An Overview of Opioid Use Disorders and Medication Assisted Treatment in Chronic Pain Conditions

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- I have no conflicts of interest to disclose.

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Objectives

- To provide a summary of the history and epidemiology of the current opioid crisis.
- To describe the neurobiology of opioid use disorders (OUD) and medications utilized to treat.
- To describe the implementation and outcomes related to OUD treatment in a primary care setting.

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Historical Background and Epidemiology

- 116 million people in the US suffer with pain – which is more than diabetes, cancer and heart disease combined[1]
- 1 in 5 adults have chronic pain[2]
- 1 in 14 adults have "high impact" pain[2]
- Annual health care costs – expenses, lost wages, productivity loss estimated to be $635 billion[1]

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Response to the Recognition of Chronic Pain in the Mid-90s

- Use of opioids increased substantially over the past 25 years despite limited evidence for efficacy in chronic non-cancer pain[3,4]
- Rise in opioids utilization corresponds to rise in opioid abuse and dependence – rates of opioid misuse (includes abuse and dependence as well as recreational use) estimated between 18 to 41%[5] and aberrant medication behavior as high as 50%[6]
- Prescriptions for opioids:
  - 1991 – 76 million
  - 2011 – 219 million[7]

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Fatal Drug Poisoning

- Between 1999 and 2002, the number of opioid analgesic poisonings on death certificates rose 91.2%
- In 2014 – 19,000 overdose deaths in the United States related to prescription opioids.

CDC MMWR Nov 4, 2011 60(43) 1487-1492

Paulozzi, L.J., Budnitz, D.S., Xi, Y, 2006. Increasing deaths from opioid analgesics in the United States. Pharmacoedidemiology and Drug Safety 15, 613-7.

Califf RM, Woodcock J, Ostroff S, 2016. A Proactive Response to Prescription Opioid Abuse. DOI:10. 1056/NEJMar1601307.

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Recognition of opioid overdose - Interventions

- CDC recognized crisis – 2007
- DEA shutters a number of pain clinics
- States developed PMP
- Health plans instituted new rules for opioids
- Medical boards increased investigations
- CDC issued further guidelines in 2016 which were interpreted often as mandates.
- Decreased initiation of opioids and often patients who were receiving long term chronic opioid therapy were abruptly cut off.

PO Coffin, AM Barreveld. N Engl J Med 2022;386:611-613.

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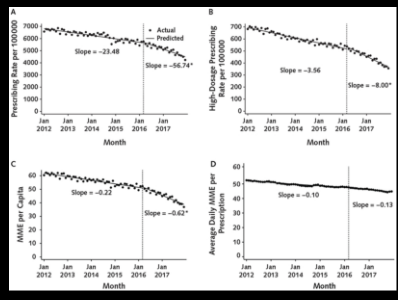
Rates of Prescribing[8]



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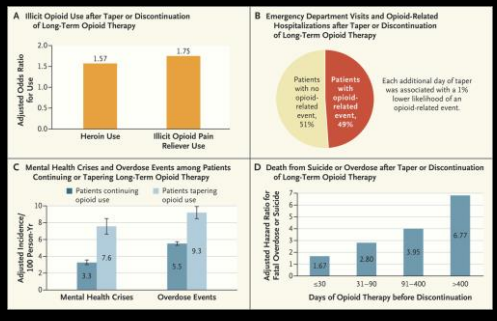
Risks Conferred by Tapering or Discontinuing Long-Term Opioid Therapy.



PO Coffin, AM Barreveld. N Engl J Med 2022;386:611-613.

The NEW ENGLAND JOURNAL of MEDICINE

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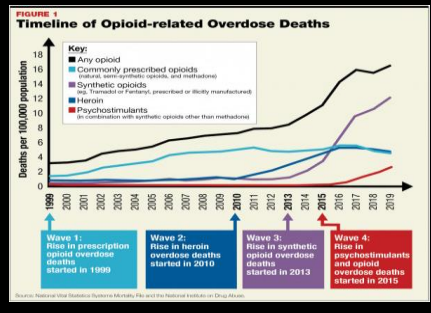
Rise of Overdose Deaths



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Current Situation – 4th Wave

