Opioid Analgesics

Pediatric Pain Management

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Contents

Opioid Medications – Generalized Characteristics

- Opiates vs. Opioids
  - Opiates: substances with active ingredients naturally derived from opium
    - Morphine, codeine, thebaine
  - Opioids
    - Synthetically manufactured substances that mimic the effects of opium
- Classification based on action
  - Full agonists (primary action via μ_1 receptors)
  - Partial agonists: less conformational change and receptor activation than full agonists
    - Low doses: may provide similar effects to full agonists
    - High doses: analgesic activity plateaus; increased adverse effects
  - Mixed agonists/antagonists: varying activity depending on opioid receptor and

	Mu	Delta	Kappa
Clinical Effect	Supraspinal chemical, thermal, & mechanical nociception Analgesia Euphoria, sedation Respiratory Depression Miosis Reduced GI Motility Hormonal Changes	Mechanical nociception Inflammatory pain Analgesia Euphoria Physical dependence Dopamine release inhibition Mu receptor modulation	Spinal-mediated thermal nociception Chemical visceral pain Sedation Miosis Dysphoria Respiratory Depression Constipation Diuresis

Opioid Medications – Generalized Characteristics

- Opioid-induced respiratory depression
  - Therapeutic opioid doses decrease minute ventilation by decreasing respiratory rate
    - Tidal volume maintained
  - Depressed ventilatory response to carbon dioxide
    - CO_2 response curve shows decreased slope and rightward shift
  - Apneic threshold increased
  - Resting ETCO2 increased
  - Partial agonists and agonist-antagonist opioids less likely to cause severe respiratory depression than selective kappa agonists

Opioid Medications – Generalized Characteristics

- Additional Side Effects
  - Acute Desensitization
    - Acute receptor agonism (minutes to hours) → activation of intracellular signaling → acute tolerance or desensitization
      - Disappears with a time course parallel to the clearance of the agonist
      - Likely related to receptor phosphorylation → receptor uncoupling from G-protein and/or internalization of the receptor
  - Hyperalgesia
    - A state of nociceptive sensitization caused by exposure to opioids
    - Paradoxical response; increased sensitivity to noxious stimuli with administration of opioids
    - Secondary to neuroplastic changes in the peripheral and central nervous system (CNS) → sensitization of pronociceptive pathways
    - Multiple proposed mechanisms
    - Signs
      - Opioid effect wanes in absence of disease progression
      - Unexplained pain reports or diffuse allodynia unassociated with original pain
      - Increased pain levels with increasing dosages
    - Treatment: dose discontinuation or decrease, augmentation with NMDA modulators
- Signs & Symptoms of Withdrawal
  - Flu-like illness, dysphoria, insomnia, pupillary dilation, piloerection, yawning, muscle aches, lacrimation, rhinorrhea, nausea, fever, sweating, vomiting and diarrhea

Opioid Medications - Morphine

- Naturally occurring opioid derived from the poppy straw of the opiate poppy
- Prototypical opioid, against which the potency of all other opioids are measured
- “Morphium” after the Greek god Morpheus, the god of dreams.
- IV, oral, buccal, sublingual, intranasal, subQ, intramuscular, and neuraxial
- Oral administration: extensive first pass metabolism
- Neuraxial administration: biphasic respiratory depression
  - Early: systemic absorption into the intravascular compartment (30-90 min.)
  - Late: slow migration through the cerebrospinal fluid (hydrophilic) and into the respiratory drive center brainstem (6-18 hours after administration)
- Primarily metabolized in the liver by glucuronidation
  - Second phase of this metabolism yields two compounds
    - Morphine-3-glucuronide (no analgesic qualities)
    - Morphine-6-glucuronide (active metabolite)
      - Potency 100x parent compound
      - ↓ lipophilicity; ↓ crossing of blood brain barrier (normal renal function)
      - Neonates and decreased renal function at risk for accumulation → respiratory depression, sedation, potential coma
  - Metabolism develops markedly over first few weeks of life
    - Morphine’s V_d and clearance increase rapidly with age during initial period of life
    - Levels equal to those of an adult by the 2 weeks to 2 months of age

