Opioids

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Objectives

- Define pain and characterize the four separate components in the pathophysiology of pain
- Categorize the available groups of narcotics (agonists, weak agonists/reuptake inhibitors, mixed agonists antagonists or partial agonists, and antagonists)
- Describe the opioid epidemic in the United States and express the severity of the problem in Ohio
- Summarize the clinical presentation, management and treatment of opioid overdose
- Review the Ohio Prescribing Limits for Opioids for Acute Pain

Physiology of Pain

Definition of Pain

- Definition per the International Association for the Study of Pain
  - "Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
    - In other words, it does not necessarily correlate with the degree of tissue damage that is present
    - Discomfort, fear of pain, and anxiety are the most common psychological symptoms that accompany pain
- Pain is an unpleasant subjective experience
  - Pain should be considered to be "whatever" the experiencing person says it is, existing "whenever" the experiencing person says it does
- Even if the patient is unable to report their pain, it still must be identified and appropriately treated

Clinical Anesthesiology, 6th edition.
. *Crit Care Med*. 2018 Sept; 46(9): e825-e873
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Epidemiology of Pain

- Pain is one of the most common causes of all physician visits
  - Chronic pain could affect approximately 40% of the adult population
  - Anywhere from 8% to 37% of adults may experience low back pain
  - An estimated 40 million people suffer from musculoskeletal pain-related conditions
  - Migraines can affect as many as 25 million adults
  - Malignancy is associated with acute and chronic pain, with 70% of cancer patients experiencing significant levels of pain
- Chronic pain is attributed to massive costs to the health-care system
  - Back pain, migraines and arthritis alone have an estimated cost of $40 billion annually

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. *Crit Care Med*. 2018 Sept; 46(9): e825-e873
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Components of Pain

- Pain is a complex phenomenon including both sensory-discriminative and motivational-affective components

- Sensory-Discriminative Component
  - Ascending projections of tracts into the cerebral cortex
  - Sensory processing at higher levels allows for the perception of the type of pain (ie. burning, aching, etc.), how intense the pain is, where the pain is located, and how long the pain lasts

- Motivational-Affective Component
  - Reflexes (somatic and autonomic), endocrine responses, attention and arousal, emotional responses
  - How the pain response makes you feel

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Nociception

- Process by which information about tissue damage is conveyed to the central nervous system

- Nociceptors
  - AKA Pain Receptors
  - Specialized primary afferents that respond to noxious stimuli in the skin, muscles, joints, viscera and vasculature
  - Distinctive because they can respond to various stimuli leading to tissue injury
    - Thermal, mechanical, and chemical

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Nociception

- Nociception involves a chain of complex physiologic processes that are made up of 4 separate components
  - Transduction
    - The conversion of the energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy/nerve impulses
  - Transmission
    - The propagation of these neural signals from the site of transduction (periphery) to the dorsal horn (spinal cord) and brain
  - Modulation
    - The process of altering pain transmission; descending inhibitory and faciliatory input from the brain that influences (modulates) nociceptive transmission at the level of the spinal cord
  - Perception
    - The appreciation of signals arriving in higher structures as pain (thalamus, cortex)

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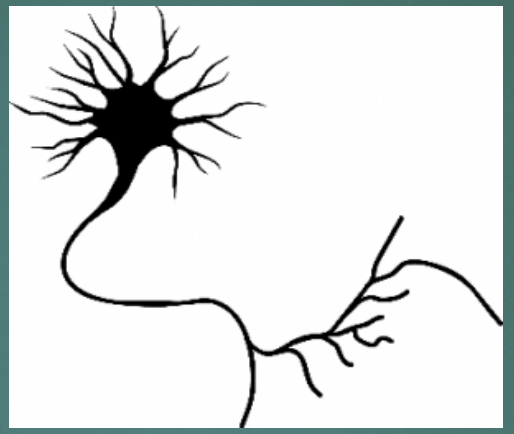
Pathophysiology of Pain

Transduction



Transmission

Perception

Modulation

http://projects.hsl.wisc.edu/GME/PainManagement/index.html.

Acute Pain vs Chronic Pain

Acute Pain

- Short-term pain
- Pain sensation stops when nociceptors no longer detect any tissue damage
- Does **NOT** persist after the initial injury has healed

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Chronic Pain

Pain persistent beyond the normal expected time for healing to occur

Pain receptors keep firing, even when tissue damage is **ABSENT**

No longer a **PHYSICAL** cause of pain but the pain is still **THERE**

No defined time frame for conversion from acute pain to chronic pain but usually considered after 3 or 6 months of ongoing pain

Note: Ohio defines chronic pain as pain lasting longer than 12 weeks

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Acute-On-Chronic Pain

- Patients who suffer from chronic pain can still experience acute pain on top of their underlying chronic pain
- Example: A 68 yo M who suffers from chronic back pain that was involved in a motor vehicle collision (MVC) and has several broken ribs and a broken femur
- Can be the most difficult to treat as the patient's underlying pain requirements must be overcome to achieve relief for the acute pain

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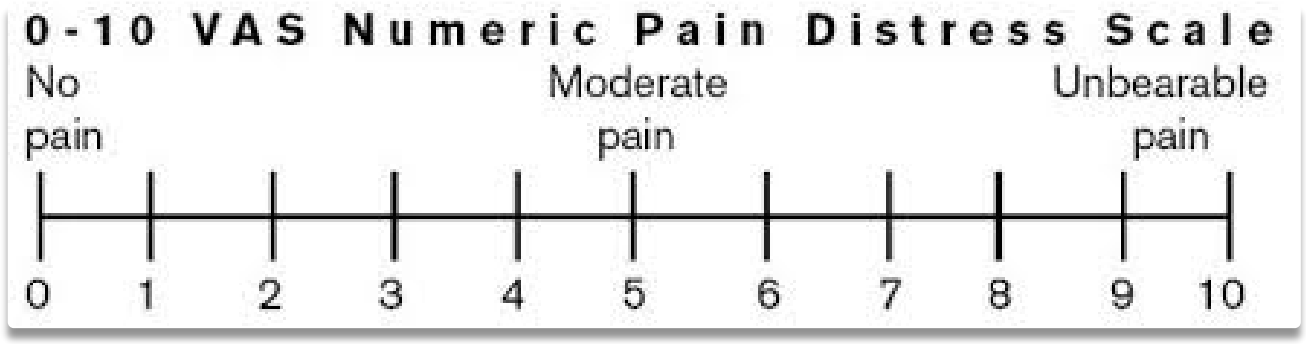
Pain Assessment

- Preferred method is self-reported pain in patients >12 years of age
  - 0 – 10 numeric rating scale is demonstrated to be most valid and feasible scale for patient's that can report their own pain



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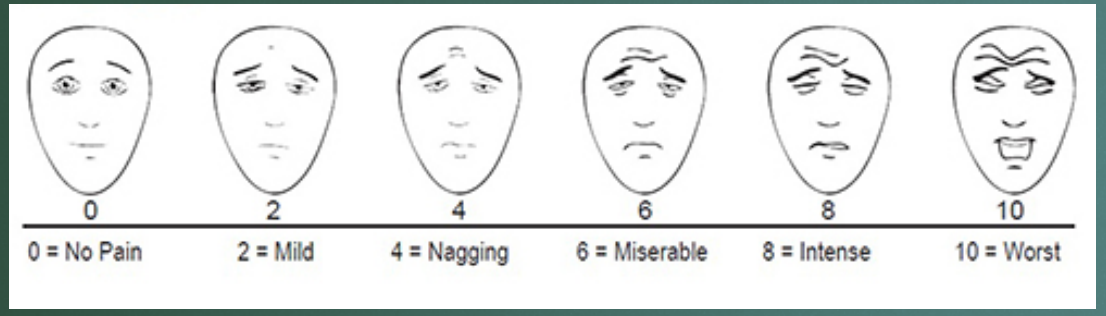
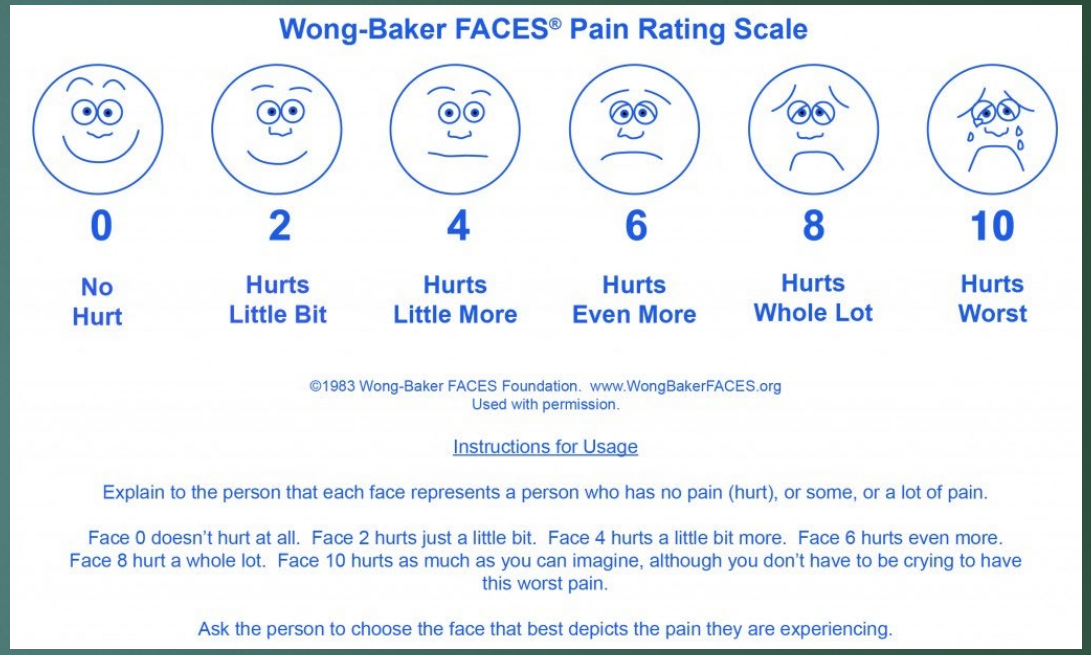
Pain Assessment

Faces of Pain Revised





Prehospital Emergency Care. 2014; 18 (Suppl 1): 25-34.

