

Opioid Use Disorder Education and Treatment ECHO Series

ECHO #1 - Medical Comorbidities

November 2, 2021

Kurt DeVine, MD, and Heather Bell, MD
Family Medicine and Addiction Physicians



MINNESOTA ACADEMY OF
FAMILY PHYSICIANS

STRONG MEDICINE FOR MINNESOTA

Medical Comorbidities Objectives:

- Differentiate the medical diagnosis that increase the risk of taking opioids
- Identify the medications that increase the risk of taking opioids
- Describe medical complications that can occur if a patient is on chronic opioids

Mental Health

Depression

- Increased risk of death, especially at higher doses
- Investigations were unable to separate unintentional OD vs. suicide
 - Turner B; Liang Y. J Gen Intern. Med. 2015;30:1081-96.



Substances/Medications

History of Substance use Disorder

- 2-4x more likely to OD than patients without history of substance abuse

CBC Guidelines References (66,24,23)

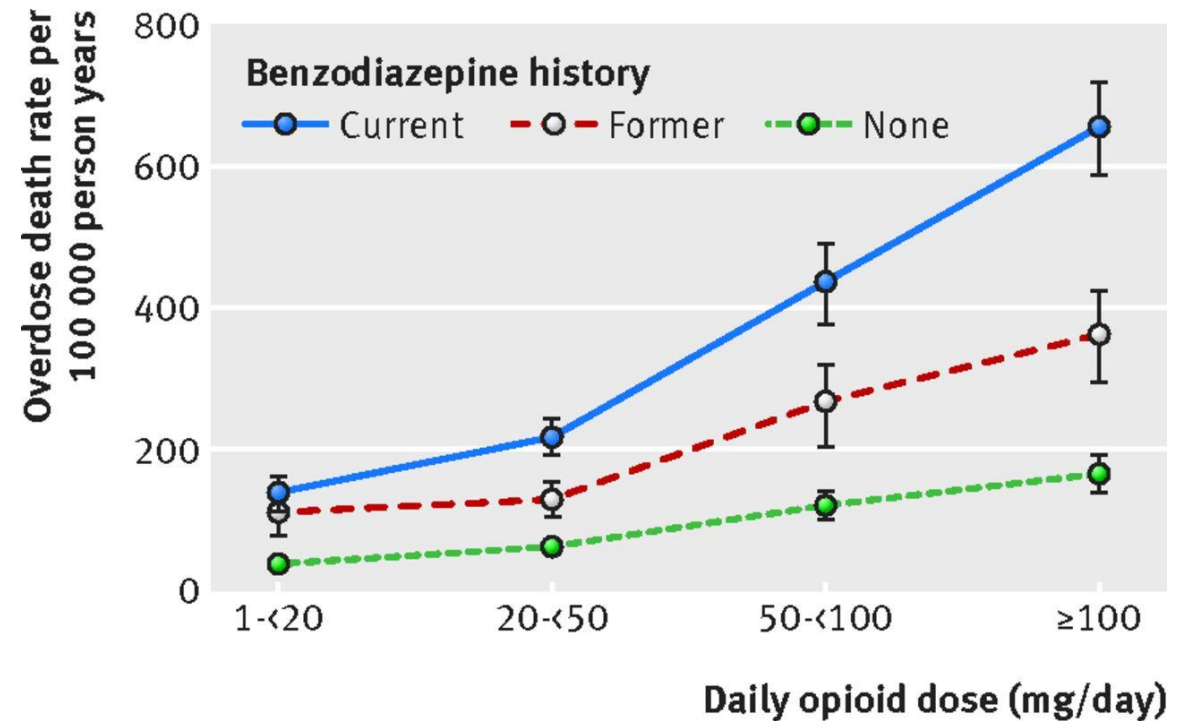


Benzodiazepines

Benzodiazepines

- Three separate studies of opioid overdose found evidence of concurrent benzodiazepine use in 31-61% of deaths

CDC (67,128,129)



Park et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350.

Benzodiazepines

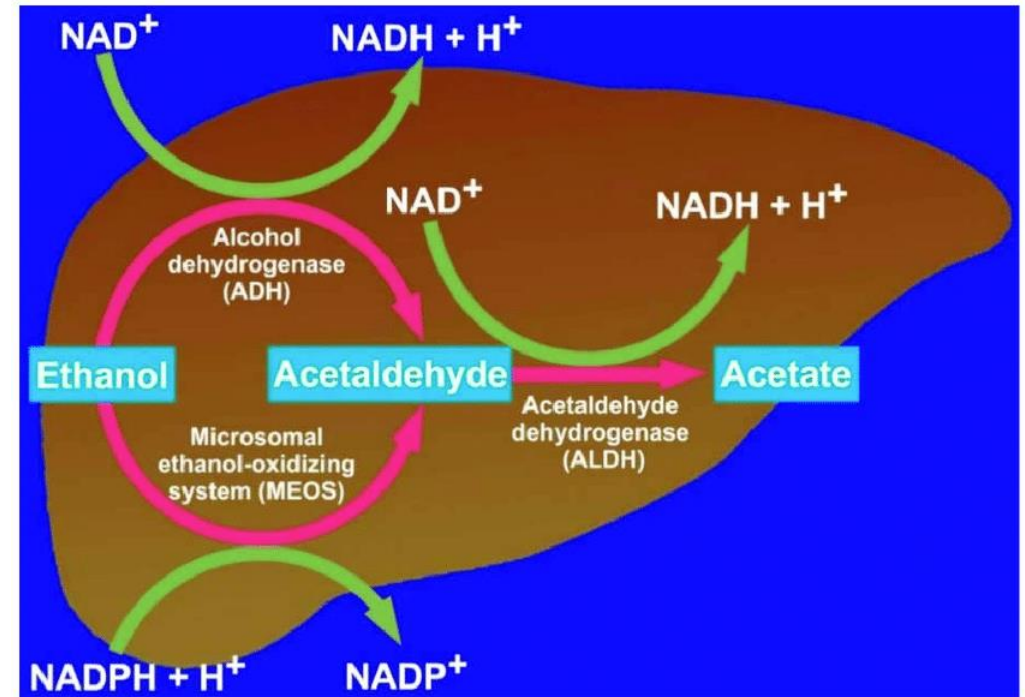
- Most common cause of polysubstance overdose fatality is combination of opioids and benzos
- Patients taking:
 - Alprazolam + Oxycodone = risk of death 10X greater than a person taking neither medication