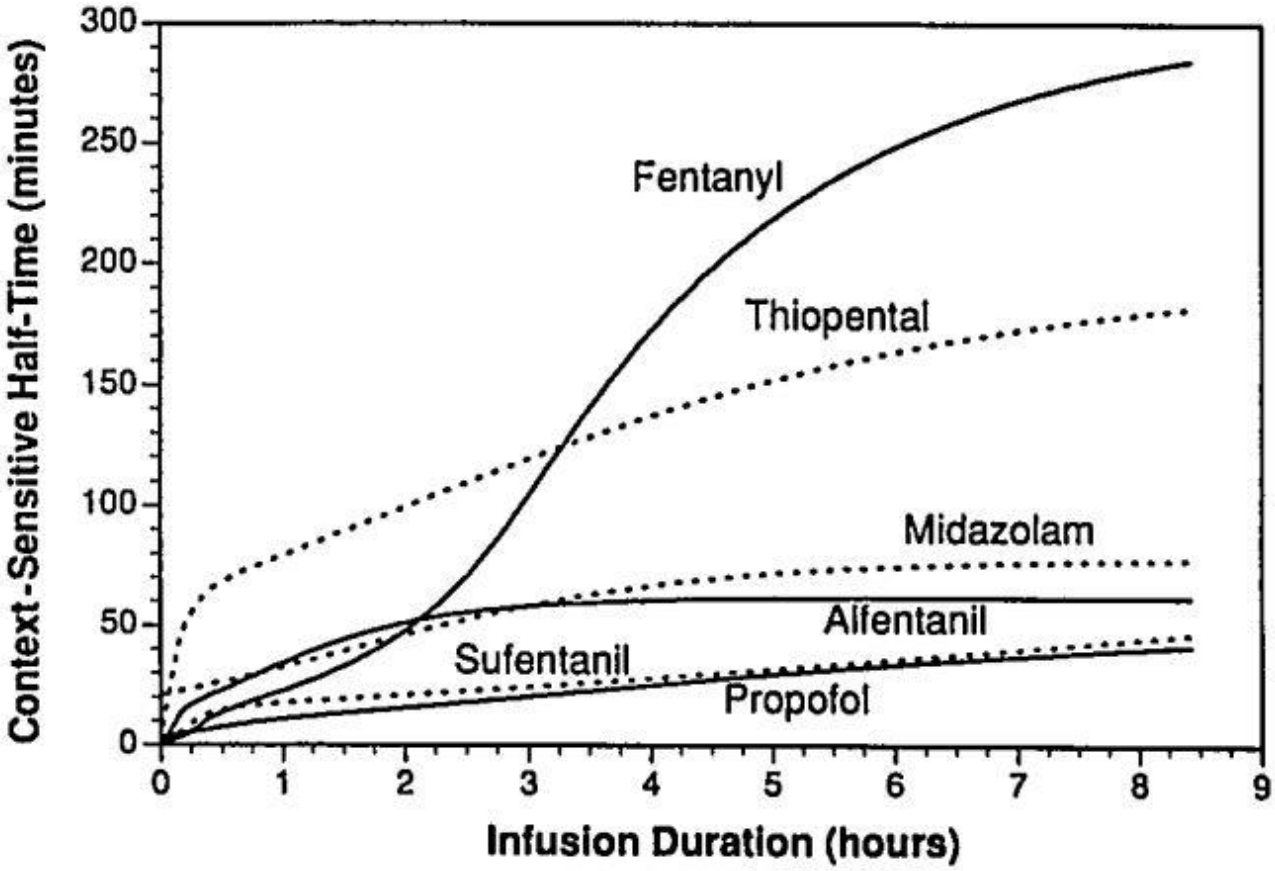
Opioid Medications - Fentanyl

- Most widely used synthetic opioid; potency 100x that of morphine
- Highly lipophilic & high membrane permeability → rapid onset/offset
  - Action terminated secondary to redistribution from active sites
  - Context sensitive half time
    - Variable, delayed time until offset after prolonged administration
    - Compartment saturation → termination by metabolism and elimination
- Routes: IV, epidural, intrathecal, transdermal, intranasal, other transmucosal
- Highly alpha-1-glycoprotein bound
  - Neonates with ↓ glycoprotein production → higher percentage unbound
- Fentanyl patches
  - Semipermeable membrane with a medication reservoir; doses of 25-100mcg/hour
  - Peak effect 12-24h; offset prolonged by deposition in skin & subQ tissue
  - Uptake variables: body temperature, body fat composition, patch location
- Increasingly common substance of abuse
  - Unreliable purity and potency: analogues with up to 10,000x that of morphine
  - Combined with heroin, other substances of abuse; frequently sold as oxycodone
  - Mortality: 2016 alone, over 20,000 deaths from fentanyl-related overdose
    - 5 times those which occurred in 2013
    - 82% involved illegally-manufactured fentanyl; only 4% from Rx medication

Opioid Medications - Fentanyl

Fentanyl

- Context Sensitive Half Time [Hughes]



Opioid Medications - Hydromorphone

- Hydrophilic, semi-synthetic (from morphine), hydrogenated ketone
- Potency approximately 5x greater than that of morphine
- Low oral bioavailability
  - Converting from IV to PO, dosage increased by approximately 4x
  - Peak effect at 15-30 minutes when given intravenous; duration 2-3 hours
- Hepatic metabolism by phase 2 glucuronidation
  - Hydromorphone-3-glucuronide
    - Active metabolite
    - Devoid of analgesic properties
    - Accumulation associated with neuroexcitatory effects
      - Allodynia
      - Agitation, confusion, hallucination
      - Myoclonus, ataxia, tonic-clonic seizures

Opioid Medications - Sufentanil

- Synthetic opioid structurally similar to fentanyl
  - Methoxymethyl group on piperidine ring → shorter duration of action
- 5-10x greater potency than fentanyl; ~500x potency of morphine
