

# Stimulant Use in Self-Care of Chronic Pain

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# Disclosure Information

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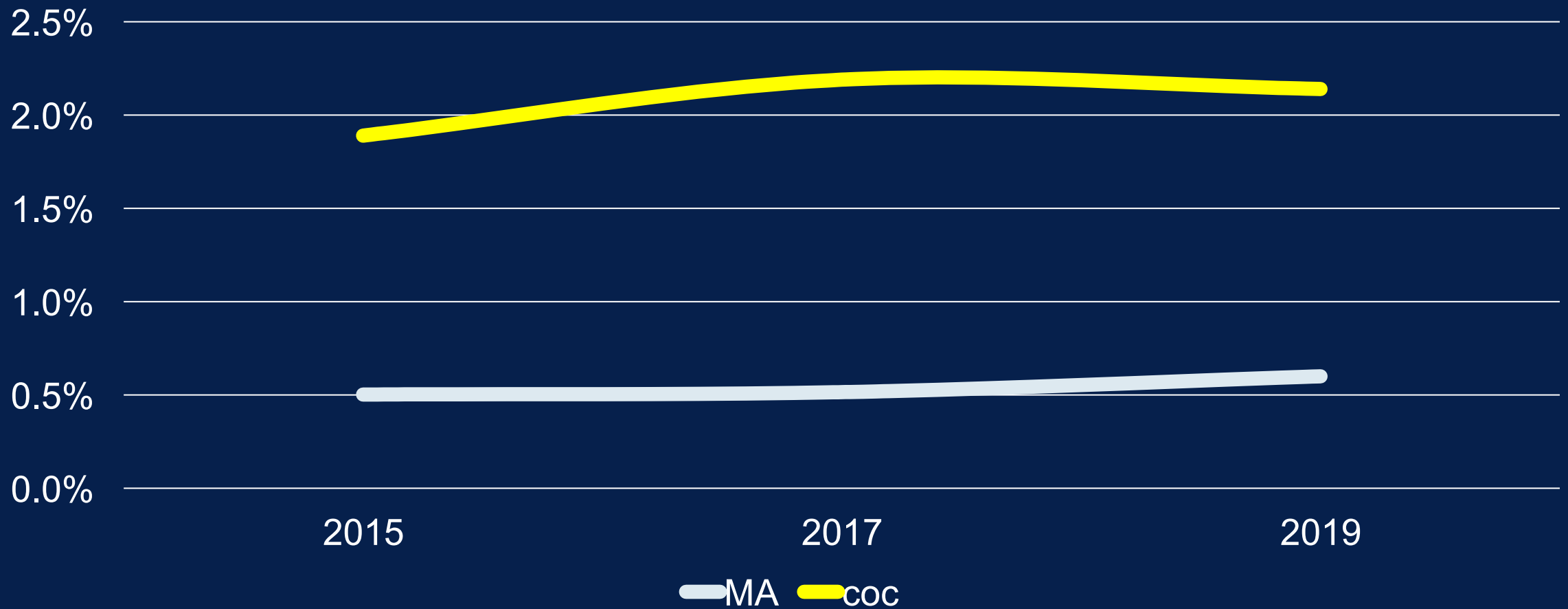
- ☀ No disclosures related to this talk
- ☀ Receipt of donated tenofovir-emtricitabine from Gilead Sciences for NIH-funded study of HIV pre-exposure prophylaxis



# Learning Objectives

- ☀ Review evidence for self-care of pain through stimulant use
- ☀ Describe a potential mechanism for analgesia from stimulants
- ☀ Debate the clinical implications of this phenomenon