FLACC	0 points	1 point	2 points
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

Prehospital Emergency Care. 2014; 18 (Suppl 1): 25-34.

Opioids

Background Terminology

- Opium: Derived from the Greek “opos” for "juice” → extract from the poppy flower
- Opiate:
  - Opiate refers to compounds structurally related to products found in opium
  - Opiates include the natural plant alkaloids such as morphine, codeine, and thebaine and many semisynthetic derivatives
- Opioid:
  - An opioid is any agent, regardless of structure, that has the functional and pharmacological properties of an opiate
- Narcotic: derived from the Greek word narkotikos, for "benumbing" or "stupor”

Opioids aka Narcotics

- Although the recent focus of pain is a "multimodal approach", opioids are still often the cornerstone of modern pain management

- A multimodal approach is a methodology of using other pain-relieving options or agents from several classes in order to decrease the amount on opioid needed to provide pain relief for the patient
  - Examples of other agents that could be utilized include:
    - Nonpharmacologic modalities
    - Acetaminophen
    - NSAIDs
    - Muscle relaxants (ie. methocarbamol, tizanidine, cyclobenzaprine, etc.)
    - Agents used for neuropathic pain (ie. gabapentin, pregabalin, carbamazepine)

- **RARELY the goal is to ELMINATE pain but rather MINIMIZE pain to a TOLERABLE level**

Mechanism of Action of Opioids

- The opioid class of medications act on specific opioid receptors in the nervous system to reduce perception to pain
  - Opioid receptors are located throughout both the central and peripheral nervous systems (CNS and PNS)
- Three classical types of opioid receptors**
  - **Mu (μ) opioid receptor – aka MOP**
  - Delta (δ) opioid receptor – aka DOP
  - Kappa (κ) opioid receptor – aka KOP
- The μ opioid receptor is located heavily in the CNS, primarily in the brain and dorsal horn of the spinal cord. When activated, a chain of biochemical responses lead to the desired analgesic effects and ultimately, pain relief
- There are several endogenous compounds responsible for the body's natural mechanisms for pain relief that act as agonists on the opioid receptor
  - Enkephalins, Dynorphins, Endorphins and Endomorphins
- The naturally occurring, semi-synthetic and synthetic opioids primarily act as an agonist at the MOP, exhibiting their analgesic effects

Opiate Receptors and Effects

Mu_1 (μ_1) (Endorphins)	analgesia, euphoria, miosis, bradycardia, hypothermia, urinary retention, hormone/NT modulation
Mu_2 (μ_2) (Endorphins)	Spinal analgesia, **constipation** (most), **respiratory depression**, **dependence**
Kappa (Dynorphins)	analgesia, DYSphoria, sedation, diuresis, miosis
Delta (Enkephalins)	analgesia, constipation (some), respiratory depression, dependence, hormone/NT modulation

Four Groups of Narcotics

- Agonists
- Weak agonist/reuptake inhibitors
- Partial agonists and Mixed agonist-antagonists
- Antagonists

Agonist vs Antagonist

OPIOIDS

Agonist

Receptor

Agonist/Receptor Interaction = Drug action/Effect

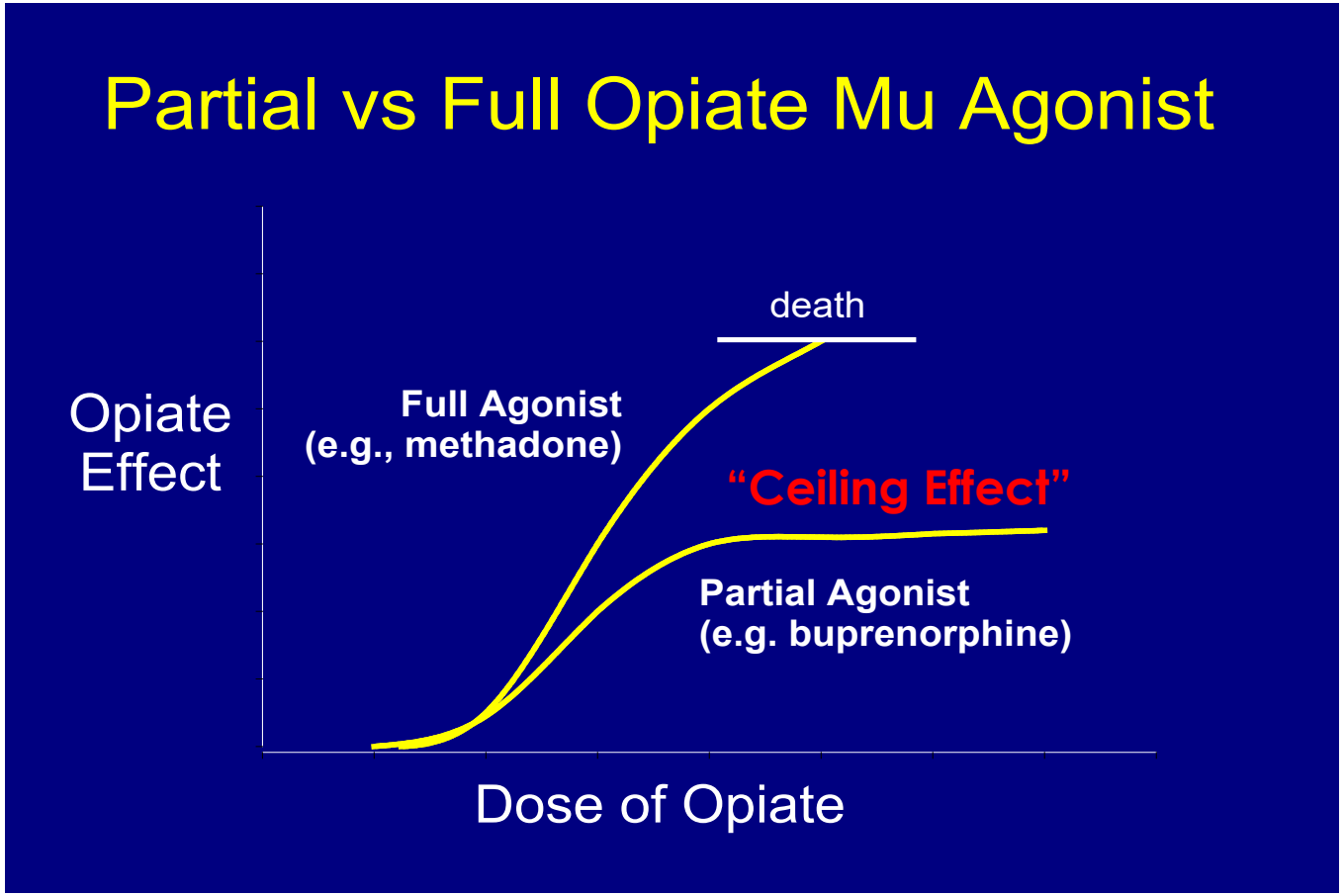
NALOXONE

Antagonist

Receptor

Antagonist/Receptor Interaction = **NO** drug action/Effect

Partial vs Full Opiate Mu Agonist



Breakdown of agents in each category

Agonists	Weak agonists/Reuptake Inhibitors	Mixed Agonist-Antagonists	Antagonists
Alfentanil	Tapentadol	Buprenorphine	Naloxone
Codeine	Tramadol	Butorphanol	Naltrexone
Fentanyl		Nalbuphine	Alvimopan
Heroin			Methylnaltrexone
Hydrocodone			Methylnaltrexone
Hydromorphone			
Levorphanol			
Meperidine			
Methadone			
Morphine			
Oxycodone			
Oxymorphone			
Remifentanil			
Sufentanil			
Carfentanil			

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Hydromorphone			
Levorphanol			
Meperidine			
Methadone			
Morphine			
Oxycodone			
Oxymorphone			
Remifentanil			
Sufentanil			
Carfentanil			

The Common Intravenous Opioid Options

- **Fentanyl**
- **Morphine**
  - **Note: also available PO**
- **Hydromorphone**
  - **Note: also available PO**
- ***All opiates are considered to be equally effective when titrated to similar pain intensity endpoints***

Crit Care Med. 2018; 46: e825-e873.

