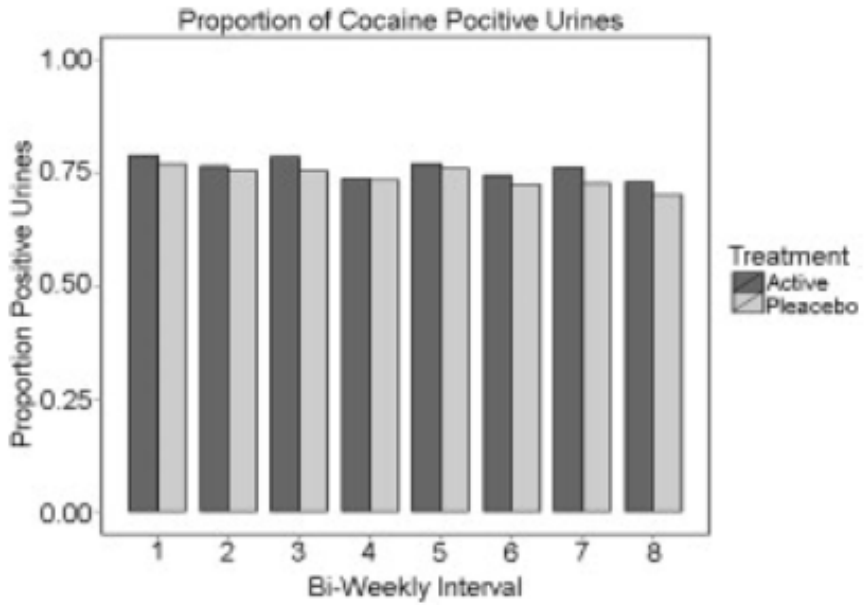
Figure 4. Scatterplot of peak antibody response by percentage of cocaine-negative urine samples. Diamonds indicate values of peak antibody response (typically at week 16) in individual vaccinated subjects plotted against their percentage of cocaine-negative urine samples using the criteria by Preston et al[35] for new uses of cocaine during weeks 8 through 20. The graph is divided into quadrants by a horizontal line at the 43-µg/mL antibody level and a vertical line at 50% cocaine-free urine samples. The numbers in each quadrant indicate the number of subjects in each quadrant. The proportion of subjects who had 50% or more cocaine-free urine samples is significantly greater in those with IgG anticocaine antibody levels of 43 µg/mL or greater than in those with lower antibody levels (Fisher exact test, P=.048).

Martell et al. *Arch Gen Psych*, 2009.

cocaine vaccine

response dependent on IgG titers and (possibly) recovery stage





Kosten et al. *Drug Alc Dep*, 2014.

rTMS

some studies demonstrating reduced cocaine craving and use/relapse targeting dlPFC

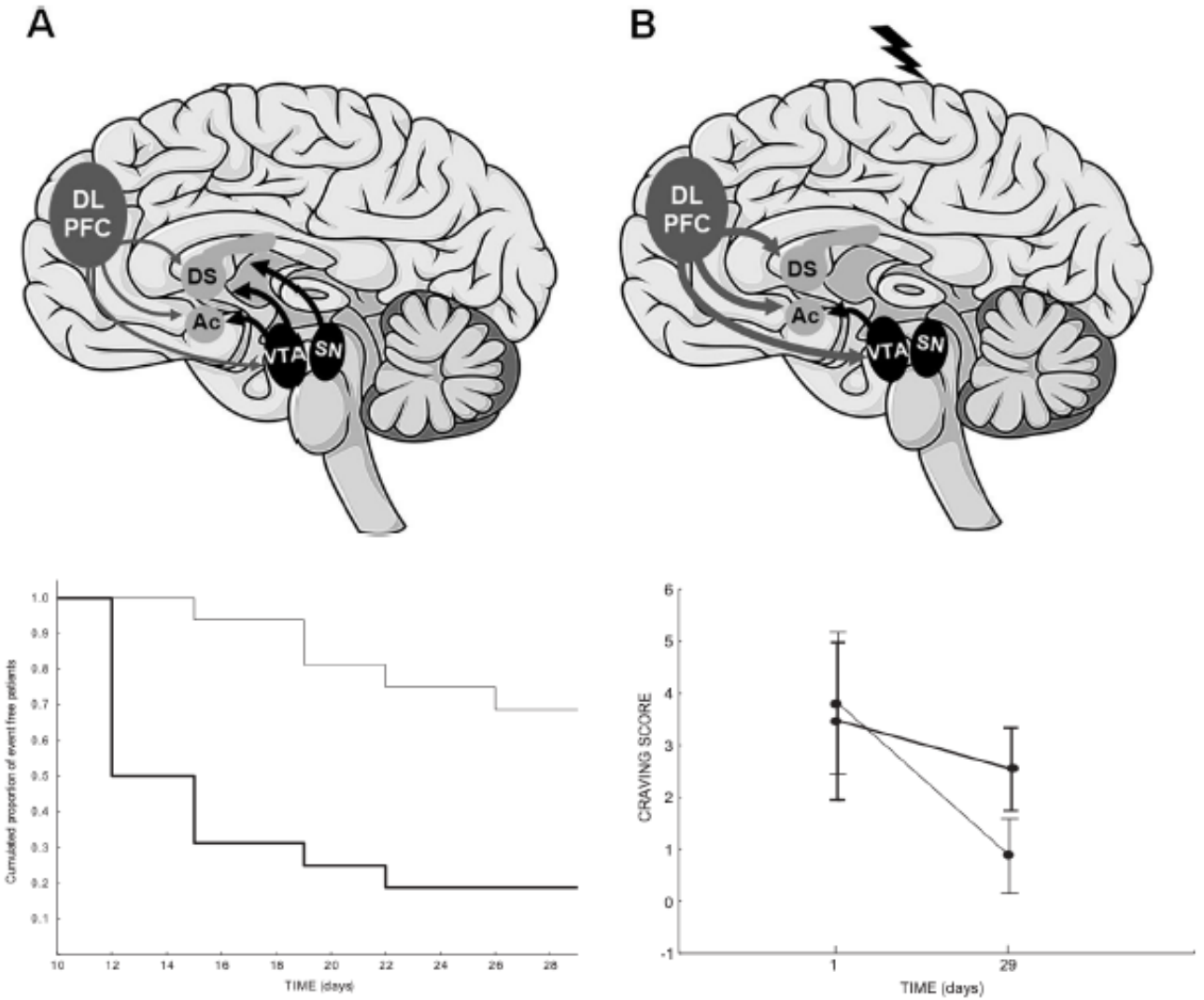


Figure 2 Kaplan Meier curve for comparison between rTMS (thin line) and controls (thick line) during Stage 1. Event is positive drug urine screen (log rank p=0.0013).

Figure 3 Significant differences in craving scores between the rTMS (thin line) and control (thick line) groups.

Antonelli et al. *Addic Behav*, 2021; Terraneo et al. Euro Neuropsychopharm, 2016.

Psychotherapeutic and psychosocial interventions

These should remain part of any first-line treatment of stimulant use disorder.

NIDA Cocaine Collaborative Study

CUD: IDC ≥ CT = SE

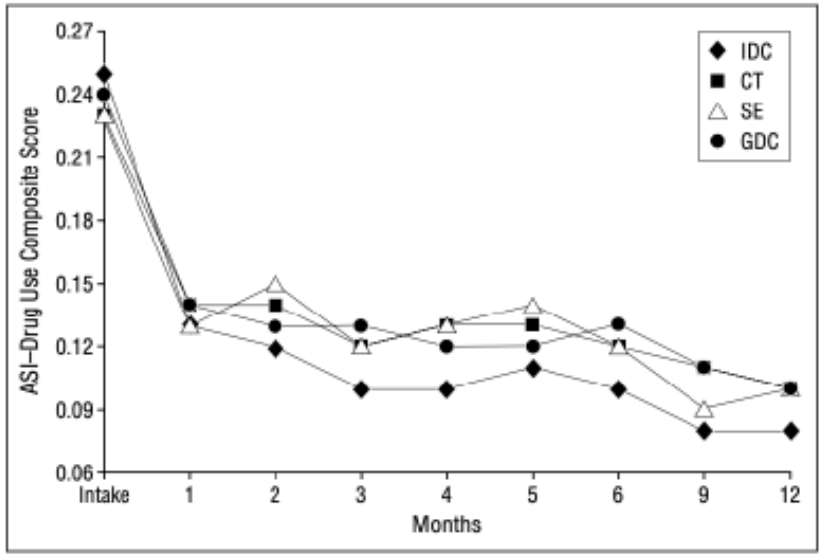


Figure 1. *Adjusted mean Addiction Severity Index (ASI)–Drug Use Composite scores by treatment condition. At intake, unadjusted ASI–Drug*

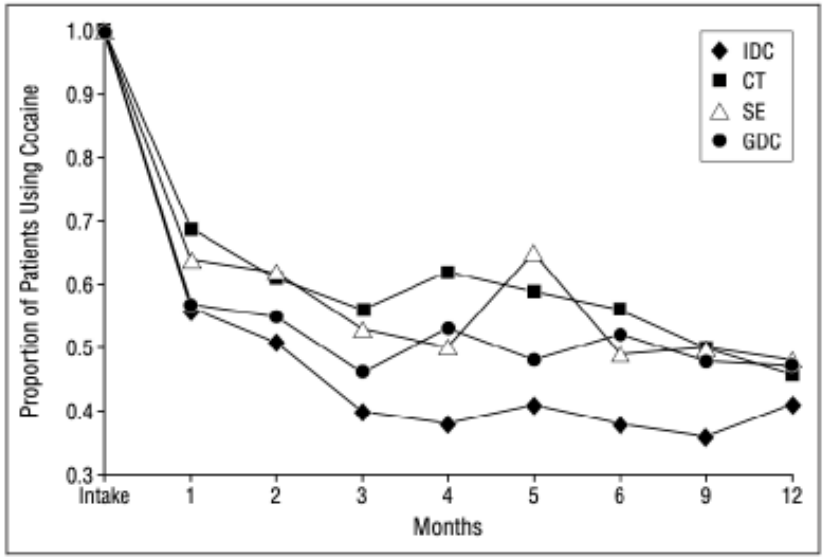


Figure 2. *Adjusted proportion of patients in each treatment condition who reported any cocaine use in the past 30 days. At intake, all patients had used*

Crist-Christoph et al. *Arch General Psychiatry*, 1999.

contingency management

rewarding desired behavior: largest effect size for <u>stimulant</u> use disorder

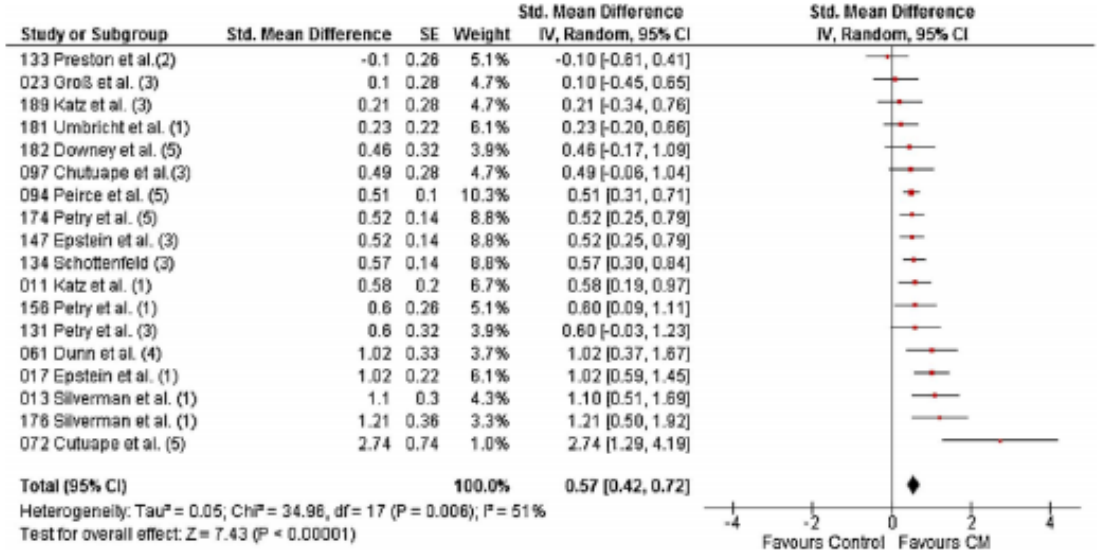


Fig. 2. Forest plot for LDA during treatment of all substances combined. (1) = Cocaine, (2) = opiates, (3) = opiates and cocaine, (4) = Tobacco, (5) = Poly-substance.

