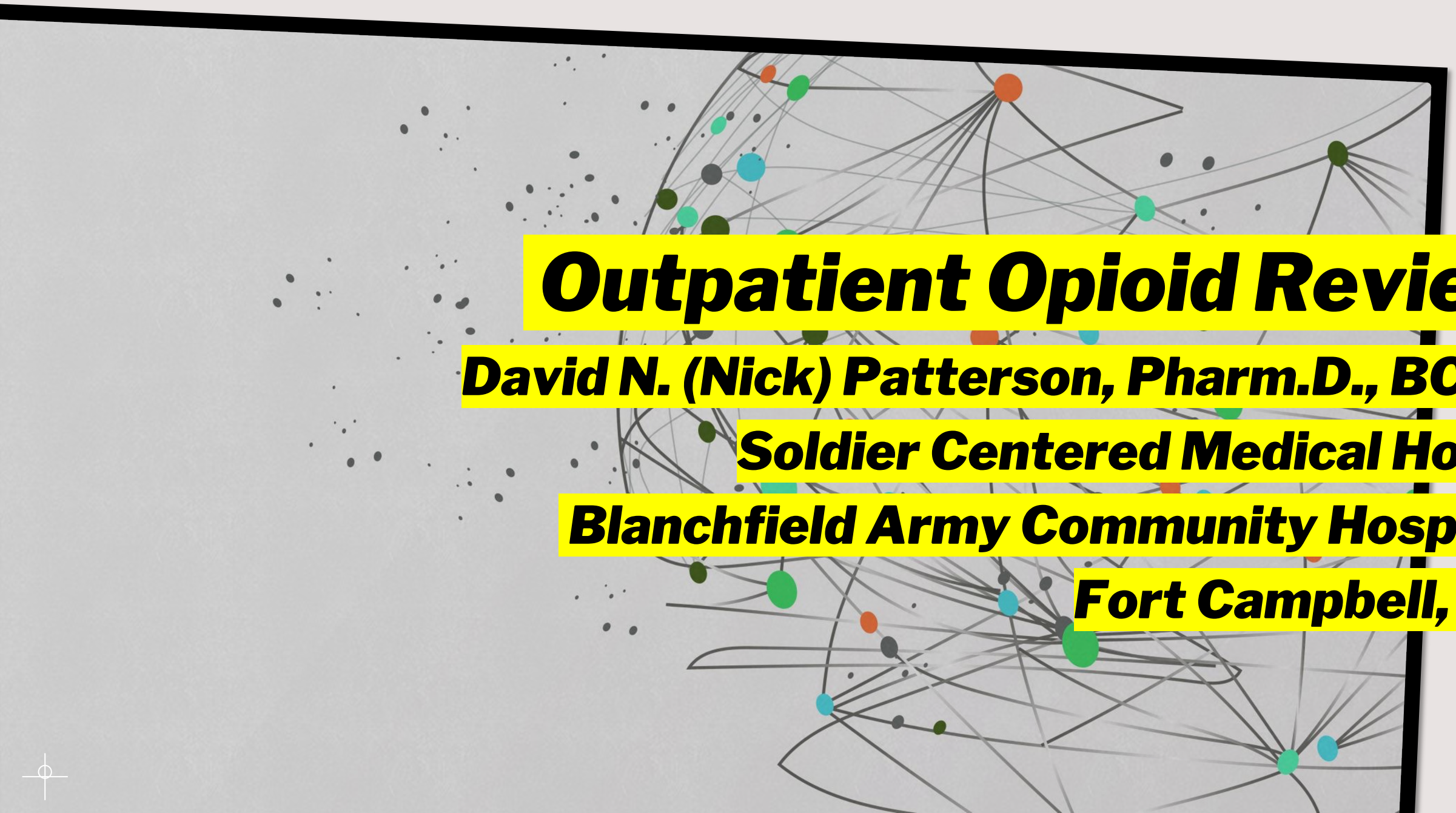


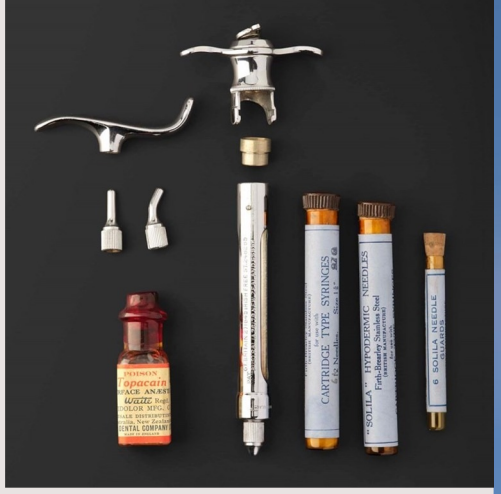
Outpatient Opioid Review

David N. (Nick) Patterson, Pharm.D., BCPS
Soldier Centered Medical Home
Blanchfield Army Community Hospital
Fort Campbell, KY

Objectives

- Compare and contrast different opioids used for outpatient pain management in the post-surgical or chronic pain environment
- Discuss opioid related dose adjustment based on pharmacogenomics and medication interactions
- Identify treatment strategies based on the most common adverse effects of opioid therapy

History of Opioids



- Originally cultivated by Sumeria (modern day Iraq) for religious ceremonies
- Greeks originally combined with hemlock during capital punishment sentences
- 9th Century B.C.: 1st appearance in literature in The Odyssey, Homer
  + "Presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow"
- 8th century A.D.: Arab traders introduced to India/China
- 1200-1300 A.D.: Documented use of narcotics for painful operations
- 1806: Morphine discovered by Seturner & named after Morpheus, god of dreams
- 1839-1842: 1st opium war between China & Britain
- 1844: hypodermic needle discovered by Irish physician Rynd then the piston syringe in 1853 by Pravaz

-Brownstein, Michael J. "A brief history of opiates, opioid peptides, and opioid receptors". Proc. Natl. Acad. Sci USA. Vol 90, pp 5391-5393. June 1993.
-Dhaliwal A, Gupta M. Physiology, Opioid Receptor. [Updated 2022 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
-Boysen PG, Patel JH, King AN. Brief History of Opioids in Perioperative and Periprocedural Medicine to Inform the Future. Ochsner J. 2023 Spring;23(1):43-49. doi: 10.31486/toj.22.0065. PMID: 36936479; PMCID: PMC10016219.
https://www.istockphoto.com/photos/opium-poppy-dripping accessed on August 12, 2023.