- ”Legacy Patients” who have been prescribed COT – can’t get providers to continue medications
- We are now dealing with synthetic opioids that are 100-1000 x the potency of morphine
- High potency synthetic opioids are now evolving, less detectable and mixed with other substances which are increasing the OD potential – ie methamphetamine, xylazine, benzodiazepines

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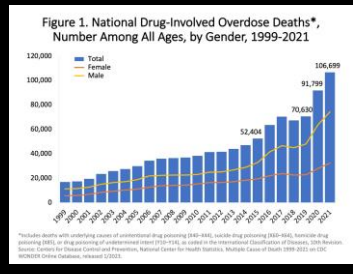
And Oh, by the way:



There were 111,355 overdose deaths in the 12-month period ending April 2023, compared with 110,394 deaths in the 12-month period ending March 2022.

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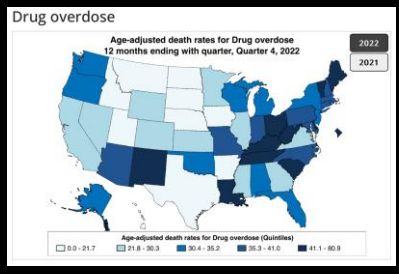
New Mexico Ranks 5th highest in country



Ahmad FB, Cisewski JA. Quarterly provisional estimates for selected indicators of mortality, 2022-Quarter 1, 2023. National Center for Health Statistics. National Vital Statistics System, Vital Statistics Rapid Release Program. 2023

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Opioid Use Disorder (OUD) and Addiction

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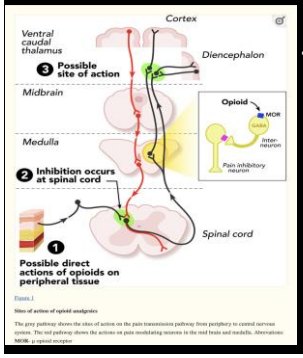
Opioid receptors/activity involved in Pain



- Four classes of opioid receptors:
  - mu*
  - delta
  - kappa
  - opioid receptor like

Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology. 2011 Dec;115(6):1363-81. doi: 10.1097/ALN.0b013e318238bba6. PMID: 22020140; PMCID: PMC3698859.

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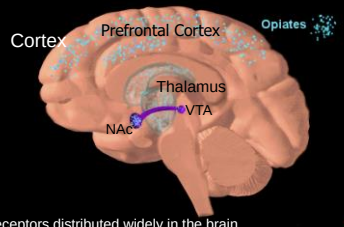
Etiology of Opioid Abuse: Neurobiology of Addiction



- Mu opioid receptors distributed widely in the brain.
- While binding in the thalamus produces analgesia, binding in the cortex produces impaired thinking/balance;
- Binding in prefrontal cortex contributes to an individual's decision about how important use of the drug is to him/her (salient value of the cue)
- Ventral tegmental area (VTA)/nucleus accumbens (NAc) is associated with euphoria that some experience (i.e. the "high")

Wise and Robble, Dopamine and Addiction, Ann. Rev. Psychol 2020 (71): 79-106
SAMHSA Buprenorphine training course

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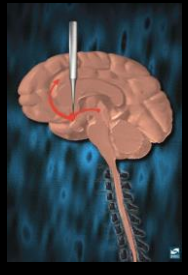
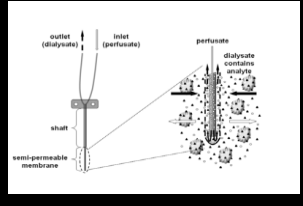
Discovery of reward pathway





Dopamine was measured – with significant elevations in the area of the probe with electrical stimulation.

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Natural Rewards

Food
Water
Sex
Nurturing

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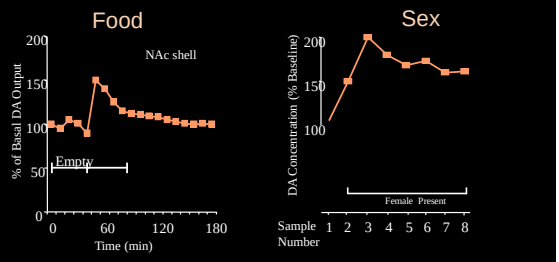
Natural Rewards Elevate Dopamine Levels



