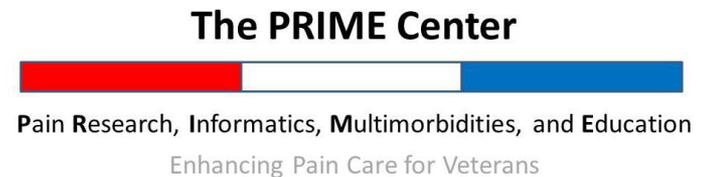


Distinguishing between the effects of prescription vs. synthetic/illicit opioids

Sequelae of opioid addiction, co-morbid mental health conditions, suicide risk

William C. Becker, MD



Questions to Discuss

Distinguishing between the effect of prescription vs synthetic/illicit opioids

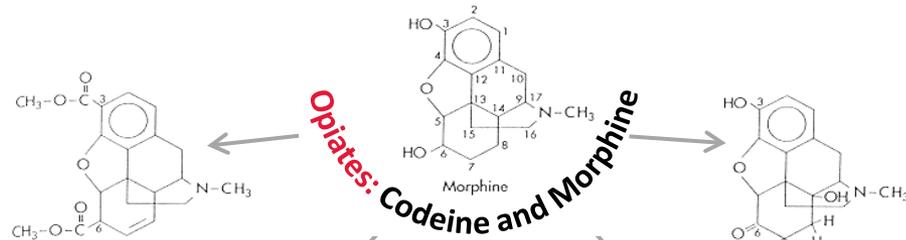
- How prevalent is synthetic/illicit use with prescribed opioid use, especially as it relates to mortality? Is there a difference in rates in the Veterans vs non-Veterans populations?
- Given the higher risk of death/overdose with use of synthetic/illicit opioids, what adjustments should the committee consider in the design and analysis of a study focused on prescribed opioids?

Sequelae of opioid addiction, co-morbid mental health conditions, suicide risk

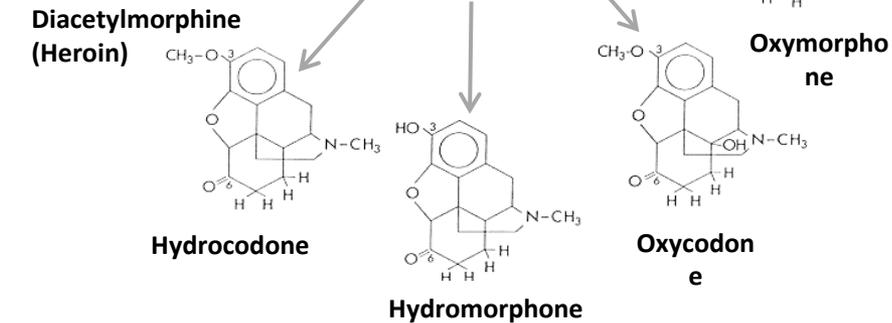
- For patients prescribed opioids, what is the likelihood of opioid addiction?
- How is addiction impacted by co-morbid conditions?
- How do these factors and the intersection of these factors impact suicide risk?

Opioids: Natural, Semi- and Synthetic

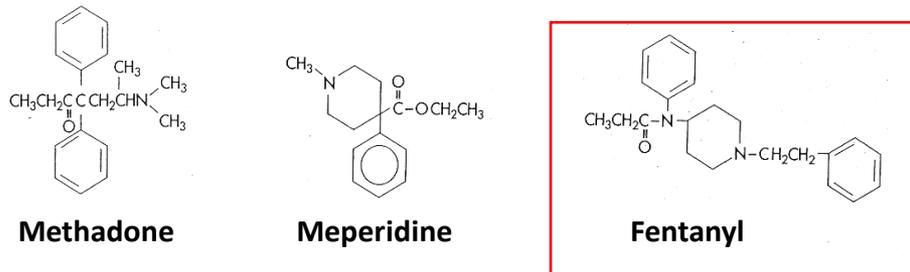
Natural (Opiates)