History of Opioids

- 1856-1860: 2nd opium war between China & Britain/France
- 1870: Physicians issue concerns about morphine becoming addictive
- 1894: 2-acetyl morphine discovered by Wright and 1898 as marketed as Heroin
  + 1962 comparative study found heroin was 2-4x more potent than morphine
- 1914: Opioid antagonist discovered by Pohl (N-allylnorcodeine)
  + 1960: naloxone synthesized
- 1932: Synthetic opioids were being produced in Germany in preparation for war
  + Germany was importing morphine from other countries at the time
  + Focused on the piperidine ring instead of modifying morphine, codeine or thebaine

-Brownstein, Michael J. “A brief history of opiates, opioid peptides, and opioid receptors”. Proc. Natl. Acad. Sci USA. Vol 90, pp 5391-5393. June 1993.
-Dhaliwal A, Gupta M. Physiology, Opioid Receptor. [Updated 2022 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
-Boysen PG, Patel JH, King AN. Brief History of Opioids in Perioperative and Periprocedural Medicine to Inform the Future. Ochsner J. 2023 Spring;23(1):43-49. doi: 10.31486/toj.22.0065. PMID: 36936479; PMCID: PMC10016219.
https://www.istockphoto.com/photos/opium-poppy-dripping accessed on August 12, 2023.

Overview of Opioids

- 20 different entities on the US market
- >60 different outpatient opioid or opioid combinations on the US market
- Not all products have abuse deterrents
- All have black box warnings (BBW), some have more:
  - Serious, life-threatening, or fatal respiratory depression may occur with use of <insert opioid here>, particularly when used concomitantly with other opioids or CNS depressants. Monitor for respiratory depression, especially during initiation of <insert opioid here> or following a dose increase
  - Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of nalbuphine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation
  - Prolonged use of <insert opioid here> during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available
- Baseline adverse effects: Constipation, euphoria, respiratory depression, sedation, itching
- All have baseline drug interactions: barbiturates, benzodiazepines, EtOH due to respiratory depression
  - Some opioids may have other interactions based on Cytochrome P450 isoenzymes

Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed August 6, 2023.

Pharmacogenomics of Opioid Dosing

- Pharmacogenomics is becoming an important and effective method used to guide personalized prescribing
- Refers to the impact of multigene variations in DNA and RNA on drug response
- Understood that standard medication doses for certain patients will be ineffective or fatal
- Pharmacogenomic information circumvents this issue by examining how naturally occurring genetic variants and/or gene expression profiles affect response to medication
- Two drug-gene pairs, (codeine-CYP2D6 and tramadol-CYP2D6), consist of clinically actionable variants with recommendations to guide/alter prescribing
- Two drug-gene pairs, (hydrocodone-CYP2D6 and methadone-CYP2B6), have optional prescribing actions
- Twenty-one drug-gene pairs are known but there are no recommended prescribing actions

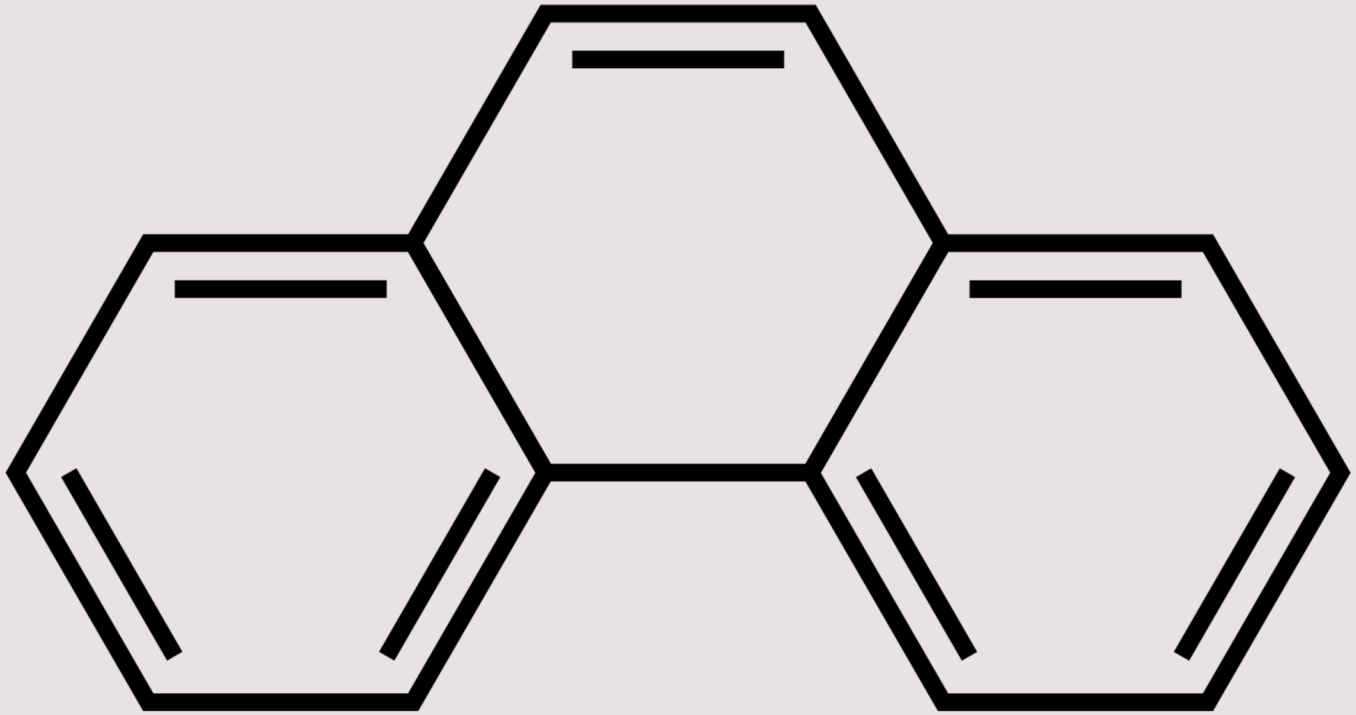
Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Classes of Opioids

- Phenanthrenes
  - Codeine/Morphine
  - Hydrocodone/Hydromorphone
  - Oxycodone/Oxymorphone
- Diphenylheptanes
  - Methadone
  - Propoxyphene
- Phenylpiperidine
  - Fentanyl
  - Meperidine
  - Remifentanil
  - Sufentanil
- Benzomorphans
  - Diphenoxylate
    - Approved in combo with atropine for diarrhea
  - Pentazocine
  - Loperamide
    - “poor man’s methadone”
- Phenylpropylamines
  - Tramadol
  - Tapentadol
- Other
  - VX-548

Fudin Jeffrey, Opioid Allergy, Pseudo-allergy, or Adverse Effect? Pharmacy Times online. Mar 6, 2018. Accessed at Opioid Allergy, Pseudo-allergy, or Adverse Effect? (pharmacytimes.com) on August 6, 2023.

Phenanthrene derivatives



https://commons.wikimedia.org/wiki/File:Phenanthrene.svg accessed on 8/1/23.