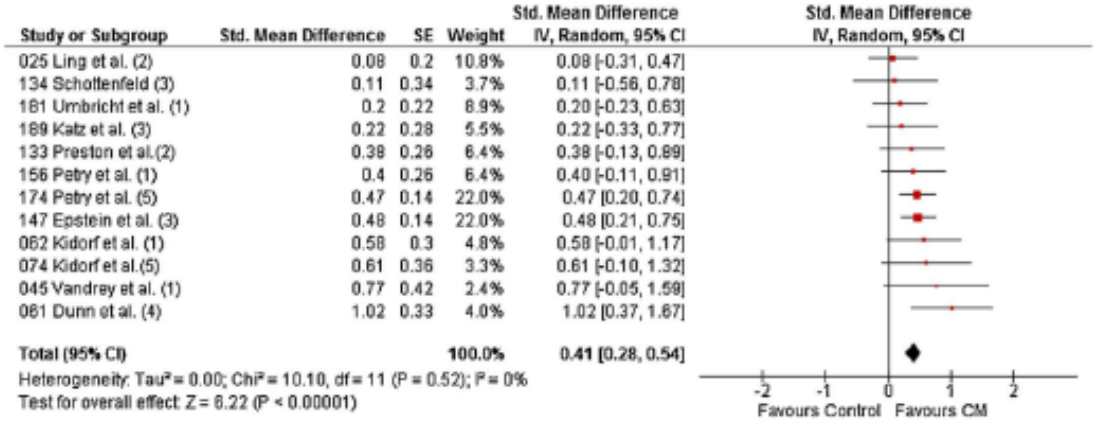


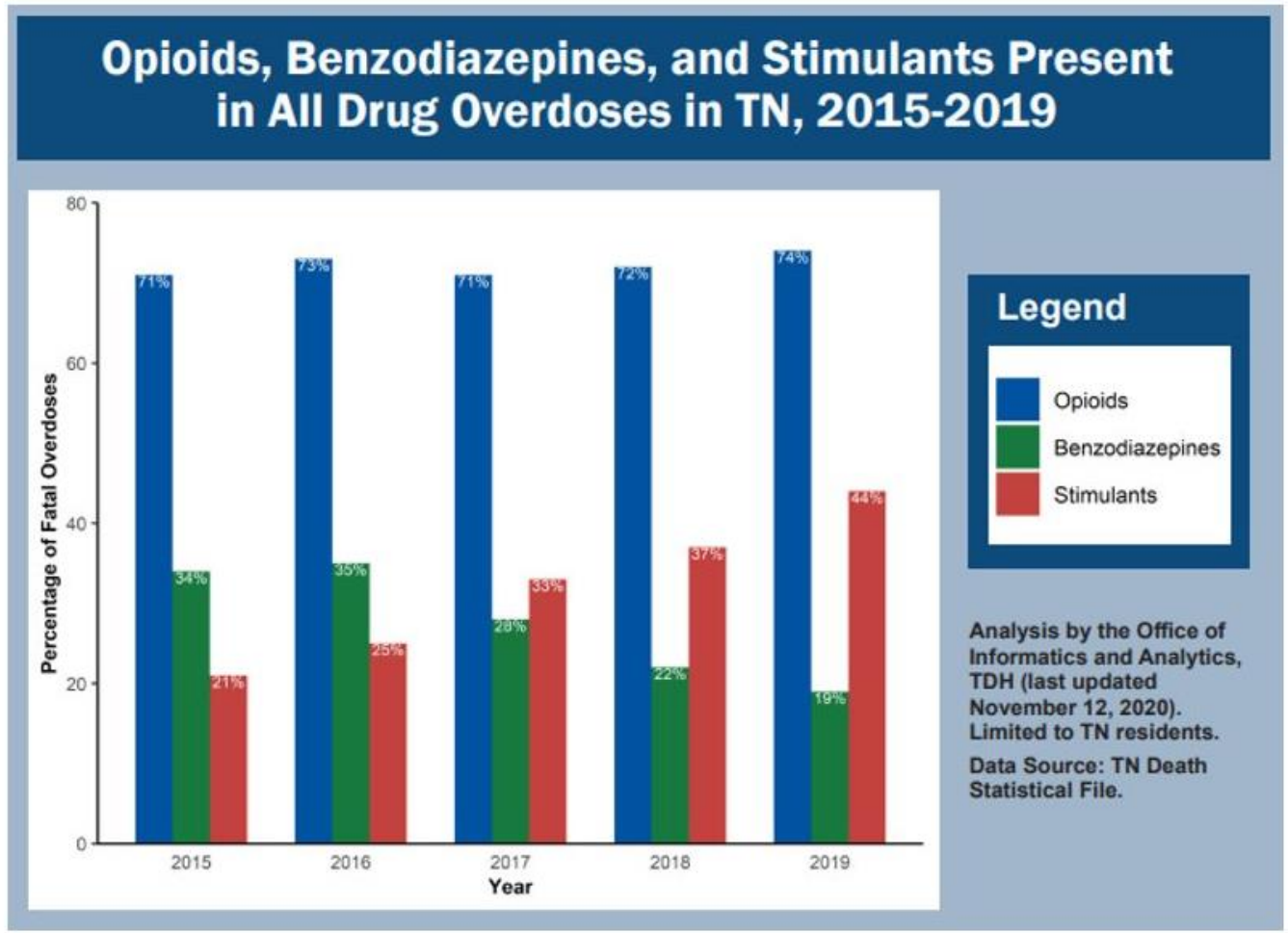
Fig. 3. Forest plot for PNS during treatment of all substances combined. (1) = Cocaine, (2) = opiates, (3) = opiates and cocaine, (4) = Tobacco, (5) = Poly-substance.

Ainscough et al. *Drug Alc Dep*, 2017.

Co-occurring OUD and StUD

How to think about concurrent stimulant use disorder when treating OUD with agonist medications.

Tennessee: multiple substance overdoses



TDOH 2021

Be wary of "wastebasket" diagnoses...

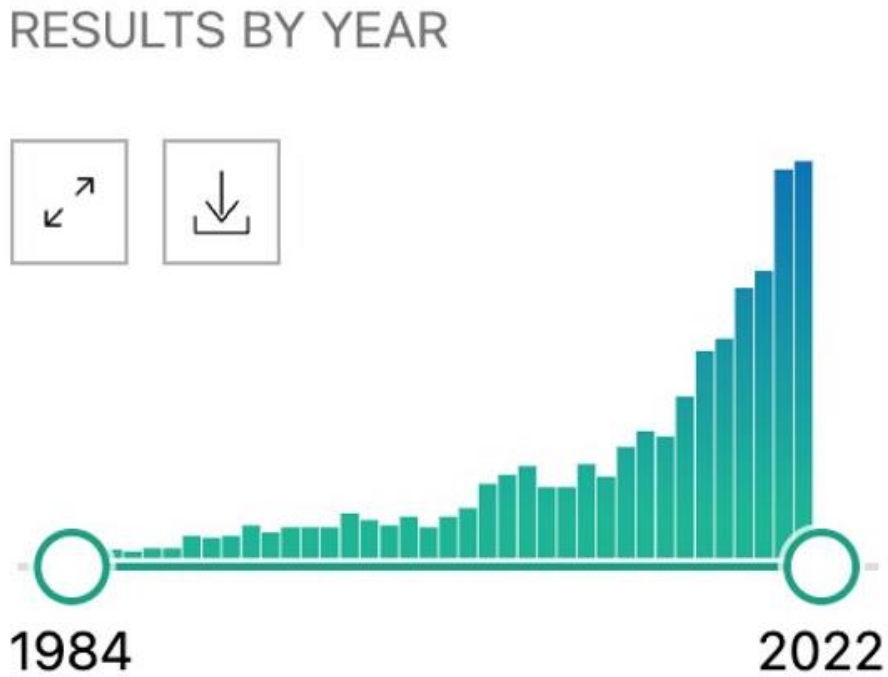
"Polysubstance use" language may sometimes lead to premature closure of diagnostic thinking and pessimism about treatment.

Polysubstance use research

There has been a relative paucity of investigation into this group.

Increasing scholarly interest across time.

Increasing calls for further research to better understand these complex relationships, including recent funding investment from NIH.



Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Institute on Drug Abuse (NIDA) National Cancer Institute (NCI) National Institute on Alcohol Abuse and Alcoholism (NIAAA
Funding Opportunity Title	Integrative Research on Polysubstance Abuse and Disorder (R61/R33 Clinical Trial Optional)
Activity Code	R61/R33 Exploratory/Developmental Phased Award
Announcement Type	New
Related Notices	See Notices of Special Interest associated with this funding opportunity • **March 10, 2020** - Reminder: FORMS-F Grant Application Forms & Instructions Must be Used for Due Dates On or After May 25, 2020- New Grant Application Instructions Now Available. See Notice NOT-OD-20-077. • **March 25, 2020** - Notice of Special Interest (NOSI): Sleep and Substance Use Disorders. See Notice NOT-DA-20-021.