# Recent Trends in Past-Year Stimulant Use

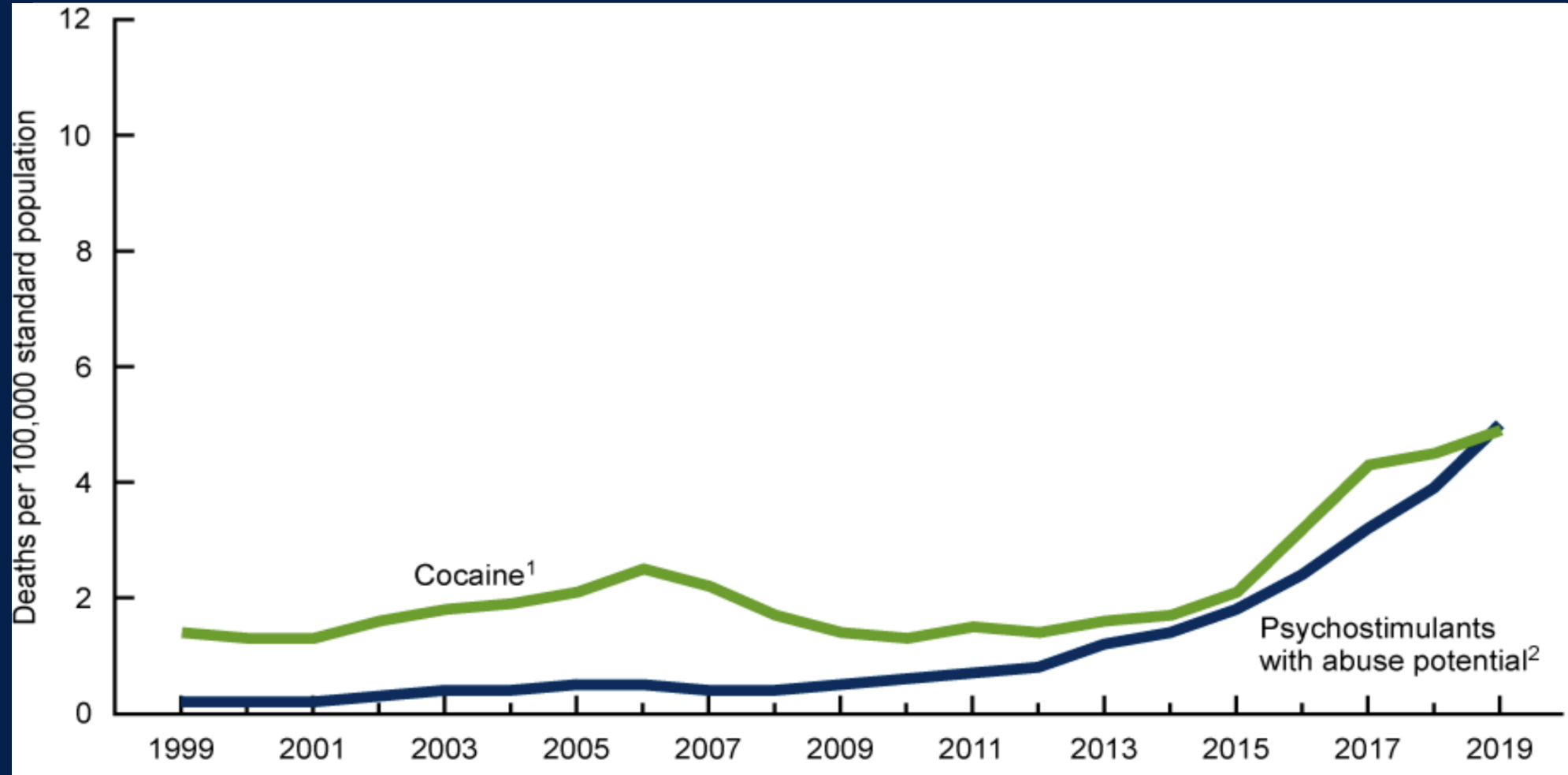


Han, JAMA Psych, 2021; Mustaquim, Add Beh, 2021

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# Age-Adjusted Stimulant Overdose Death, US



Hedegaard, NCHS Data Brief No. 394, 2020

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# High-Impact Chronic Pain

	Prevalence
High-impact chronic pain	8% (20 million)
45y +	>10%
< high school education	14%
Unemployed	16%
<100% federal poverty level	15%
<65 y with public insurance	17%
>65 y with public insurance	24%

- ☀ From 2012-18, per capita rate of opioid prescribing declined from 81.3 to 51.4 Rx/100 persons, with associated increased non-prescribed opioid use and stimulant use.
- ☀ Increased non-prescription opioid use often has been attributed to self-treatment of pain or opioid use disorder, with less clarity regarding stimulant use.

# Case

- ☀ Bruce, 45yo man with HIV prescribed oxycodone 30mg TID to treat peripheral neuropathy for the past 15 years, joins your practice after his provider retires
- ☀ Other interventions didn't help or weren't tolerated
- ☀ He attends clinic regularly, has no early refills or other concerning behaviors
- ☀ Urine drug screen is consistently positive for oxycodone and no other opioids, but is often positive for methamphetamine

Doc - it  
takes the  
pain away



Traditionally, the **BROMPTON COCKTAIL** consisted of morphine or heroin, cocaine, and a highly pure form of **ETHYL ALCOHOL** (or gin). Sometimes, the mixture also contained an anti-nausea agent, such as Thorazine.