Suggested dosing in acute pain (opioid naïve patients)

- Fentanyl
  - Initial dose 1 mcg/kg; consider starting 0.5 mcg/kg in geriatric patients
  - Repeat doses 0.5 mcg/kg
  - Pediatric patients: 1 mcg/kg/dose
- Morphine
  - Initial dose 0.1 mg/kg; consider starting 0.05 mg/kg in geriatric patients
  - Repeat doses 0.05 mg/kg
  - Pediatric patients: 0.025 – 0.05 mg/kg/dose
- Hydromorphone
  - Initial dose 0.5 – 1 mg; consider starting no more than 0.5 mg in geriatric patients
  - Repeat doses 0.25 – 0.5 mg
  - Pediatric patients: 0.01 – 0.015 mg/kg/dose
- **If concerned for respiratory status or mentation, can always initiate lower doses and repeat as tolerated**

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Prehospital Emergency Care. 2014; 18 (Suppl 1): 25-34.

Opioid	Relative Potency	Onset of Action (IV)	Duration of Action (IV)	Potential for Accumulation	Other Information
Fentanyl	+++	1 – 2 min	0.5 – 1 hr	Hepatic Impairment	Synthetic opioid
Morphine	+	5 – 10 min	3 – 5 hr	Renal/Hepatic Impairment	Naturally-occurring opioid; causes histamine release
Hydromorphone	++	5 – 15 min	3 – 4 hr	Hepatic/Renal Impairment	Semi-synthetic opioid

Common Oral Opioid Options

OXYCODONE

HYDROCODONE

MORPHINE

HYDROMORPHONE

OXYMORPHONE

METHADONE

Suggested dosing in acute pain (opioid naïve patients)

- Hydrocodone/APAP 5/325 mg
  - 1 – 2 tabs PO q4-6h prn
- Oxycodone 5 mg (with or without 325 mg APAP)
  - 5 – 10 mg PO q4-6 prn
- Morphine IR
  - 10 mg PO q4h prn
- Hydromorphone
  - 1 – 2 mg every 4-6h prn
- Oxymorphone
  - 5 - 10 mg every 4-6h prn
  - Not seen commonly in opioid naïve patients

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Opioid	Relative Potency to Morphine	Onset of Action (PO)	Duration of Action (PO)	Potential for Accumulation	Other Information
Morphine	--	IR: ~30 min	IR: 3 – 5 hours ER: 8 – 24 hours	Renal/Hepatic Impairment	Naturally-occurring opioid; causes histamine release
Hydrocodone (most commonly used as combination product with APAP)	~2/3 as potent	15 – 60 mins	4 – 6 hours	Concern for hepatotoxicity risk with APAP (>4 gm/day)	ER formulation available
Oxycodone (commonly used as combination product with APAP; also used commonly alone)	~1.5x more potent	IR: 10 – 15 mins	IR: 3 – 6 hours ER: ≤ 12 hours	Heparin Impairment; Concern for hepatotoxicity risk with APAP (>4 gm/day)	
Hydromorphone	~5x more potent	5 – 15 min	3 – 4 hours	Hepatic/Renal Impairment	Semi-synthetic opioid
Oxymorphone	~10x more potent	ER peak effect ~2 – 3 hours	ER half life ~9 – 12 hours	Renal/Hepatic Impaiment	Opana ER withdrawn from the market; generic Oxymorphone ER remains available

LexiComp.®

Equianalgesic Conversion of Opioids		
Drug	IV/IM Dose	Oral Dose
Morphine	10 mg	30 mg
Hydromorphone (Dilaudid®)	1.5 mg	7.5 mg
Oxycodone	--	20 mg
Hydrocodone	--	30 mg
Meperidine (Demerol®)	75	--
Codeine	--	200 mg
Fentanyl	0.1 mg (100 mcg)	Not established

Equianalgesic Conversion of Opioids

Meperidine

- No longer recommended for pain management due to existence of safer alternatives
- Active metabolite normeperidine can accumulate in patients, specifically in elderly patients and patients in renal failure
- Can lead to neurotoxicity
  - Symptoms of neurotoxicity include anxiety, tremors, and **seizures**
  - Note: Naloxone (reversal agent) does not reverse and can even worsen neurotoxic effects
- Clinical use – post-operative shivering and rigors
  - Dosing: 12.5 – 50 mg

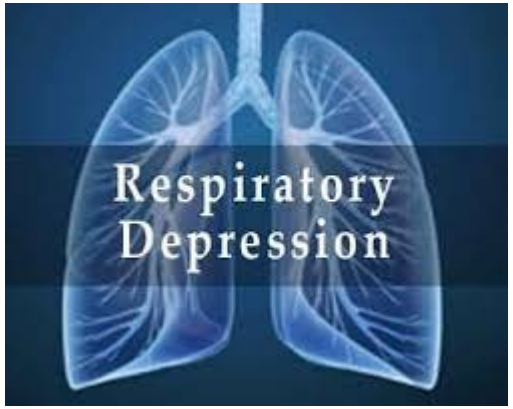
Methadone

- Generally not used for acute pain
- Primarily used for chronic pain and opioid use disorder
  - Can be used short-term for medically supervised opioid withdrawal
- Dosing in chronic pain
  - 2.5 mg – 5 mg every 8-12h
  - Gradual titration: May increase by 2.5 mg per dose no more often than every 5 – 7 days
- Warnings/Precautions unique to Methadone: QT prolongation, serotonin syndrome

Contraindications and Adverse Reactions to Opioids

- Contraindications
  - Reported hypersensitivity or anaphylaxis
  - Allergenic cross-reactivity for opioids is limited. However, due to similarities in chemical structures, the possibility for cross-sensitivity exists
  - If documented allergy to naturally-occurring opioids such as codeine or morphine, may have less chance of reaction to a semi-synthetic or synthetic compound (ie. Hydromorphone or Fentanyl)

- Adverse Reactions
  - CNS depression
  - Respiratory depression
  - Constipation
  - Hypotension