Alcohol

Alcohol

- Microsomal ethanol oxidizing system (MEOS)
- ETOH and opioids metabolized in part by the hepatic MEOS system
- Separately they augment MEOS system
- Together slower disposals rates = increased toxicity



Alcohol

- Ethanol may modify some opioid receptors and also the effects of opioids
- Patients with OUD and patients on methadone have unusually high rates of AUD

J. Advances in Alcohol and Substance Use



Alcohol

- Involved in 18.5% of opioid abuse ER visits and 27.2% of benzodiazepine related visits
- ETOH related to 20% of OD deaths with opioids or benzos

MMWR Oct 10, 2014. 63(40)881-885.



Alcohol

- Ethanol and oxycodone cause greater ventilation depression than either alone
- Magnitude is clinically relevant
- Older adults more affected

Effects of Ethanol and Oxycodone. Anesthesiology (126)3:534-542.March 2017



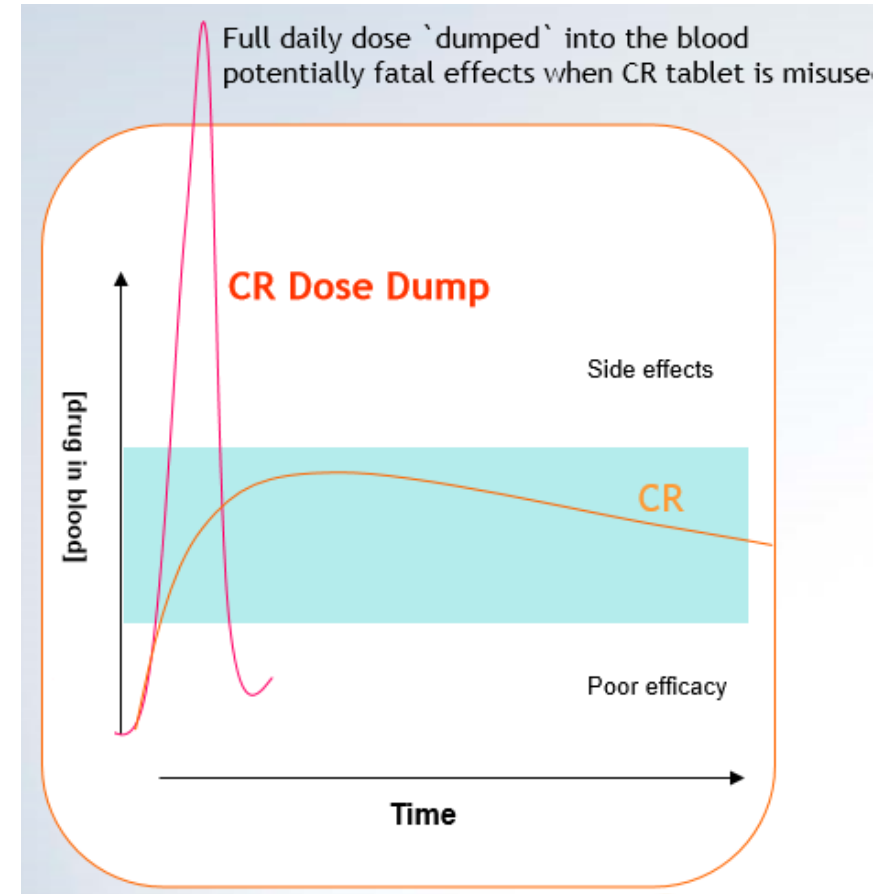
Alcohol

- Major concern with alcohol + opioids is possibility of “dose dumping”
- Dose Dumping:
 - Unintended rapid release of the entire amount or a significant fraction of the drug from an ingested dose



Alcohol

- Alcohol is linked to dose dumping across specific long-acting opioid formulations
- Results of which are:
 - Increased OD potential
 - Increased abuse potential



Akhmad, AS. Dose Dumping. Clinical Pharmaceutical. Nov 2017.

Alcohol

- One Hydromorphone ER capsule mixed with alcohol causes a 16-fold increase in plasma concentration
- Mechanism is poorly understood

Risk, Management and Monitoring of Combination
Opioid, Benzodiazepines, and or Alcohol Use.
Post Grad Med. 2013 July.