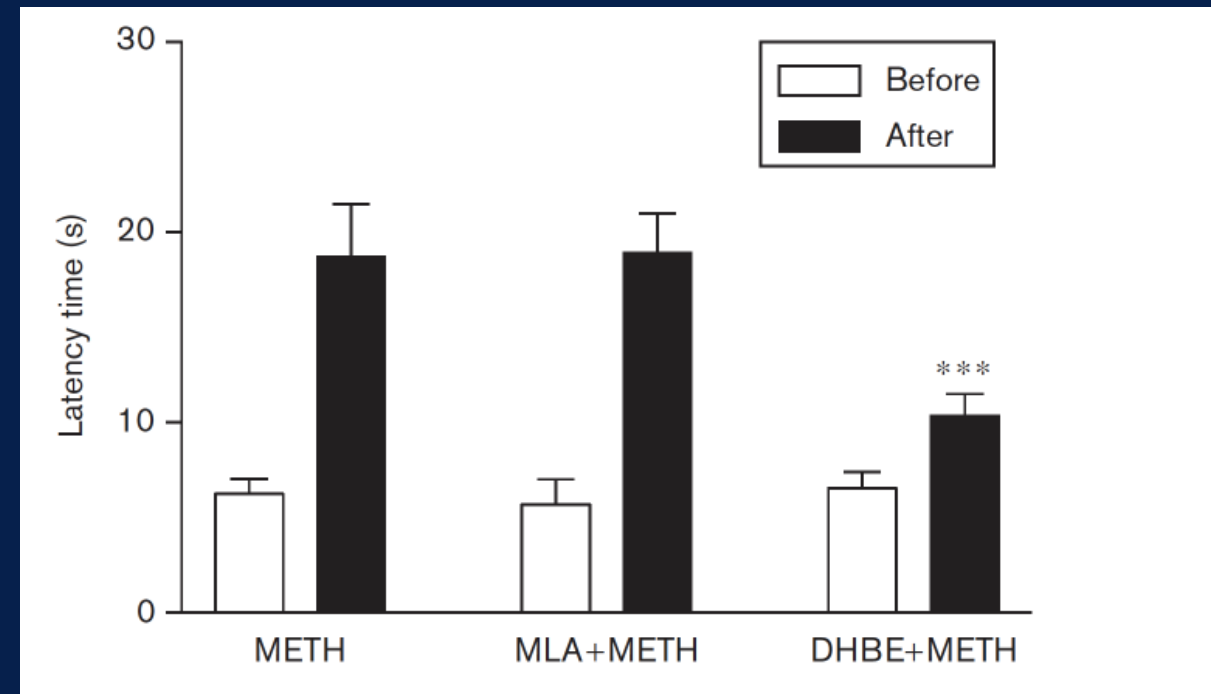
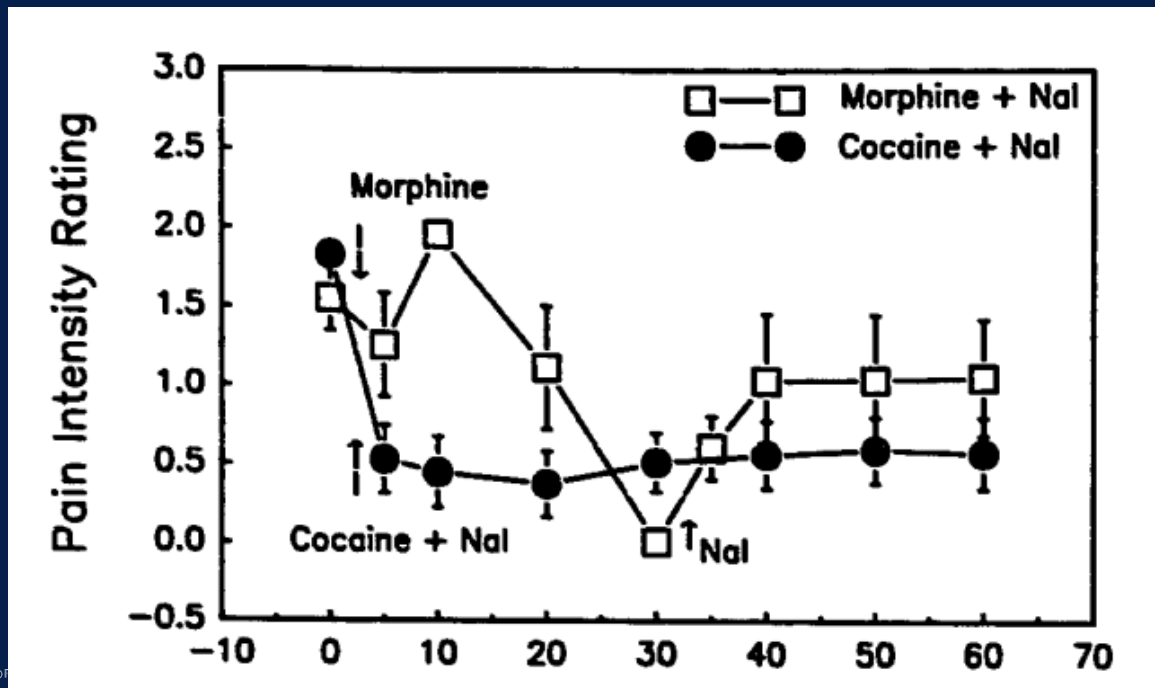