- Intravenous, intramuscular, neuraxial, sublingual tablet (2018)
- Renal Failure
  - Hepatic metabolism without active metabolites
  - Improved context-sensitive half life over that of fentanyl
- Among highest therapeutic index of commercial opioids (~27,000)
- More effective analgesia; less respiratory depression when compared to fentanyl

Opioid Medications - Oxycodone

Oxycodone

- Semisynthetic opiate derived from the alkaloid compound thebaine
- Full μ receptor agonism; partial κ and δ agonism
- ~1.5x potency of morphine
- Oral solution, immediate release tablet, extended release tablet, and tamper-resistant formulations
- Frequently combined with acetaminophen
  - Improved analgesia
  - Theoretical decrease in abuse potential
- Onset of action (IR formulation) 10-30 min; peak plasma at 30-60 min
- Oxymorphone
  - Active metabolite
  - Responsible for 10-15% of drug action
  - In renal or hepatic dysfunction, may accumulate and cause a pronounced level of respiratory depression and sedation

Opioid Medications - Codeine

Codeine

- Opioid agonism primarily via active metabolite, morphine
- Substantial genetic variability in CYP2D6 results in varied metabolism, from no effect to high sensitivity
  - Ultra-rapid metabolizers
    - Convert codeine to morphine more rapidly and completely
    - ~30% North African and Ethiopian patients
    - ~6% African American, caucasian, and Greek patients
    - Somnolence, decreased arousability, disorientation, confusion, apnea, hypoxia
- Discouraged use in pediatrics by multiple organizations
  - World Health Organization
  - US Food and Drug Administration
  - European Medicines Agency

Opioid Medications - Methadone

- Synthetic opioid first tested as a treatment for heroin addiction in 1964
- Mechanism
  - Full μ opioid agonism
    - l-Isomer/R-met
  - NMDA antagonism
    - d-Isomer/S-met
  - MAOI
    - TCAs may increase effect
- Fecal excretion primarily (some renal)
  - Multiple applications
    - Acute pain
    - Chronic pain
    - Opioid weaning in dependence
      - NMDA thought to mitigate hyperalgesia
  - Analgesic effect of 12-36 hours after single dose
  - Peak analgesia 10-15 minutes with IV dosing
  - Variable half-life of 12-100 hours
    - Steady state maximal effect ~ 5 days
  - Oral bioavailability 65-95%