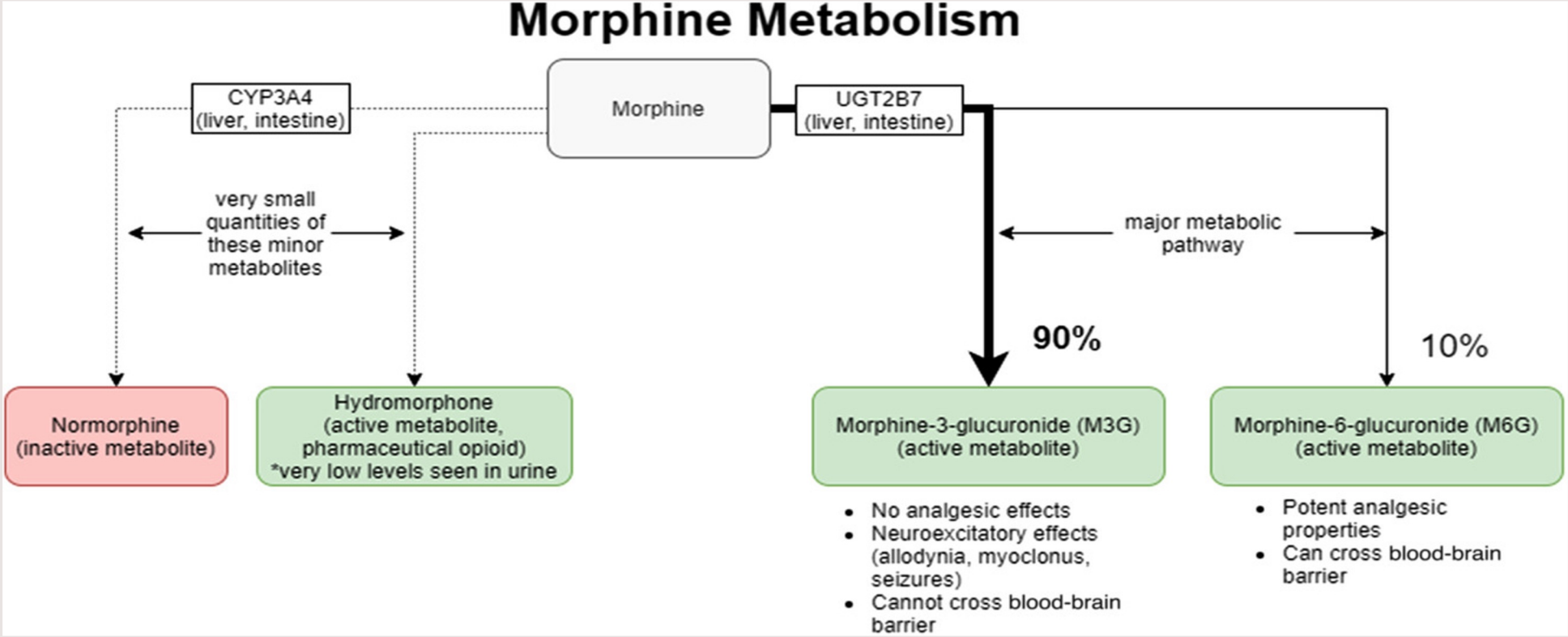
Morphine (MSIR/MS CONTIN)

- Discovered in 1803 by 21yo German pharmacist assistant Freidrich Serturner
  + All experiments performed on….himself
- U.S. Approval date: 1941
- Indications: acute and chronic pain
- Pharmacokinetics
  + Onset of action: IR: 30 mins ER: 2-4 hours
  + Duration of action: 3 to 5 hours (IR) or 8-24 hours (ER)
- Available forms
  + MSIR tabs/supps/oral solution: normally administered every 4 hours
  + Kadian: daily to q12h
  + MS Contin: q8h-q12h

Holly L. Geyer. A brief history of morphine use. The discovery of morphine is an interesting story thousands of years in the making. January 17, 2023. https://mcpress.mayoclinic.org/opioids/history-of-morphine/ accessed on 7/26/23
Brownstein, Michael J. “A brief history of opiates, opioid peptides, and opioid receptors”. Proc. Natl. Acad. Sci USA. Vol 90, pp 5391-5393. June 1993.
Lexi-Drugs/morphine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.

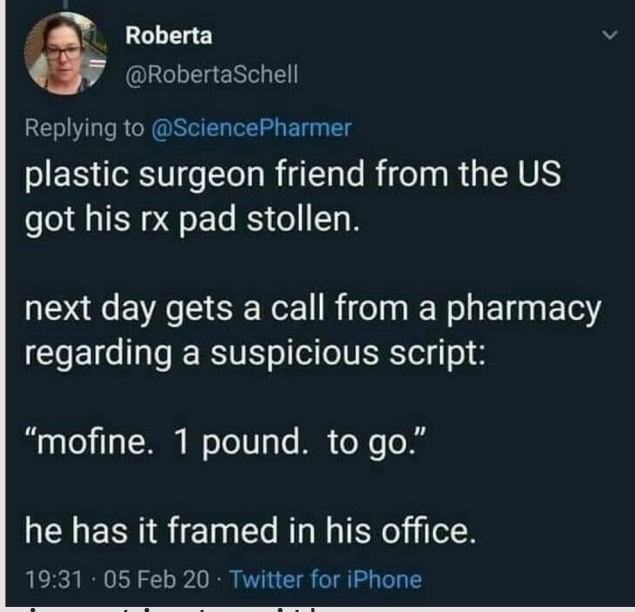
Morphine Metabolism

- Hepatic via conjugation with glucuronic acid primarily to morphine-6-glucuronide (M6G) (active analgesic) morphine-3-glucuronide (M3G) (inactive as analgesic which contributes to CNS stimulation)
- Minor metabolites: morphine-3-6-diglucuronide, normorphine, morphine 3-ethereal sulfate, hydromorphone



Ofoegbu A & Ettienne EB. Pharmacogenomics and Morphine. Clinical Pharmacology. Vol 61. Issue 9. September 2021: 1149-1155.

Morphine (MSIR/MS CONTIN)



- Dose adjustment
  - + Renal: Clearance is similar in altered or normal renal function
    - M3G (CNS stimulant/lower seizure threshold) & M6G [active analgesic]) accumulate in patients with reduced kidney function
  - + Hepatic: There are no dosage adjustments provided in the
    - In cirrhosis, increases half-life & AUC-suggest dosage adjustment
- BBW:
  - + Patients should not consume EtOH beverages or use Rx or nonprescription products that contain EtOH while taking morphine ER caps due to increased plasma levels & a potentially fatal overdose of morphine
  - + Ensure accuracy when prescribing, dispensing, and administering morphine oral solution. Dosing errors due to confusion between mg and mL, and other morphine solutions of different concentrations, can result in accidental overdose and death
- Clinical Pearls:
  - + High risk of pseudo allergy: vasodilation with itching

Holly L. Geyer. A brief history of morphine use. The discovery of morphine is an interesting story thousands of years in the making. January 17, 2023. https://mcpress.mayoclinic.org/opioids/history-of-morphine/ accessed on 7/26/23
Brownstein, Michael J. “A brief history of opiates, opioid peptides, and opioid receptors”. Proc. Natl. Acad. Sci USA. Vol 90, pp 5391-5393. June 1993.
Lexi-Drugs/morphine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://www.reddit.com/r/trashy/comments/rz5f2k/to_go/?rdt=44719 accessed on August 12, 2023.