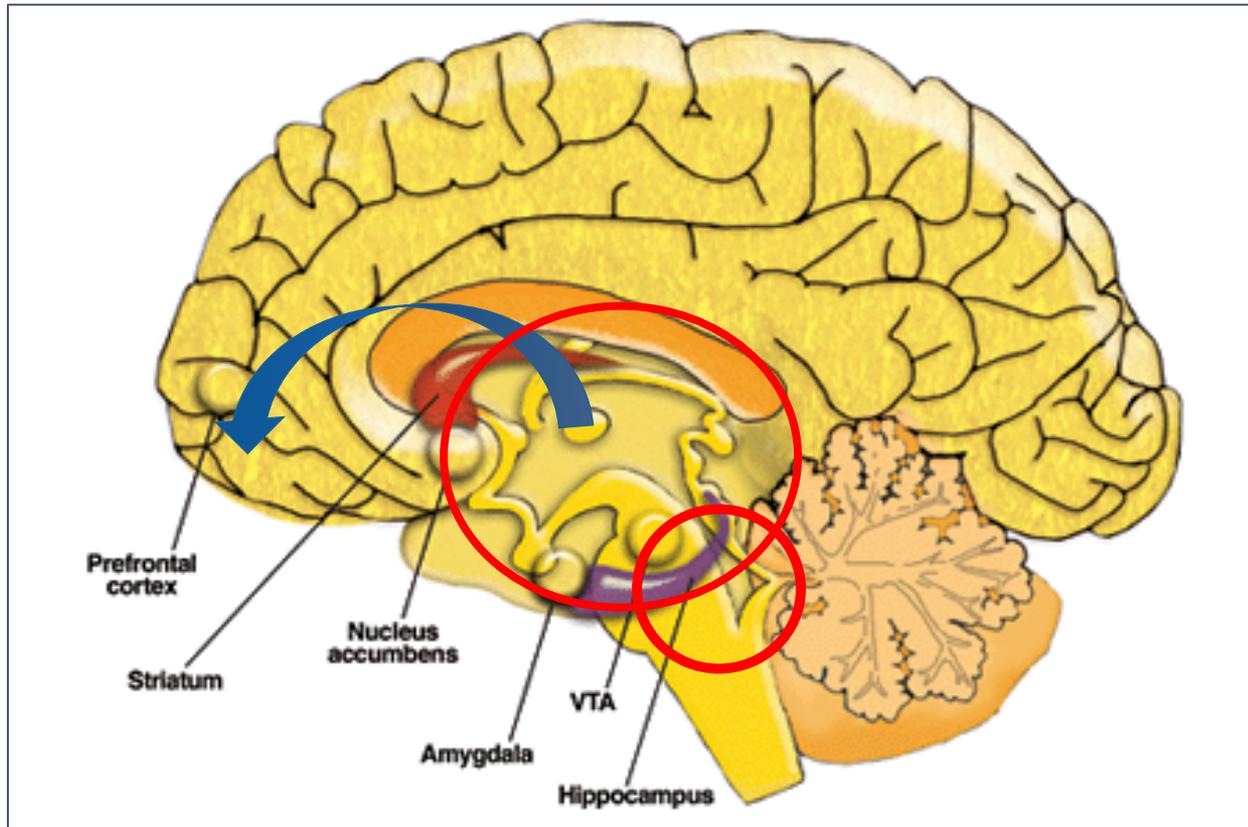
Semisynthetic



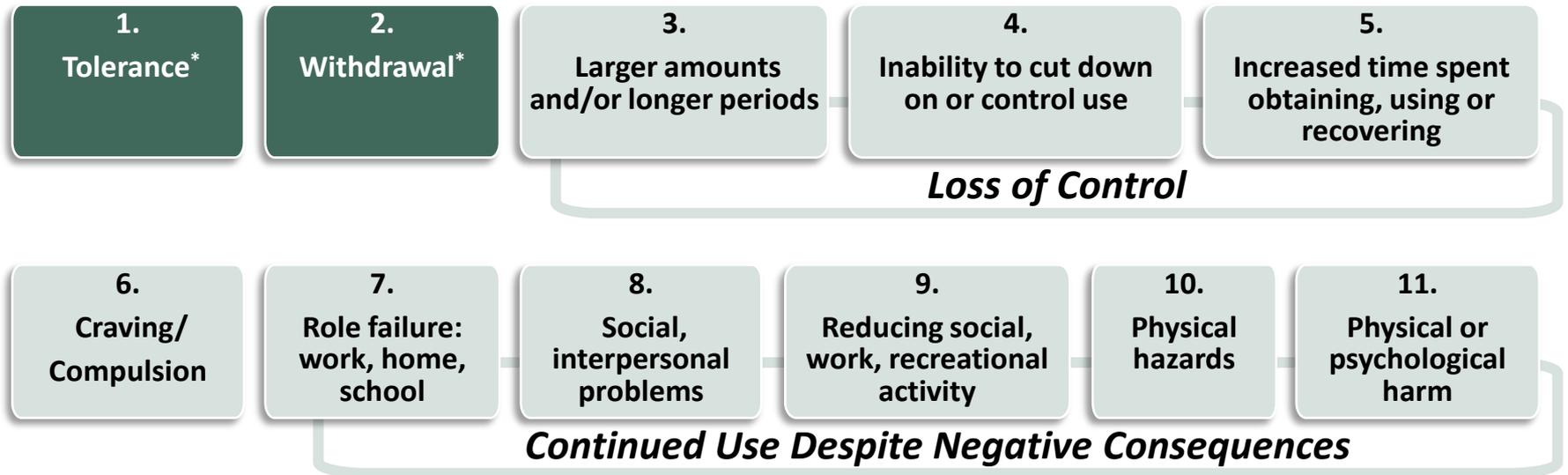
Synthetic



Blood-brain Barrier: Reward and Risk



Opioid Use Disorder (OUD): Criteria



*This criterion is not considered to be met if taking opioids under appropriate medical supervision

Mild OUD: 2-3 Criteria
Moderate OUD: 4-5 Criteria
Severe OUD: ≥ 6 Criteria

APA. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.)

Problematic Opioid Use in Long-term Opioid Therapy for Chronic Pain

Systematic Review of 38 Studies (26% primary care, 53% pain clinics)

Misuse rates: 21% - 29%

(95%CI: 13%-38%)

- **Misuse:** Use contrary to the prescribed use, regardless of the presence or absence of harm or adverse effects

Addiction rates: 8% - 12%

(95% CI: 3%-17%)

- **Addiction:** Pattern of continued use with experience of, or potential for, harm