The concept of "polysubstance use"

- Not "addictive personality" -- an historical theory with significant disconfirming evidence
- Simultaneous or sequential use of different substance classes
  - Mean of 3.5 substance classes used among SUD population
  - Cannabis and cocaine often "secondary", compared to other classes
- Differing conceptual frameworks proposed:
  - Common factors or a "gateway"?
- Evidence that the Gateway and Common Liability models are complementary
  - Epidemiological findings of gateway-type progression within common liability cohorts
  - Shared effects of maladaptive learning and long-term memory via *CREB*-mediated mechanisms, including delta-FosB accumulation in NAcc

Kandel and Kandel. *Acta Paed* 2015; Crummy et al. *Front Neurosci* 2020

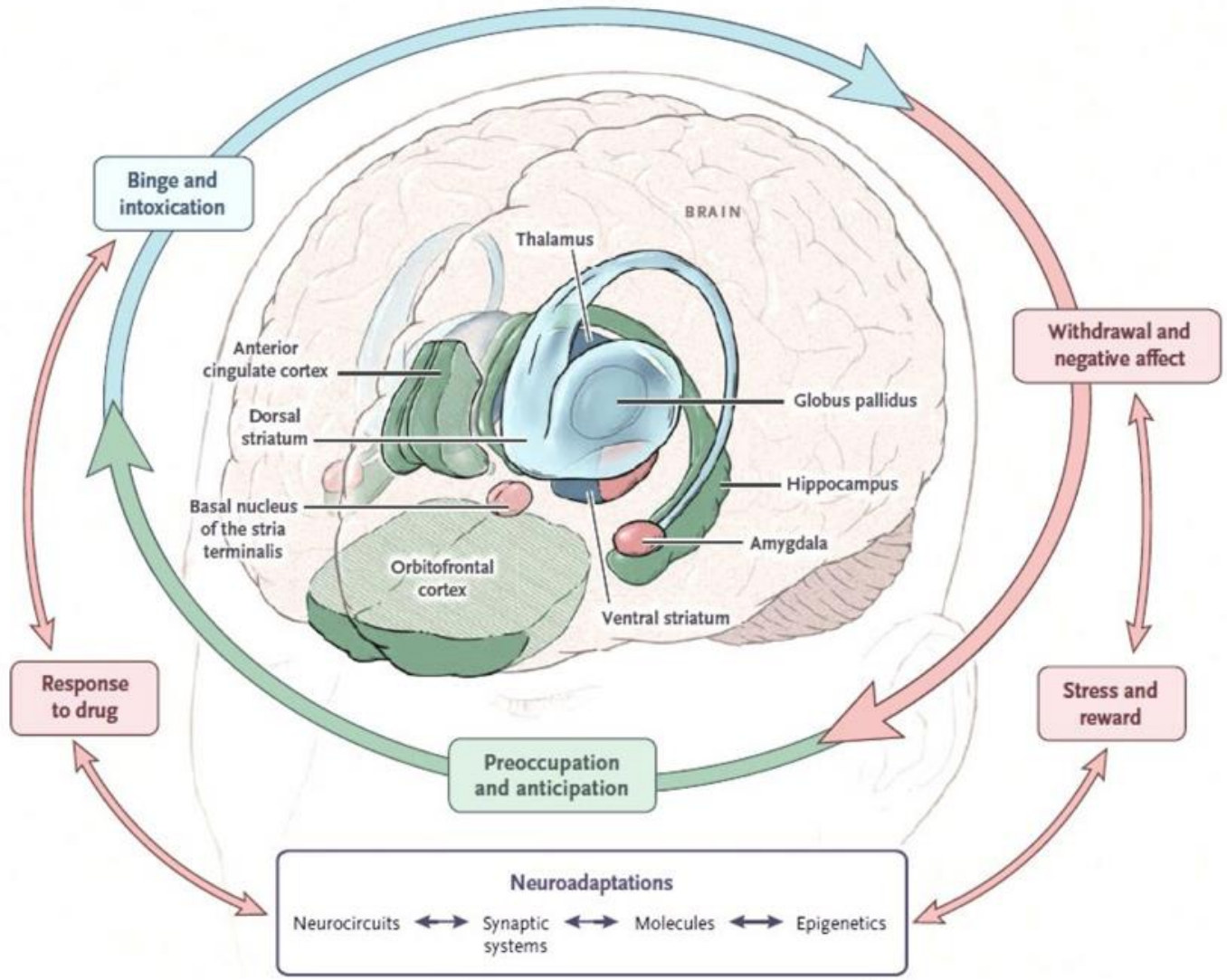
Shared neurobiology

The canonical 3-part model of addiction does not differ by specific substance category.

1. Binge-intoxication and reward system

2. Negative affect-withdrawal and anti-reward systems

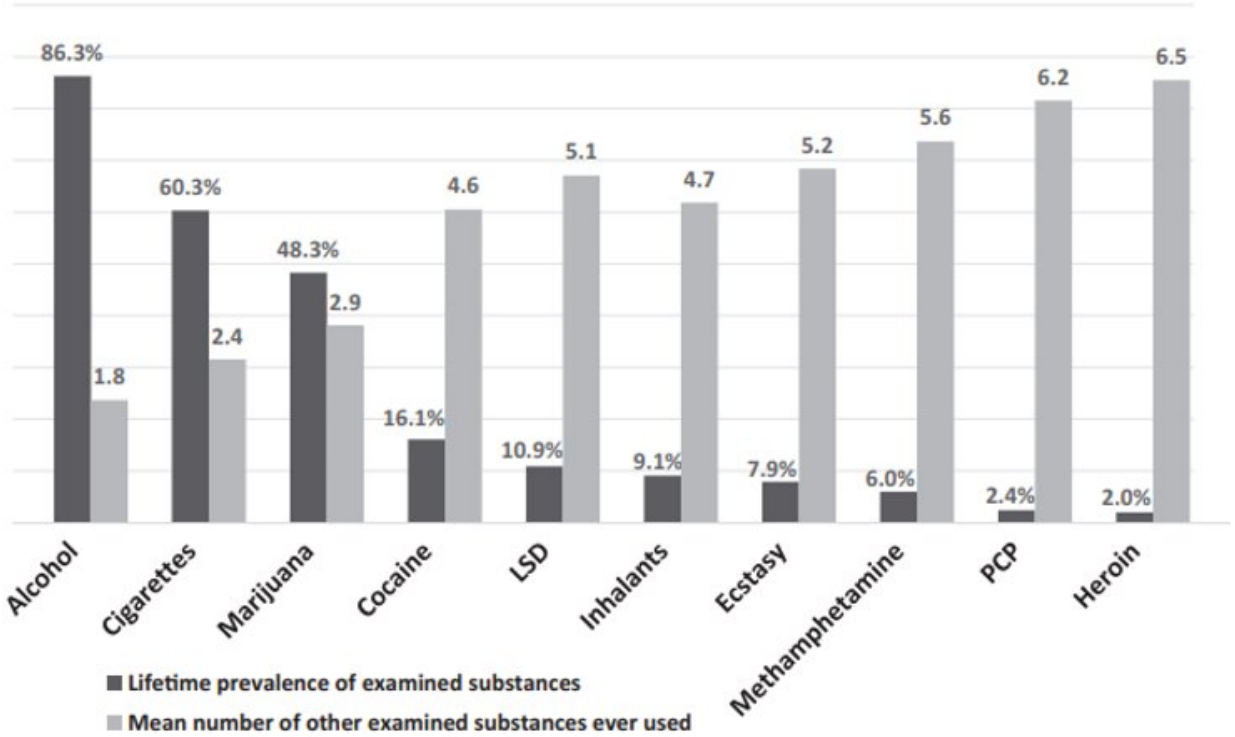
3. Cognitive control and cortical executive function



Koob et al. *Neuropsychopharm* 2010

Lifetime overlap of substance use

Fig. 1 Overlap of substances used across the lifetime. Weighted lifetime prevalence of substance use and mean number of other substances ever used by adults age 18 and older in the United States ($n = 51{,}000$; Source: 2018 U.S. National Survey on Drug Use and Health [adapted from Eric Wish, University of Maryland, Center for Substance Abuse Research]).



Compton et al. *Mol Psych* 2021

Reasons for co-use

- Additive/synergistic euphoric effect
- Compensation for undesired effects of another substance
  - Reported heroin-to-cocaine cross-titration
  - Compensation for negative internal states
  - Khantzian's "self-medication" hypothesis
  - PTSD co-occurrence associated with OR 2.41-4.15 for OUD + 2 other SUDs
- A "general predisposition for all substances"

Compton et al. 2021; Hassan et al. 2019; Khantzian 1997; Hunt et al. 1984

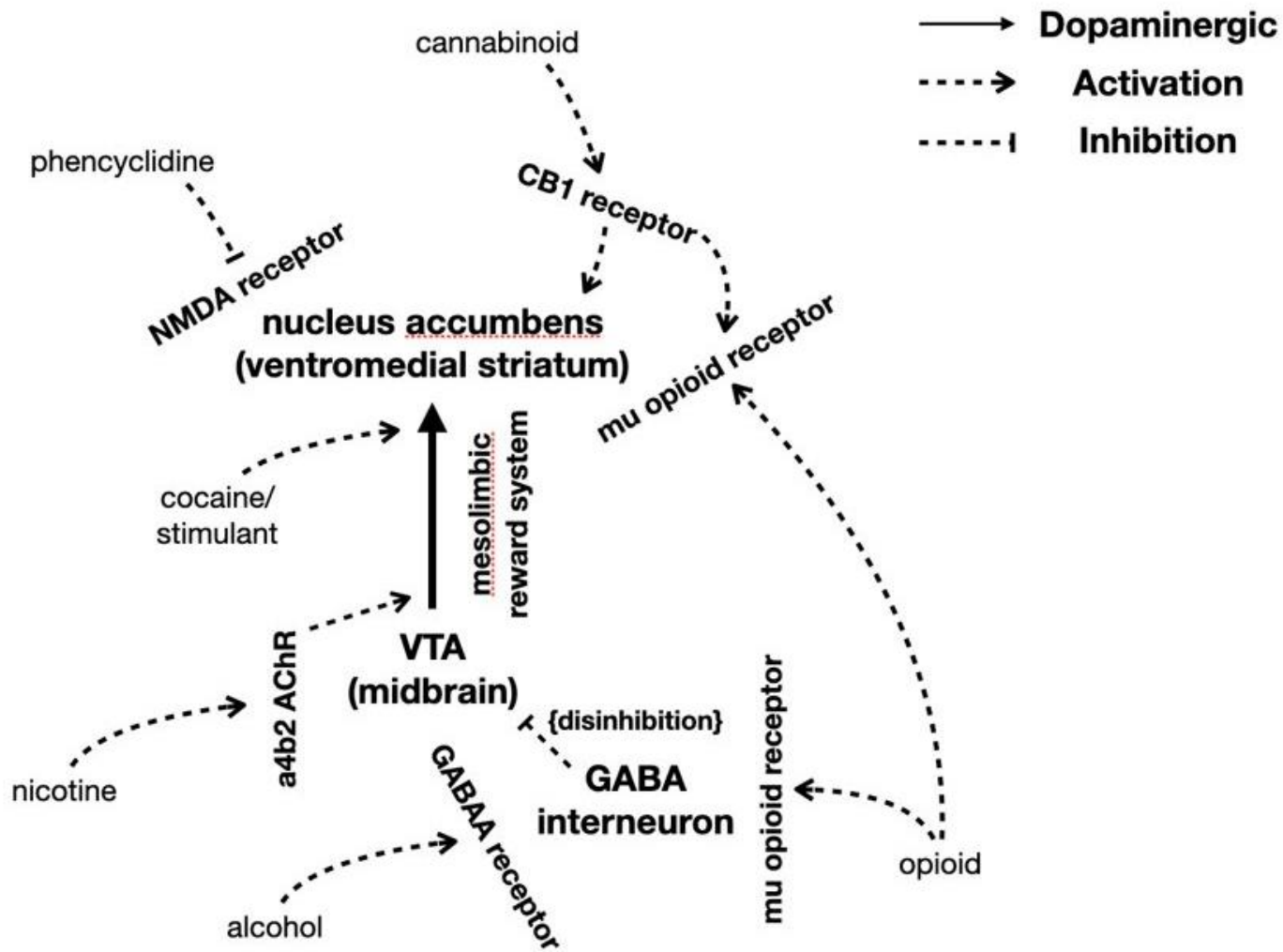
Synergistic effects

Cocaine and/or amphetamines affect DA release and reuptake at NAcc.