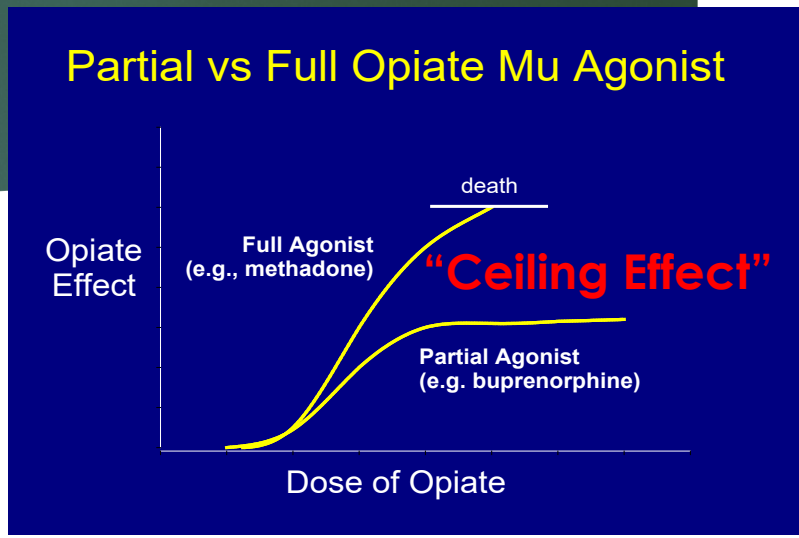


Partial Agonists
Mixed Agonists/Antagonists

Buprenorphine

Buprenorphine/Naloxone

Buprenorphine

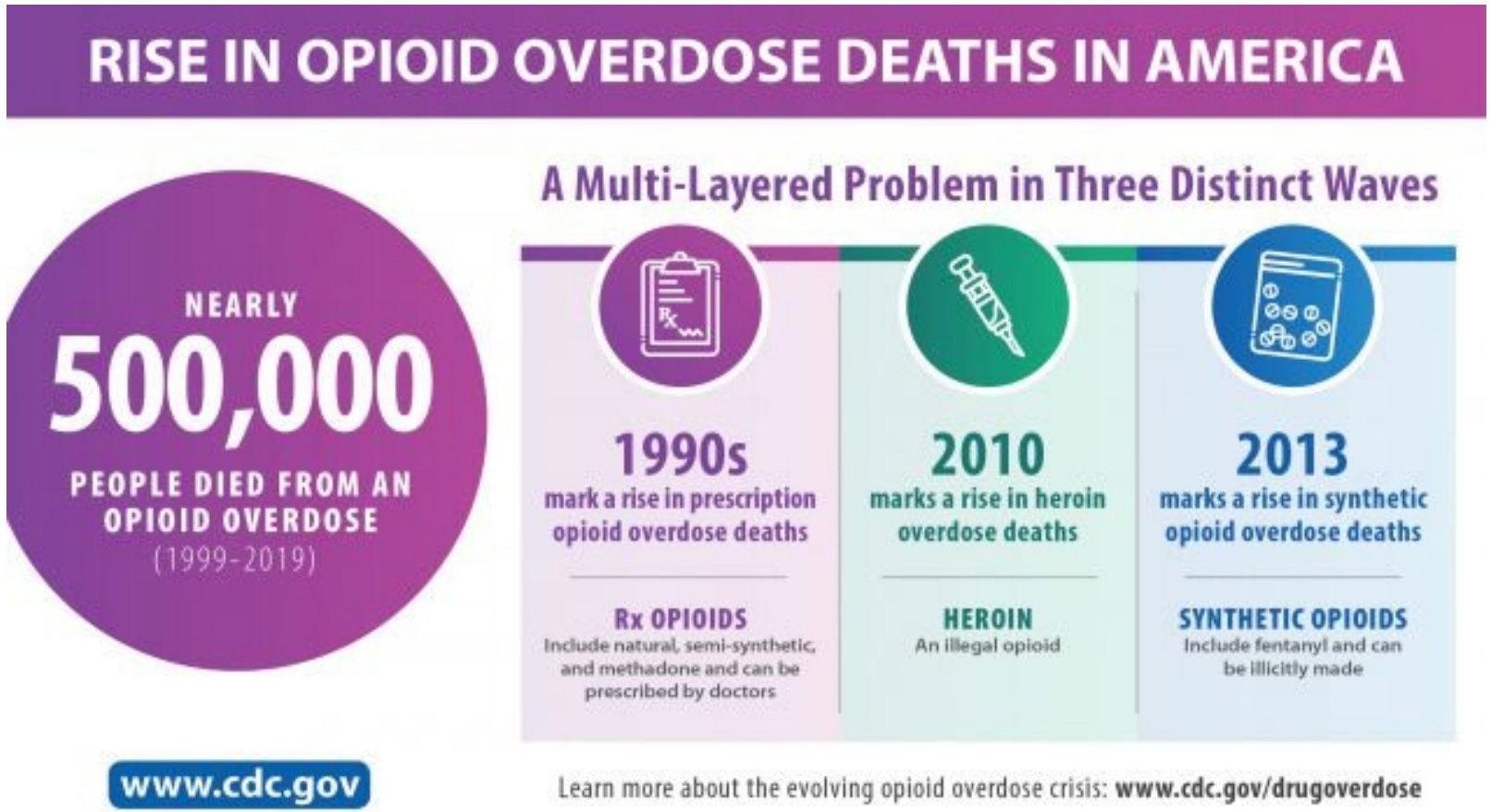


- Partial Agonist
- Used primarily for chronic pain and opioid use disorder
  - Transdermal patch available for chronic pain
  - ER injections, subdermal implants and sublingual tablets available for opioid use disorder
  - IM/Slow IV IR injections can be used for short term acute pain
- Benefit in chronic pain and opioid use disorder is that "ceiling" effect
- Prescribing in the US:
  - ER injection is limited to healthcare providers who meet qualifying requirements notifying the Secretary of Health and Human Services (HHS) of their intent to prescribe this for opioid dependence and have been assigned a unique ID number to include on every prescription
  - Subdermal Implants are limited to prescribers who have completed a live training program and must perform a qualifying surgical procedure in the preceding 3 months
  - Sublingual tablets require an "X" DEA number for prescribing

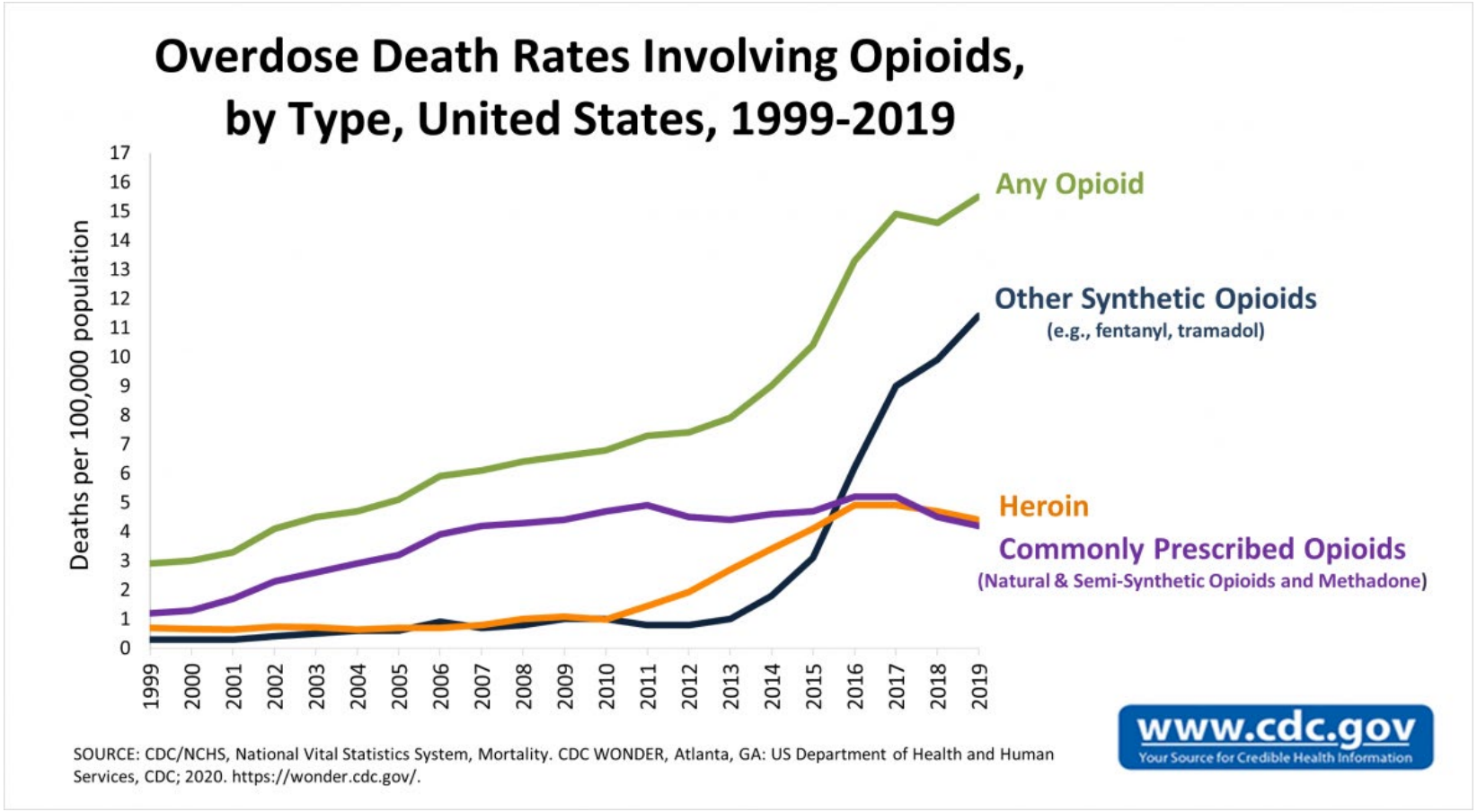
Buprenorphine/Naloxone

- Mixed Agonist/Antagonist
- Used in Opioid Use Disorder
  - Available as buccal film, sublingual film, and sublingual tablets
- Goal is to use medication to prevent relapses to traditional opioids while suppressing opioid withdrawal symptoms
- Requires "X" DEA number to prescribe
- Can be difficult to treat patients coming in with acute pain that are on chronic buprenorphine/naloxone therapy. Close monitoring for respiratory depression is needed as these patients may require high doses of opioids to achieve pain relief