Vowles KE, et al. *Pain*. 2015

from Boston University SCOPE of Pain, with permission

Medication Factors Increasing Risk

Medication Factors	Risk	
Daily dose >100 mg morphine equivalents	Overdose	OUD
Long-term opioid use (>3 months)	Overdose	OUD
Extended release/long-acting (ER/LA) opioid formulation	Overdose	
Initial 2 weeks after starting ER/LA opioid	Overdose	
Combination opioids and benzodiazepines	Overdose	

Volkow ND, et al. *N Engl J Med*. 2016

from Boston University SCOPE of Pain, with permission

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Small Group of Patients with Rapidly Escalating Trajectory

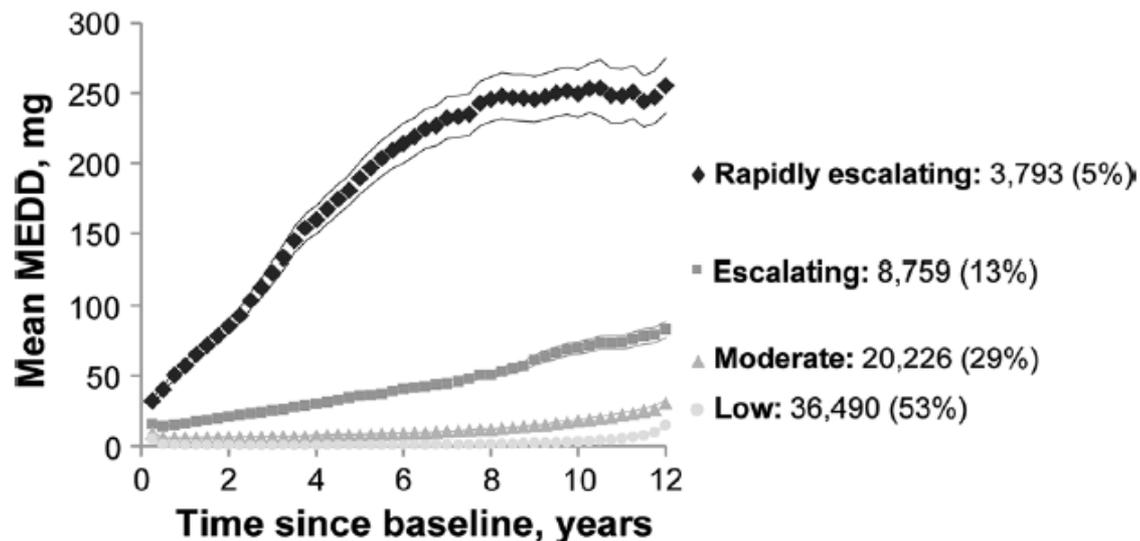


Fig. 2 Prescription opioid dose trajectories among 69,268 opioid-exposed patients in the US Veterans Aging Cohort Study 1998–2015