Cough Syrup

Cough Syrup

- FDA: “The risks of slowed or difficult breathing, misuse, abuse, addiction, overdose and death with medications outweigh the benefits in patients younger than 18”
- Cough syrup as a cough suppressant is not supported by available evidence

Current Opinion Allergy Clinical Immun.2007 Feb 7(1)32-36



Cough Syrup

- Neither codeine nor hydrocodone had any effect on cough duration or intensity in the study

Wester Journal of Med. 2000 Oct 173(4)283



Cough Syrup

- Norman Edelman, MD, CMO at American Lung Association:
“We’ve never had good evidence that cough suppressants and expectorants help with cough...”
- Study on 270 children:
“Children who received honey coughed less frequently, less severely, and were less likely to lose sleep due to the cough when compared to other treatments”

Cough Syrup

Cough syrup

+

=

Pop, jolly ranchers,
beer or wine coolers

Purple drank

Sizzurp

Lean

Purple

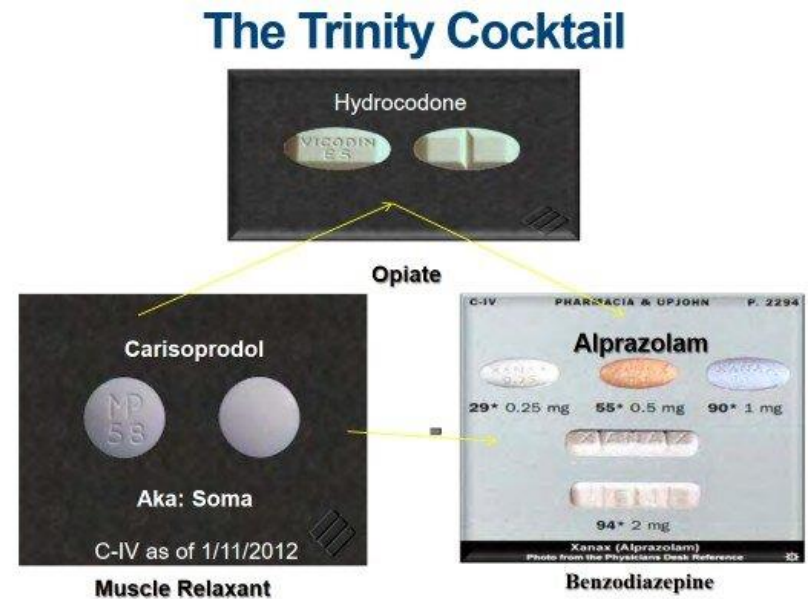


Soma

Soma

- Opioids + Alprazolam + **SOMA** = “*Holy Trinity*”
- Combination can be addictive and result in significant respiratory depression
- Major metabolite is meprobomate
 - Acts like a barbiturate

The Perfect Storm: Opioid Risks and The Holy Trinity. Pharmacy Times. Sept. 24, 2014



“Z”-Drugs

Z-Drugs

- 2016- Black Box Warning (for opioid co-use)
- Adding a z-drug to opioids:
 - Increased the risk of unintentional OD by nearly 4X in the first 30 days of prescription



The risk of overdose with concomitant use of z-drugs and prescription opioids. Am J Psychiatry. 2021 July; 178(7)643-650.

Age

Older Adult Definition

MUCH “OLDER” than
Kurt?

Poll....?



Older Adult

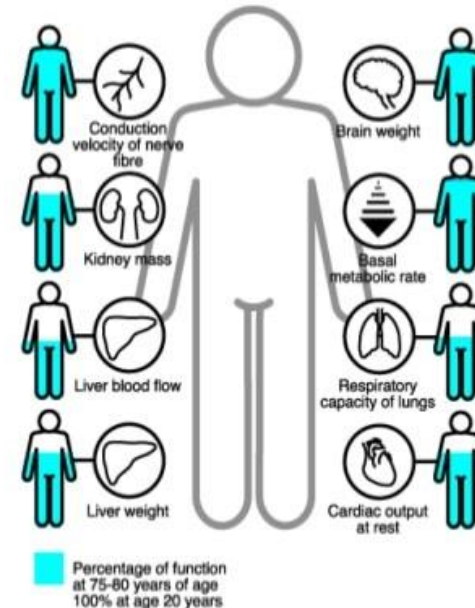
- 4X more likely to fall on opioids than on NSAIDs
- First 14 days from initiating opioids, risk of fall 4.5X



Older Adult cont.

- Things to think about in the elderly receiving opioids:
 - Decreased distribution volume
 - Liver metabolism is often decreased
 - Renal excretion often compromised
 - Age often is related to all polypharmacy

Effect of Aging on Body Physiology



- **Decrease in :**
 - Conduction velocity of nerves
 - Brain weight
 - Cerebral flow
 - Kidney mass
 - Basal metabolic rate
 - Liver blood flow
 - Liver weight
 - Capacity of lungs
 - Cardiac output
- **More prone to electrolyte imbalances**

Older Adult cont.

- AND...
- Never discount the effect of alcohol mixed with chronic (or acute) opioids in the elderly.
- MANY studies show significant changes in respiratory depression and apnea that worsen with age



Pulmonary

COPD

- 50% of patients with COPD get opioids for chronic pain
 - Musculoskeletal pain > “breathlessness”



COPD cont.

- Ahmed et al showed that opioids are associated with adverse outcomes, and therefore should not be given to those patients for reasons not supported with scientific evidence such as musculoskeletal pain

Ahmed et al. International Journal of Obstructive Pulmonary Disease. 2016;11:2651-2657

COPD cont.

- COPD affects 4-10% of Canadian population
 - 5-year mortality 40-70% depending on severity
 - 2-year mortality with severe COPD 50% when on opioids
 - Increased risk of: ER visits, hospitalizations, use of antibiotics/steroids
 - Some evidence not dose related

Nicholas t. Vozoris et al. European Respiratory Journal. July 2016. DOI 10.1183/13993003.01967-2015



COPD cont.



- 2016 study evaluating risks of adverse outcomes associated with incident opioid use among older adults with COPD
 - Retrospective study, patients >65 years old
 - Adverse respiratory outcomes within 30 days of incident opioid use

Zoris, Vo. European Respiratory Journal. 2016;48:683-93.