Crisis
EPIDEMIC
Opioid
Battle


RISE IN OPIOID OVERDOSE DEATHS IN AMERICA
NEARLY
500,000
PEOPLE DIED FROM AN OPIOID OVERDOSE
(1999-2019)
A Multi-Layered Problem in Three Distinct Waves
1990s
mark a rise in prescription opioid overdose deaths
Rx OPIOIDS
Include natural, semi-synthetic, and methadone and can be prescribed by doctors
2010
marks a rise in heroin overdose deaths
HEROIN
An illegal opioid
2013
marks a rise in synthetic opioid overdose deaths
SYNTHETIC OPIOIDS
Include fentanyl and can be illicitly made
www.cdc.gov
Learn more about the evolving opioid overdose crisis: www.cdc.gov/drugoverdose

www.cdc.gov


Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019
Deaths per 100,000 population
0
1
2
3
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9
10
11
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16
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1999
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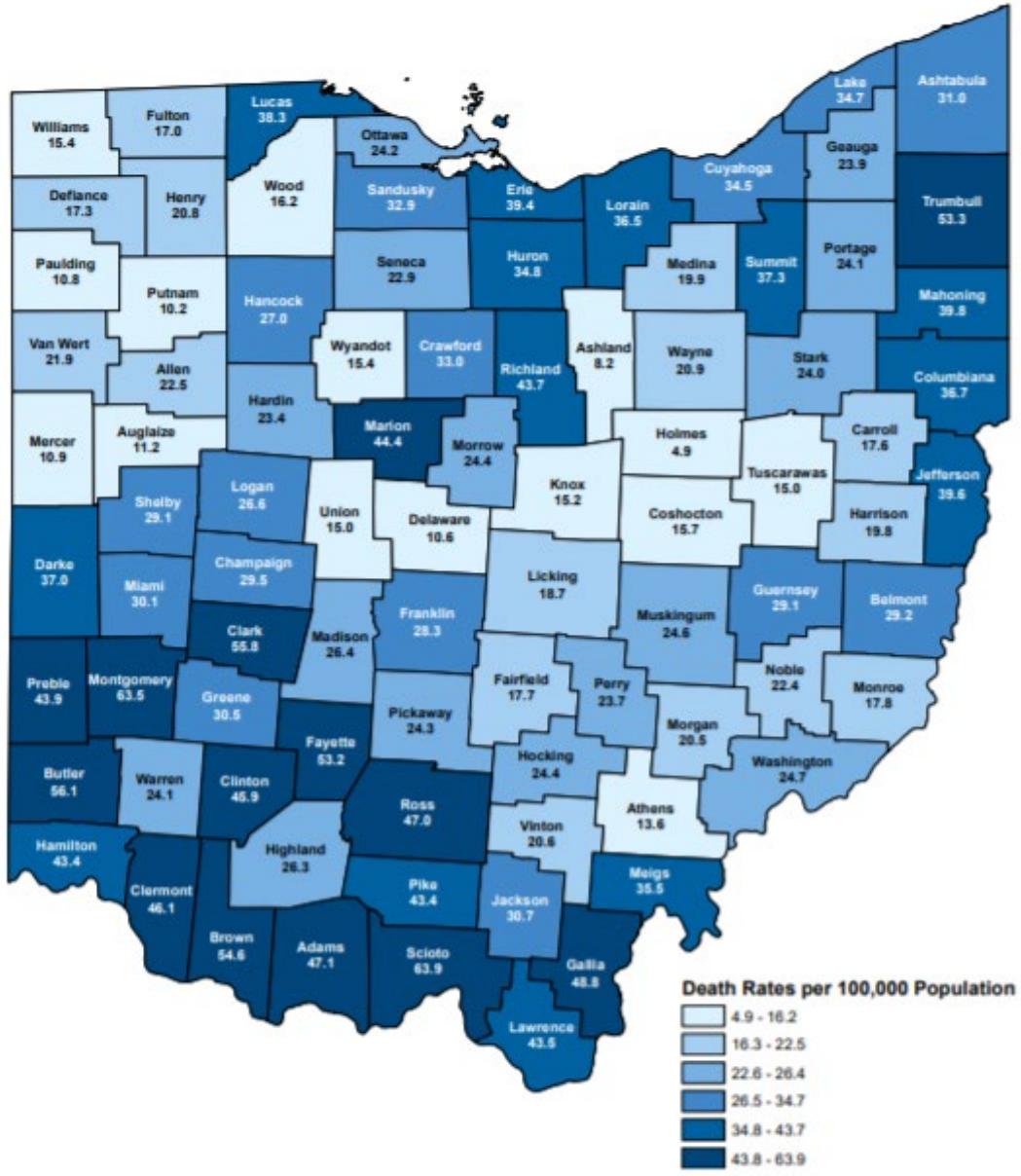
2019
Any Opioid
Other Synthetic Opioids
(e.g., fentanyl, tramadol)
Heroin
Commonly Prescribed Opioids
(Natural & Semi-Synthetic Opioids and Methadone)
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.
www.cdc.gov
Your Source for Credible Health Information

Figure 12. Average Age-Adjusted Rate of Unintentional Drug Overdose Deaths by County, Ohio, 2014-2019



Source: Ohio Department of Health, Bureau of Vital Statistics, U.S. Census Bureau (Vintage 2019 population estimates). Analysis: ODH Violence and Injury Prevention Section. Includes Ohio residents who died due to unintentional drug poisoning (underlying cause of death ICD-10 codes X40-X44). County is based on county of residence.

Ohio Department of Health.

Heroin

- Street Names: China White, Smack, Snow, Junk, Mexican Mud, Mexican Tar, Brown Sugar, Big H, Dope, White Lady
- Heroin addiction continues to increase among 18 – 25 year olds
- Between 2010 and 2016, the number of heroin-related overdose deaths has increased 5-fold
  - More than 15,469 people died in 2016
- Possible contributors to rising rates of heroin use include:
  - Increased availability
  - Lower cost
  - Increased purity

www.cdc.gov
www.streetdrugs.org

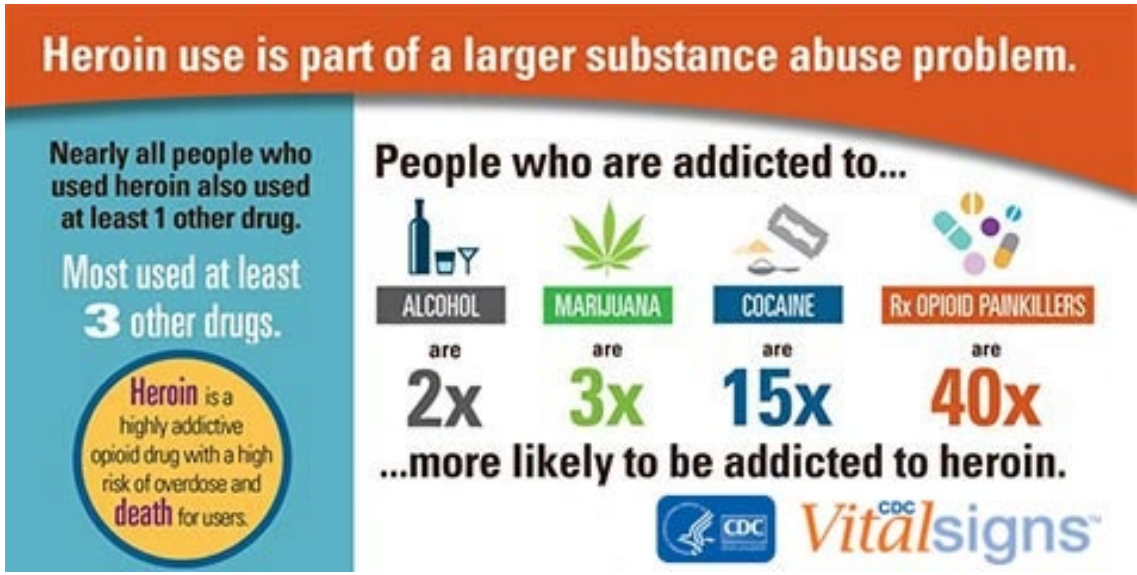
Heroin, cont.

Traditional heroin (China)

Black tar heroin (Mexico)

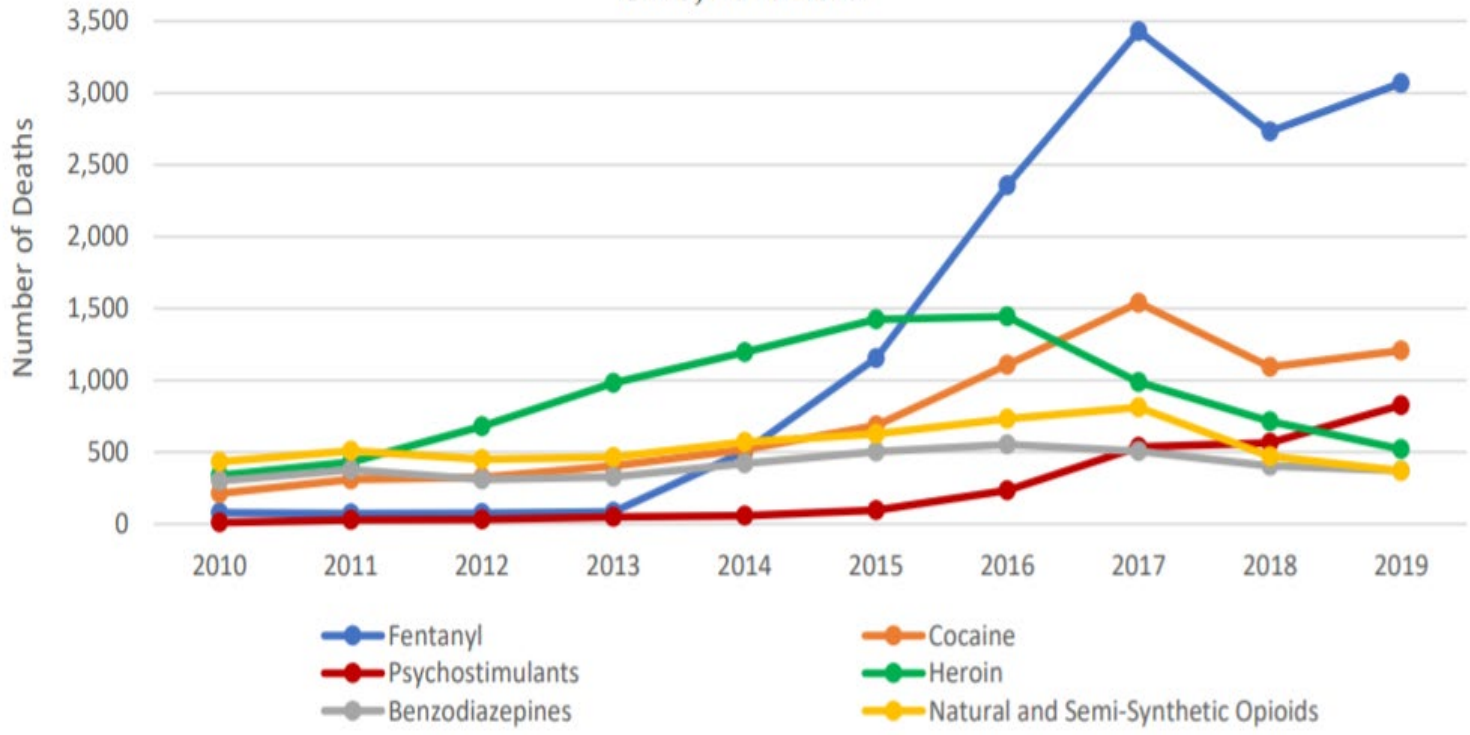
Heroin, cont.