Rentsch, et al. *AIDS & Behavior*. 2019

Patient-related Risk Factors

Patient Factors	Risk	
Mental health disorder (e.g. depression, anxiety)	Overdose	OUD
Substance use disorder (e.g., alcohol, tobacco, illicit and prescription drug)	Overdose	OUD
Family history of substance use disorder		Misuse
Adolescent		OUD
Age >65	Overdose	
Sleep-disordered breathing	Overdose	
Legal history (e.g., DUI, incarceration)		Misuse
History of overdose	Overdose	

Akbik H, et al. *J Pain Symptom Manage.* 2006
 Ives J, et al. *BMC Health Serv Res.* 2006
 Liebschutz JM, et al. *J Pain.* 2010

Michna E, et al. *J Pain Symptom Manage.* 2004
 Reid MC, et al. *J Gen Intern Med.* 2002
 Volkow ND, et al. *N Engl J Med.* 2016

from Boston University SCOPE of Pain, with permission

OD: Other important physiologic and clinical considerations

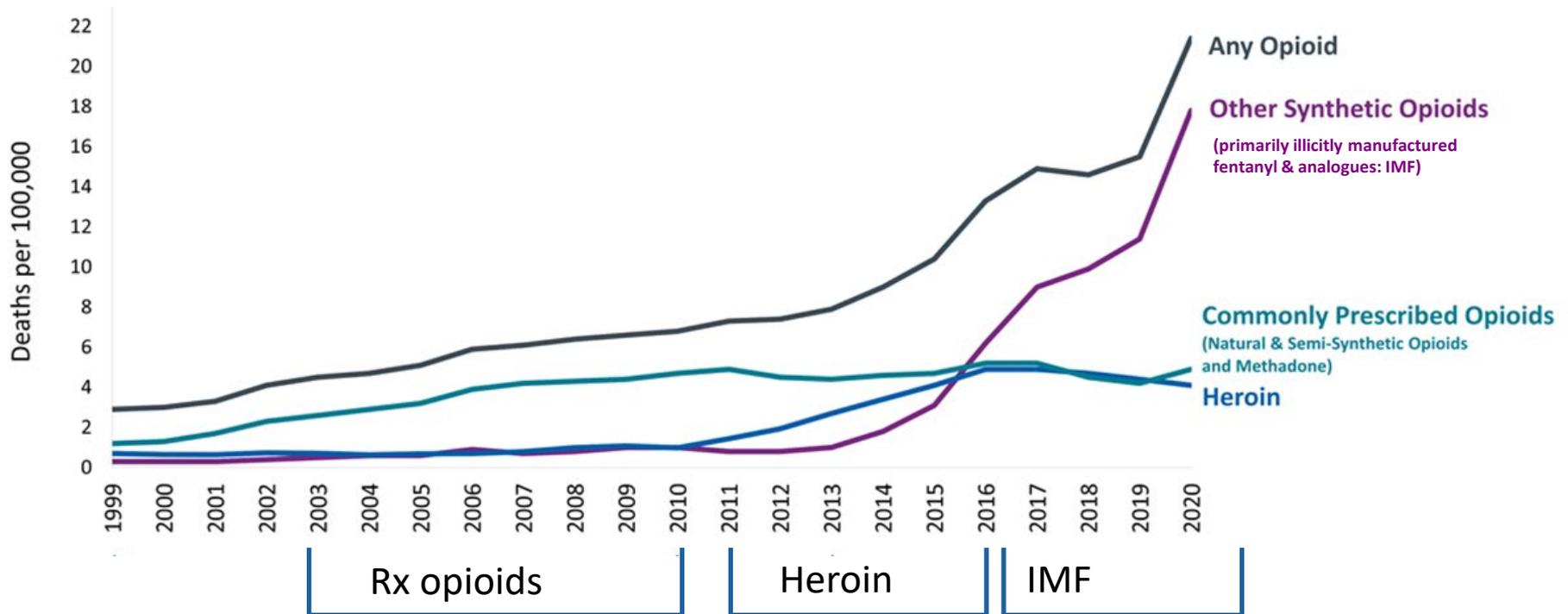
- Salience, expectancy, context of use matter; pain is not protective
- Adverse social determinants of health, life stressors, trauma impact risk, severity, treatment outcomes
- Co-occurring mental health conditions (other SUDs, mood, anxiety disorders):
 - Shared genetic, neurophysiologic and environmental roots
 - Highly co-prevalent
 - Impact severity and complexity of clinical presentation
- Acute and chronic pain both highly co-prevalent