NIDA

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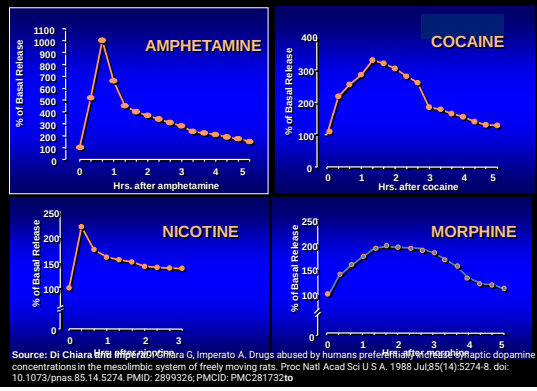
Drugs Elevate Dopamine Levels More or For Longer



Source: Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988 Jul;85(14):5274-8. doi: 10.1073/pnas.85.14.5274. PMID: 2899326; PMCID: PMC281732to

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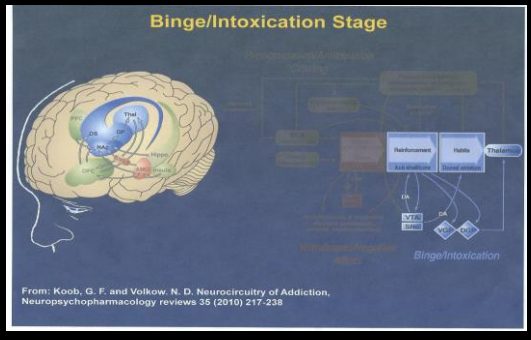
Binge/Intoxication Stage



From: Koob, G. F. and Volkow, N. D. Neurocircuitry of Addiction, Neuropsychopharmacology reviews 35 (2010) 217-238

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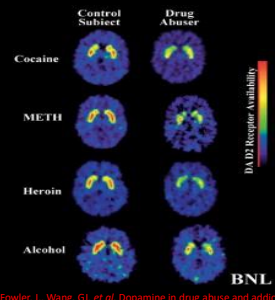
The Brain's adjustment for homeostasis – downregulation of receptors



Volkow, N., Fowler, J., Wang, GJ. *et al.* Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry* **9**, 557–569 (2004). https://doi.org/10.1038/sj.mp.4001507

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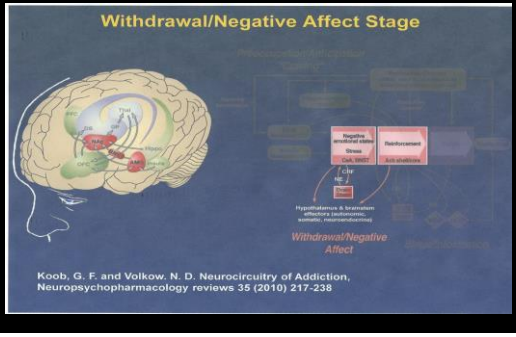
Withdrawal/Negative Affect Stage



Koob, G. F. and Volkow, N. D. Neurocircuitry of Addiction, Neuropsychopharmacology reviews 35 (2010) 217-238

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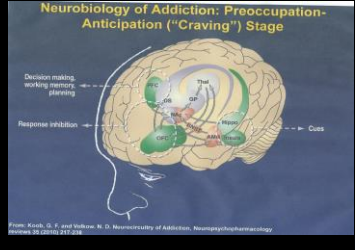
Neurobiology of Addiction: Preoccupation-Anticipation ("Craving") Stage



PFC and Orbital Frontal Cortex are involved in telling right from wrong, putting the brakes on bad behavior and inhibiting harmful behavior. In addiction these are impaired. Glutamate, is also released by the areas which are cue driven, and stimulates dopamine.

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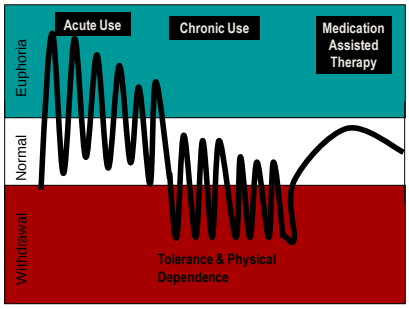
What this addiction cycle looks like



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Definition of Addiction – ASAM adopted in 2017

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment and an individual's life experience.
- People with addiction use substances or engage in behaviors that become compulsive and continue despite harmful consequences.
- Prevention and treatment approaches are generally as successful as those for other chronic diseases.