- Who is most at risk of developing a heroin addiction?
  - People addicted to prescription opioids
  - People addicted to cocaine
  - People addicted to marijuana and alcohol
  - People without insurance
  - Males
  - 18 – 25 year olds
  - People living in large metropolitan areas



www.cdc.gov

Figure 10. Number of Unintentional Drug Overdose Deaths Involving Select Drugs, Ohio, 2010-2019



Ohio Department of Health.

Fentanyl

Wikipedia

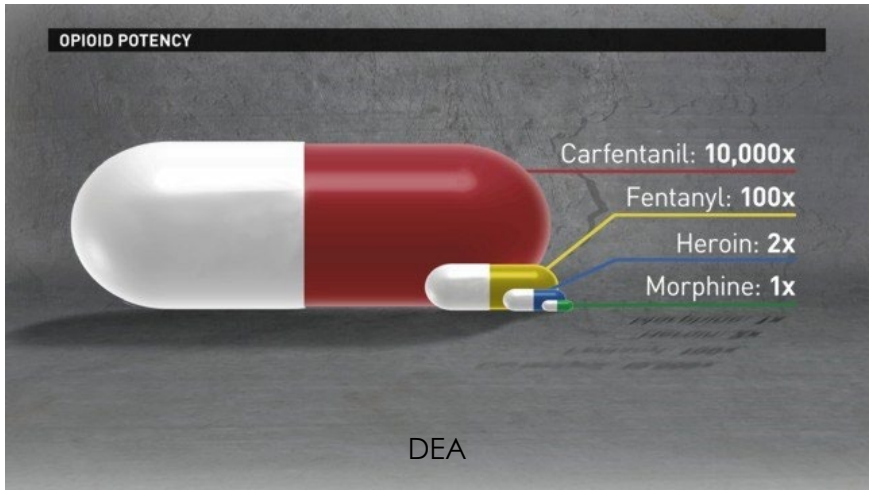
- Heroin now commonly being cut with fentanyl
  - Street name: Tango and Cash
- Fentanyl is 25 – 40x more potent than heroin
  - This is why overdoses are drastically on the rise
- Not only are fentanyl and fentanyl analogs affecting the user but first responders and healthcare workers are being put at risk
- The American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) have issued a statement on the handling of illicit compounds believed to contain fentanyl or fentanyl analogs by first responders
  - Use nitrile gloves when handling
    - If incidental dermal exposure occurs, wash with liberal amounts of water
  - Water-resistant coveralls should be worn if entering highly contaminated spaces
  - If significant amounts of airborne exposure to opioids anticipated, N-95 respirators should be worn

Carfentanil

- A fentanyl analog
- A newer drug being used to cut heroin in the last 5 years
- Available commercially as an animal sedative; specifically used in elephants
- 10,000 times more potent than morphine; 100 times more potent than fentanyl
- The equivalent of 1 grain of salt is enough to kill a human being
- Carfentanil can be absorbed through the skin and must be handled with same precautions as fentanyl

Relative potency of Heroin, Fentanyl, and Carfentanil

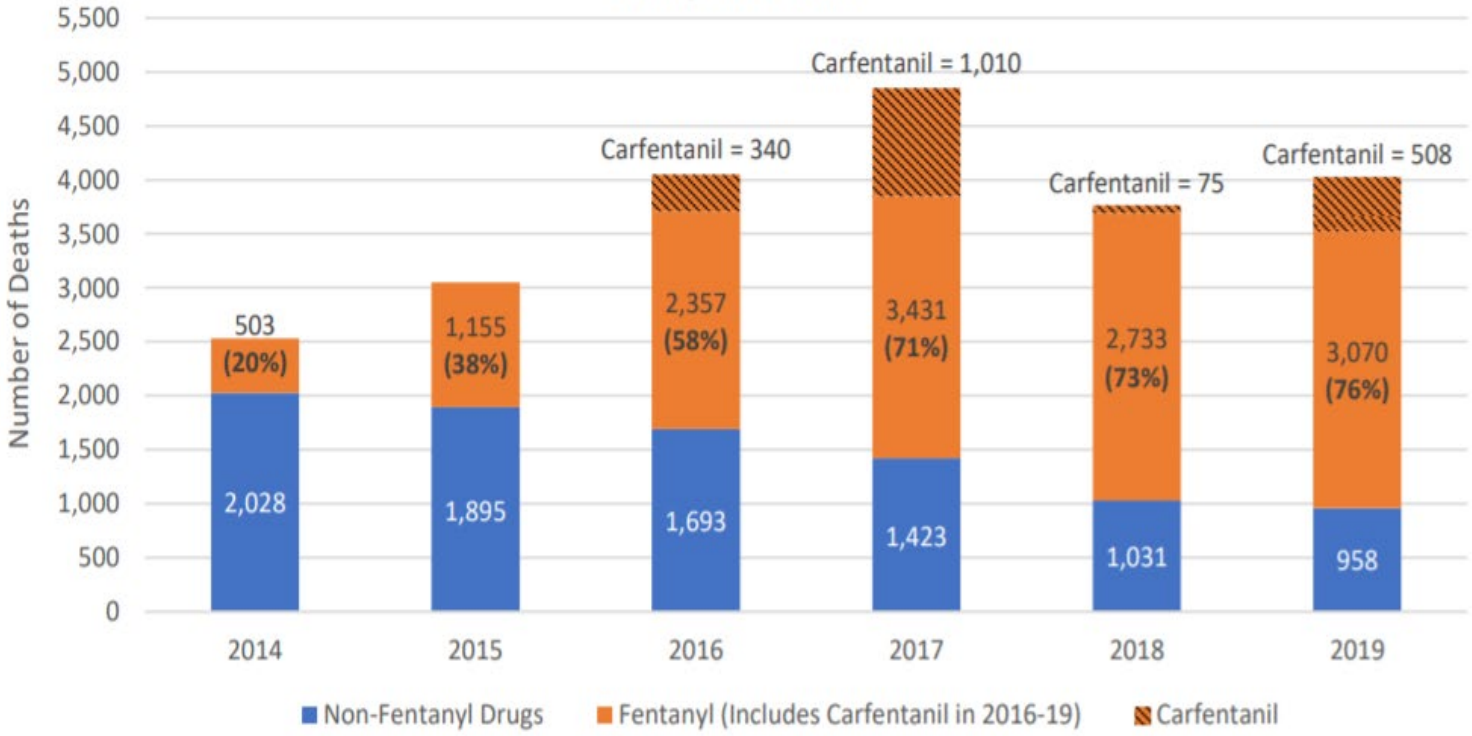
- In order to get high, the average person needs
  - Heroin 15 – 30 mg
  - Fentanyl 1 mg
  - Carfentanil less than 1 salt sized grain



DEA

New Hampshire Forensic Lab

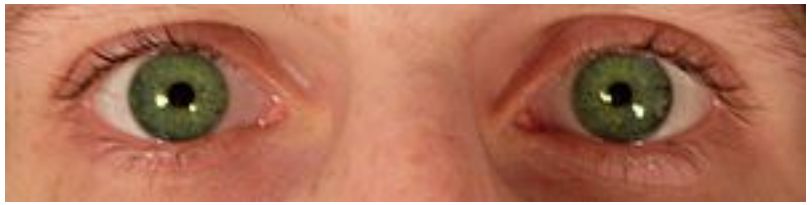
Figure 8. Number and Percentage of Fentanyl-Related Unintentional Drug Overdose Deaths, Ohio, 2014-2019



Ohio Department of Health.