Opioids disinhibit DA neurons via VTA GABA interneuron down-regulation.

Benzodiazepines target a1 subunit GABA-Ar, selectively affecting interneurons, resulting in disinhibition.

Nicotine directly depolarizes VTA DA neurons and increases "bursting" tone from PFC glutamatergic neurons.



Compton et al. *Mol Psych* 2021; Kast and Avery. *Springer* 2020

Summary of findings

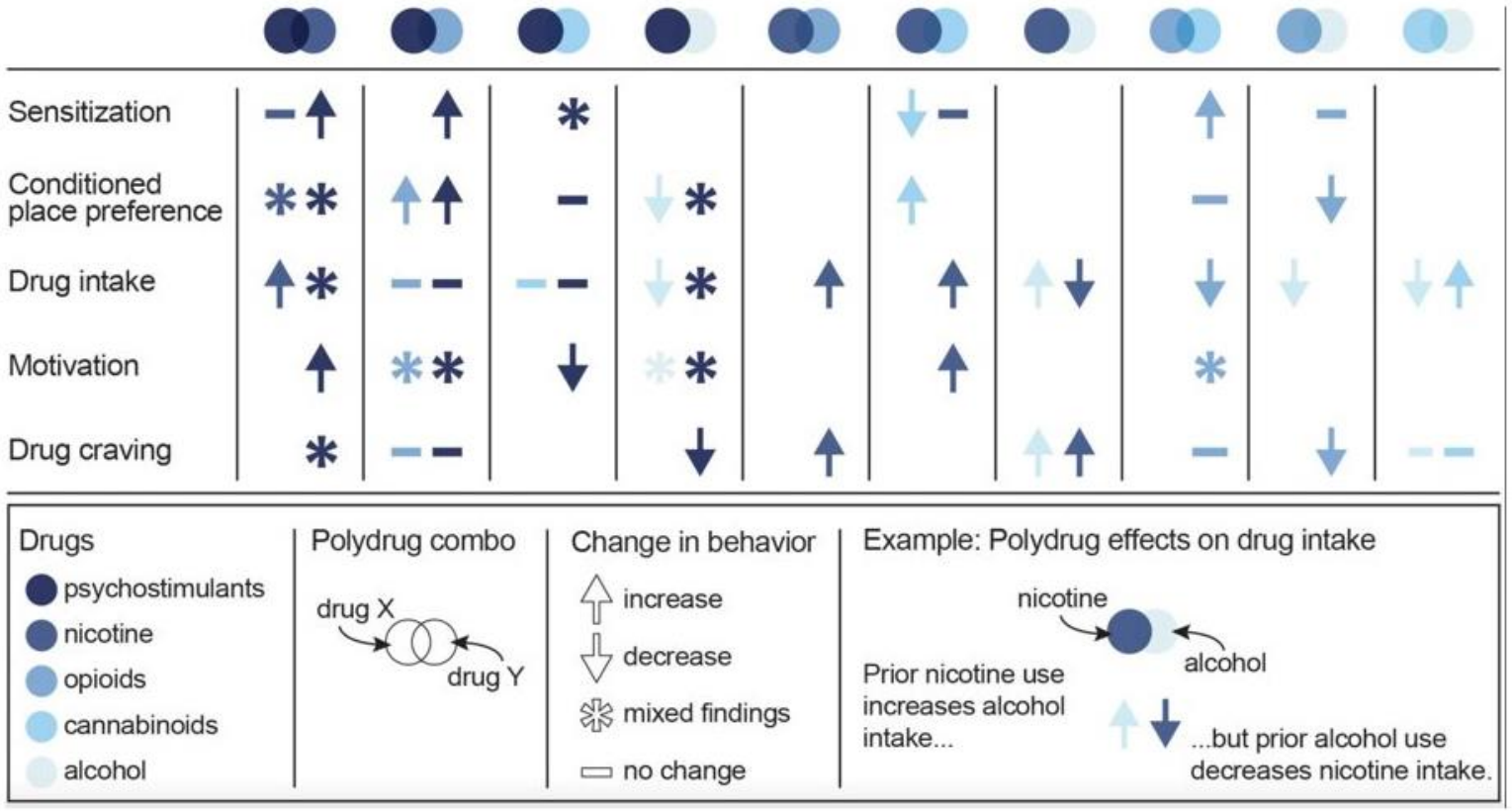
Opioids appear to enhance behavioral response to stimulants.

Nicotine + stimulant use mutually reinforcing.

Cannabis + nicotine use mutually reinforcing and worsens withdrawal.

Cannabis + cocaine use produce longer-lasting euphoria.

Adolescent alcohol exposure shows predisposing effect for stimulant and opioid use in animal studies.



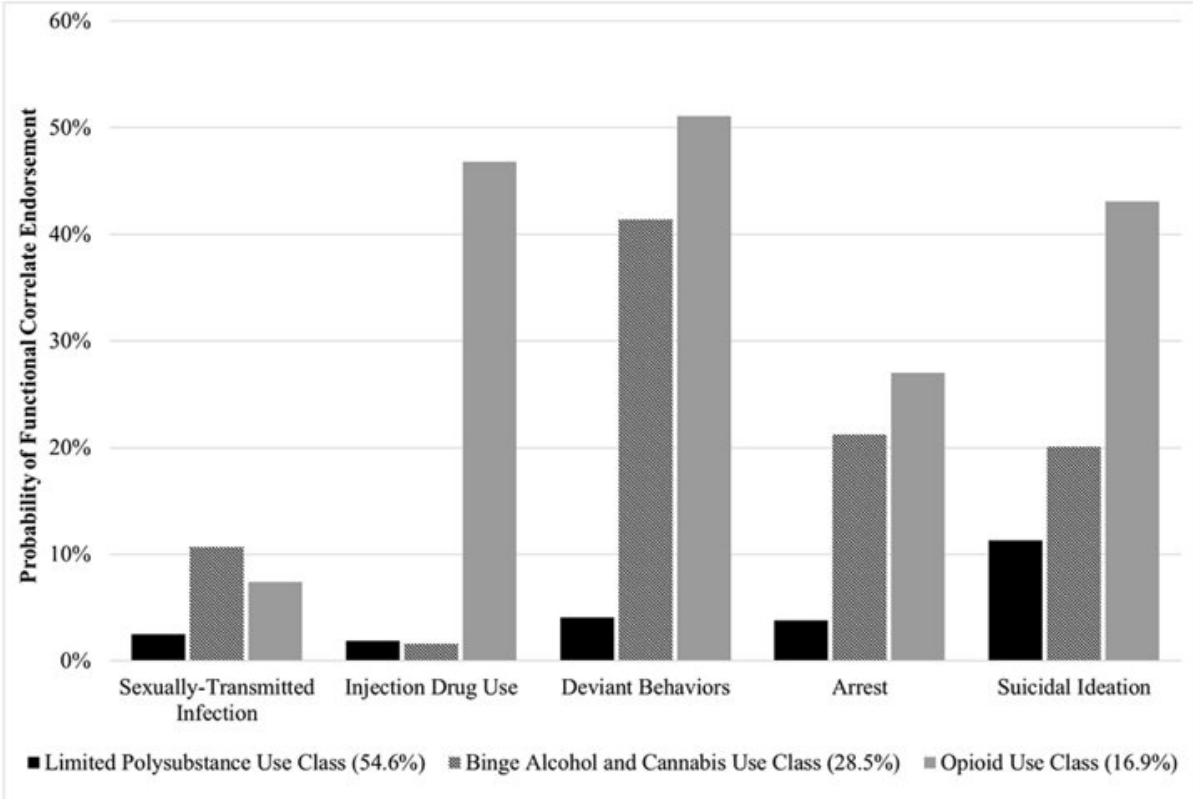
Crummy et al. *Front Neurosci* 2020

Functional outcomes

Polysubstance use has been found to worsen treatment retention, relapse rates, and mortality.

Also associated with unmet health needs, higher acute care/ED visit rates, risky and violent behaviors.

In the 2015-17 NSDUH cohort, individuals with current benzodiazepine misuse had differential functional impairment dependent upon co-use of other substances.



Votaw et al. *Subst Use Misuse* 2020; Crummy et al. *Front Neurosci* 2020

Harm reduction

Interventions for every patient.

abstinence “only”

criticisms.

- often viewed as optimal target by treatment providers
- abstinence may not be…
  - feasible (e.g. chronic pain, severity of social determinants or mental illness)
  - desired (spectrum of motivation, ambivalence, “readiness”)
  - only mechanism for improving other outcomes
- many harms are not from the substance used (e.g. blood-borne pathogens)

PWID and infectious complications

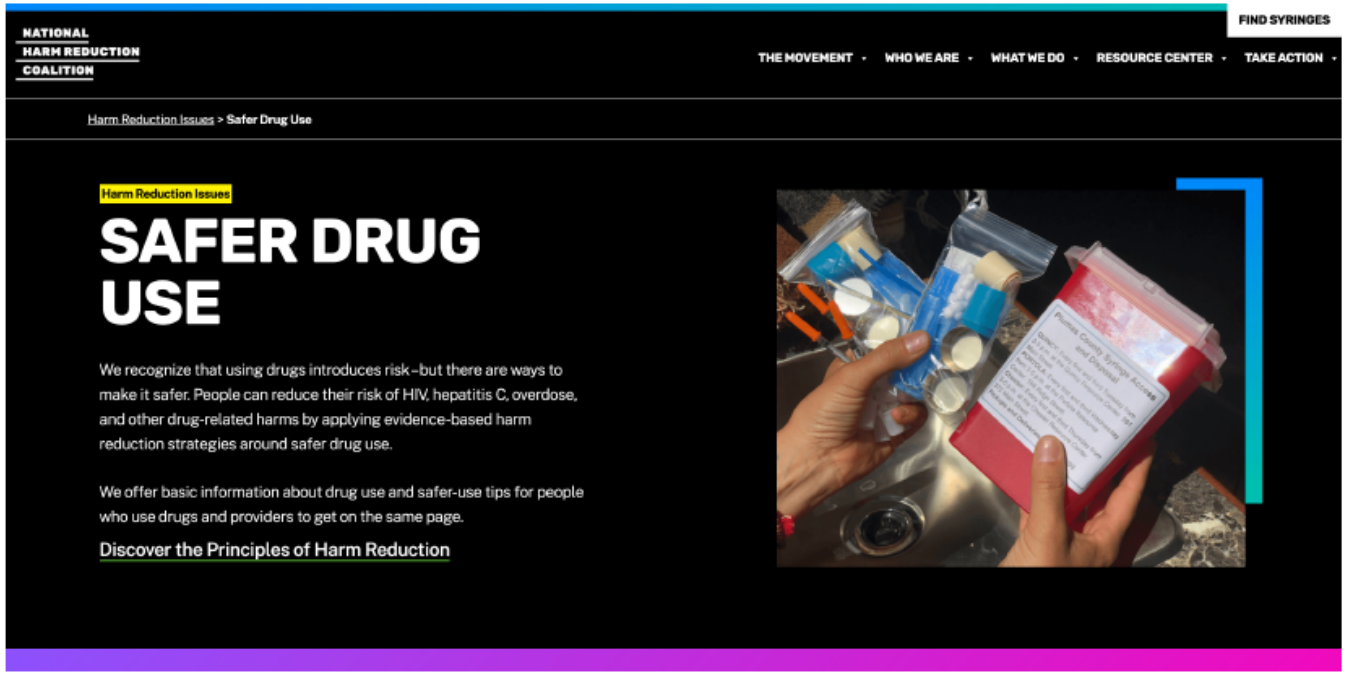
persons who injects drugs

- **60%** of PWID hospitalizations are due to infections
- **viral** infectious complications of injection use:
  - HIV: 10% of new US cases CDC
  - HCV: 70% of new US cases, 193% increase in TN CDC, TDH
  - HBV: 32% increase in TN 2014-18 TDH
  - HAV: TN since 2019 >3k cases, >1.8k hospitalizations, 28 deaths CDC

harm-reduction interventions for PWID

for every PWID, every admission

- ✓ screening: TB, STI, HIV, viral hepatitis
- ✓ vaccination: HAV, HBV
- ✓ HCV DAA
- ✓ HIV PrEP, PEP
- ✓ SNAP: Street Works Nashville
- ✓ overdose education and naloxone rescue kit prescription



interventions for every patient

model for harm-reduction.