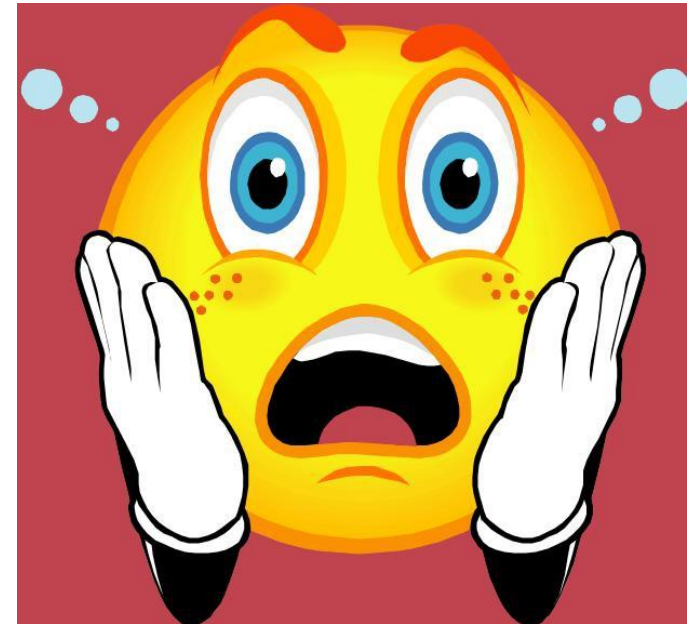
COPD cont.

- 2016 study continued...
 - Population based cohort of 130,979 patients with COPD + opioid use
 - Previous studies have shown high dose opioids associated with all cause mortality
 - This study was the first to show the link between opioid use AND respiratory-related morbidity and mortality REGARDLESS of dose

COPD cont.

- 2016 study continued...

AND



All cause mortality persisted in all sub-groups, including individuals with the “least” severe COPD

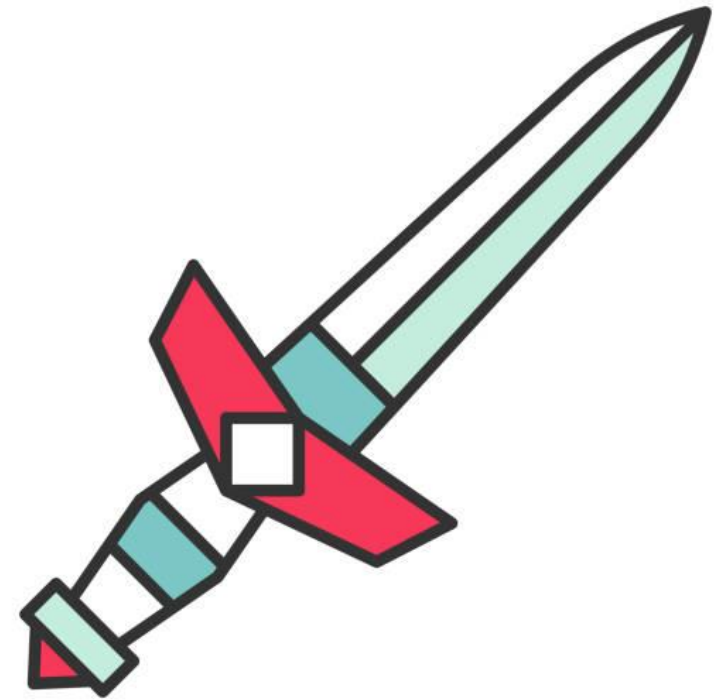
Sleep Apnea

- Opioids predispose to central sleep apnea and to a lesser extent obstructive sleep apnea
- 24% increase of CSA in long-term opioid users
J. Of Clinical Sleep Med. Vol 12. No. 04. Medium increased risk for central sleep apnea...in long term opioid users
- Methadone and high dosing >200 MME and combination with benzos increases risk



Sleep Apnea cont.

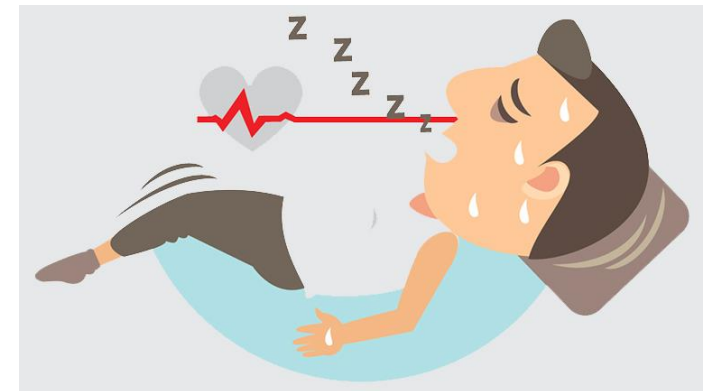
- The two-edged sword:
 - Central sleep apnea can be caused by chronic opioids (licit or illicit)
 - Patients with sleep apnea are at increased risk of complications from opioids



Sleep Apnea cont.

“Patients with sleep disordered breathing (including OSA + CSA) have increased incidence of nocturnal arrhythmias, myocardial ischemia or infarction, and sudden death”

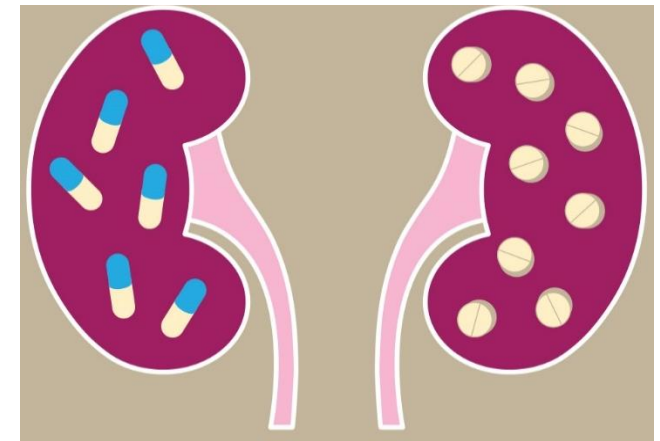
Prescription of long-acting opioids and mortality in patients with chronic non cancer pain. JAMA.2016;315(22)2415-23.



