Taking the Pain Out of Opioid Therapy

Ascension

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Disclosure

I have no relevant financial relationships with any ACCME-defined commercial interest to disclose. I will not discuss off label use and/or investigational use in my presentation.

Objectives

- Review basic pain concepts and the WHO analgesic step ladder
- Describe the mechanism of action of opioids and their side effects
- Recall conversions of common opioids and resources of opioid conversion information
- Identify additional patient care needs for patients on opioids

Pain Concepts

- *Pain*- unpleasant sensory or emotional experience associated with actual or potential tissue damage or nerve dysfunction
  - Subjective to each patient
  - "The fifth vital sign"
- One in five US adults reported to have chronic pain in 2016

Pain Management. In: Schwinghammer TL DiPiro JT et al. *Pharmacotherapy Handbook*. 11ed. McGraw Hill; 2021.
Kuehn, B. JAMA 2018;320(16):1632.

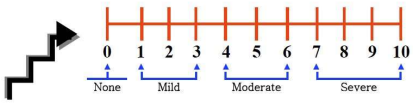
Pain Concepts

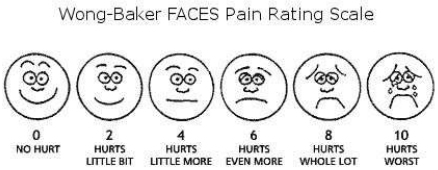
Pain Work-Up

- "PAINED"
  - Place
  - Amount
  - Intensifiers
  - Nullifiers
  - Effects
  - Descriptors

Critical Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2





Scullion BF and Ryan L, Pain Management. In: Attridge RL et al. *Internal Medicine: A Guide to Clinical Therapeutics*.McGraw Hill; 2013.
Images from: https://www.verywellhealth.com/pain-scales-assessment-tools-4020329
https://www.researchgate.net/figure/Critical-care-pain-observation-tool-CPOT_fig3_337928045

Pain Concepts

Classifications of Pain

- *Nociceptive*
  - *Somatic*- skin, bone, joint, connective tissue
    - Throbbing, aching, pressure
  - *Visceral*- internal organs, vasculature
    - Deep, cramping, stabbing, diffuse
- *Neuropathic*- peripheral or central nervous system damage
  - Burning, tingling, numbness, shooting

Scullion BF and Ryan L, Pain Management. In: Attridge RL et al. *Internal Medicine: A Guide to Clinical Therapeutics*.McGraw Hill; 2013.

Pain Concepts

Classifications of Pain

- *Acute*
  - After injury
  - Resolves when heals
  - Usually nociceptive pain
- *Chronic*
  - Persistent
  - If triggered by injury, does not resolve once healed
  - Nociceptive or neuropathic pain

Scullion BF and Ryan L, Pain Management. In: Attridge RL et al. *Internal Medicine: A Guide to Clinical Therapeutics*.McGraw Hill; 2013.