American Society of Addiction Medicine. (2011). Public policy state- ment: Definition of addiction. Chevy Chase, MD: Author. Retrieved from http://www.asam.org/quality-practice/definiti on-of-addiction

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DSM-5 Criteria

- Opioids taken in larger amounts, longer than intended
- Unsuccessful efforts to cut down or control use
- A great deal of time spent obtaining, using, or recovering from use
- Craving
- Recurrent use results in failure to fulfill work, home, school obligations
- Continued use resulting in interpersonal/social problems
- Recurrent use in hazardous situations
- Important social, occupational or recreational activities are reduced due to use
- Continues use despite knowledge of physical, psychological problems related to use
- **Tolerance and withdrawal: NOT criteria if opioids are used solely under appropriate medical supervision**

SEVERITY:
Mild (2-3)
Moderate (4-5)
Severe (≥6)

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Pharmacology of opioids

And Medications used for OUD

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Full opioid agonist:

- Full agonist binding activates the μ opioid receptor
- Additive effect when combined with other full agonists
- Is highly reinforcing and has higher potential for abuse
- Abrupt discontinuation will result in withdrawal
- Hydrocodone, hydromorphone, morphine, heroin, methadone[8]

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Opioid Efficacy in Chronic Pain

- Most literature surveys & uncontrolled case series
- RCTs are short duration <4 months with small sample sizes <300 pts
- Mostly pharmaceutical company sponsored
- Pain relief modest
- Limited functional improvement

Balantyne JC, Mao J. NEJM 2003
Kalso E et al. Pain 2004
Eisenberg E et al. JAMA. 2005
Furlan AD et al. CMAJ 2006
Martell BA et al. Ann Intern Med 2007

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Variability in Response to Opioids

Mu Receptor

- G protein-coupled receptor family, signal via second messenger (cAMP)
- >100 polymorphisms in the human MOR gene
- Mu receptor subtypes
  - Not all patients respond to same opioid in same way
  - Not all pain responds to same opioid in the same way
  - Incomplete cross-tolerance between opioids

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The Good and Bad about Methadone

Good

- Inexpensive
- Long acting to treat OUD
- No significant toxic metabolites
- No accumulation in renal disease
- NMDA antagonist
- Treatment in a structured setting
- Have shown: reduction in illicit use, criminal activity, HIV infection, overdose, improvement in health, retention in treatment and suicide rates

Bad

- Highly variable metabolism
- Unpredictable half-life
- Conversion to other opioids is a challenge/unpredictable equipotency
- QTc prolongation
- Multiple drug interactions
- Sleep apnea/respiratory suppression
- Limits geographically to clinic
- Stigma
- Perceived as outside the medical mainstream

Miller, S et al, ASAM Principles of Addiction Medicine, sixth edition 2019, chapter 57

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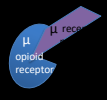
Partial opioid agonist: Buprenorphine



- Partial agonist binding activates the μ opioid receptor and kappa antagonist
- Competitive agonist with high binding affinity/slow disassociation
- Is less reinforcing than full agonists (lower risk for abuse)
- Abrupt discontinuation will result in withdrawal
- Available as sublingual, buccal, transdermal, and injection

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The Use of Buprenorphine/Naloxone to treat co-occurring pain and opioid dependence

- Buprenorphine/Naloxone:
  - Partial opioid agonist
  - In 2002, Drug Abuse Treatment Act approved sublingual formulations of buprenorphine for treating opioid addiction
  - Effectively treats opioid addiction by reducing illicit opioid use, improving treatment retention (55-60%)[9], and increasing negative urine toxicology screens[10]
  - Buprenorphine is considered to produce analgesia at least 30 times the potency of morphine.[11]
  - Mainstreaming Addiction Treatment Act of 2022 expanded ability of all healthcare providers with standard controlled substance license to prescribe buprenorphine eliminating the X-waiver.[12]

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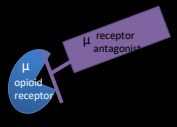
Opioid antagonists: Naloxone and Naltrexone*



- Antagonist binding to the μ opioid receptor occupies without activating
- Is not reinforcing
- Blocks abused opioid agonist binding

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Naltrexone

- Opioid antagonist
  - Binds competitively, but blocks opioid effect
- As oral tablet usual dose is 50 mg daily
  - t ½ = 14 hours, 50% blockade gone after 72 hours
- Comes in depo form – 380 mg IM every 4 weeks
  - Peak plasma concentration in 2-3 days, declines in 15 days
- Blocks opioid analgesia – blockade can be overcome with 6-20x the usual dose of opioids without significant respiratory depression
- Will not be effective for pain control
- Decreases cravings and useful in stable patients for relapse prevention.