- safer injection practices
  - ✓ educational intervention
  - ✓ booklets and online resources
  - ✓ opportunity to build a relationship

equipment	hygiene	site
new syringe and needle for every injection	wash hands	arms and hands are safer
use your own clean cooker or spoon	clean surface for works/prep	avoid neck and groin
use sterile or clean water	clean injection site with alcohol wipe	
use clean cotton filter	avoid sharing any equipment	
sturdy container for used syringe-needles		

interventions for every patient

model for harm-reduction.

- syringe-needle access
  - ✓ HIV effect size: 0.42-0.66
  - ✓ -6% in cities with SNAPs
  - ✓ +6% in cities without SNAPs
  - ✓ ↑ engagement in HIV/SUD care

Published by Oxford University Press on behalf of the International Epidemiological Association
© The Author 2013; all rights reserved. Advance Access publication 27 December 2013
International Journal of Epidemiology 2014;43:235–248
doi:10.1093/ije/dyt243

HIV/AIDS

Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis

Esther J Aspinall,[1,2]* Dhanya Nambiar,[3] David J Goldberg,[2] Matthew Hickman,[4] Amanda Weir,[1,2] Eva Van Velzen,[2] Norah Palmateer,[2] Joseph S Doyle,[3,5,6] Margaret E Hellard[3,5,6] and Sharon J Hutchinson[1,2]

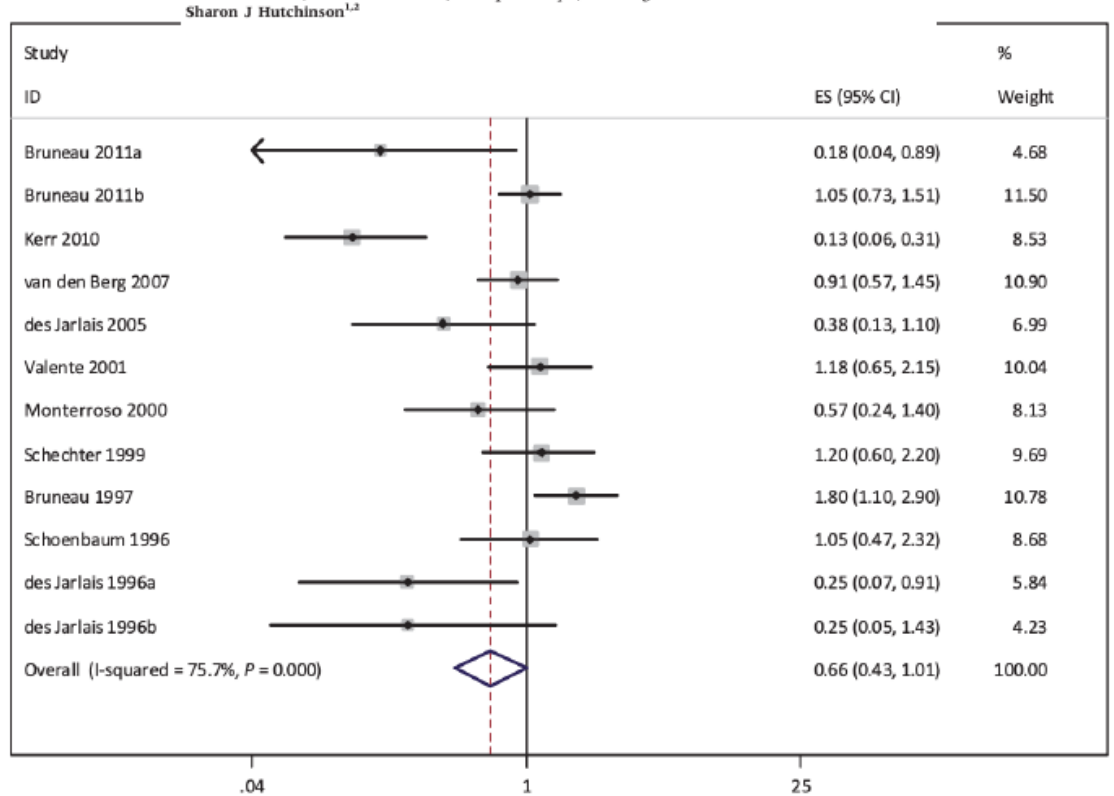


Figure 2 Forest plot of studies examining the association between NSP exposure and HIV incidence
Note: Weights are from random-effects analysis using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. ES; effect size

interventions for every patient

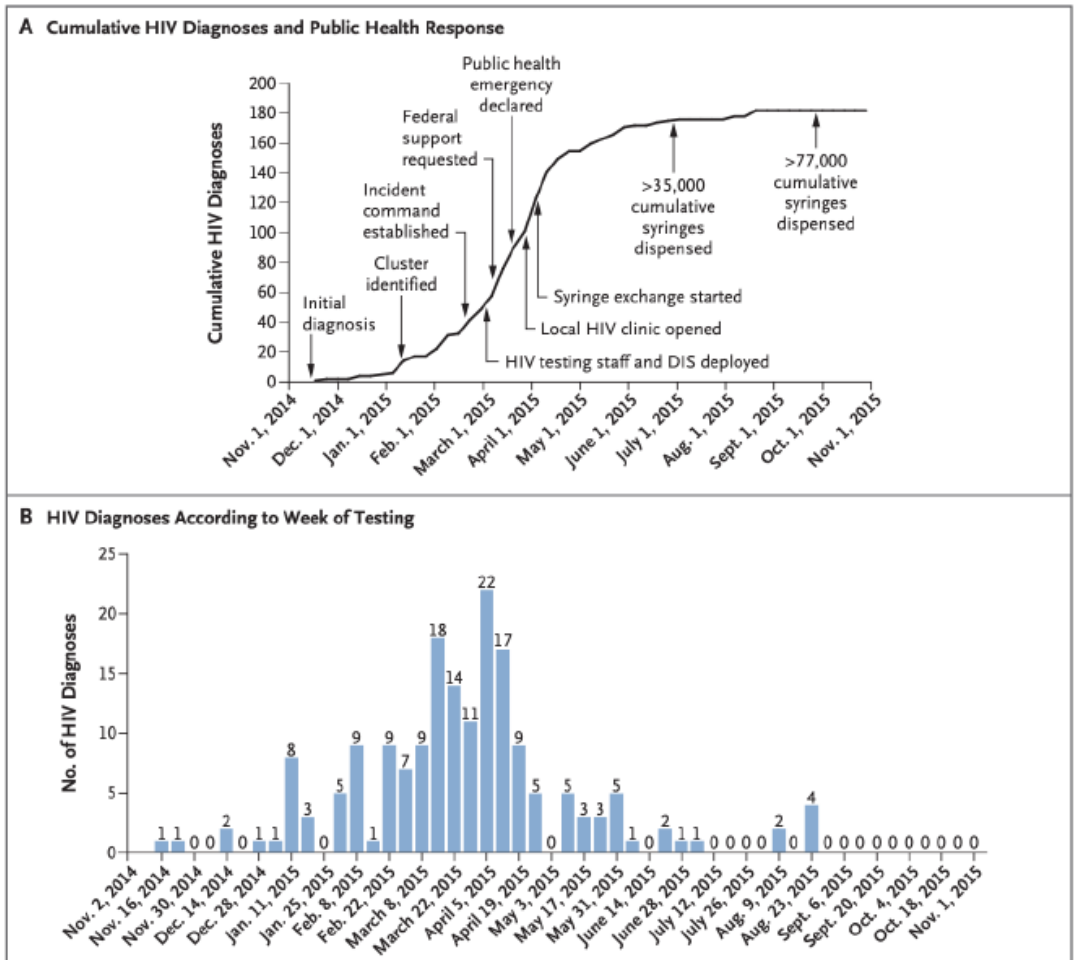
model for harm-reduction.

- syringe-needle access
  - rural Indiana case study
    - ✓ flattened curve with SNAP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015



interventions for every patient

model for harm-reduction.

- syringe-needle access
  - rural Indiana case study
    - ✓ injection predominant mode of transmission

The NEW ENGLAND JOURNAL of MEDICINE

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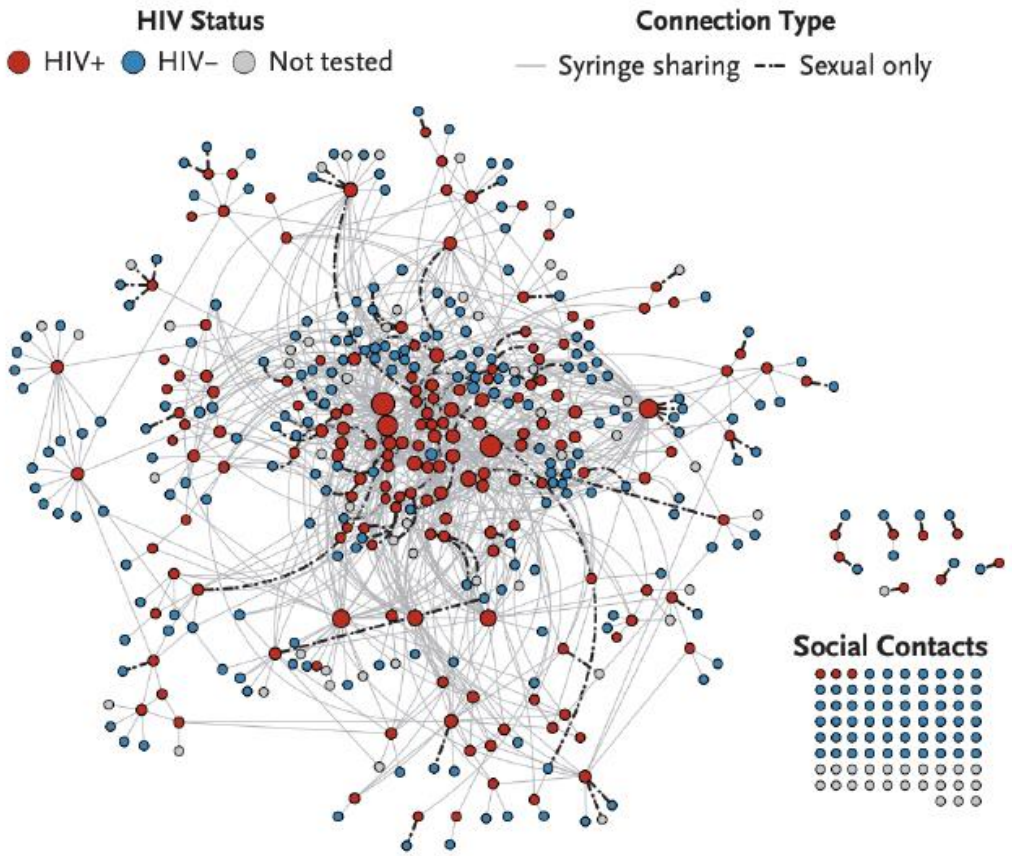


interventions for every patient

model for harm-reduction.