# Stimulants and Pain in Animal Models

- ☀ Cocaine reduces hot plate response in rats

- ☀ Not a/w opioid pathway

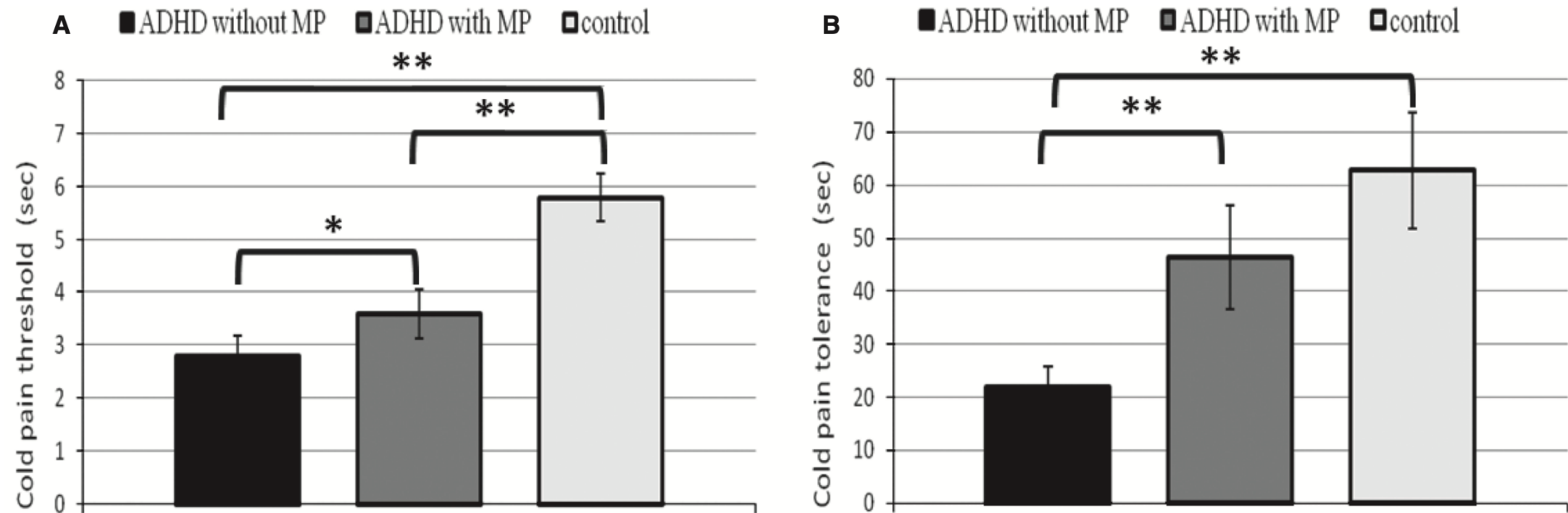
- ☀ Methamphetamine reduces hot plate response in mice



Lin, Brain Res, 1989; Camarasa, Pharmacology, 2009

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# Methylphenidate increases cold pain threshold and tolerance in adults with ADHD



**Figure 1.** Cold pain threshold and cold pain tolerance in the three study conditions. Mean  $\pm$  SEM of cold pain onset (A) and cold pain tolerance (B) in the controls (white bars), the Attention Deficit Hyperactivity Disorder (ADHD) subjects “with methylphenidate (MP)” (gray bars), and the ADHD subjects “without MP” (black bars). The y-axis represents time in seconds for threshold and tolerance. Asterisk represents significant results in the Wilcoxon signed-rank test when comparing within-group differences and the Mann–Whitney *U*-test when comparing between-subject effects. \*  $P < 0.05$ , \*\*  $P < 0.001$ .

# Methylphenidate increases cold pain threshold and tolerance in healthy adults

**Cold pain threshold and tolerance prior to and following treatment with MP and placebo.**

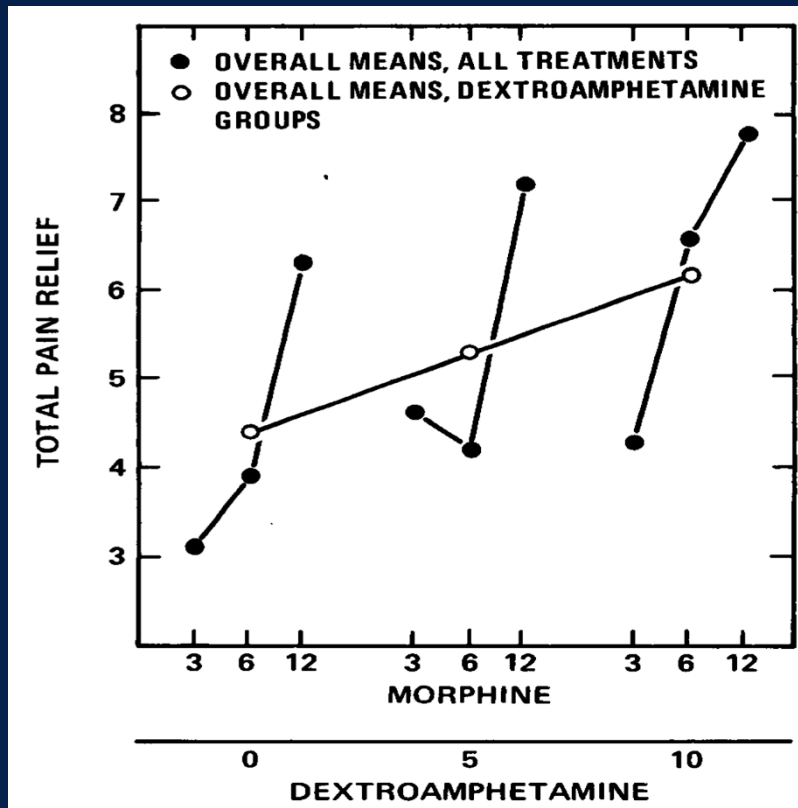
	MP			Placebo		
	Pretreatment	Posttreatment	Significance (Wilcoxon)	Pretreatment	Posttreatment	Significance (Wilcoxon)
Cold pain threshold, s						
Median (IQR)	3.5 (3.7)	4.6 (4)	$Z = -3.3, P = 0.001$	4.0 (2)	4.0 (2.5)	$Z = -1.28, P = 0.20$
Mean (SD)	4.1 (2.6)	5.4 (3.1)		4.5 (2.6)	4.3 (2.7)	
Min-max	1-14	1.5-13		1-12	1-14	
Cold pain tolerance, s						
Median (IQR)	31.0 (55)	41.0 (103)	$Z = -3.2, P = 0.001$	29.0 (40)	32 (37.8)	$Z = -1.65, P = 0.10$
Mean (SD)	57.8 (54.5)	73.8 (61.8)		52.5 (53.7)	57.0 (52.9)	
Min-max	10-180	13-180		7-180	6-180	

IQR, interquartile range; SD, standard deviation.