Renal

Chronic Kidney Disease

- Renally excreted opioids and metabolites can accumulate and cause life threatening symptoms
 - Tramadol: if needed
 - Methadone: metabolizes in the liver = minimal accumulation in chronic kidney disease
 - Codeine: not recommended
 - Morphine: avoid if creatinine clearance <30
 - Hydrocodone: 25% renal
 - Oxycodone: can be used, dose adjusted
substantial renal excretion



Endocrine

Obesity

- Associated with chronic non-cancer pain specifically:
 - Knee, hip, back
 - Headaches, stomach pain

Comorbidity of Obesity and Pain. J. Pain. 2007 May 8(5):430-6.
- As BMI increases, there is a proportional increase in incidence of pain
- As of 2007, an association between opioid use and obesity had not been demonstrated

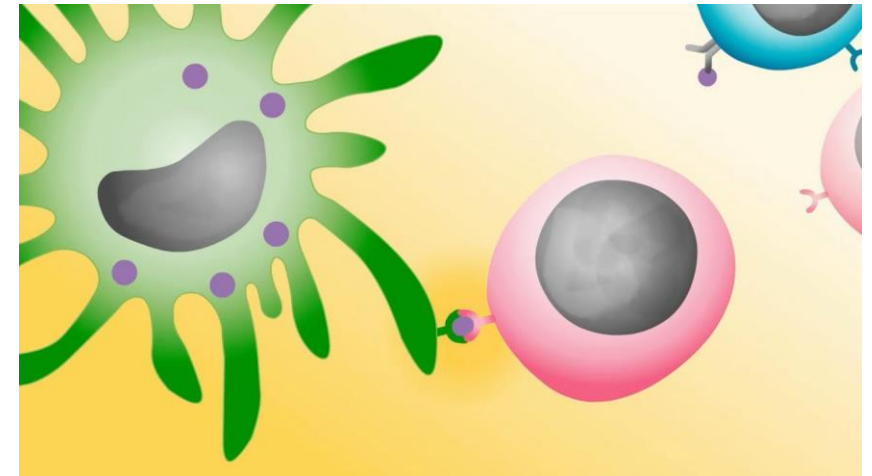


Opioid Long-Term Effects

Immunologic

Immunologic

- Inhibitory effects on:
 - Antibody and cellular immunity
 - Natural killer cell activity
 - Cytokine expression
 - Phagocytic activity



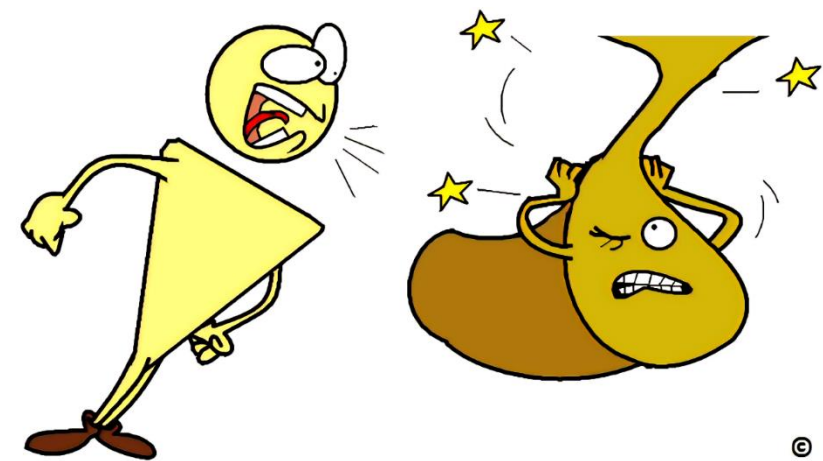
*First described in 1890 in work on guinea pigs

* Pain Physician. 2008;11:5105-20.

Hormonal

Hormonal

- Decreased total and free testosterone*
- Abnormalities of many other hormones:
 - Estrogen
 - Luteinizing hormone
 - GNRH
 - DHEA



Hormonal

- Results in:
 - A very long list of concerns
 - Common concerns:
 - Sexual dysfunction
 - Depression
 - Decreased energy levels
 - Osteoporosis in women