- PrEP for HIV
  - 50-75% risk reduction in PWID
  - ***2014 CDC recommendation***

Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial

Kachit Choopanya, Michael Martin, Pravan Suntharasamai, Udomsak Sangkum, Philip A Mock, Manoj Leethochawalit, Sithisat Chiamwongpaet, Praphan Kitisin, Pitinan Natrujirote, Somyot Kittimunkong, Rutt Chuachoowong, Roman J Gvetadze, Janet M McNicholl, Lynn A Paxton, Marcel E Curlin, Craig W Hendrix, Suphak Vanichseni, for the Bangkok Tenofovir Study Group

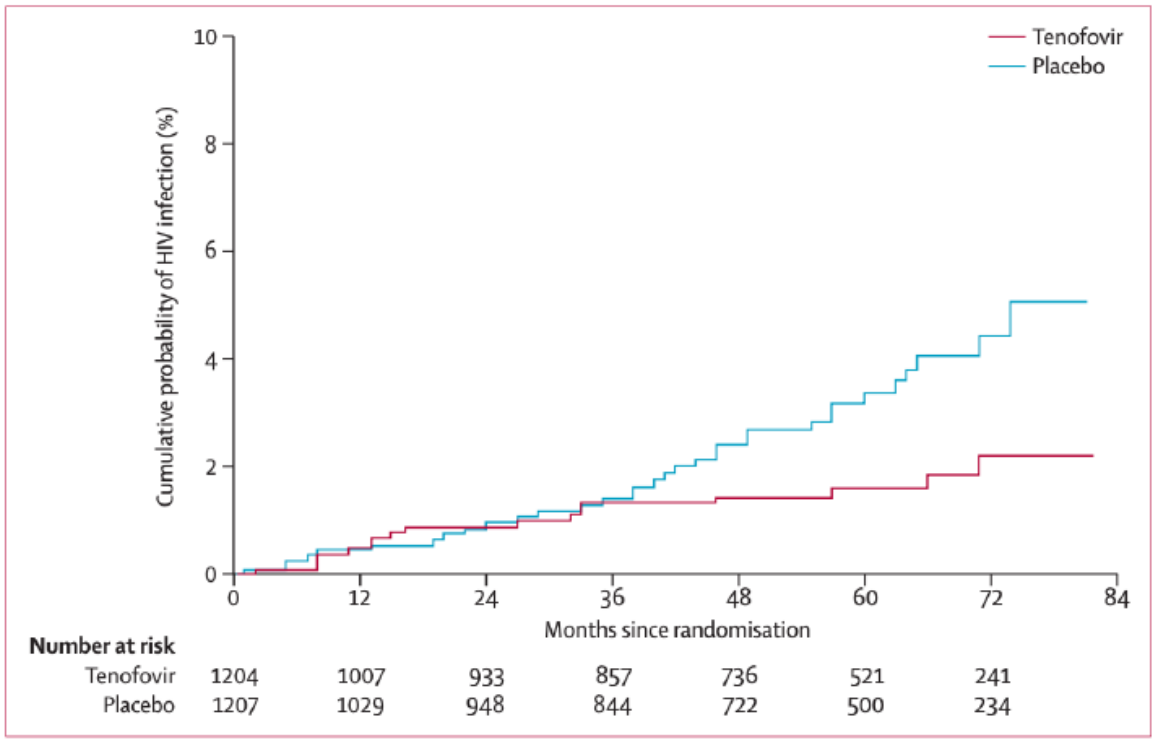


Figure 2: **Kaplan-Meier estimates of time to HIV infection in the modified intention-to-treat population**

interventions for every patient

model for harm-reduction.

- HCV diagnosis and DAA
  - 70% of new HCV due to IVDU
  - >90% sustained viral response
  - ***AASLD + IDSA guidelines***

International Journal of Drug Policy 47 (2017) 196–201

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic

Brianna L. Norton[a,*], Julia Fleming[a], Marcus A. Bachhuber[a], Meredith Steinman[b], Joseph DeLuca[a], Chinazo O. Cunningham[a], Nirah Johnson[c], Fabienne Laraque[c], Alain H. Litwin[a]

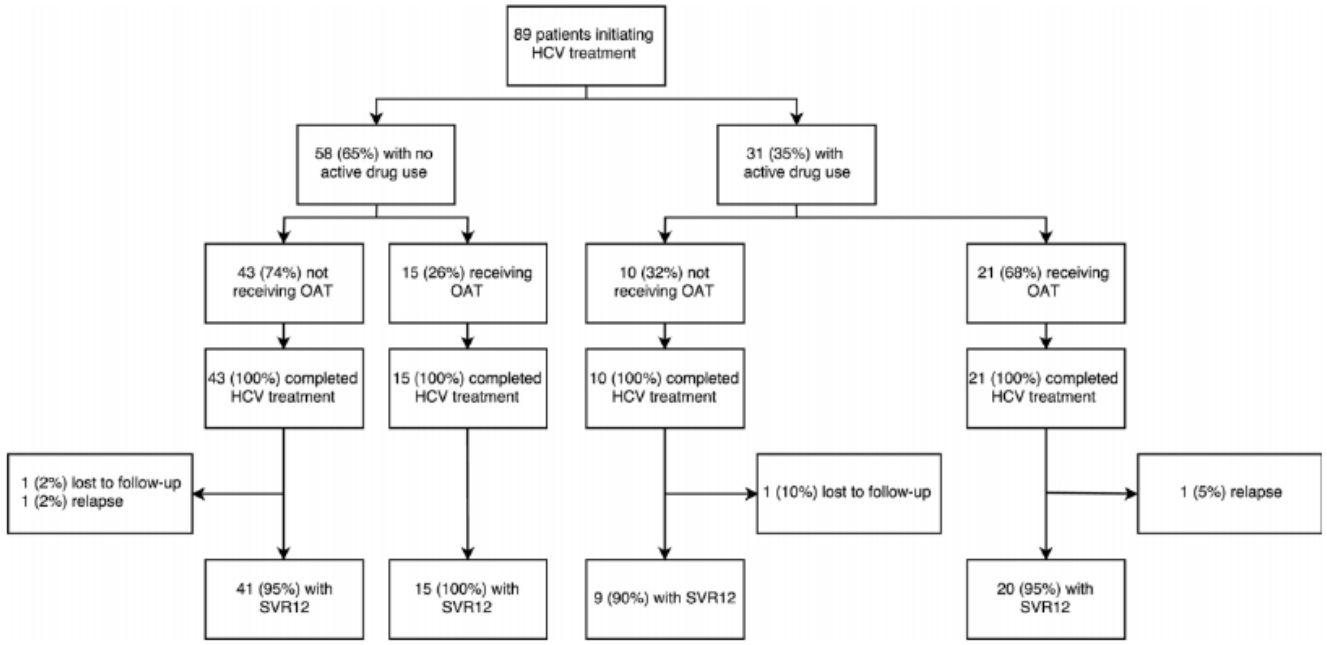
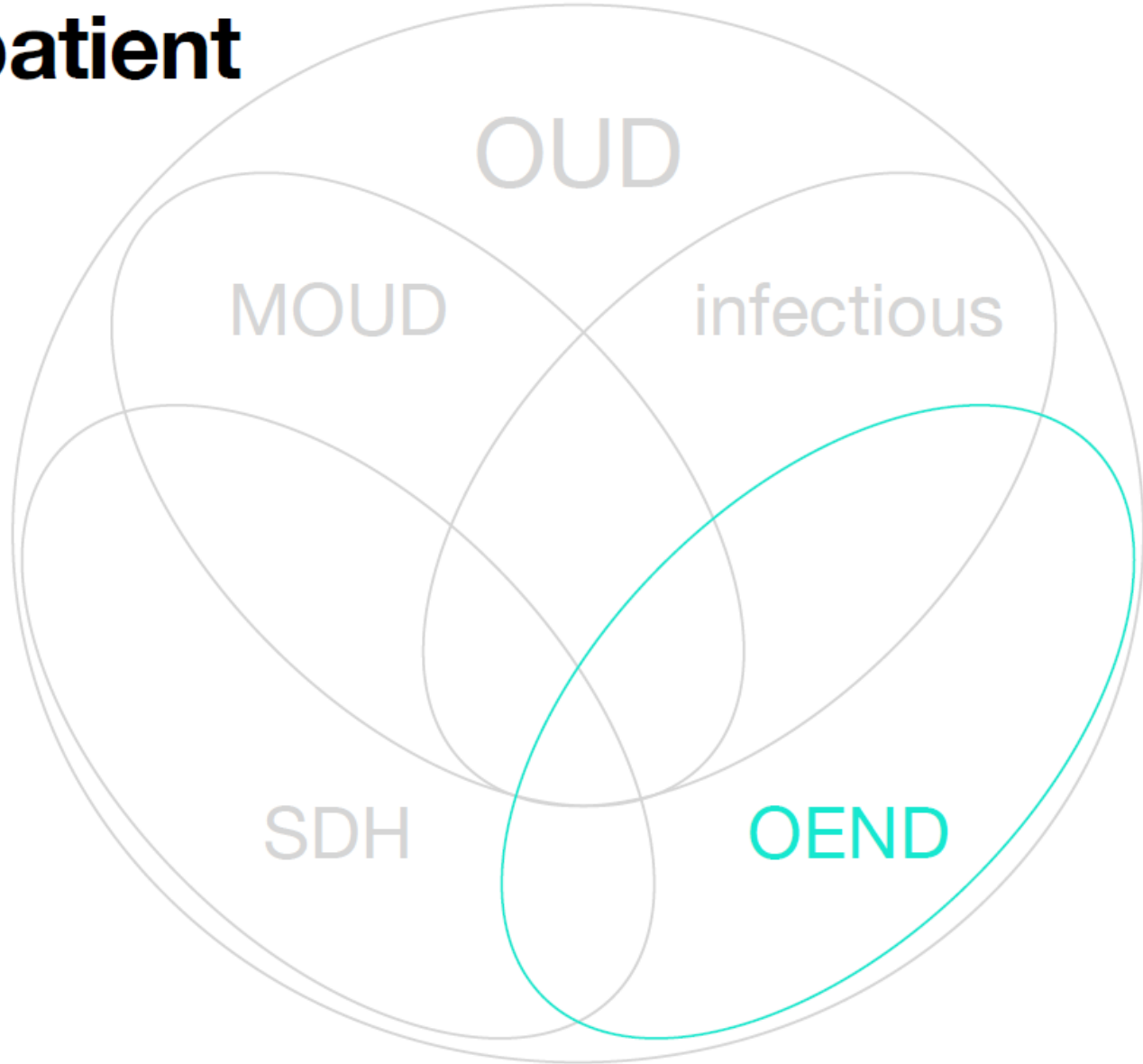


Fig. 1. Hepatitis C virus SVR rates among patients initiating direct acting antiviral therapy in an urban primary care clinic, by drug use and drug treatment status.

interventions for every patient

model for harm-reduction.