# D-amphetamine reduce adverse effects of opioids

☀ Enhances post-op morphine pain relief & reduces sedation

☀ Reduces AEs, increases liking among PWUD



Opioid Signs/Symptoms	Morphine	d-amphetamine	Morphine + d-amphetamine
Sick stomach	21%	0%	13%
Itchy skin	27%	11%	17%
Coasting	11%	3%	5%
Nodding off	5%	0%	2%

# Patient reports of substance use for pain

☀ *I've got drunk before, to get rid of the pain. I've taken cocaine before, to get rid of the pain. It didn't get rid of it long, but as soon as you hit it, for 30 or 40 seconds, no pain.*

# Methamphetamine & HIV Symptom Management

20 HIV+ Men	All used methamphetamine (55% prior to having HIV)
Perceived benefits of methamphetamine use	
Enhanced sexual pleasure	All participants
Less depression	"I took meth for depression, but now that I'm on psych meds, I don't need it anymore"
Managing neuropathic pain	<p>"I play the piano, and the pain in my fingers is so severe sometimes I can't stand it. The meth takes that pain away."</p> <p>"I use meth a lot for pain, because it helps get relief faster than going to the emergency room and waiting 2 hours or more."</p>

# Management of HIV Neuropathy

	United States (N=326)		International (N=228)	
Strategy	Frequency	Effectiveness (1-10)	Frequency	Effectiveness (1-10)
<b>Street drugs</b>	<b>12%</b>	<b>5.1</b>	<b>8%</b>	<b>6.9</b>
Cigarettes	42%	4.7	28%	6.4
Alcohol	22%	5.0	13%	6.6
OTC Medications	38%	5.7	25%	6.8
Prescription opioid	28%	6.3	16%	6.8
Cannabis	23%	6.8	19%	7.0
Acupuncture	11%	7.4	16%	7.1

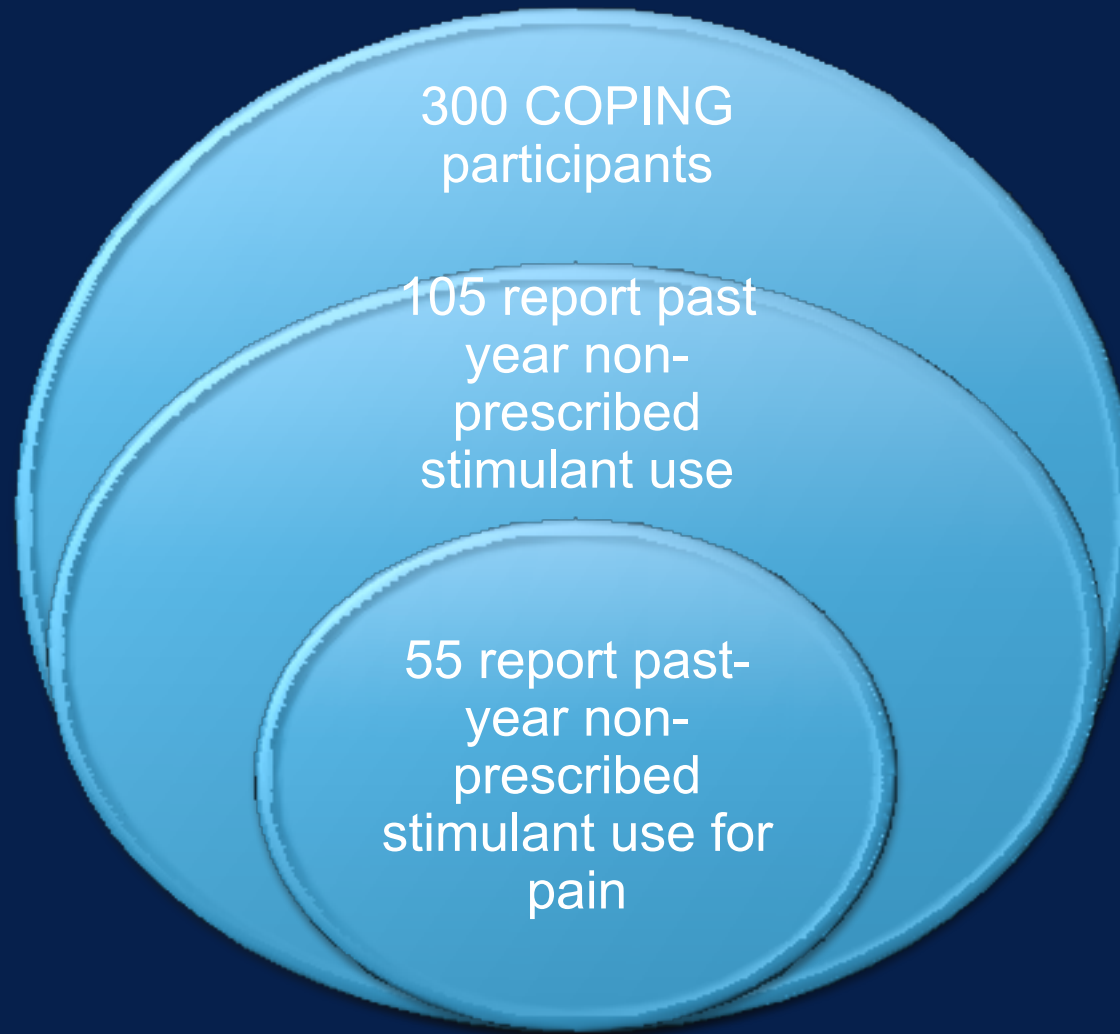
Among those reporting substance use for pain, more severe neuropathic pain was associated with using amphetamines for pain self-treatment (2007; N=450)