Opioid Medications - Methadone

- Highly lipophilic
- Biphasic elimination phase
  - Alpha phase (distribution phase)
    - 8-12 hours
    - Approximates period of analgesia
  - Beta phase (clearance)
    - 30-60 hours
    - Avoid withdrawal syndrome
    - Insufficient for analgesia
  - Reason for BID dosing for analgesia and daily dosing for opioid maintenance
- Conversion from morphine based on MEDD
- QTc prolongation → Torsades de Pointe
  - Monitor EKG
  - Treatment magnesium

Morphine to Methadone Conversion	
Morphine (mg/day)	Methadone (mg/day)
20	5
40	10
60	15
90	20
120	20
180	22.5
200	25
300	30

Opioid Medications - Meperidine

- Meperidine
  - Synthetic opioid; derived from phenylpiperidine
  - Analgesic effects via action at the μ receptor; anti-shivering via κ receptor agonism
  - 1/10 as potent as morphine; elimination half-life ~ 3 hours
  - Routes: intravenous, oral, intramuscular, subcutaneous
    - Injection with local anesthetic properties
    - Effects at sodium channel
  - Hepatic metabolism by hydrolysis and N-demethylation
    - Normeperidine
      - Active metabolite of meperidine
      - About ½ of the analgesic properties of meperidine; 2x the seizure-inducing activity
      - Delirium, dysphoria, and tremor
  - Cardio-depressive effects and tachycardia
  - Chemical structure similar to atropine
    - Anticholinergic effects
    - Less miosis than other opioids
  - Serotonergic activity
    - Associated with serotonin syndrome: excitation, delirium, hyperpyrexia, and convulsions
    - Avoid co-administration with SSRIs, SNRIs, and MAOIs
  - Previously considered low risk of addiction
    - Increased euphoria from meperidine than with oxycodone and hydromorphone
    - Rapid onset of action
    - High abuse potential

Opioid Medications - Tramadol

- Atypical opioid of the benzoid class [Bozkurt]
  - Potency 10% that of morphine
  - Multiple means of action
    - Opioid agonism (primarily μ)
    - Inhibition of serotonin and norepinephrine
    - Serotonin 5-HT_{2C} antagonism
    - Minimal effects at NMDA receptors
  - Decreased seizure threshold
    - Co-administration with meperidine
    - Naloxone further increases risk
  - Risk of serotonin syndrome
    - Monoamine oxidase inhibitors and tricyclic antidepressants
  - As of 2017, FDA contraindicated in patients under 12 years old
    - “Serious risks, including slowed or difficulty breathing and death, which appear to be a greater risk in children younger than 12 years”

Opioid Medications - Nalbuphine

- Nalbuphine (Nubain®)
  - Antipruritic (opioid-induced pruritus) and analgesic effects
  - High-efficacy partial agonist of the κ-opioid receptor
  - Moderate-efficacy partial agonist, agonist, or antagonist of μ receptor
    - Antagonist activity
      - Doses ≤ analgesic dose
      - Coadministration with mu agonists may result in partial reversal or blockage of opioid-induced respiratory depression
      - May precipitate withdrawal in chronic opioid users
  - Low affinity δ-opioid (DOR) and sigma receptors
  - Respiratory depression equivocal to equianalgesic morphine doses
    - Ceiling effect (increased doses > 30 mg without further respiratory depression)

Opioid Medications - Naloxone

- Non-selective and competitive opioid receptor antagonist
  - Potent antagonist at μ receptor
  - Moderate antagonistic properties at δ and κ opioid receptors
- Incremental doses of 0.5-1mcg/kg to avoid withdrawal symptoms in chronic opiate users or opiate-dependent patients
  - Restlessness, agitation, tachycardia, hypertension, ventricular fibrillation, dyspnea, pulmonary edema, diaphoresis, nausea, vomiting
- Infusion at 1-2 mcg/kg/h for opiate-induced pruritus
- Half-life of 60-90 minutes
  - Effects terminate prior to elimination of most μ agonists
  - Infusion or re-dosing as necessary to prevent recurrence of sedation and respiratory depression
- Multiple routes of administration, including a nasal spray formulation and single-use filled syringe kits