Pain Concepts

World Health Organization Analgesic Step Ladder

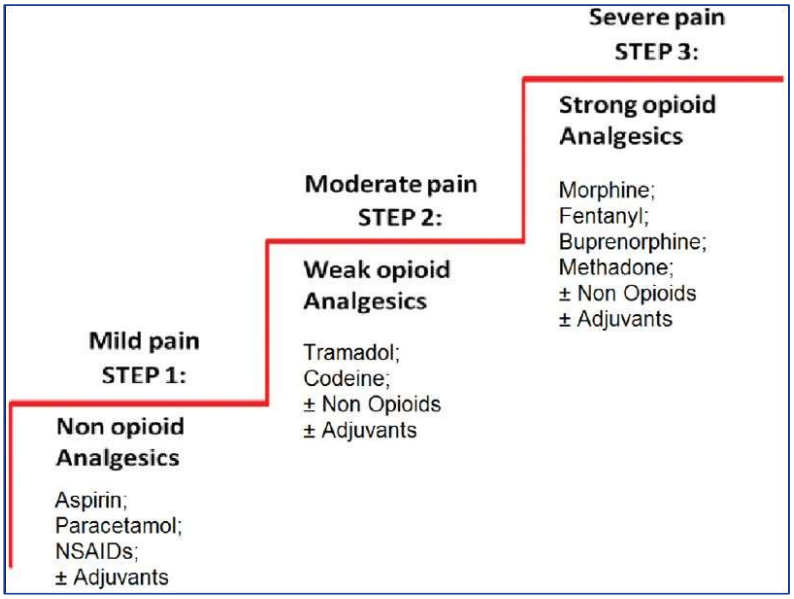


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Image from: https://www.indianjpain.org/viewimage.asp?img=IndianJPain_2019_33_4_11_276063_f1.jpg

Pain Concepts

Analgesics

- Non-Opioid Analgesics
  - NSAIDs
  - Acetaminophen
  - Aspirin
- Adjuvants
  - Tricyclic antidepressants
  - Duloxetine
  - Lidocaine
  - Steroids
  - Dexmedetomidine (ICU)
  - Ketamine (ICU)

Pain Management. In: Schwinghammer TL DiPiro JT et al. *Pharmacotherapy Handbook.* 11ed. McGraw Hill; 2021.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Opioid Analgesics

Site of Action

- Mu (μ), delta (δ), and kappa (κ) opioid receptor activation decreases the following:
  - Cellular cAMP
  - Protein kinase A activation
  - Release of neurotransmitters
- Mu (μ) and delta (δ) opioid receptor activation also causes:
  - Membrane hyperpolarization → suppression of depolarization

Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018. 11

Opioid Analgesics

Classification

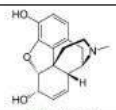
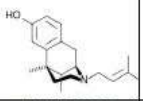
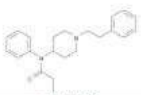
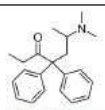
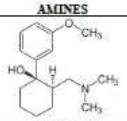
- Action
  - *Agonist*- high efficacy; promotes activation
  - *Partial Agonist*- less efficacy than agonist
  - *Antagonist*- prevents activation of receptor
- Type
  - *Natural (opiate)*- fully derived from nature (ex: opium, morphine, codeine)
  - *Semi-synthetic*- derived from opiates (ex: hydrocodone, hydromorphone)
  - *Synthetic*- fully made in the laboratory (ex: methadone, fentanyl)

Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018. 12

Opioid Analgesics

Classification

- Chemical Structure

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

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Image from: https://www.pharmacytimes.com/view/opioid-allergy-pseudo-allergy-or-adverse-effect
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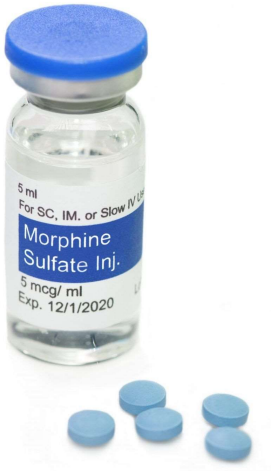
Opioid Analgesics

Natural Opioids (Opiates)

- Morphine
  - Bioavailability ~33%, but can vary
    - Oral form has first pass effect, decreased potency
  - Two metabolites- M-3G and M-6G
  - t½ morphine = 2-3 hrs, t½ M-6G = 12 hrs
  - Routes- PO, IM, IV, PR
  - Caution in cirrhosis, not recommended in renal failure



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Morphine sulfate injection. Package Insert. Hospira Inc; 2011.
Morphine sulfate tablets. Package Insert. Roxane Laboratories; 2012.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.
Image from:https://danapointrehabcampus.com/blog/2020/04/morphine-about-uses-and-abuse/

Opioid Analgesics

Natural Opioids (Opiates)

- Codeine
  - Bioavailability = 50%
  - Active drug with active metabolite (morphine)
  - t½ = 4 hrs
  - Antitussive effects
  - Routes- PO (tablet, solution), IV (rare)
  - Not recommended in renal failure

Codeine sulfate oral solution. Package Insert. West-Ward Pharmaceuticals Corp; 2017.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.
Image from:https://www.akorn.com/prod-details-list.php?group=Promethazine+Hydrochloride+and+Codeine+Phosphate+Oral+Solution%2C+CV&search=50383