Volkow ND, et al. *N Engl J Med.* 2016

Ballantyne & Mao, et al. *N Engl J Med.* 2003

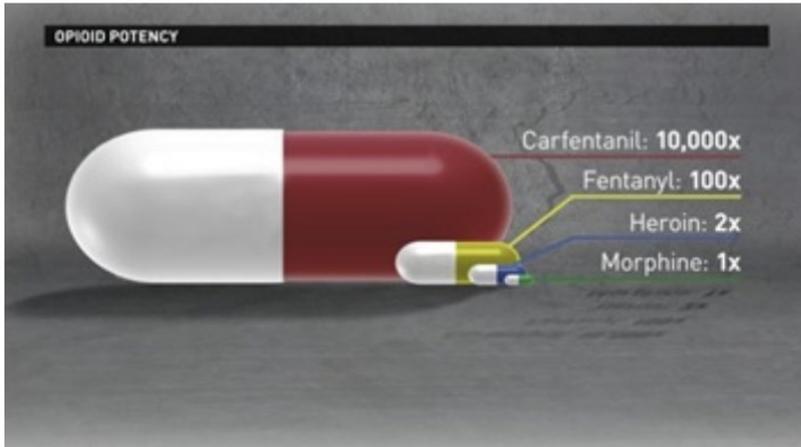
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Trends in U.S. Opioid Overdose Deaths