Opioids in Renal Failure [Dean]

- Typically Avoided
  - Codeine
    - Morphine and morphine-6-glucuronide active metabolites
  - Morphine
    - Metabolized to morphine-3-clucuronide (55%) and morphine-6-glucuronide (10%) and renally excreted
    - M6G accumulation leads to respiratory depression, hypotension, narcolepsy
  - Hydrocodone
    - Metabolized to hydromorphone
      - Hydromorphone-3-glucuronide: potential for neuroexcitatory effects
  - Meperidine
    - Normeperidine active metabolite; accumulation □ decreased seizure threshold
- Used with Caution
  - Oxycodone
    - Active metabolite oxymorphone; plasma levels typically negligible
  - Hydromorphone
- Typically Used
  - Fentanyl: metabolized by liver; lacks active metabolites
  - Sufentanil: metabolized by liver; lacks active metabolites. Decreased context sensitive half time.
  - Alfentanil: metabolized by liver; lacks active metabolites
  - Methadone
    - Fecal and urinary excretion without active metabolite
    - Typically considered safe in renal disease
  - Remifentanil
    - Nonspecific plasma esterases; inactive metabolites

Acetaminophen and Acute Hepatic Failure

- Acetaminophen Toxicity
  - Most common cause of acute liver failure in US
  - Up to 500 annual cases of unintentional overdose leading to acute liver failure
    - ~150 deaths per year [Fontana]
  - Acute hepatic failure: severe, acute liver injury with encephalopathy & impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or preexisting liver disease & with an illness of fewer than 26 weeks duration
- Hepatic metabolism: primarily non-toxic, inactive metabolites excreted by the kidneys
  - Glucuronidation (45-55%), Sulfate conjugation (20-30%), N-hydroxylation and dehydration, typically followed by glutathione conjugation
    - N-acetyl-p-benzoquinone imine (NAPQI): intermediate toxic metabolite
      - Therapeutic doses: NAPQI detoxified 1° by glutathione conjugation (min. oxidation by cytochrome P450)
      - Overdose: overwhelmed glutathione pathway → enhanced oxidation → high levels of oxidation byproducts → fulminant hepatic failure & necrosis
- Dosing in Pediatrics [Dimitropoulos]:
  - Do not exceed 50 to 70 mg/kg in 24 hours
  - Dose-dependent toxicity (toxicity varies according to baseline glutathione levels, etc.)
    - **Single dose: minimal toxic dose 150 mg/kg; toxicity likely >250mg/kg in 24h**
    - Chronic overdose: minimum toxic threshold 150-175 mg/kg daily over 2-4 days
- Combination opioid formularies often avoided in pediatrics as a result
  - Tylenol #3, Vicodin® [hydrocodone], Percocet® [oxycodone]

Opioids and Substance Use Disorders – Terms [Yaksh]

- Acute Desensitization
  - Acute receptor agonism (minutes to hours) → activation of intracellular signaling → acute tolerance or desensitization
    - Disappears with a time course parallel to the clearance of the agonist
    - Likely related to receptor phosphorylation → receptor uncoupling from G-protein and/or internalization of the receptor
- Tolerance
  - The need for larger doses of medication to maintain original effect
    - Tolerance to analgesic effects tends to parallel tolerance to side effects.
    - Varied rates of tolerance development, from little to no tolerance (pupillary miosis) to rapid tolerance (euphorogenic effects)
    - Resolution several weeks after withdrawal of substance
    - Degree of cross-tolerance exists (i.e. different μ agonists)
- Dependence
  - Production of withdrawal symptoms with cessation of drug exposure or with antagonist administration
  - Increased adenylyl cyclase, release of excitatory amino acids & cytokines, activation of microglia & astrocytes, initiation of apoptosis
  - Term is not synonymous with addiction
- Addiction
  - A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
- Pseudoaddiction: caused by poorly controlled pain; can mimic addiction
- Substance Use Disorder
  - DSM-V combines categories of substance abuse and substance dependence into single disorder measured on a continuum from mild to severe