Morphine Products

No abuse deterrent forms on the market

No longer available

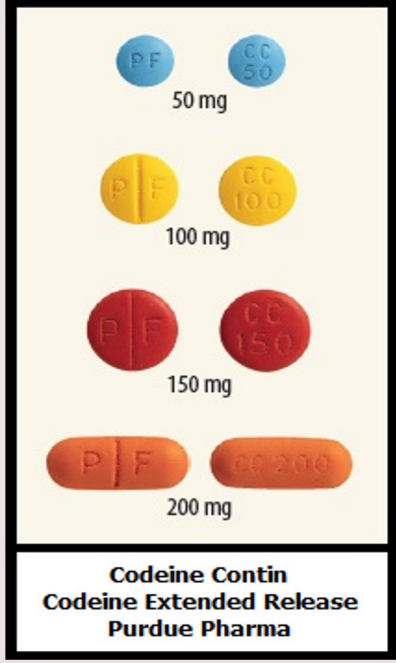
- Embeda (no longer marketed): morphine/naltrexone
  + Abuse deterrent form
- Avinza (no longer available): morphine ER
- Morphabond ER/Arymo ER (no longer available)
  + Abuse deterrent forms

Available

- Morphine oral liquid
  + 10mg/5ml, 10mg/0.5ml, 100mg/5ml
- Morphine rectal supps
  + 5mg, 10mg, 20mg, 30mg
- Morphine IR (MSIR)
  + 15mg, 30mg
- Kadian: (Generic only) morphine ER caps
  + 10mg, 20mg, 30mg, 40mg, 50mg, 80mg, 100mg, 200mg
- MS Contin: Morphine ER tabs (NB & generic)
  + 15mg, 30mg, 60mg, 100mg, 200mg

Embeda. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022321s016lbl.pdf accessed on 7/26/23.
Kadian. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020616s057lbl.pdf accessed on 7/26/23.
MS Contin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019516s034lbl.pdf accessed on 7/26/23
Lexi-Drugs/morphine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.

Codeine (Codeine Contin)

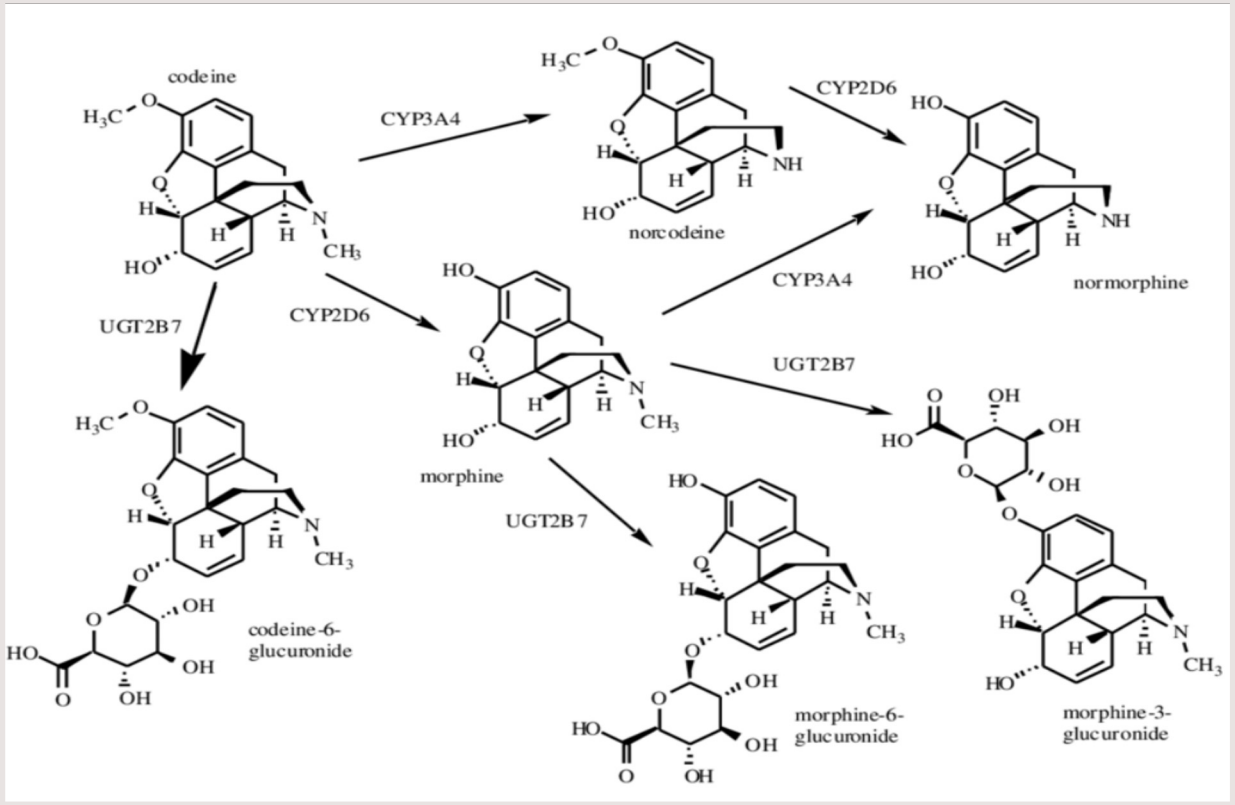


- AKA Methylmorphine
- First isolated by French pharmacist Pierre-Jean Robiquet in 1832
- MME: Morphine: Codeine 1:4.5
- Indications: mild-moderate pain/Cough
- Pharmacokinetics:
  + Onset of action: 30-60 mins | Duration: 4-6 hours
- Adverse effects if different from opioids: None
- Special populations:
  + Older adult: Clearance reduced in older adults (with or without renal impairment) resulting in a narrow therapeutic window & increased risk of adverse effects
  + Pediatric: Respiratory depression: Risk factors include conditions: postoperative status, OSA, obesity, severe pulmonary disease, neuromuscular disease, & other meds that cause respiratory depression
    - Deaths have also occurred in breastfeeding infants after being exposed to high concentrations of morphine because the mothers were UM

https://www.britannica.com/science/pharmacology accessed on 7/25/23.
Lexi-Drugs/codeine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://www.opiateaddictionresource.com/media/images/codeine_tablets/ accessed on August 12, 2023

Codeine Metabolism

- Hepatic via UGT2B7/UGT2B4 to codeine-6-glucuronide, via CYP2D6 to morphine (active), and via CYP3A4 to norcodeine
- Morphine is further metabolized via glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide



https://www.researchgate.net/figure/Mean-stdev-pharmacokinetic-parameters-for-codeine-and-its-metabolites-based-on_tbl1_24267947 accessed on 8/2/23.