Opioid Analgesics

Semi-Synthetic Opioids

- Hydromorphone
  - Bioavailability = 50%
  - t½ = 2-5 hrs
  - Structurally similar to morphine
    - 5-7x more potent than morphine
  - Renal failure→ potential neuroexcitation
- Hydrocodone
  - Bioavailability = 25%
  - Active metabolite = hydromorphone
  - t½ = 4 hrs
  - Usually in combination products
  - Caution in liver disease

Dilaudid (hydromorphone injection). Package Insert. Purdue Pharma; 2008.
Norco (hydrocodone bitartrate and acetaminophen tablet). Package Insert. Actavis; 2014.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Synthetic Opioids

- Oxycodone
  - Bioavailability = 50%
  - t½ = 2-4 hrs
  - PO (immediate release and extended release)
  - Structurally similar to morphine
  - Caution in liver disease
- Meperidine
  - t½ = 2-5 hrs
  - Toxic metabolite = normeperidine (seizure); t½ = 15-30h
  - Structurally similar to atropine (tachycardia)
  - Drug of choice for rigors
  - Do not use >48 hrs in CNS disease, renal disease, or geriatrics

Oxycontin (oxycodone HCl ER tablet). Package Insert. Purdue Pharma; 2018.
Meperidine HCl for injection. Package Insert. Sanofi-Aventis; 2008.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Synthetic Opioids

- Tramadol
  - Bioavailability = 70%
  - t½ = 13 hrs
  - Seizure activity seen in <1%
    - Increase risk EtOH abuse, stroke, head injury, renal insufficiency, SSRI/SNRI/TCA
  - Increased risk of serotonin syndrome
- Tapentadol
  - Bioavailability = 32%
  - t½ ~ 4 hrs
  - High fat, high calorie meal with admin may increase overall exposure
  - Caution in hepatic dysfunction

Ultram (tramadol hydrochloride tablet). Package Insert. Ortho-McNeil Pharmaceuticals Inc; 2008.
Nucynta (tapentadol hydrochloride tablet).. Package Insert. Ortho-McNeil Pharmaceuticals Inc; 2009.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Synthetic Opioids

- Fentanyl
  - IV t½ = 3.5 hrs; fast onset, fast offset
  - Routes- IV, transdermal, transmucosal, buccal
  - NOT for opioid-naive patients
  - Safe in renal failure
  - Transdermal patches
    - May need bridge pain control
    - SQ fat is reservoir
    - Heat considerations
    - Fold and flush to dispose

Fentanyl citrate injection. Package Insert. Akron; 2012.
Duragesic (fentanyl transdermal patch). Package Insert. Janssen; 2003.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.
Image from: https://www.medimfarm.ro/Products/Product/10610/fentanyl-actavis-50micrograme-h-x-5

Opioid Analgesics

Synthetic Opioids

- Methadone
  - Bioavailability = 80%
  - No metabolites
  - t½ = 8-59 hrs (highly lipophilic)
  - Prolonged duration of action with repeat dosing
  - Respiratory depression due to decreased brainstem responsiveness to CO_2
  - Titration considerations
  - Good option for hepatic or renal failure

Dolophine (methadone hydrochloride tablet). Package Insert. Roxane Laboratories; 2015.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Opioid Equivalency

Equianalgesic Opioid Dosing

Drug	Equianalgesic Doses (mg)	
	Parenteral	Oral
Morphine	10	30
Buprenorphine	0.3	0.4 (sl)
Codeine	100	200
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tramadol	100*	120

*Not available in the US

McPherson ML. *Demystifying Opioid Conversion Calculations: A Guide For Effective Dosing.* Amer Soc of Health-Systems Pharm, Bethesda, MD, 2010. Copyright ASHP, 2010. Used with permission. NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

Image from: https://www.hcplive.com/view/equianalgesic-opioid-dosing-calculation-isnt-simple-math
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