Opioids and Substance Use Disorders – History [Jones]

- Addictive potential known for centuries (1860s)
  - United States civil war [Yaksh]
    - Administration of “soldier’s joy” (morphine & opium) → “soldier’s disease”
      - Opiate addiction secondary to using opioids to address soldiers’ chronic pain states
      - “The Dr. put me on morphine and I can’t stop that,” Chappell wrote to William R. Terry. “Can’t get it often except people give it to me.” A.M. Chappell (1886)
      - Addictive potential of opioids → search for opioid analgesics without addictive potential
- C.R. Alder Wright (1874)
  - Discovery of the synthetic opioid, diacetylmorphine. Later branded as “heroin” by Bayer corporation from 1890s-1913 and marketed as “non-addictive” cough suppressant and sedative
- Porter and Jick (1980)
  - Retrospective publication; 1-paragraph letter to editor published in New England Journal of Medicine
  - "There were only four cases of reasonably well documented addiction in patients who had no history of addiction… The addiction was considered major in only one instance.” – Porter and Jick of the Boston Collaborative Drug Surveillance Program
- Portenoy (1986)
  - Retrospective review of 38 patients
  - 2 of 38 patients with chronic pain developed substance use disorder when receiving opioid
  - “We conclude that opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse.”
- World Health Organization addressed the under-treatment of postoperative and cancer pain in 1986 with Cancer Pain Monograph

Opioids and Substance Use Disorders – History [Jones]

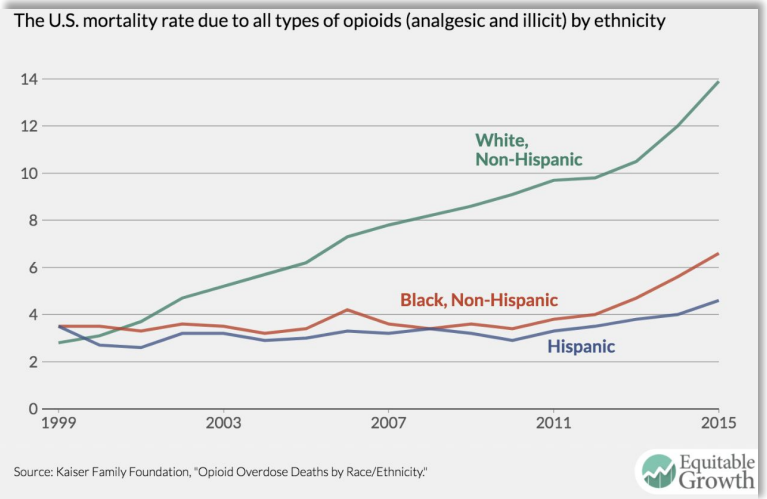
- Ronald Melzack (1990)
  - Article in *Scientific American*
  - "Contrary to popular belief, the author says, morphine taken solely to control pain is not addictive."
- American Pain Society (1995)
  - "Pain as the fifth vital sign" campaign – James Campbell
  - Encouraged proper, standardized evaluation and treatment of pain symptoms
- Purdue Pharma (1995)
  - Oxycontin approved
- Veteran's Health Administration (1999)
  - Adoption of pain as fifth vital sign initiative
- The Joint Commission (2000)
  - Published standards for pain management emphasizing the need for quantitative assessments of pain as recommended by the Institute of Medicine
- Federation of State Medical Boards and Drug Enforcement Agency
  - Promised less regulatory scrutiny over opioid prescribers
  - Decreased physician reluctance to prescribe opioids more liberally
  - Physicians mandated to provide adequate pain control by the TJC
  - Hospitals investing more readily in opioid therapy received better patient satisfaction rates

Opioids and Substance Use Disorders – History [Jones]