Alford, D, Managing Acute and Chronic Pain in Patients on MAT, PCSS-Mat Webinarm Aug. 12, 2014

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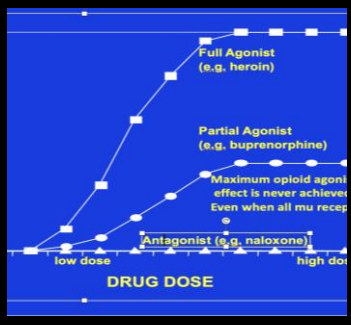

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The following slides are from my previous work at both the New Mexico VA Hospital and University of Colorado.

This work was published in 2012 and also presented at ASAM national conference in 2015.

Pade PA, Cardon KE, Hoffman RM, Geppert CM. Prescription opioid abuse, chronic pain, and primary care: a Co-occurring Disorders Clinic in the chronic disease model. J Subst Abuse Treat. 2012 Dec;43(4):446-50. doi: 10.1016/j.jsat.2012.08.010. Epub 2012 Sep 11. PMID: 22980449.

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Today's Problems with Treatment Delivery

- Providers:
  - Addiction providers uncomfortable treating pain
  - Pain Management providers uncomfortable treating addiction
  - PCPs uncomfortable treating both and PCPs prescribe the opioids
  - Lack of training of providers in addiction
  - Regulations surrounding opioids
  - Perceive patients as difficult and time-consuming.
- Patients
  - Stigmatization to addiction
  - Believe pain is primary problem not addiction
  - Fear their pain will not be addressed
  - SUD programmatic treatment is overwhelming
  - Not ready for treatment
  - Many will agree to treatment in Primary Care but are reluctant to go psychiatric facility.

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Improvement Change: Creation of Co-occurring Disorders Clinic (CODC)

- Establishment of unique clinic within Ambulatory Care Service to evaluate, treat, manage and monitor co-morbid pain and addiction:
  - High risk opioid patients
    - history of substance use disorder
    - family history of substance use disorder
    - younger age
    - psychiatric illness
  - Noncompliant patients
  - Complex pain regimens
  - Prescribed high dose opioids

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CODC Clinical Activities

- Pain Medication Assessment
- Substance Use Disorder Assessment
- Psychiatric Assessment
- Opioid use Risk Assessment
- Opioid use Monitoring
- Buprenorphine/Naloxone treatment for opioid dependence
- Complex Pain Medication Management
- Adjuvant treatments: TENS units, intra-articular injections, trigger point injections
- Motivational Interviewing
- Supportive Counseling
- Overdose counseling and Narcan training

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Opioid Risk Assessment And Monitoring

- Risk:
  Detailed History, Physical Exam and Chart Review
  Screening tools: SOAPP, BPI, ORT, DIRE instrument administration
  Collateral information with patient consent
- Monitoring: Frequency of visits determined by risk
- Extensive urine toxicology screening
- State Prescription Monitoring Program Access and Query with consent
- Detail chart review
- COMM instrument administration

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CODC Data and Outcomes Over 1.5 years

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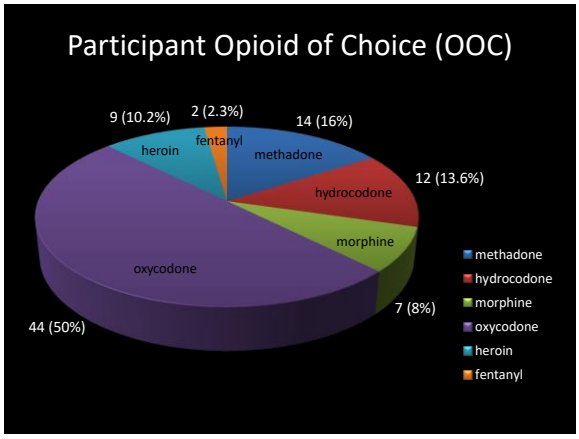