Codeine Pharmacogenomics (2D6)

- Globally: normal metabolizers (NM) make up 43-67% of the population
- Non-normal estimated to make up 33-57%
  + Ultrarapid (UM)
    - Increased conversion to morphine even at low doses causing increased risk of toxicity
    - Strong recommendation to avoid use due to potential for toxicity; use alternative non-tramadol opioid. Be alert to adverse effects
    - Most common in North Africans (40%) and least common in East Asians (1.4%)
  + Extensive (EM)
    - Normal conversion to morphine, however unpredictable variability leading to issues like ultrarapid metabolizers
    - Strong recommendation to use label-recommended dosing

Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Codeine Pharmacogenomics (2D6)

- Phenotype:
  + Intermediate (IM)
    - Reduced conversion to morphine, usually no clinical analgesic significance
    - Moderate recommendation to use label-recommended dosing, if less effective, consider alternative non-tramadol opioid
  + Poor (PM)
    - Reduced conversion to morphine causing reduced analgesia, with persistent central adverse effects (sedation, nausea, xerostomia
    - Strong recommendation to avoid use due to lack of efficacy; use alternative non-tramadol opioid. Be alert to insufficient pain relief
    - Most common in British, (12.1%) and least common in Asian and Oceanian (0.4%)

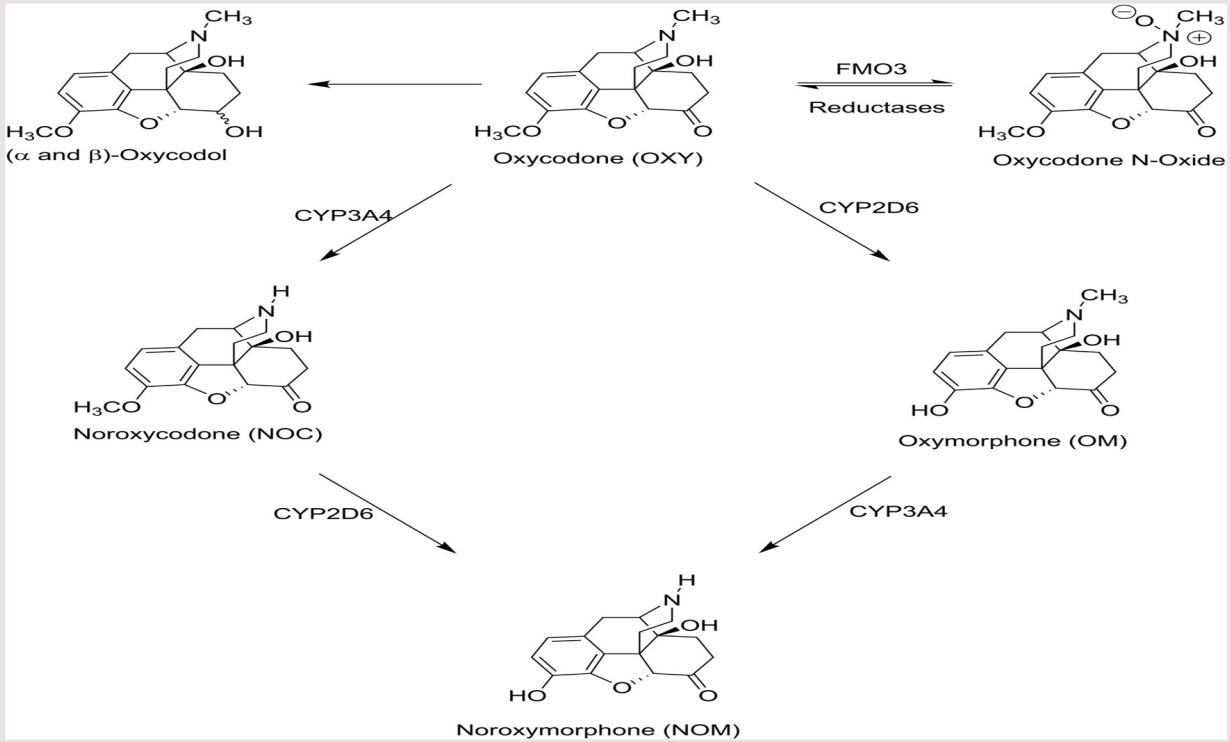
Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Oxycodone (OxyIR/Oxycontin/Percocet/Percoda n)

- Approval date: 1928, synthesized from thebaine in 1916
- MME: Morphine: Oxycodone: 1.5:1
- Dose: 5-10 mg PO every 4 to 6 hours as needed
- Pharmacokinetics
  + Onset of action: 10-15 mins
  + Duration of action: 3-6 hours
  + Dose adjustment
    - Renal:
      + No specific dose adjustments provided in the manufacturer's labeling
      + Oxycodone is excreted as parent drug (~10%) and active to weakly active metabolites (~47%) with varying degrees of analgesic activity
      + T1/2 is prolonged with accumulation of active metabolites
      + Use of other opioids may be preferred for management of severe pain in patients with kidney impairment
    - Hepatic:
      + Initiate therapy at 33% to 50% the usual dosage and titrate carefully
      + Severe impairment, consider extending the dosing interval based on response and tolerability (eg, every 6 to 12 hours)

https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
-Oxycodone: Drug information. Hudson, OH: Lexicomp, 1978-2023. http://online.lexi.com/. Updated date. Accessed 1/29/23
https://www.reddit.com/r/pharmacy/comments/9r4u01/came_across_some_cool_old_ones_today/ accessed on August 12, 2023.

Oxycodone Metabolism:



- Hepatic via CYP3A4 to noroxycodone (has weak analgesic activity), noroxymorphone, and alpha- and beta-noroxycodol
- CYP2D6 mediated metabolism produces oxymorphone (has analgesic activity; low plasma concentrations [<15%])

Cashman JR, Gohdes M, de Kater A, Schoenhard G. Oxycodone *N*-Oxygenation, Oxycodone N-Oxide Retro-reduction. Drug Metabolism and Disposition February 1, 2020, 48 (2) 106-115.
Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Oxycodone (OxyIR/Oxycontin/Percocet/Percodan)

- Pharmacogenomics
  - Several case studies also report that PMs require higher oxycodone doses, whereas UMs experience greater analgesic effect and toxicity due to increased metabolism to oxymorphone
  - Due to the weak and limited evidence, the recommendation is that data are not yet adequate to allow calculations for dose adjustment
  - Accepted convention is that UMs have increased metabolism to oxymorphone, but without changes to analgesia or toxicity
- BBW if different than opioids:
  + The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer
  + Inducers: rifampin, carbamazepine, phenobarbital,
  + Inhibitors: clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil

Oxycodone controlled-release (OxyContin) prescribing information. Purdue Pharma. April 2010. Available at: www.purduepharma.com/PI/Prescription/Oxycontin.pdf. Accessed August 6, 2023
Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Oxycodone (OxyIR/Oxycontin/Percocet/Percodan)

- 4 abuse deterrent products available:
  - + Oxycontin & generic
    - Difficult to crush and forms a viscous gel if dissolves
    - Deterrence from IV/Nasal
  - + Roxybond (oxycodone IR)
    - Difficult to crush and forms a viscous gel if dissolves
    - Deterrence from IV/Nasal
  - + Xtampza ER (oxycodone ER cap)
    - Capsules contain microspheres of oxycodone and inactive ingredients that hinder dosage dumping via intranasal and oral abuse
    - Microspheres cannot be readily dissolved and will solidify within a needle to prevent injection.
    - Deterrence from IV/Nasal/Oral
  - + Targin (Oxycodone ER + naloxone)
    - Contains naloxone (opioid antagonist) which is not active PO but blocks opioid associated euphoria when injected or inhaled.
    - Deterrence from IV/Nasal

Rosenquist R. Abuse deterrent opioids: In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on July 26, 2023.)

Oxymorphone (Opana)

- Synthesis of 14-hydroxydihydromorphinone in 1955 by Ulrich Weiss at the New York Botanical Garden
  - Originally available in parenteral formulation in 1959 by Endo Pharmaceuticals (filed for bankruptcy in 2022 d/t the lawsuits over its role in the opioid epidemic
- MME oral: Morphine: Oxymorphone 3:1
- Indications: Acute and Chronic pain
- Dosing:
  - IR: 5-10mg every 6 hours as needed
  - ER: Start at 5mg Q12h & may titrate upwards
    - Largest CR dose is 40mg

Lexi-Drugs/oxymorphone. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
https://www.healthcarepackaging.com/markets/pharmaceutical/news/13293328/fda-tells-endo-to-pull-opioid-opana-er-from-market accessed on August 12, 2023.

Oxymorphone (Opana)

- Pharmacokinetics
  - + Onset of action: 30-60 mins
  - + Bioavailability: 10%
  - + Duration of action:
    - IR: 7-9 hours | ER: 11-15 hours
  - + Metabolism: No phase I metabolism (through CYP enzymes)
    - Phase II metabolism:
  - + Dose adjustment
    - Renal:
      - + <50ml/min: Start at 50% initial dose & titrate slowly
    - Hepatic: Moderate-severe hepatic impairment-contraindicated
- Drug interactions: azelastine, orphenadrine, olopatadine nasal spray

Lexi-Drugs/oxymorphone. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023
Sloan P. Review of oral oxymorphone in the management of pain. Ther Clin Risk Manag. 2008 Aug;4(4):777-87.
https://www.outsourcing-pharma.com/Article/2016/08/25/Grunenthal-says-anti-crush-tech-Endo-uses-for-Opana-ER-helps-prevent-abuse accessed on August 12, 2023.

Oxymorphone (Opana)

- 11/1/14-11/1/15-Scott County Indiana
- Perfect storm for abuse
  - + Abuse deterrent forms on market in 2012-not effective
  - + Low bioavailability, high lipophilicity
  - + 3-5 times higher affinity for MOR than morphine
  - + IV form 10 times more potent than morphine
- 181 cases of new HIV infections diagnosed
- 88% of these patients reported injection ER oxymorphone
  - + 92.3% were coinfected with HCV
- 159/181 cases shared the same phylogenetic analysis of the HIV type 1 pol sequence
- Majority of patients reported sharing syringes

Peters PJ, Pontones P, Hoover KW, et al. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015. N Engl J Med. 2016. 375: 229-239.
Smith HS, McCleane G. OPIOIDS ISSUES. Current Therapy in Pain, 2009.
https://www.stats.indiana.edu/profiles/profiles.asp?scope_choice=a&county_changer=18143 accessed on August 12, 2023.

Oxymorphone (Opana

- Abuse deterrent forms-None
- Endo pharmaceuticals did release an “abuse deterrent form” of Opana ER
  + Version was withdrawn from market in 2017 after FDA recommendation
  + INTAC technology was supposed to resist crushing and gel when mixed with liquid
    - While this passed FDA scrutiny, users were able to continue to crush the tablet for insufflation with common tools
    - With excess fluid, still has high syringe ability
- Oxymorphone ER still available, not abuse deterrent

Brooks M. Endo Pharma Agrees to Pull Abuse-Deterrent Opioid. Medscape. June 6, 2017. https://www.medscape.com/viewarticle/882578?form=fpf accessed on 8/2/23.
https://cen.acs.org/articles/95/i45/Abuse-deterrent-opioids-Worth-effort.html accessed on August 12, 2023.

Hydrocodone

(Vicodin, Norco, Hysingla, Lorcet

- Released in 1943, acquired growing popularity as a drug considered as a “middle-level” opioid
- Semi-synthetic opiate derivative with analgesic and antitussive effects
- Chemical name: (4R,4aR,7aR,12bS)-9-methoxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinoline-7-one
- Original drug name dihydrocodeinone was given when it was first marketed in Germany
- Rescheduled from CIII to CII in the United States by Food and Drug Administration (FDA) in 2012
- Indications: Acute & Chronic pain, cough

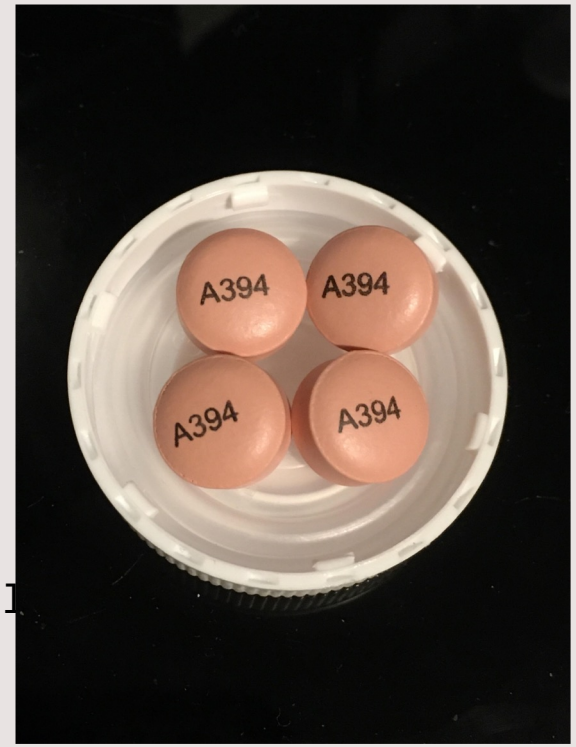
Front. Pharmacol., 01 October 2018 Sec. Neuropharmacology Volume 9 - 2018 | https://doi.org/10.3389/fphar.2018.01122
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023

Hydrocodone

- MME: M:H-1:1
- Dose: IR: 5-10mg every 6 hours| ER: start 10mg q 12 or 24 hours
- Pharmacokinetics
  + Onset of action:
    - IR: Reaches maximum serum concentrations within 1 h
    - ER: 14-16 hours (range is 6-30 hours depending on the dose)|Steady state in 48 hours
  + Duration of action
    - IR: 4-6 hours
    - ER: 24 hours
  + Dose Adjustment:
    - Renal: 50% dose decrease in ESRD
    - Hepatic: 50% dose decrease in severe hepatic impairment

Lexi-Drugs/hydrocodone. Lexicomp app. UpToDate Inc. Accessed August 12, 2023.
https://www.ebay.com/itm/155470898631 accessed on August 12, 2023.