- Modern pharmaceutical companies
  - Encouraged the use of opioids as humane treatment option
    - Avoidance of opioids by the physician considered to be inhumane
    - Ensuing litigation for the under-treatment of pain
  - Purdue Pharma - Oxycodone (OxyContin)
    - Marketed as significantly decreased likelihood for misuse or abuse
    - 1997-2002, Oxycontin prescriptions increased from 670,000 to 6.2 million
    - Purdue Pharma (2007) plead guilty to federal charges of OxyContin misbranding
      - Intentionally downplayed risk of addiction posed by OxyContin
      - Mislead healthcare industry by overstating opioid benefits for chronic pain
  - Endo Pharmaceuticals and Johnson & Johnson facing related litigation
- Overall opioid consumption in U.S. increase
  - 46,946 kg consumed in 2000
  - 165,525 kg consumed in 2012
- American Academy of Pain Medicine, American Geriatric Society, American Pain Society facing litigation

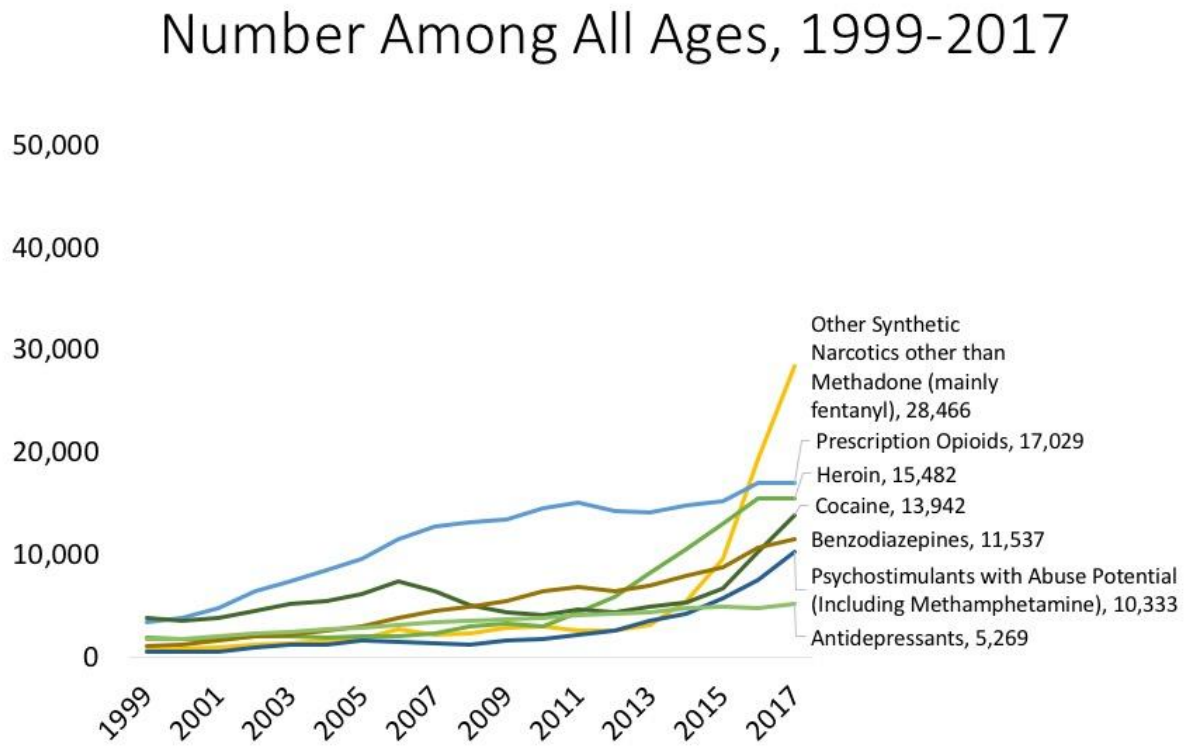
Opioids and Substance Use Disorders – Current

- CDC Statistics on Prescription Opioid Use
  - Up to 25% of patients receiving opioid for noncancer pain experience struggle with addiction
  - In 2016, more than 46 people died each day from overdoses involving prescription opioids
    - 130 people daily from opioid overdose in general
    - Now surpassed the 42 daily deaths which result from HIV/AIDS
  - Prescription opioids contribute to 40% US opioid overdose deaths
  - Prescription opioid overdose rates highest among people 25-54yo
  - Approximately 75% of new heroin users misused prescription opioids prior to using heroin
- Peri-procedural doses in pediatrics associated with risk of substance use disorders [Schroeder]
- Why the publicity now? Affected demographics:



Substance Use Disorder - Fentanyl

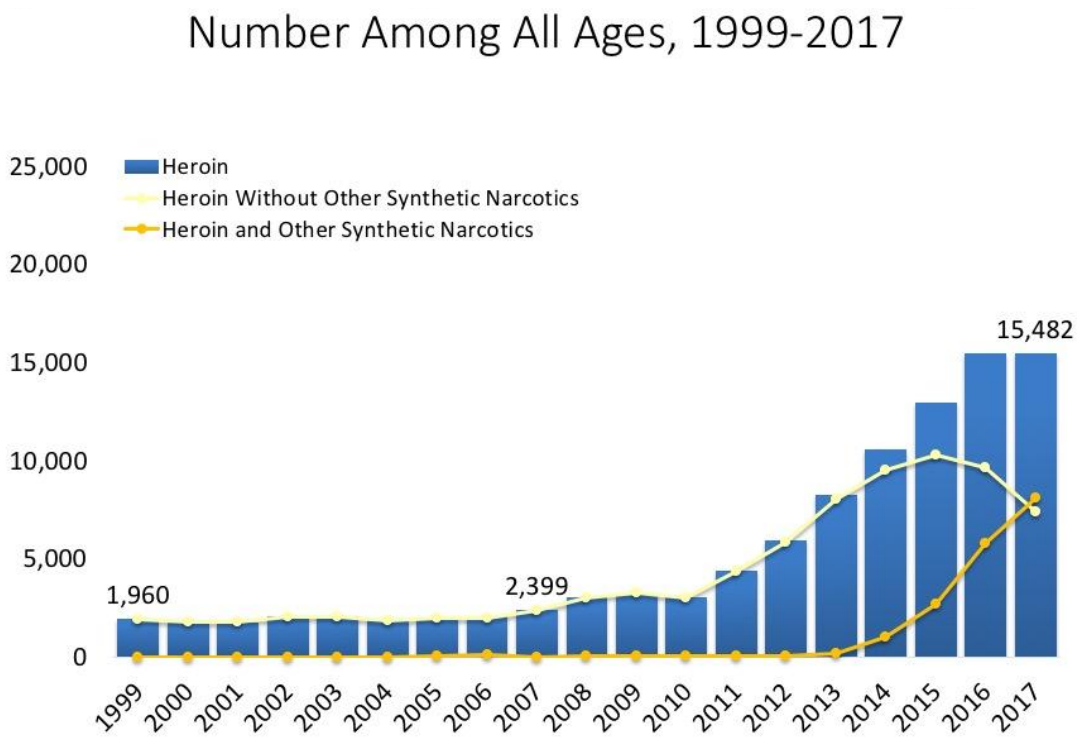
- National Overdose Deaths



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Substance Use Disorder - Fentanyl

- National Overdose Deaths



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Substance Use Disorders – Preventative Strategies

- 1° goal: decreased opioid administration with maintenance of adequate analgesia
  - Adjunctive medications to address all components of pain
    - Muscular spasm: methocarbamol, tizanidine, cyclobenzaprine, baclofen, etc.
    - Anxiety: α-2 agonists, benzodiazepines
    - NSAIDs: ibuprofen, naproxen, ketorolac, selective cox-2 inhibitors
    - Acetaminophen
    - Peripheral and Neuraxial Blockade
- Medication selection and mitigating euphoria
  - Oral vs. intravenous
  - Oral: Oxycodone vs. Morphine [Wightman]
    - Oxycodone [Remillard]
      - Increased active transport across blood-brain barrier [Okura]
      - Increased phasic dopaminergism in the ventral tegmental area, nucleus accumbens, and striatal reward centers [Weele]
      - Possible increase in kappa opioid receptor-mediated withdrawal dysphoria
  - IV: Hydromorphone vs. Morphine [Gulur]
- Medication administration
  - Bolus vs. infusion administered over 10-15 minutes
  - PCA: decreased dose and decreased frequency interval
- Patient and Parent Education

QUESTIONS???

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