- overdose education and naloxone distribution (OEND)
  - >25k rescues s/p >150k OEND
  - 25-45% reduction in deaths
  - no compensatory use increase
  - good samaritan laws
  - less ED visits



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BMJ 2013;346:f174 doi: 10.1136/bmj.f174 (Published 31 January 2013)

RESEARCH

Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

Table 4| **Models of overdose education and nasal naloxone distribution implementation and unintentional opioid related overdose death rates in 19 communities* in Massachusetts, 2002-09**

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio† (95% CI)	P value
Absolute model:			
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	0.93	0.73 (0.57 to 0.91)	<0.01
High implementation: >100 enrollments	0.82	0.54 (0.39 to 0.76)	<0.01
Relative model:			
No implementation	Reference	Reference	
Low implementation: <median	0.85	0.71 (0.57 to 0.90)	<0.01
High implementation: >median	1.00	0.78 (0.60 to 1.01)	0.06

interventions for every patient

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Contents lists available at ScienceDirect

Addictive Behaviors

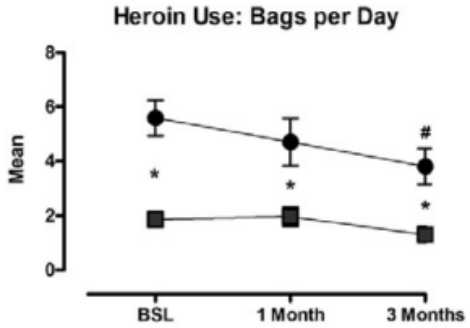
journal homepage: www.elsevier.com/locate/addictbeh

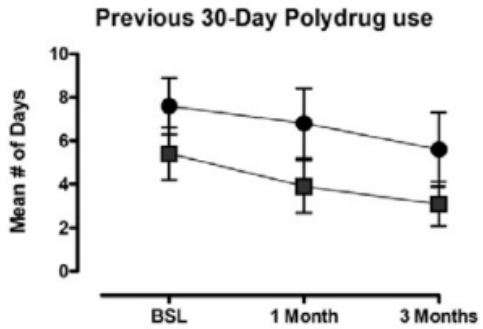
Short Communication

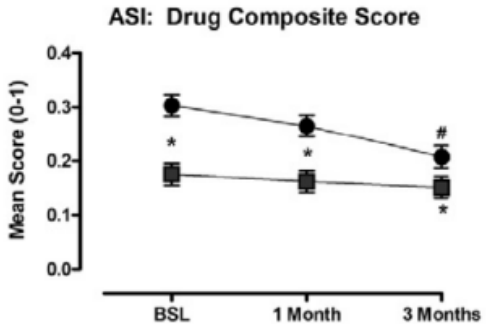
No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone

Jermaine D. Jones *, Aimee Campbell, Verena E. Metz, Sandra D. Comer

J.D. Jones et al. / Addictive Behaviors 71 (2017) 104–106







interventions for every patient

model for harm-reduction.

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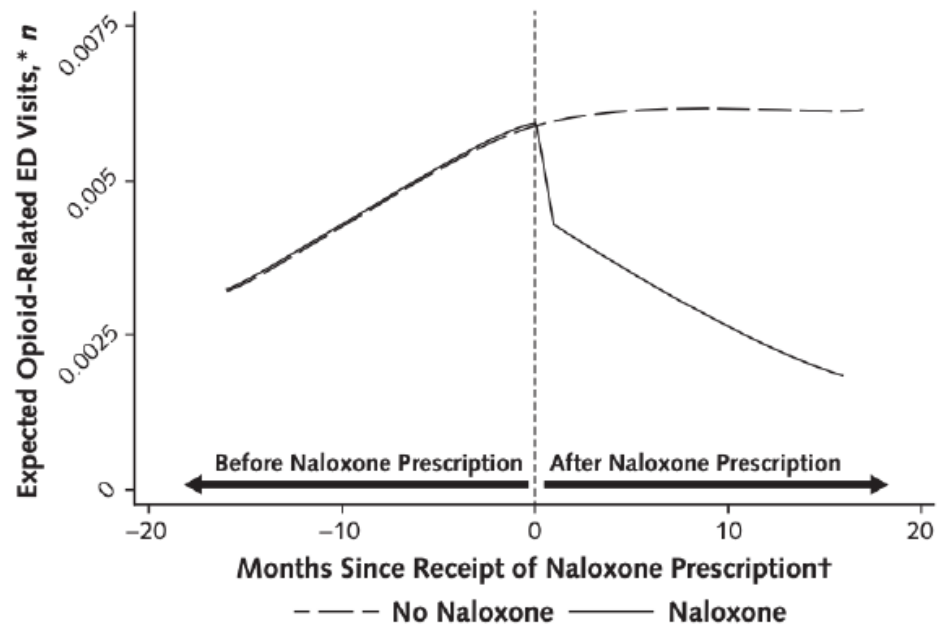
  - 25-45% reduction in deaths
  - no compensatory use increase
  - good samaritan laws
  - less ED visits

Annals of Internal Medicine ORIGINAL RESEARCH

Nonrandomized Intervention Study of Naloxone Coprescription for Primary Care Patients Receiving Long-Term Opioid Therapy for Pain

Phillip O. Coffin, MD, MIA; Emily Behar, MA; Christopher Rowe, MPH; Glenn-Milo Santos, PhD, MPH; Diana Coffa, MD; Matthew Bald, MD; and Eric Vittinghoff, PhD

Figure 1. Expected number of opioid-related ED visits per month, by receipt of naloxone prescription.

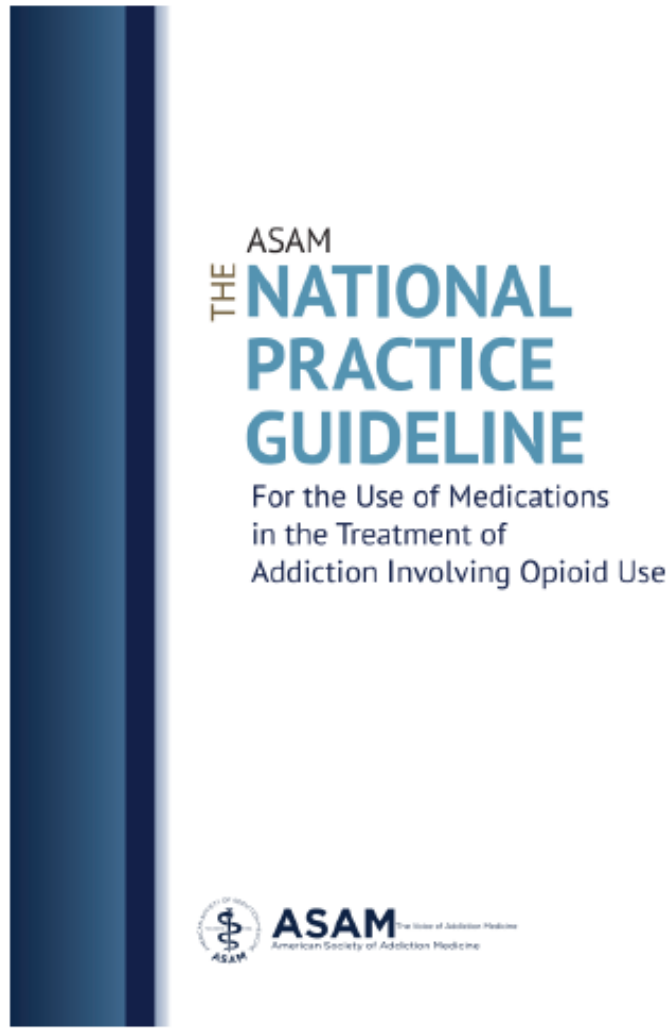


interventions for every patient

model for harm-reduction.

- 2015 ASAM national guideline:

  "The use of marijuana, stimulants, or other addictive drugs should ***not*** be a reason to suspend OUD treatment"



Outpatient parenteral antibiotics

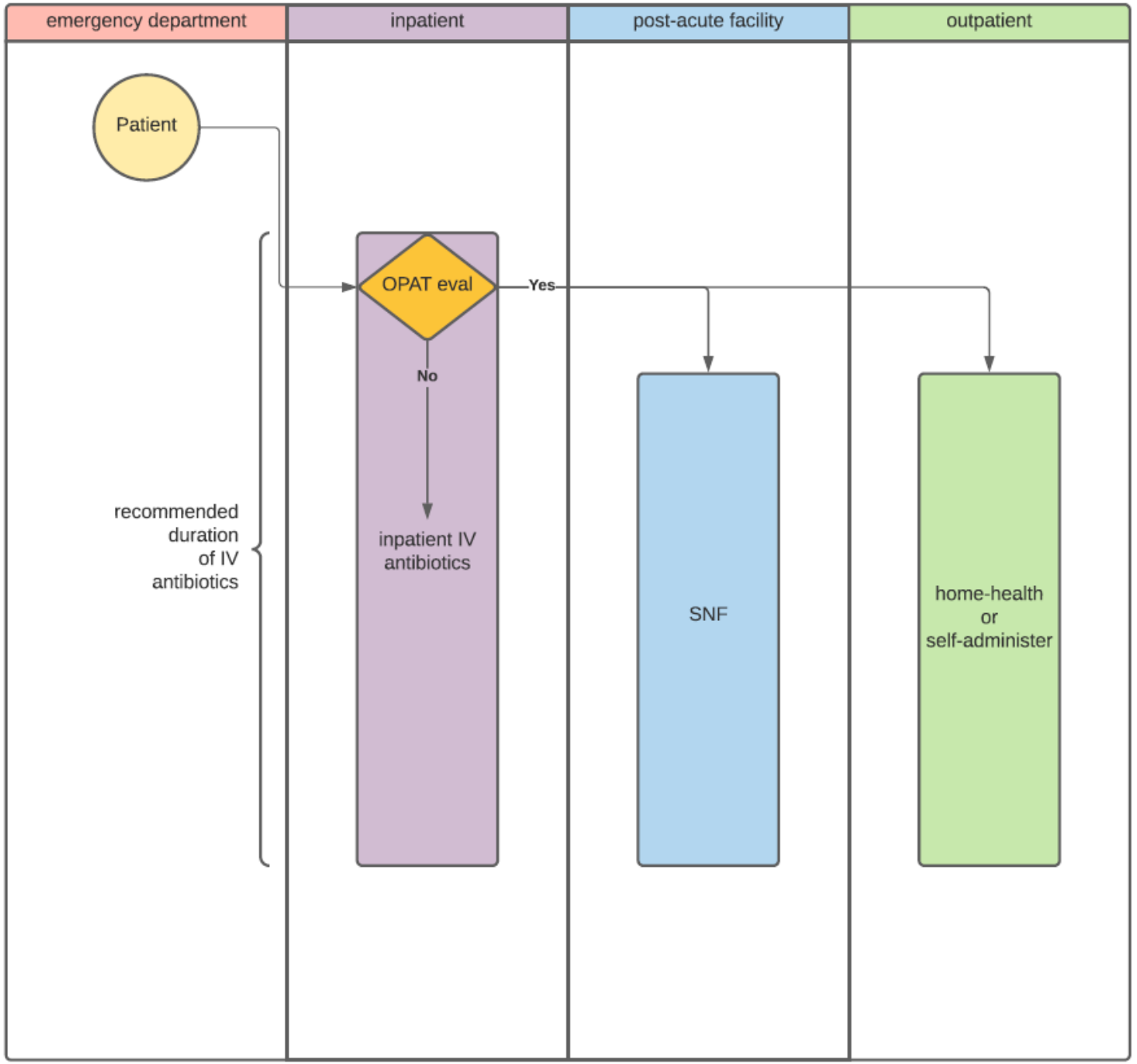
OPAT in PWID

PWID and infectious complications

persons who injects drugs

- **60%** of PWID hospitalizations are due to infections
- **bacterial** infectious complications of injection use:
  - SSTI: 50% of all PWID infectious admissions
  - sepsis/bacteremia: 50% of all PWID infectious admissions
  - IE: increased from 15 to 29% of all IE admissions nationally (2010-2015)
  - IE: more recently, academic medical centers report **40-60%** of all cases
  - osteomyelitis: 10% of all PWID infectious admissions in statewide database