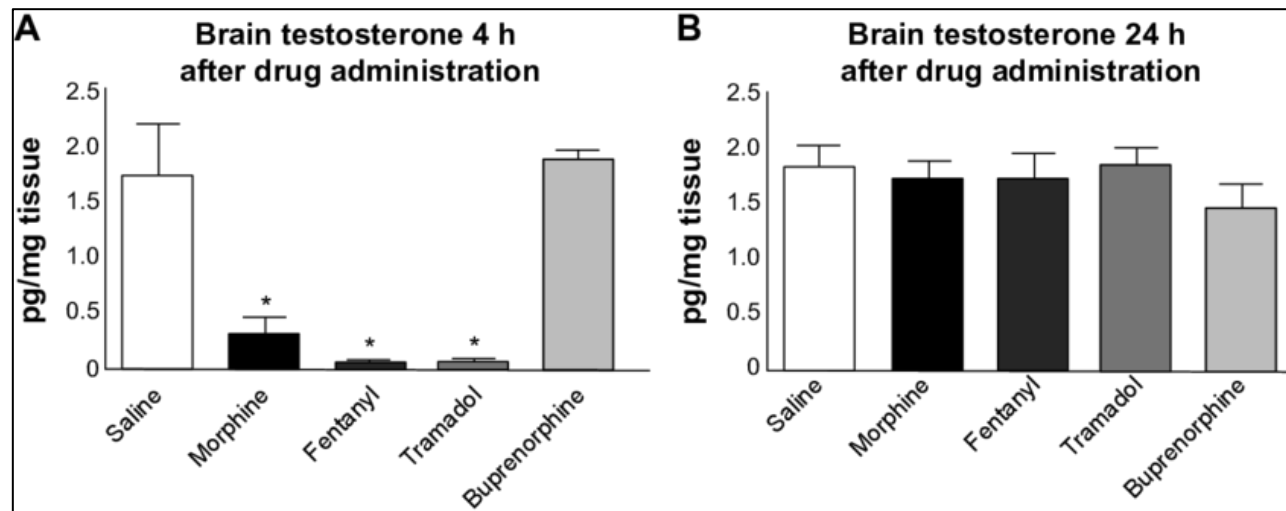


Testosterone... In the Weeds...

Kurt Style

Opioid-Induced Androgen Deficiency

- Previous studies show:
 - Morphine induces a dramatic long-lasting decrease in testosterone
 - May occur after even a few hours and can reach catastrophic levels <1ng/mL
 - Testosterone levels recover in days after opioid discontinuation



Coluzzi F et al. The unsolved case of “bone-impairing analgesics”: The endocrine effects of opioids on bone metabolism. *Therapeutics and Clinical Risk Management*. 2015;11:515-23.

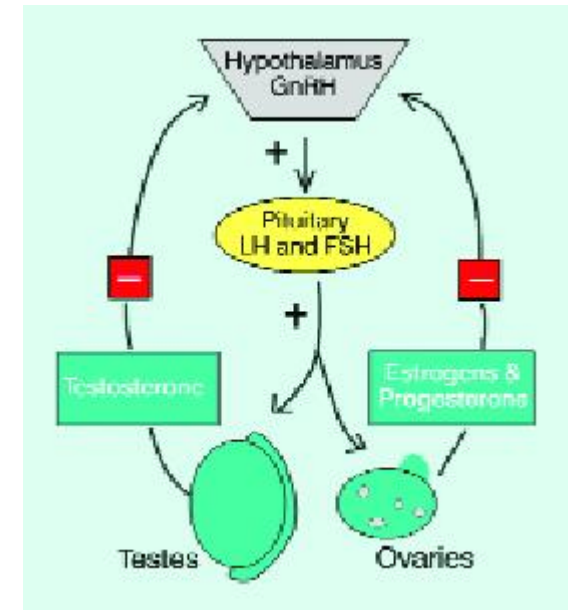
Opioid-Induced Androgen Deficiency

- Opioids inhibit the hypothalamus production of GNRH
- Via 5-Alpha reductase and p450 aromatase:
 - Increased metabolism of blood and brain testosterone



Opioid-Induced Androgen Deficiency

- Multiple studies have shown a DIRECT correlation between testosterone deficiency and chronic opioid use
 - 2002 Roberts et al: intrathecal opioids affected HPG axis in one week of initiation
 - 2004 Rajagopal et al: 40 cancer survivors: 90% on opioids were hypo-gonadal, only 40% of control group were hypogonadal



Opioid-Induced Androgen Deficiency

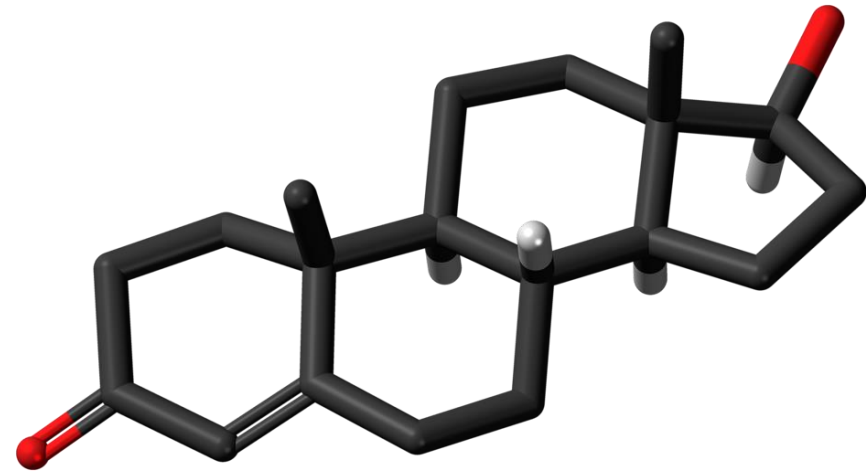
- Retrospective studies show >100 MME is likely where dropping testosterone may occur
- Duration?
 - Higher risk of hypogonadism when on opioid >1 month
- HPG axis affected in first week