www.cdc.gov/drugoverdose

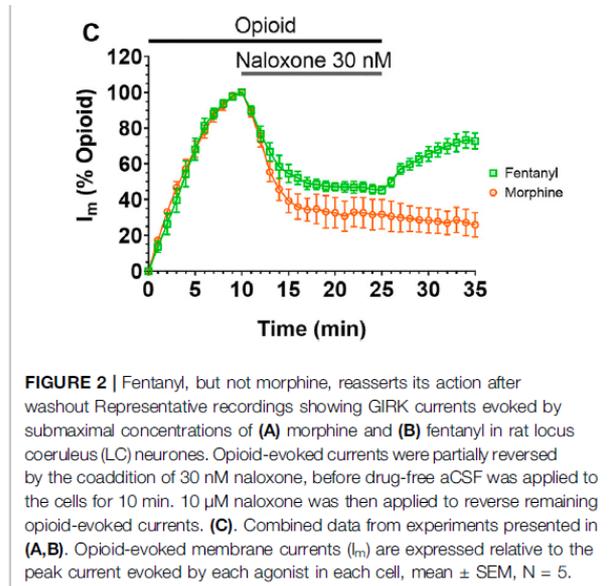
IMF: Potent, Lethal, Unpredictable



April 2, 2018: Inadvertent Overdose in First Responders.
Emergency Medicine News

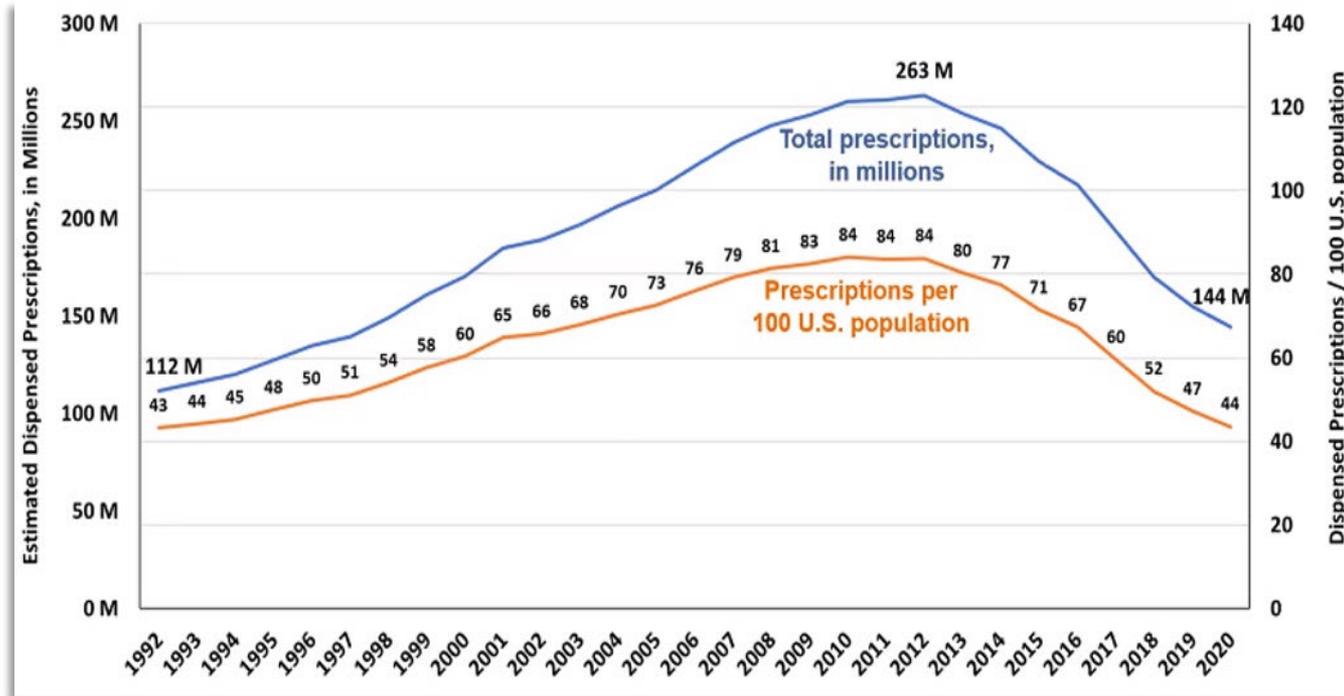


www.dea.gov



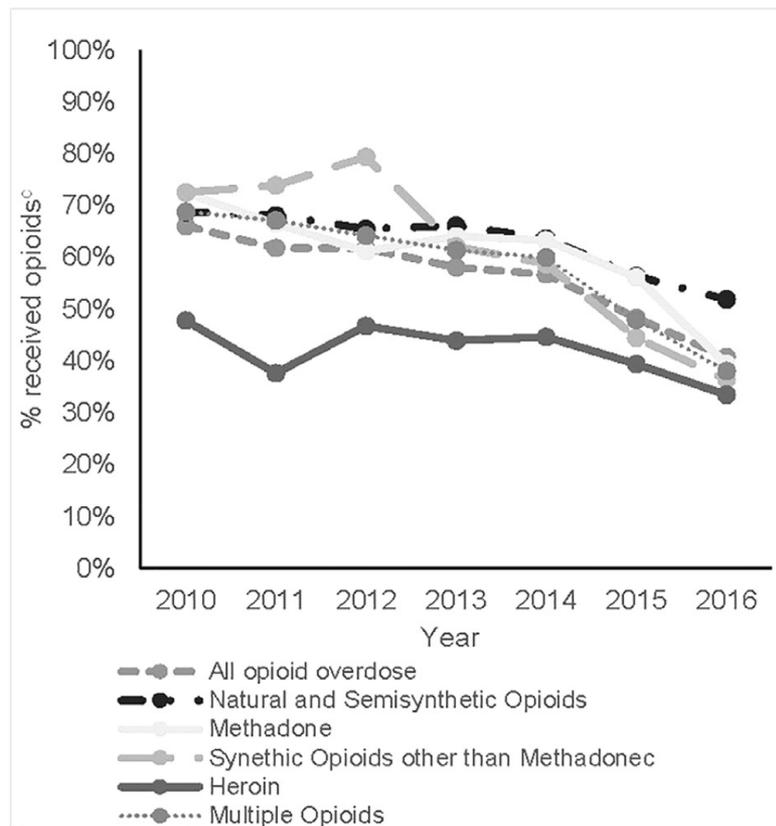
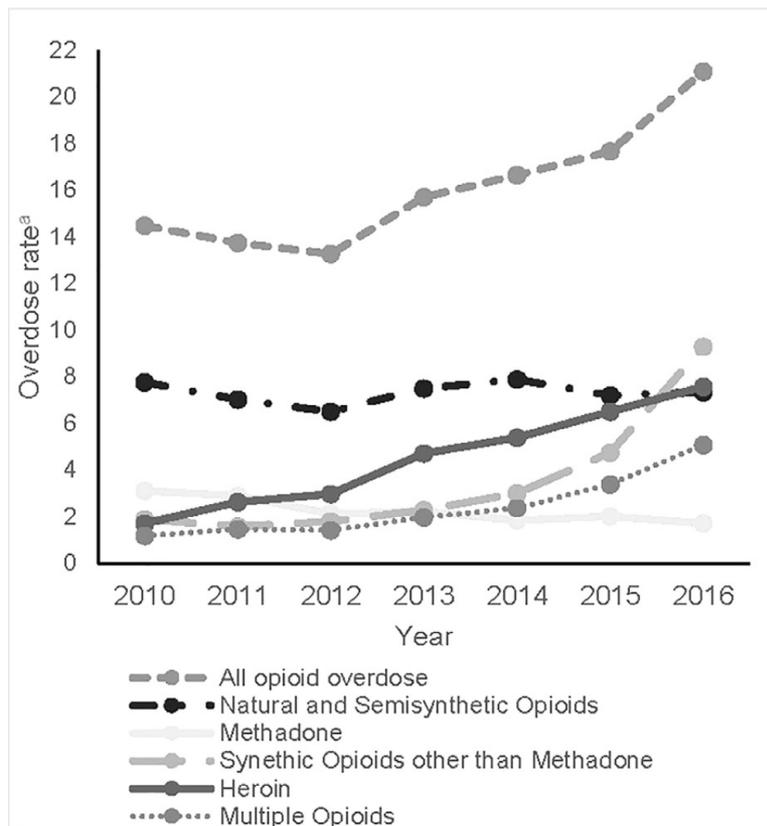
Sutcliffe et al. *Advances in Drug and Alcohol Research*, 2022