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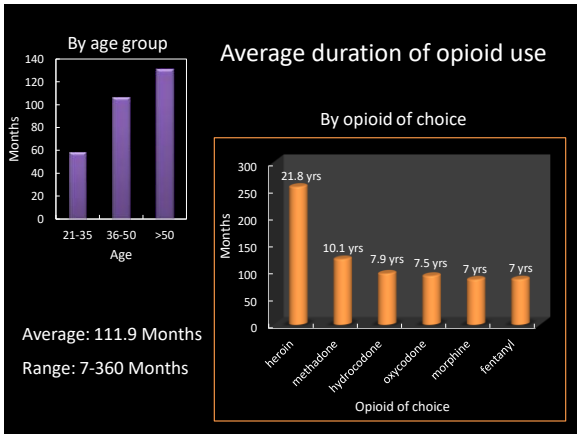

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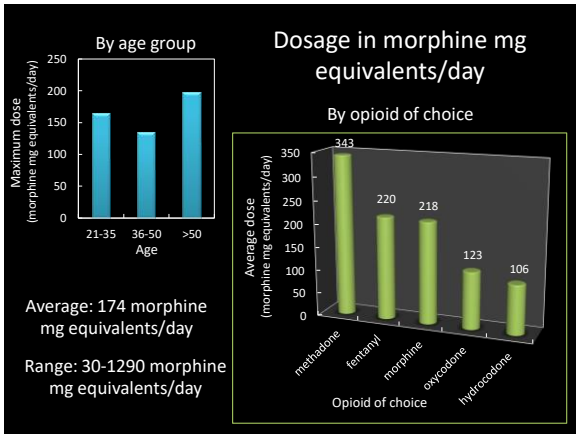

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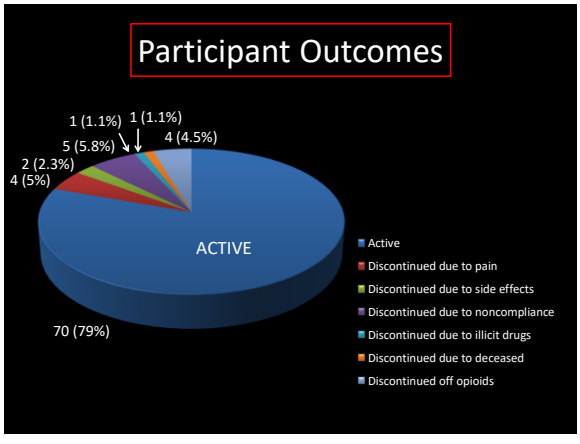

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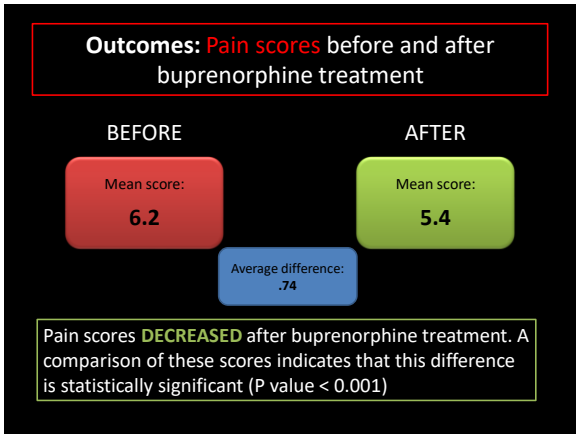

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Two Last Thoughts

Stigma

- Effects chronic pain patients and people with SUD
- Leads to poor outcomes and not getting effective treatment.
- Systemic issue in the health professions

NIDA. 2022, June 1. Stigma and Discrimination. Retrieved from https://nida.nih.gov/research-topics/stigma-discrimination on 2024, January 6

SUDs as a pediatric disease

- Median age of initial use of substances in adults is 16.
- Earlier onset of substance use predicts greater addiction severity and morbidity.
- Please tell your patients to safely secure all controlled substances!

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Develop- mental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. The American Journal of Psy- chiatry, 160(6), 1041-1052.

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4. Chabal, C., M. K. Erjavec, et al. (1997). "Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors." Clin J Pain 13(2): 150-155.
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