Opioid-Induced Androgen Deficiency

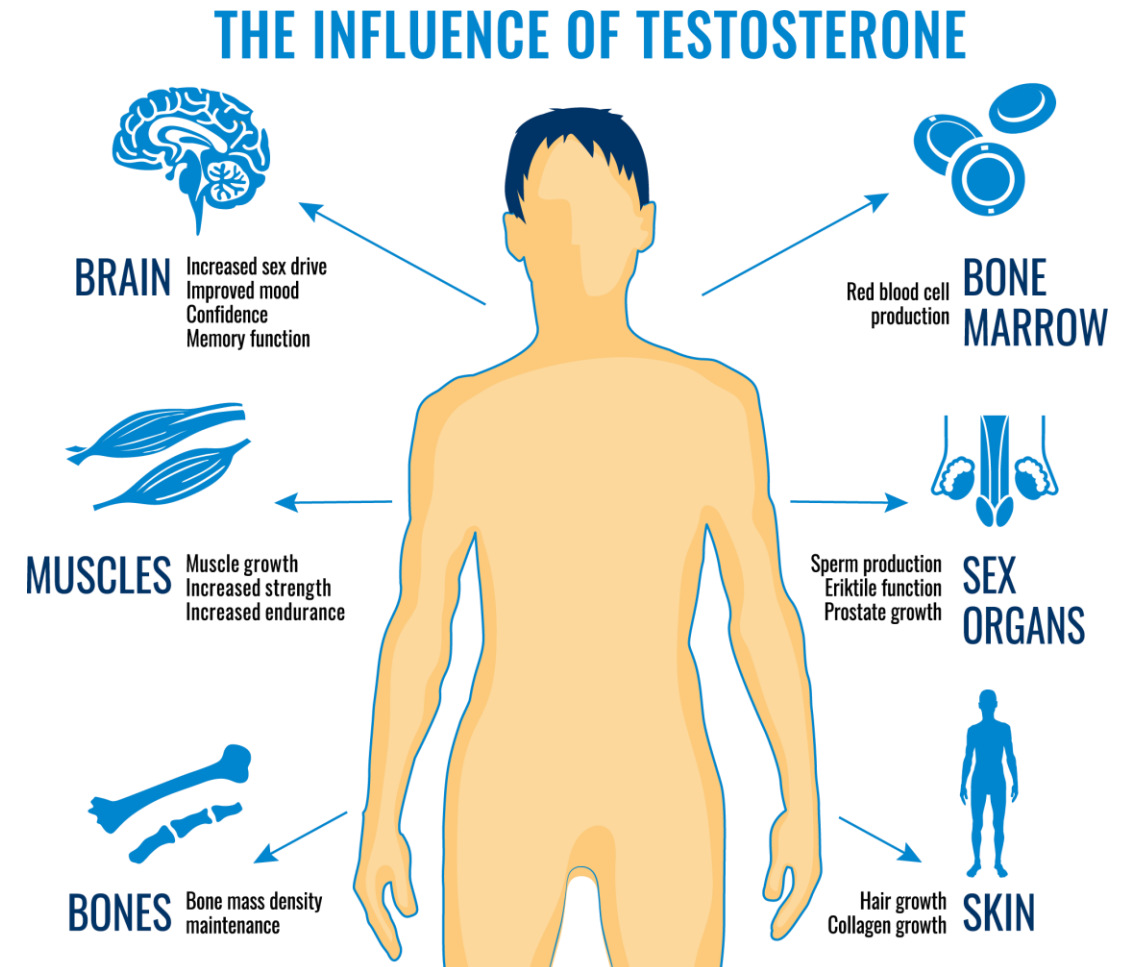
- Reversible:
 - Normal serum testosterone often seen in days to weeks from opioid discontinuation (even in long-term users)

Finch et al. Clin J Pain. 2002



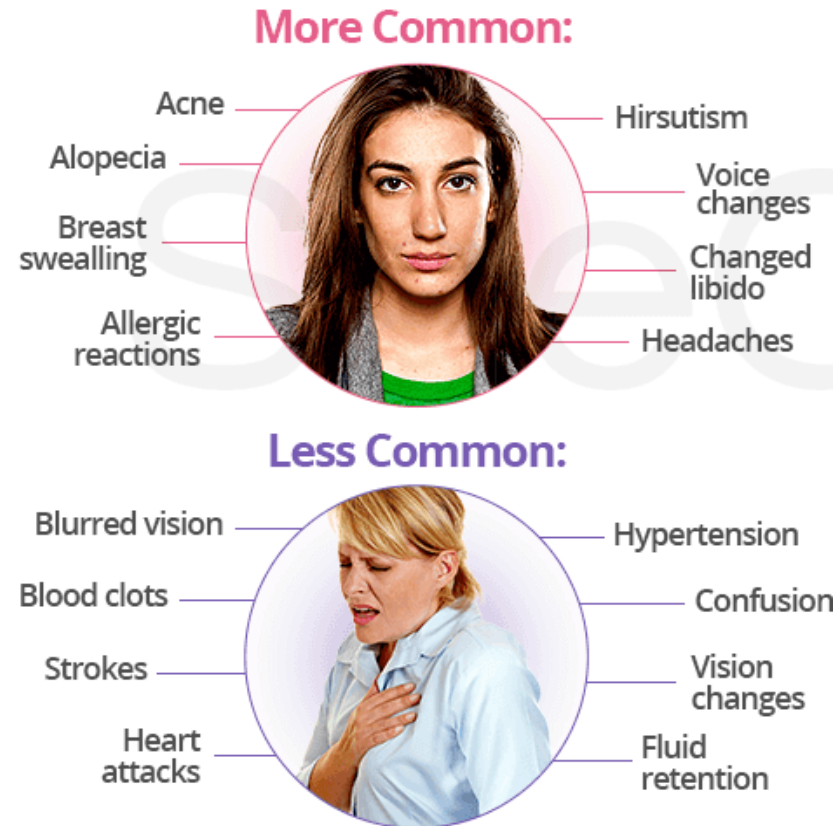
Opioid-Induced Androgen Deficiency

- Chronic opioid patients receiving testosterone:
 - Have lower all cause mortality
 - Decreased other adverse health outcomes
- Lower risk of:
 - CAD/Stroke
 - Other - adverse cardiac events/femoral hip fracture/anemia