# COPING Study

- ☀️ Prospective cohort study of 300 San Francisco primary care patients receiving long-term opioids for chronic non-cancer pain who also have a lifetime history of non-prescribed opioid, cocaine, or methamphetamine use.
- ☀️ 2016-2021
- ☀️ Interviews, exam, functional status assessments, cold pressor tests, qualitative substudy



# Stimulant Use Among COPING Participants



## Self-Reported Stimulant Use for Chronic Pain: Bivariate Associations with Self-Care of Pain with Stimulants

	Used Stimulants for Pain (N=55)	Used Stimulants but NOT for Pain (N=50)	P-Value
<b>Average pain (1-10)</b>	<b>8</b>	<b>7</b>	<b>0.049</b>
<b>Neuropathic pain score</b>	<b>4.5</b>	<b>3.4</b>	<b>0.017</b>
Pain catastrophizing	38%	30%	0.38
Cold pain threshold	7.48s	8.03s	0.93
Cold pain tolerance	13.2s	13.0s	0.87
No non-opioid pain meds	24%	38%	0.11
Used complementary therapies	42%	44%	0.82
BSI score (median)	16.0	12.5	0.086
PTSD screen	40%	36%	0.67
<b>PHQ-8 Mod-Sev</b>	<b>49%</b>	<b>28%</b>	<b>0.027</b>

## Self-Reported Stimulant Use for Chronic Pain: Bivariate Associations with Self-Care of Pain with Stimulants

	Used Stimulants for Pain	Used Stimulants but NOT for Pain	P-Value
Drug injection	55%	40%	0.14
Heroin use	44%	32%	0.22
Maximum MME (median)	180	164	0.72
Opioid Rx Discontinued	24%	20%	0.65
At least weekly stimulant use	56%	46%	0.29

## Multivariable Logistic Regression Analysis of Characteristics Associated with Reporting Stimulant Use to Treat Pain (N=105)

	aOR	95% CI
Female gender (male reference)	3.2	1.06-9.63
Neuropathic pain score (DN4)	1.34	1.05-1.70

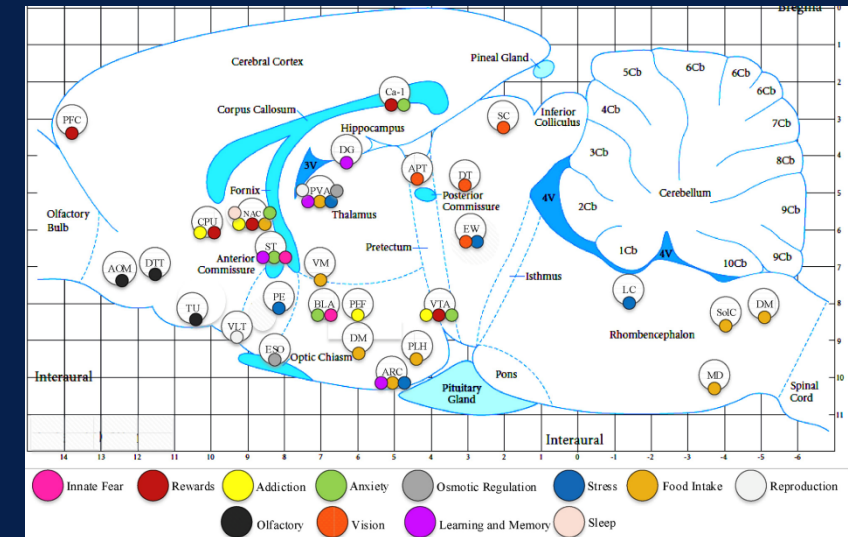
Also controlled for age, race, education, homelessness, pain score, depression, use of non-opioid meds for pain

# PLWH and chronic pain, discontinued from opioids, report self-care of pain with stimulants

- ☀ I: When was the last time that you used cocaine?
- ☀ R: Maybe last week. . .Because I had no opiates to help the pain. No methadone. So I sniffed it [cocaine]. . .the pain went away.
- ☀ R: I only use [methamphetamine] when like ... I miss going to the [methadone] clinic that day to actually dose ... for me ... a shot of methamphetamine will sometimes be better than ... a pain pill to take the pain away ... and **not all doctors understand that.**