Signs and Symptoms of an Opioid Overdose

- Confusion
- Diaphoresis
- Extreme drowsiness
- Respiratory depression
  - Apnea in severe overdose
- Seizures
- Decreased GI motility/constipation
- Urinary retention
- Miosis



- "Going on the nod"
- Bradycardia/Dysrhythmias/Cardiac arrest
- Coma

Management of suspected Opioid Overdose

- Evaluate and correct any emergent life-threatening complications
  - Airway
  - Breathing
  - Circulation

- If known oral ingestion and within 1 hour, consider gastric lavage or activated charcoal
  - Activated charcoal single adult dose 25 – 100 g
  - Activated charcoal MOA: adsorbs toxic substances, thereby preventing absorption by the GI tract and systemic toxicity

- Antidote available → **NALOXONE (NARCAN®)**

Agonist vs Antagonist

OPIOIDS

Agonist

Receptor

Agonist/Receptor Interaction = Drug action/Effect

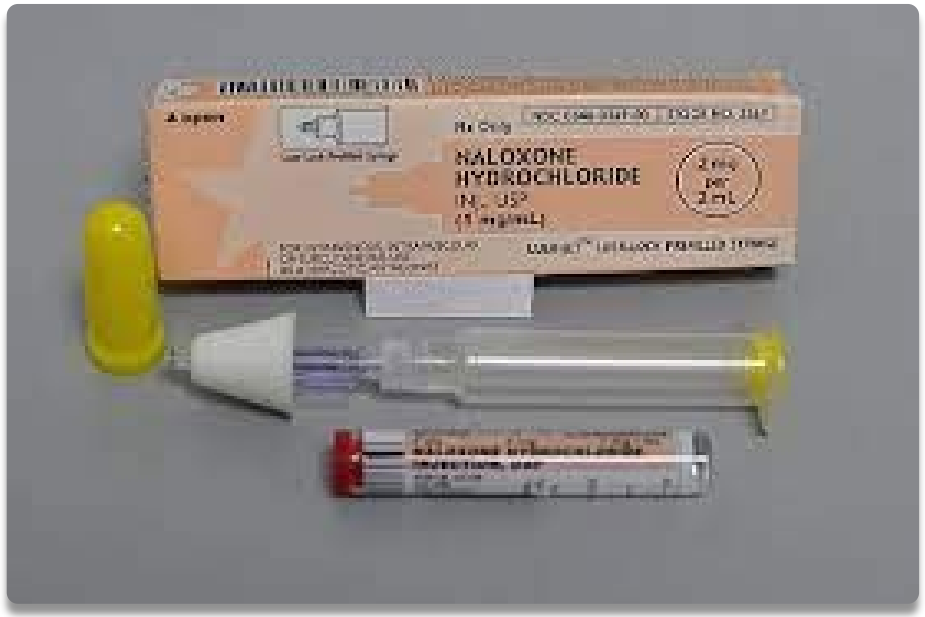
NALOXONE

Antagonist

Receptor

Antagonist/Receptor Interaction = **NO** drug action/Effect

Treatment: Naloxone (Narcan®)



- Goal of Naloxone – Reverse respiratory depression associated with opioid overdose
  - Reminder: Naloxone does **NOT** reverse the neurotoxicity associated with meperidine's active metabolite normeperidine
- MOA: Mu opioid receptor competitive antagonist; displaces opioids from their receptor sites
- Multiple routes of administration
  - IV preferred
  - Intranasal preferred if no IV access
  - IM, SubQ, IO, Endotracheal, Nebulization

Lexi-Drugs.®

Lexi-Tox.®

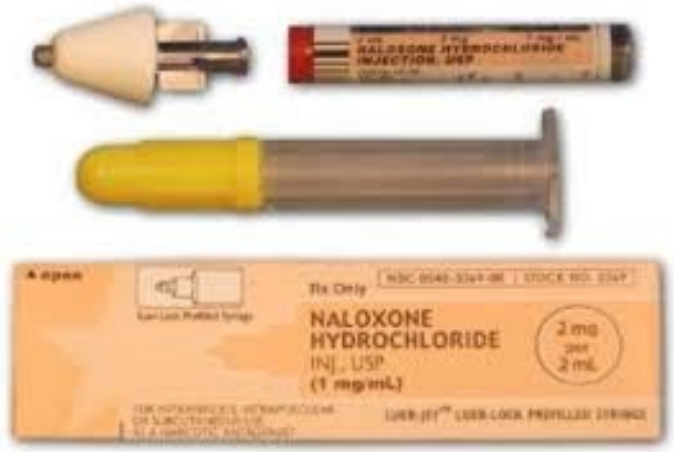
Treatment: Naloxone (Narcan®)

- Adult Dosing
  - IV/IM/SubQ Initial Dose: 0.4 – 2 mg; repeat every 2 – 3 minutes as needed
    - In patients with known opioid dependence, consider starting lower doses of 0.1 – 0.4 mg
      - Doses too high may throw patients in to immediate opioid withdrawal
    - If no response after total 10 mg administered, consider other causes of respiratory depression
  - Repeat doses may be needed after initial reversal depending on duration of the associated opioid
  - If exposure to a long-acting or extended release opioid, may need to initiate a continuous infusion of naloxone

Lexi-Drugs.®
Lexi-Tox.®

Treatment: Naloxone (Narcan®)

- Intranasal
  - Narcan® Nasal Spray: 4 mg as a single dose
    - May repeat every 2 – 3 minutes in alternating nostrils until medical assistance is available
  - Generic naloxone with mucosal atomization device
    - Dose: 2 mg (1 mg per nostril)
    - May repeat in 3 – 5 minutes if inadequate response



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Treatment: Naloxone (Narcan®)

- Pharmacokinetics:
  - Onset of action
    - IV ~2 minutes
    - Intranasal ~8 - 13 minutes
  - Duration of action
    - 30 – 120 minutes depending on route of administration
  - Half-life elimination
    - IM/IV/SubQ 0.5 – 1.5 hours
    - Intranasal ~2 hours

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Opioid Pharmacokinetics in Adults

- Fentanyl (IV)
  - Onset of action almost immediate
  - Duration of action: 30 minutes – 1 hour
  - Elimination half-life: 2 – 4 hours
- Heroin
  - Onset of action rapid
  - Duration of action: ~3 – 4 hours
  - Elimination half-life: mean 3 minutes
    - Active Metabolites: 2 – 3 hours
- Oxycodone IR
  - Onset of action: 10 – 15 minutes
  - Time to peak plasma concentration: 1.2 – 1.9 hours
  - Duration of action: 3 – 6 hours
  - Apparent half-life: 3.2 – 4 hours
- Oxycodone ER
  - Time to peak plasma concentration: 4 – 5 hours
  - Duration of action: ≤12 hours
  - Apparent half-life: 4.5 hours

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Naloxone Infusions

- Indicated for patients who were exposed to long-acting opioids or extended release products
  - Should also be considered in symptomatic body packers (drug mules) where continued exposure to drug is expected

- Dosing (2 methods)
  - Method 1: Calculate dosage per hour based on effective intermittent dose used and duration of adequate response seen
  - Method 2: Use two-thirds (2/3) of the initial effective naloxone bolus on an hourly basis
  - One half (1/2) of the initial bolus dose should be re-administered 15 minutes after the initiation of the continuous infusion to prevent a drop in naloxone levels
  - Usual dose: 0.25 – 6.25 mg/hr

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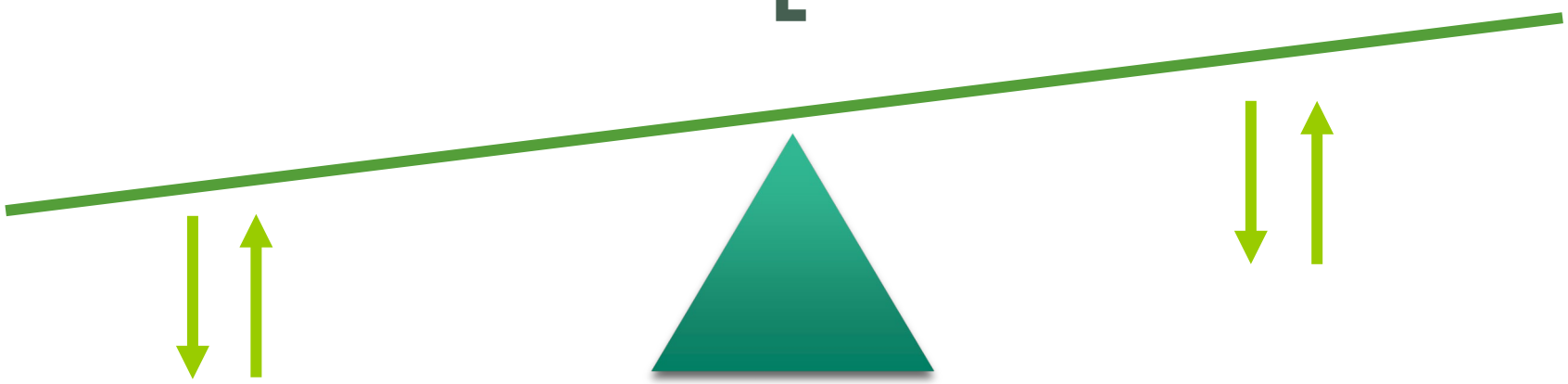
Naloxone Infusions – A Balancing Act

Adequate Ventilation

G
O
A
L

Prevention of Withdrawal



Prescribing Opioids for Acute Pain: Ohio Edition

Ohio Prescribing Limits
for Opioids for Acute Pain (effective 31 August 2017)

NOTE: these rules apply to outpatient prescriptions only

Acute Pain is defined as pain arising from an injury or condition and is expected to resolve within days to weeks.
Chronic pain is that which lasts beyond 12 weeks.