Opioid-Induced Androgen Deficiency

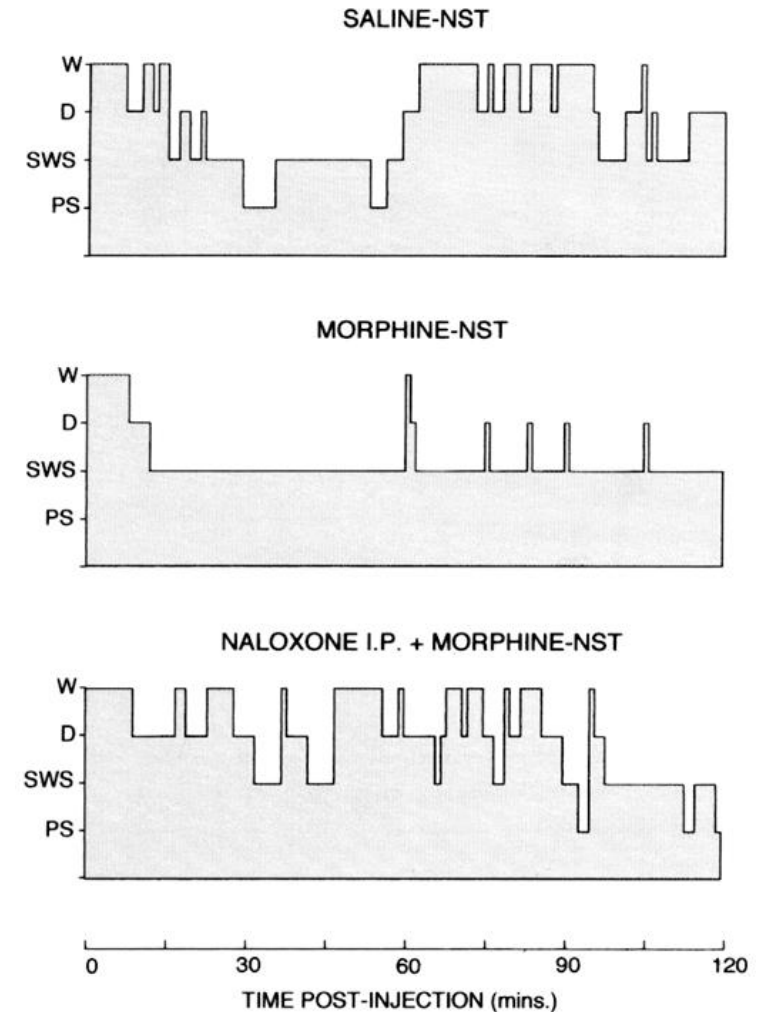
- On testosterone more likely to have:
 - Obesity
 - Hyperlipidemia
 - Hypertension



Sleep

Sleep

- Opioid induced sleep disturbances
 - Increased number of shifts in sleep-wake states
 - Decrease total sleep time and efficiency
 - Decreased REM sleep

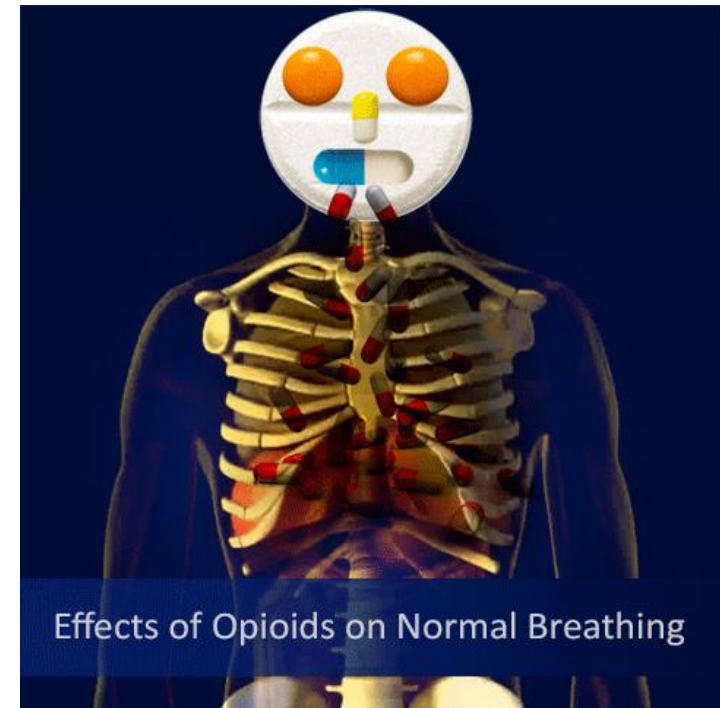


Reinoso-Barbero F, de Andres I. Effects of Opioid Microinjections in the Nucleus of the Solitary Tract on the Sleep-Wakefulness Cycle States in Cats. *Anesthesiology*. 1995, Vol.82,144-152.

And a Few Other Things...

Respiratory Risk of Opioids

- Decreased respirations
- Pneumonia (aspiration, immunocompromise)
- COPD exacerbation
- (Sleep apnea: central and obstructive more prominent)



Post-Operative “No-No’s”

- Benzos + opioids together:
 - Associated with increased mortality
- Long-acting opioids:
 - Associated with increased mortality
- Methadone
 - OT prolongation, mortality if used for pain



Post-Operative “No-No’s” cont.

- Codeine:
 - Renal insufficiency, mortality, falls and fractures
 - Black box warning pediatrics, breast feeding, post-op tonsil/adenoid
- Tramadol:
 - Renal insufficiency, seizures, high rates of forming chronic use
 - Black box warning pediatrics, breast feeding
- Meperidine:
 - Renal insufficiency, serotonin syndrome, seizures, mortality

Opiate Addiction Influences on Mental Health Conditions



For questions regarding content from this boot camp:

Heather Bell

heather.bell1012@gmail.com

Kurt Devine

kmdevine.truk@gmail.com



@echocsct



Podcast:
The Addiction
Connection



MINNESOTA ACADEMY OF
FAMILY PHYSICIANS

STRONG MEDICINE FOR MINNESOTA