## Potential Mechanism: Cocaine and amphetamine-regulated transcript peptide (CART)

- ☀️ Neurotransmitter initially found in hypothalamus in 1995, now known to be widely distributed
- ☀️ Induced by administration of cocaine or amphetamines
  - ☀️ Methamphetamine increases CART in n. accumbens
- ☀️ Induces or enhances:
  - ☀️ anti-nociception on its own
  - ☀️ anti-nociception of morphine for neuropathic but not inflammatory pain
  - ☀️ anti-hyperalgesia effect of fluoxetine
  - ☀️ reduced anxiety of alcohol withdrawal in rats



# But does it help chronic pain?

☀ If long-term opioids are really helpful, then perhaps we should be considering stimulants as well.

☀ If long-term opioids are rarely helpful, is stimulant use also treating something else?

☀ Addiction

☀ Brief moment of salience

☀ **Social pain / dissociative effect**

# The pain of life

- ☀ Physical versus social pain
- ☀ Reward systems in transition from acute to chronic pain
- ☀ Chronic pain often worsened by social stress
- ☀ Patients with complex chronic pain are the ones who usually want longterm opioid therapy
- ☀ Exogenous opioids overwhelm endogenous opioid system
- ☀ “Diminishing natural rewards from normal sources of pleasure, and increasing social isolation”
- ☀ Withdrawal “not only painful but distressing”

*“I stood at a distance, and aloof from the uproar of life”*

- Confessions of an Opium Eater, 1821

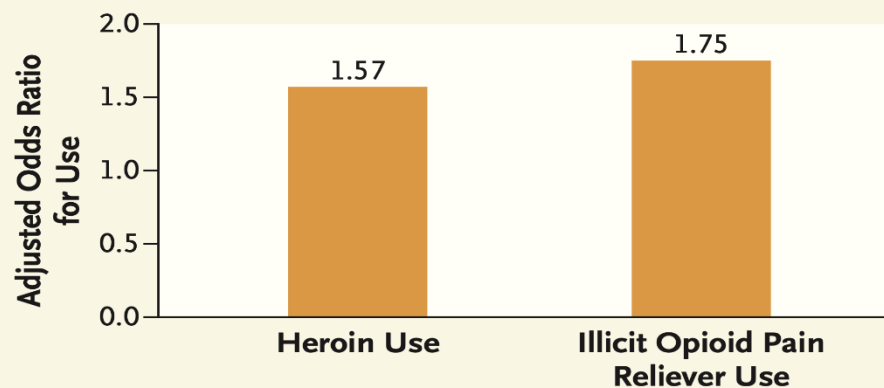


# Back to the Case: What to do with Bruce

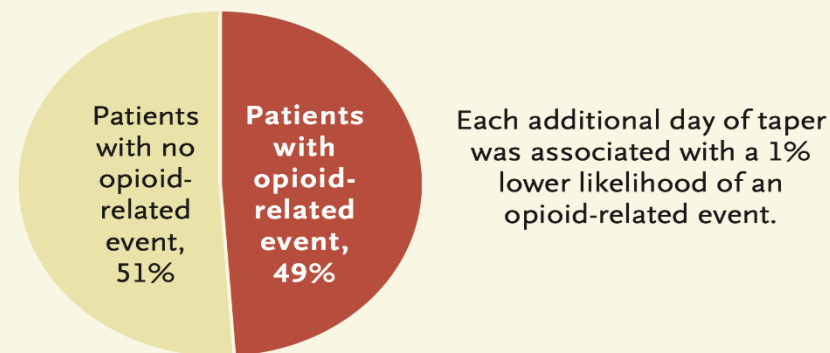
- ✱ Common approach: stop opioids when a patient is using stimulants
- ✱ Stimulants increase anxiety, which *should* increase pain and reduce opioid benefits anyway
- ✱ Concerns about potential diversion

# Risks of Stopping Opioids

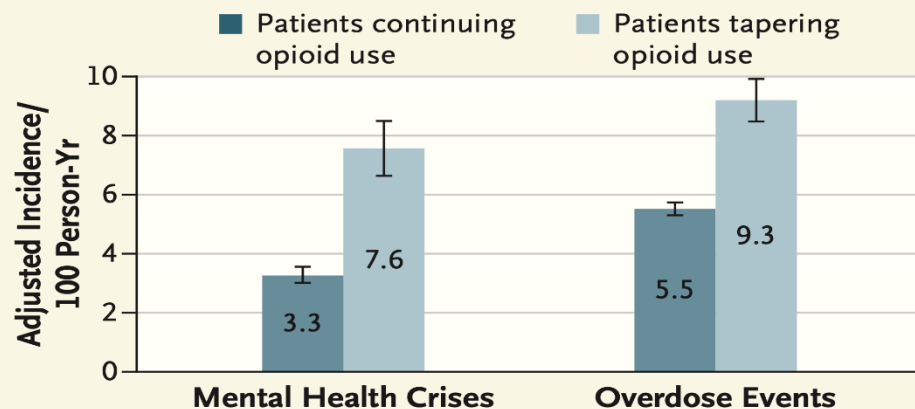
**A Illicit Opioid Use after Taper or Discontinuation of Long-Term Opioid Therapy**