Opioids considered long-acting (egs methadone, oxycodone) should not be prescribed for acute pain.

The Ohio morphine equivalent dose (MED) calculations are the same as for the CDC morphine milligram equivalent (MME) calculations
To assist prescriber's in calculating a patient's morphine equivalent dose, the State of Ohio Board of Pharmacy has developed a conversion chart that can be accessed at: www.pharmacy.ohio.gov/MEDtable.

In general, the rules limit the prescribing of opioid analgesics for acute pain, as follows:

1. No more than seven days of opioids can be prescribed for adults.
2. No more than five days of opioids can be prescribed for minors and only after the written consent of the parent or guardian is obtained.
3. Health care providers may prescribe opioids in excess of the day supply limits only if they provide a specific reason in the patient's medical record.
4. Except as provided for in the rules, the total morphine equivalent dose (MED) of a prescription for acute pain cannot exceed an average of 30 MED per day.
5. The new limits do not apply to opioids prescribed for cancer, palliative care, end-of-life/hospice care or medication-assisted treatment for addiction.
6. The rules apply to the first opioid analgesic prescription for the treatment of an episode of acute pain.

Start Talking!

Consent Form

for Prescribing Opioids to Minors

Patient Name:
Date of birth:

Prescription name & quantity:
Number of refills:

The prescribed drug is a controlled substance containing an opioid. This means the medication has been identified by the United States Drug Enforcement Administration as having a potential for abuse, dependence or misuse.

I certify that I have discussed the following with the minor patient and the patient's parent, guardian or authorized adult:

(a) The risks of addiction and overdose associated with a controlled substance containing an opioid;

(b) The increased risk of addiction to controlled substances of individuals suffering from both mental and substance abuse disorders;

(c) The dangers of taking controlled substances containing opioids with benzodiazepines, alcohol or other central nervous system depressants;

(d) Any other information in the patient counseling information section of the labeling for the medication required by Federal law.

_____

Signature of prescriber Date

_____

Parent/Guardian Date

_____

Adult Authorized to Consent to Minor's Treatment* Date

*An adult to whom a minor's parent or guardian has given written authorization to consent to the minor's medical treatment. The prescription must be limited to not more than a single 72-hour supply if the person consenting to treatment is an adult authorized to consent to a minor's treatment. See, Section 3719.061, Ohio Revised Code.

See the Start Talking! website for tips on talking to kids about drugs
StartTalking.ohio.gov

Patient Name
Date of Birth or
Medical Record Number

https://www.ohioafp.org/wp-content/uploads/2017/06/Start-Talking-Model-Consent-Form.pdf

Calculating Morphine Milligram Equivalent (MME)

Note: The table below is **not** an opioid conversion table. It is **not** designed nor intended to be used to convert one opioid to another. Refer to specific opioid conversion tables or references.

This table is intended only to determine the morphine milligram equivalent total daily dose for patients receiving different oral (PO) opioid medications concurrently. (see the example sample calculation below for the correct intended use of this table)

CDC Morphine Milligram Equivalents (MME)

OPIOID (doses in mg/day except where noted)	**CONVERSION FACTOR**
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1 – 20 mg/day	4
21 – 40 mg/day	8
41 – 60 mg/day	10
≥ 61 – 80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Source: www.cdc.gov/drugoverdose/prescribing/guideline.html

To calculate MME:

Step 1) DETERMINE the total daily amount of each opioid the patient takes.

Step 2) CONVERT each opioid to its MME — multiply the dose of each opioid by the conversion factor in the above table.

Step 3) ADD them together.

- Patients prescribed higher opioid dosages are at higher risk of overdose death.
- Dosages > 50 MME/day are at TWICE the risk to overdose than dosages < 20 MME.
- Use the above conversion factor to calculate daily MME only – it is NOT to be used as a tool to convert from one opioid to another.
- Use extra precautions when increasing to ≥ 50 **MME**˚ per day such as:
  - Monitor and assess pain and function more frequently
  - Discuss reducing dose or tapering and discontinuing opioids if benefits do not outweigh harms.
  - Consider offering naloxone.
- Avoid or carefully justify increasing dosage to ≥ 90 **MME**˚ per day.

˚These dosage thresholds are based on overdose risk when opioids are prescribed for pain and should not guide dosing of medication-assisted treatment for opioid use disorder.

Recommendation #6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.

Source: CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016. JAMA;315(15):1624-1645

Sample calculation:

Patient is receiving OxyContin 10 mg PO twice a day and hydrocodone/acetaminophen 7.5 mg/325 mg PO every 6 hours as needed for breakthrough pain. What is their daily MME?

So what are some appropriate acute pain prescriptions???

- Remember the rules:
  - No more than a 7 day supply for adults
  - No more than 30 Morphine Equivalent Dose (MED) per day

- Hydrocodone/APAP 5/325 mg tabs
  - Conversion factor to Morphine = 1
  - Therefore, can prescribe no more than 30 mg of Hydrocodone per day for 7 days
  - Possible script: Hydrocodone/APAP 5/325 mg tabs
    - Sig: Take 1 tab PO q4h prn pain
    - Total quantity: 42 tabs

So what are some appropriate acute pain prescriptions???

- Remember the rules:
  - No more than a 7 day supply for adults
  - No more than 30 Morphine Equivalent Dose (MED) per day

- Oxycodone IR tabs
  - Conversion factor to Morphine = 1.5
  - Therefore, can prescribe no more than 20 mg of Oxycodone per day for 7 days
  - Possible script: Oxycodone 5 mg tabs
    - Sig: Take 1 tab PO q6h prn pain
    - Total quantity: 28 tabs

References:

- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013 Jan;41(1):263-306.
- Basic and Clinical Pharmacology, 12th edition, 2011, Ed: Bertram G. Katzung, McGraw Hill, Chapter 31, 32, 58.
- Centers for Disease Control and Prevention. Opioid Overdose. https://www.cdc.gov/drugoverdose/opioids/heroin.html. Accessed March 15, 2018.
- Clinical Anesthesiology – 6th edition, 2018.. Butterworth, Mackey, Wasnick. McGraw Hill/Lange, Chapter 10.
- Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018 Sept; 46(9): e825-e873.
- Gausche-Hill M, Brown KM, Oliver ZJ, Sasson C, Dayan PS, Echmann NM, *et al*. An evidence-based guideline for prehospital analgesia in trauma. *Prehospital Emergency Care*. 2014; 18 (Suppl 1): 25-34
- Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; March 20, 2018.
- Lexicomp Online® , Lexi-Tox® , Hudson, Ohio: Lexi-Comp, Inc.; March 20, 2018.
- MacKenzie M, Zed PJ, Ensom MHH. Opioid pharmacokinetics-pharmacodynamics: clinical implications in acute pain management in trauma. *Annals of Pharmacotherapy*. 2016; 50(3): 209-218.
- McCord J, Jneid H, Hollander JE, de Lemos JA, Cercek B, Hsue P, *et al*. Management of cocaine-associated chest pain and myocardial infarction. *Circulation*. 2008; 117: 1897-1907.
- Nelson L, Odujebe O. Cocaine: Acute Intoxication. *UpToDate*. Waltham, Mass.: UpToDate; 2018. www.uptodate.com. Accessed March 20, 2018.
- Ohio Department of Health. Increasing Heroin Overdose in Ohio: Understanding the Issue. http://mha.ohio.gov/portals/0/assets/research/reports/heroinoverdosereportfin43014.pdf. Accessed March 14, 2018.
- Pain management. University of Wisconsin: School of Medicine and Public Health. http://projects.hsl.wisc.edu/GME/PainManagement/index.html. Accessed February 19, 2020.
- Pathan H and Williams J. Basic opioid pharmacology: an update. *British Journal of Pain.* 2012; 6(1): 11-16.
- Pharmacology & Physiology in Anesthetic Practice – 6th edition, 2022. Flood, Rathmell. Wolers Kluwer, Chapters 6 and 7.
- Pharmacotherapy– A pathophysiological approach – 8th edition, 2011, Ed: Dipiro, Talbert, Yee, Matzke, Wells, Posey, McGraw Hill, Chapter 14
- Street Drugs. https://www.streetdrugs.org/. Accessed March 16, 2018.