Hydrocodone Forms

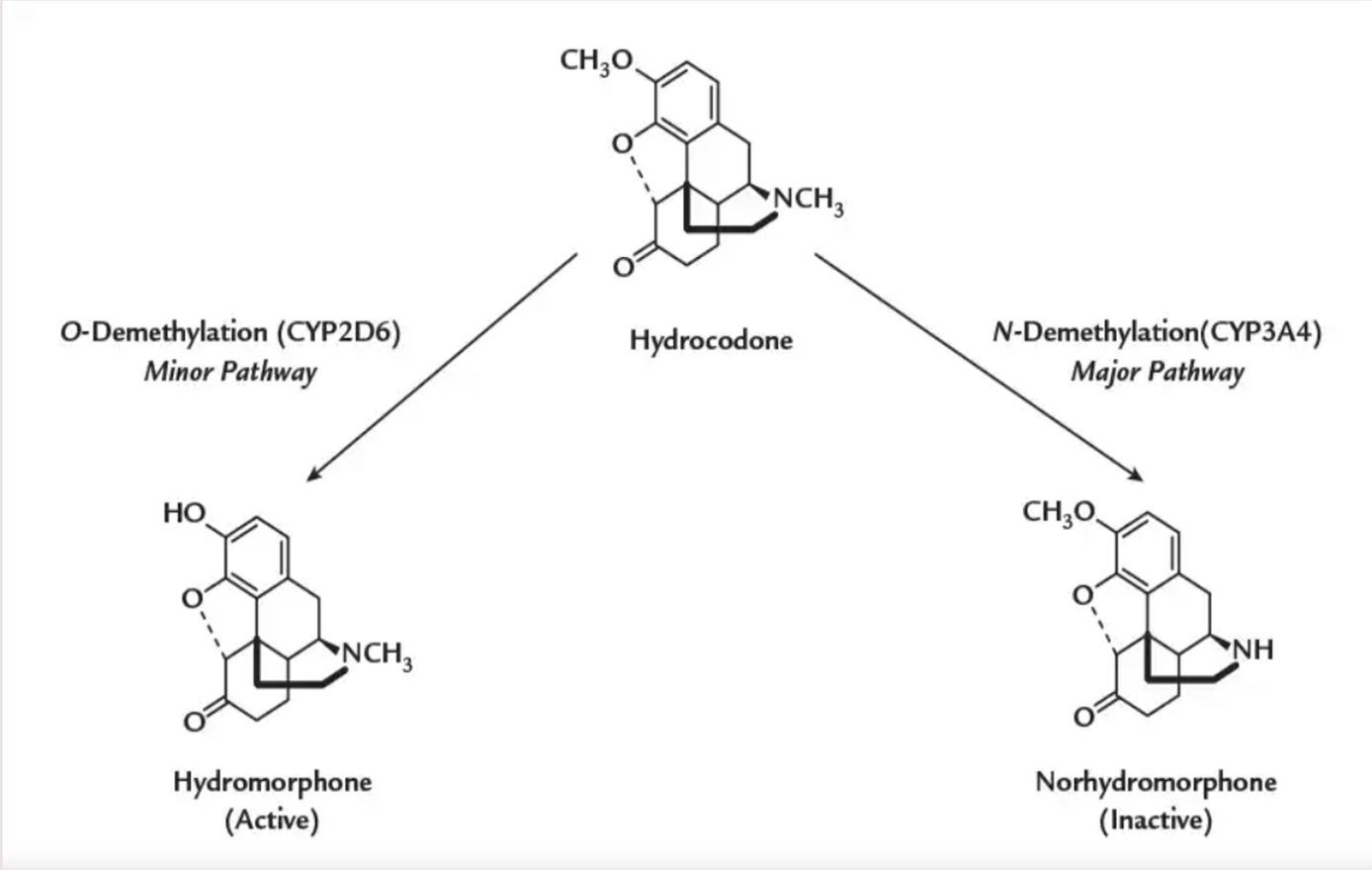


- 1 abuse deterrent form:
  - + Hysingla ER: Difficult to crush and if dissolved, forms a viscous gel
  - + Deterrence from using IV, nasal, or oral
- Hydrocodone Products:
  - + Hydrocodone ER oral cap (Q12 hour form)-Zohydro (NB dc/d)
  - + Hydrocodone ER oral tab (Q24 hour form)-Hysingla NB and generic
  - + Hydrocodone APAP IR tabs, solution, and elixir
  - + No hydrocodone IR products on market without APAP

Front. Pharmacol., 01 October 2018 Sec. Neuropharmacology. Volume 9 - 2018 | https://doi.org/10.3389/fphar.2018.01122
Purdue's Hysingla (single-entity hydrocodone) Receives FDA Approval. May 18, 2015. https://www.practicalpainmanagement.com/resources/news-and-research/purdues-hysingla-single-entity-hydrocodone-receives-fda-approval accessed on 7/26/23
Rosenquist R. Abuse deterrent opioids: In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on July 26, 2023.)

Hydrocodone Metabolism

- Hydrocodone is a prodrug (inactive), must have bioconversion to its active metabolite hydromorphone
- Pain relief correlates with plasma hydromorphone but not with hydrocodone concentration. Ability to convert hydrocodone to its active drug is essential
- Hydrocodone is transformed to hydromorphone through O-demethylation catalyzed by CYP2D6
- The principal metabolites of hydrocodone are:
  - norhydrocodone
  - **hydromorphone**



Kapil, Ram Prakash et al. "Effects of paroxetine, a CYP2D6 inhibitor, on the pharmacokinetic properties of hydrocodone after coadministration with a single-entity, once-daily, extended-release hydrocodone tablet." *Clinical therapeutics* 37 10 (2015): 2286-96 .