OPAT


emergency department
inpatient
post-acute facility
outpatient
Patient
OPAT eval
Yes
No
inpatient IV antibiotics
recommended duration of IV antibiotics
SNF
home-health or self-administer

outpatient parenteral antibiotic therapy

OPAT

- Rucker et al. 1974: first program for cystic fibrosis patients
- Mitchell et al. 2017: 128 studies, >60k OPAT episodes
  - no difference in duration, improved outcomes
  - more line-related complications, but same re-admission and death rates
  - high patient satisfaction
- Durojaiye et al. 2018: cost 15-44% of comparable inpatient antibiotics
- Lai et al. 2013: 79.6% completed OPAT as planned (n = 313 of 393), estimated $4 million per year savings (~$10k per patient)

OPAT in PWID vs. non-PWID

Suzuki et al. 2018 meta-analysis

Open Forum Infectious Diseases

REVIEW ARTICLE

Outpatient Parenteral Antimicrobial Therapy Among People Who Inject Drugs: A Review of the Literature

Joji Suzuki,[1,2] Jennifer Johnson,[2,3] Mary Montgomery,[2,3] Margaret Hayden,[3] and Christin Price[2,3]

[1]Department of Psychiatry and [2]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts; [3]Harvard Medical School, Boston, Massachusetts

Hospitalizations for people who inject drugs (PWID) with infectious complications requiring prolonged antibiotic therapy are increasing in the context of the opioid epidemic. Although outpatient parenteral antimicrobial therapy (OPAT) is routinely offered to patients without a history of injection drug use (IDU), PWID are often excluded from consideration of OPAT. To better assess the evidence base for the safety and effectiveness of OPAT for PWID, we conducted a review of the published literature. Results suggest that OPAT may be safe and effective for PWID, with rates of OPAT completion, mortality, and catheter-related complications comparable to rates among patients without a history of IDU. Rates of hospital readmissions may be higher among PWID, but instances of misuse of the venous catheter were rarely reported. More research is needed to study the safety and effectiveness of OPAT among PWID, as well as studying the combination of OPAT and addiction treatment.

Keywords. injection drug use; outpatient parenteral antimicrobial therapy; people who inject drugs.

outcomes	PWID	non-PWID
experience	n = 800, 10 studies	n = >60,000
treatment completion	72-100% (>80% in 9/10)	80-90%
deaths	n = 8 (1% of total, 0-10% per study)	0.1-0.4%
readmission	~20%	3.6-12.6% (15.3-36% for SSTI, IE, osteomyelitis)
PICC-related complications	0.75-4.2 per 1,000 line-days (2.7-9.4%)	3.2-.3 per 1,000 line-days
PICC misuse	very low rates (2% in 1/10)	unreported, though ~1% of IE re-admitted with new SUD diagnosis

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Keywords. injection drug use; outpatient parenteral antimicrobial therapy; people who inject drugs.

- increasingly common: **84%** of OPAT centers internationally **provide to PWID**
- savings: **$11k-25k per OPAT episode**

PWID: OPAT vs. SNF

D'Couto et al. 2018

Open Forum Infectious Diseases

MAJOR ARTICLE FIDSA

Outcomes According to Discharge Location for Persons Who Inject Drugs Receiving Outpatient Parenteral Antimicrobial Therapy

Helen T. D'Couto,[1,3] Gregory K. Robbins,[1,2,3] Kevin L. Ard,[1,2,3] Sarah E. Wakeman,[3] Justin Alves,[2] and Sandra B. Nelson[1,2,3]

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Background. Opioid use disorder poses a significant public health risk. Persons who inject drugs (PWID) suffer from high mortality and morbidity secondary to serious infectious diseases, often requiring prolonged courses of outpatient parenteral antibiotics. The goal of this study was to determine the outcomes of PWID discharged to home or to a skilled nursing or rehabilitation facility (SNF/rehab) with parenteral antibiotic treatment under an outpatient parenteral antimicrobial therapy (OPAT) program.

Methods. This is a retrospective observational study. The study population was identified via hospital and OPAT databases using substance use disorder diagnoses and confirmed through chart review. The study population included hospitalized PWID with injection drug use in the preceding 2 years who were discharged between 2010 and 2015 to complete at least 2 weeks of parenteral antibiotics and monitored by the OPAT program. Retrospective chart review was used to describe patient characteristics and outcomes.

Results. Fifty-two patients met inclusion criteria, 21 of whom were discharged to home and 31 were discharged to a SNF/rehab. Of the patients discharged to home, 17 (81%) completed their planned antibiotic courses without complication. Twenty (64%) patients discharged to a SNF/rehab completed the antibiotic courses without complication. Six (11%) patients had line infections, 6 (11%) had injection drug use relapse, and 12 (23%) required readmission.

Conclusions. Persons who inject drugs discharged home were not more likely to have complications than those discharged to a SNF/rehab. Home OPAT may be a safe discharge option in carefully selected patients.

Keywords. central venous access; discharge planning; OPAT; PWID.

Table 2. Outcomes of Patients Discharged to Home Versus Rehabilitation

Patient, Diagnosis, and Treatment Factors	Discharged to Home (n = 21)	Discharged to Rehab (n = 31)	*P* Value (Fisher's Exact Test)
Any Complication	4	11	.23
Line Complications	1	5	.38
Injection Drug Use Relapse	1	5	.38
Loss to Follow-up	1	4	.64
Readmission	3	9	.72
Death	1	0	.40

PWID: which readmissions matter?

Rudasill et al. 2019

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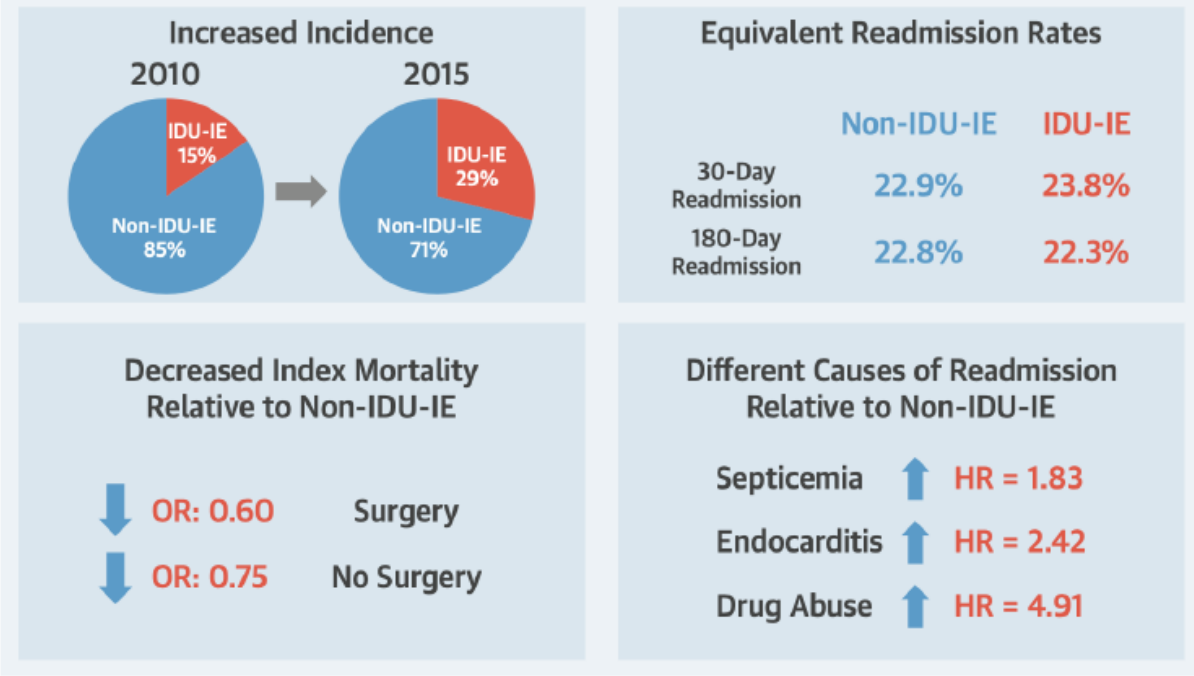
Clinical Outcomes of Infective Endocarditis in Injection Drug Users

Sarah E. Rudasill, BA,[a] Yas Sanaiha, MD,[a] Alexandra L. Mardock, BA,[a] Habib Khoury, BS,[a] Hanning Xing, BS,[a] James W. Antonios,[a] James A. McKinnell, MD,[b] Peyman Benharash, MD[a]

CENTRAL ILLUSTRATION Infective Endocarditis in Injection Drug Users



Rudasill, S.E. et al. J Am Coll Cardiol. 2019;73(5):559–70.

Infective endocarditis in injection drug users is increasing in incidence and is associated with decreased index mortality, equivalent rates of 30- and 180-day readmission, and increased risk of readmission for septicemia, endocarditis, and drug abuse.

2018 IDSA OPAT guidelines:
case-by-case for PWID

OPAT criteria for PWID

considerable variability

- criteria range significantly across institutions:
  - risk “score”
  - absolute prerequisites
  - clinical assessment using specified risk factors

criteria	Singapore	UAB	Brigham	MGH
housing stability	+	+	+	
support person	+			+
no other active PWID/SUD			+	
contract	+			
cravings score		+		
comorbidity		+		
prior overdoses		+		
prior relapses		+		+
multi-substance		+		
family history		+		
trauma		+		
motivation		+		+
MOUD			+	+
last use				+
in-hospital behavior			+	
recovery coaching			+	
scoring		+		

does MOUD affect outcomes?

MOUD and IE outcomes

Thakarar et al. 2019

PLOS ONE

RESEARCH ARTICLE

Mortality, morbidity, and cardiac surgery in Injection Drug Use (IDU)-associated versus non-IDU infective endocarditis: The need to expand substance use disorder treatment and harm reduction services

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outcome	MOUD	no MOUD
n (%)	10 (24%)	32 (76%)
90-day mortality	1 (3%)	6 (15%)
ED visits <90d	4 (10%)	16 (41%)

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