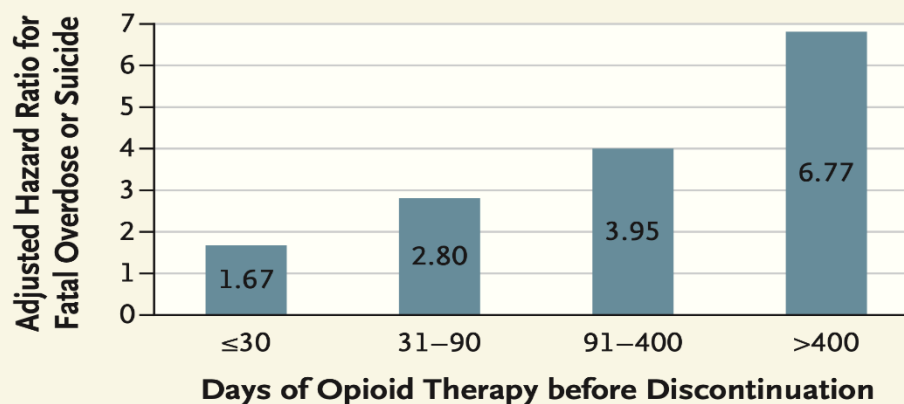
**B Emergency Department Visits and Opioid-Related Hospitalizations after Taper or Discontinuation of Long-Term Opioid Therapy**



**C Mental Health Crises and Overdose Events among Patients Continuing or Tapering Long-Term Opioid Therapy**



**D Death from Suicide or Overdose after Taper or Discontinuation of Long-Term Opioid Therapy**



# Back to Bruce: Alternative Response

- ☀️ Talk with patients about motivations for stimulant use
- ☀️ Consider neuropathic therapies (e.g., anticonvulsants that may also play a role in managing stimulant use disorders)
- ☀️ Multimodal pain management strategies

# Integrative Pain Management Program

- ☀ Tenderloin district, San Francisco
- ☀ 12w program with
  - ☀ Weekly “home group”
  - ☀ Physical movement, mindfulness, nutrition, medication education
  - ☀ Acupuncture, massage, health coaching
- ☀ 146 patients treated at IPMP
- ☀ Compared to controls who were awaiting care
- ☀ Mean daily MME=197
- ☀ Most with problematic substance use

	IPMP	Control
Pain interference	- 2.59	- 0.98
Pain intensity	- 0.78	- 0.01
Social satisfaction	+3.06	+0.58
Global mental health	+2.76	+0.32
Pain self-efficacy	+5.15	-2.11

# Should opioids be stopped?

- ☀️ Pause before considering a unilateral opioid taper
- ☀️ Draft 2022 CDC Opioid Prescribing Guideline:
  - ☀️ “Clinicians should not dismiss patients from care based on a toxicology test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids or other drugs from alternative sources and the clinician missing opportunities to facilitate treatment ...”
  - ☀️ “Unless there are indications of a life-threatening issue, such as warning signs of impending overdose, e.g., confusion, sedation, or slurred speech, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages.”

# If Cutting Opioids: Patient-Centered Taper

1. Ask patient about risks/benefits of opioids, review risks
2. Develop a plan WITH the patient
  - A. Validate patient experiences, recognize power dynamics, be flexible
  - B. Address related issues
    - ✱ Social (housing, finances, partner violence)
    - ✱ Mental health
    - ✱ Alternative pain management strategies
  - C. Discuss the risks of tapering
  - D. Have patient determine which medications to taper and at what rate
  - E. Always consider buprenorphine

# Does the patient have a stimulant use disorder?

- ☀ Review DSM-V criteria
- ☀ Consider available treatment options:
  - ☀ CBT
  - ☀ Contingency management
  - ☀ Off-label use of medications such as bupropion, mirtazapine, ER-naltrexone, topiramate

# What about prescribing stimulants?

- ☀ Some data that methylphenidate, amphetamines, modafinil increase abstinence from cocaine and methamphetamine
- ☀ Long-acting/abuse deterrent formulations generally preferred
- ☀ Concerns include diversion/adherence, cardiac conditions
- ☀ Best data for co-morbid ADHD; maybe co-morbid chronic pain?



# Final Takeaways/Summary

- ☀ Stimulants have analgesic properties, particularly for pain with neuropathic elements, and may augment opioid-induced analgesia while reducing side effects
- ☀ Pain self-care may motivate stimulant use, although this may extend to use of multiple other substances, and may have transient benefits and/or be entangled with social pain
- ☀ A positive urine drug screen for stimulants in a patient prescribed opioids for chronic pain should lead to a discussion with the patient, rather than automatic taper/discontinuation of opioids
- ☀ Multimodal chronic pain care is needed
- ☀ Future pain management strategies might consider neurotransmitters involved in stimulant-related analgesia

# Acknowledgments

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- ☀️ Participants for sharing their voices
- ☀️ Research team at the Center on Substance Use & Health

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