Decline in U.S. Opioid Prescribing



www.fda.gov

Similar Trends in Veterans Health Administration



Lin et al / Am J Prev Med 2019;57(1):106–110

Decreased prescribing but increased overdose

Individuals prescribed opioids: Cohort effect with time lag

- Development of OUD → misuse of one's own prescription or transition to higher potency illicit sources (heroin, IMF)
- Development of physiologic opioid dependence → prescription abruptly discontinued → accessing higher potency illicit sources

Individuals who use opioids without a prescription

- Over time, increasing likelihood of exposure to increasingly lethal opioids earlier in opioid-taking careers
- Possibly even first use

Suicide and Opioid Use and Pain

- Opioid use disorder associated with increased risk of suicide¹
- Higher dose opioid therapy increased with increased risk of suicide¹
- Painful diagnoses associated with increased risk of suicide¹
- In chronic pain:
 - Evidence for non-opioid treatments as effective, safer for initial therapy
 - Persons already on opioids require separate considerations

¹Bohnert and Ilgen, NEJM. 2019

Effectiveness of Opioids for Pain

- Minor post-surgical pain (e.g. dental extractions) → non-opioids superior¹
- Minor emergency department pain (e.g. ankle sprain) → non-opioids superior²
- Chronic non-cancer pain (e.g. low-back pain)
 - Equivalent benefit to non-opioids with significantly increased harms³
 - Benefit may wane over time despite dose escalations
 - Dose escalations may paradoxically worsen pain and have other potential harms (e.g. risk of invasive pneumococcal infection⁴)

¹Moore RA, et al. *Cochrane Library*. 2015

⁴Edelman EJ, et al. *JAMA IM*. 2019

²Busse, et al. *Annals IM*. 2020

³Krebs EE, et al. *JAMA*. 2018

What adjustments should the committee consider in the design and analysis of a study focused on prescribed opioids?

- As person-level “time to transition” to increased potency opioids may be highly variable (and evolve over several years), IMF- and heroin-associated deaths should have a long look-back period for prescription opioid exposure
- Accounting for out of system exposure
- Accounting for inpatient exposure
- Carefully considering periods of opioid discontinuation

Path forward

Implement evidence-based pain care

- Decrease new starts of opioids for chronic pain
- Increase availability/accessibility of evidence-based, non-pharmacological pain treatments
- Judicious use of non-opioid pharmacologic treatments
- Frame treatment around engagement in active modalities and whole person wellness
- De-implement ineffective long-term opioid therapy by offering choice of switch to buprenorphine vs. taper

Improve access to evidence-based Medications for Opioid Use Disorder

Improve access to harm reduction services and facilities in healthcare and non health care settings