Opioid Equivalency

- Determine total amount of each opioid per day
- Multiply dose of each opioid by multiplier
  - Morphine milligram equivalent (MME)
- Add all MME together for total daily MMEs

Calculating 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

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

Image from:https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf
Center for Disease Control. *Calculating Total Daily Dose of Opioids for Safer Dosage.*Factsheet.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Opioid Analgesics

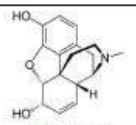
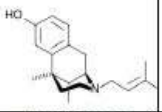
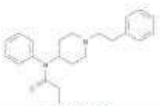
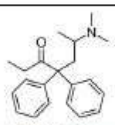
Opioid Equivalency

- Converting opioids
  - New opioid MME dose should be lower than original
    - Incomplete cross-tolerance
- ≥50 MMEs per day increased risk of overdose
  - Monitor and assess more frequently
  - Taper when possible
  - Offer naloxone
- ≥90 MMEs per day should be avoided or "carefully justified"

Center for Disease Control. *Calculating Total Daily Dose of Opioids for Safer Dosage*.Factsheet.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*.13ed. McGraw Hill; 2018.

Opioid Analgesics

Opioid Allergy Cross-Reactivity

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
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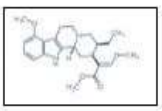
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK
*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group **6-position is substituted with a ketone group and tolerability is similar to hydroxylation				

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFSMB
http://paindr.com/wp-content/uploads/2018/02/Opioid-Structural-Classes-Figure_-updated-2018-02.pdf

Mitragynine (Kratom) 

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Additional Considerations

Additional Considerations

Opioid Side Effects

- Central Nervous System
  - Sedation, mood changes, myoclonus, hallucinations
- Gastrointestinal
  - Constipation, nausea, vomiting
- Pruritus
- Cardiovascular
  - Bradycardia (most), tachycardia (meperidine), hypotension

Pain Management. In: Schwinghammer TL DiPiro JT et al. *Pharmacotherapy Handbook.* 11ed. McGraw Hill; 2021.
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Additional Considerations

Additional Therapies for Opioid Patients

- Non-opioid analgesics and adjuvants previously discussed
- Bowel regimens/methylnaltrexone
- Physical/occupational therapies, activity
- Naloxone

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Additional Considerations

Naloxone

- Opioid reversal agent
  - Competes for opioid binding sites
  - Reversal of respiratory depression
- Dosage forms = intranasal, IM (injectable or autoinjector), IV (hospital use)
- Onset within minutes → caution; possibly combative
  - t½ varies (1-3 hrs)
- Need emergency medical attention after administration
  - Duration of opioids may > naloxone → relapse of respiratory depression

Naloxone hydrochloride (nasal spray). Package Insert. Adapt Pharma Inc.; 2015.
Pain Management. In: Schwinghammer TL DiPiro JT et al. *Pharmacotherapy Handbook.* 11ed. McGraw Hill; 2021.
Yaksh T and Wallace M. Opioids, Analgesia, and Pain Management, In: Brunton et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.*13ed. McGraw Hill; 2018.

Additional Considerations

Tolerance/Dependence/Withdrawal

- *Tolerance*- reduction in efficacy due to chronic exposure
- *Dependence*- if drug is stopped abruptly/tapered too quickly, patient will go into withdrawal
- *Withdrawal*- syndrome due to abrupt discontinuation of opioids
  - Symptoms include sweating, agitation, anxiety, nausea, tachycardia
- *Addiction*- patient has lost control over use; negative/harmful consequences

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Scullion BF and Ryan L, Pain Management. In: Attridge RL et al. *Internal Medicine: A Guide to Clinical Therapeutics.*McGraw Hill; 2013.

Summary

- Pain can be nociceptive or neuropathic, and is subjective
- Opioid side effects include pruritus, nausea, sedation, and bradycardia
- Common opioid conversion factors are extremely important for transitions between opioid medications and patient safety
- Additional considerations for our opioid patients include bowel regimens, activity, and rescue naloxone if needed

Taking the Pain Out of Opioid Therapy

Ascension

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