Hydrocodone Pharmacogenomics (CYP2D6)

- Hydrocodone has actionable pharmacogenomic variants
- Unavailable in most countries
- Data on UMs are not yet sufficient to guide prescribing
- CYP2D6 IMs and PMs have reduced capacity to metabolize hydrocodone into hydromorphone
- It is unclear whether this translates to clinical differences in analgesia or toxicity
- Usual conservative approach of using hydrocodone
  + If there is no analgesic effect, consider an alternative opioid not metabolized by CYP2D6
    - **NOT** codeine, tramadol, or oxycodone

Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

Hydromorphone (Dilaudid/Exalg

- Hydrogenated ketone of morphine
- Synthesized in Germany in 1921 & introduced into clinical practice in 1926.
- MME: Morphine:Hydromorphone-4:1
- Indications: Acute and chronic pain
- Dose:
  + Oral: 1-2mg every 4-6 hours: moderate pain: 8mg/day severe pain: 12mg/day
  + Supp: 3mg every 6-8 hours
  + ER: once daily
- Onset of action:
  - IR: 15-30 mins
  - ER: 6 hours
- Duration of action:
  - IR: 3-4 hours
  - ER: 13 hours

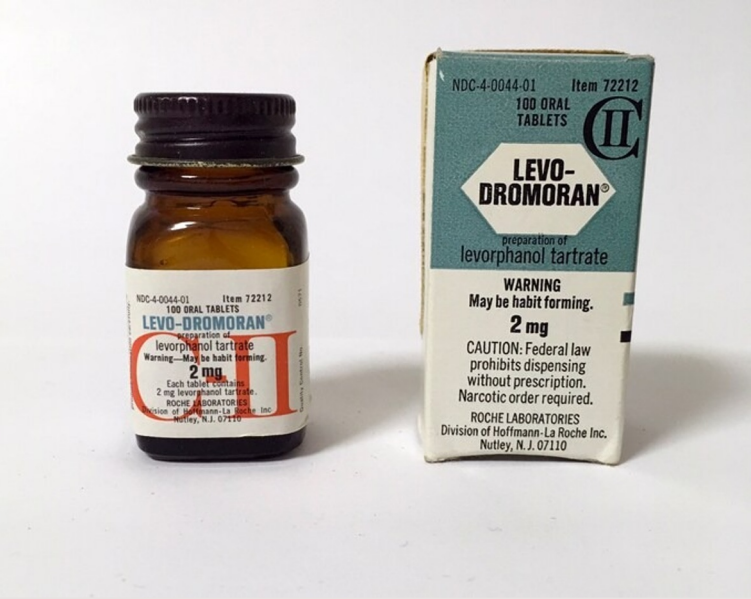
Lexi-Drugs/ Hydromorphone. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
https://www.etsy.com/listing/675791959/vintage-dilaudid-knoll-pharmaceutical accessed on August 12, 2023.
https://www.webmd.com/drugs/2/drug-11338/hydromorphone-rectal/details accessed August 12, 2023.

Hydromorphone (Dilaudid/Exalgo)

- Metabolism: metabolized to hydromorphone-3-glucoronide
- Dose adjustment
  - + Renal:
    - 37% of hydromorphone metabolized to hydromorphone-3-glucuronide, a potentially neuroexcitatory metabolite, which can accumulate with kidney impairment
    - Careful titration of dosing with close monitoring of response and adverse reactions due to drug and metabolite accumulation is important with all degrees of kidney impairment
  - + Hepatic:
    - Mild to severe impairment: Initiate with 25% to 50% of the usual starting dose depending on the degree of impairment
  - + Hydromorphone IR & ER
  - + No abuse deterrent forms

Lexi-Drugs/ Hydromorphone. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://www.empr.com/home/news/covidien-launches-exalgo-for-chronic-pain-relief/ accessed on August 12, 2023.

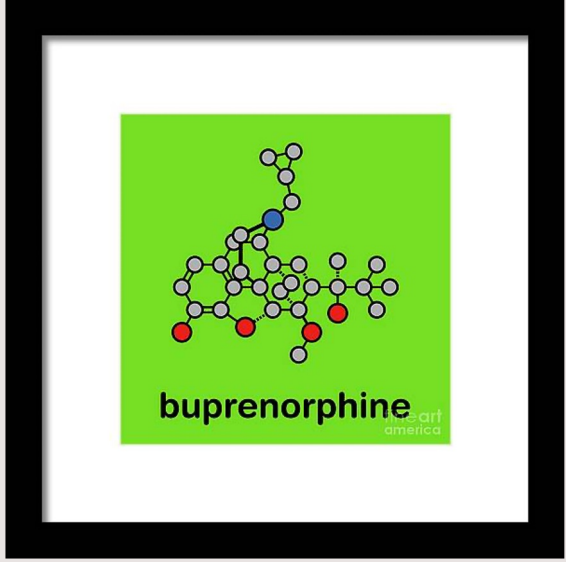
Levorphanol (Levo-Dromoran



- Used in the U.S. since 1953
- MME: Morphine:Levorphanol-12:1: but higher doses lead to a higher ratio
- MOA if different than opioid: NMDA antagonist/SNRI
  + Related to dextromethorphan
- Indication: Acute pain
- Onset of action: 10-60 mins| Duration of action: Up to 8 hours
- Metabolism: glucuronidation to levorphanol-3-glucuronide (active)
- Adverse effects if different from opioids: hallucinations/delirium
  + Most likely d/t Kappa opioid receptor activation

Lexi-Drugs/levorphanol. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
Prommer E. Levorphanol: revisiting an underutilized analgesic. Palliat Care. 2014 May 11;8:7-10. doi: 10.4137/PCRT.S13489. PMID: 25278763; PMCID: PMC4168847.
https://www.etsy.com/no-en/listing/675787527/vintage-levo-dromoran-roche-laboratories accessed on August 12, 2023.

Buprenorphine



- Developed in 1966 by R&C corp
  + Provided to the Addiction Recovery Center in Lexington, KY through the 1970s
- MME conversion factor: Morphine:Buprenorphine-1:10
  + Not expected to be associated with OD risk in the same manner as full opioid agonists
- Labeled indications
  + Buccal film/Transdermal patch: Chronic pain
  + No option for treatment of acute pain
- MOA if different from other opioids:
  + Partial mu agonist and weak kappa antagonist activity
  + Due to it being a partial mu agonist, its analgesic effects plateau at higher doses and can behave like an antagonist

Lexi-Drugs/buprenorphine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
Christian Heidbreder, Paul J. Fudala, Mark K. Greenwald, History of the discovery, development, and FDA-approval of buprenorphine medications for the treatment of opioid use disorder,Drug and Alcohol Dependence Reports, Volume 6, 2023: 2772-7246

Buprenorphine

- Dose
  + Film:
    - 75mcg daily and progress to 300mcg q 12H
  + Patch:
    - 5mcg/hour patch change every 7 days
    - Titrate up to 20mcg/hr patch every 7 days
- Adverse effects if different from other opioids:
  + Black Box Warning
    - Use of sublingual buprenorphine products (tablets and films) may result in dental adverse events (eg tooth decay, **dental caries**, dental abscesses/infection, tooth erosion, fillings falling out, total tooth loss)

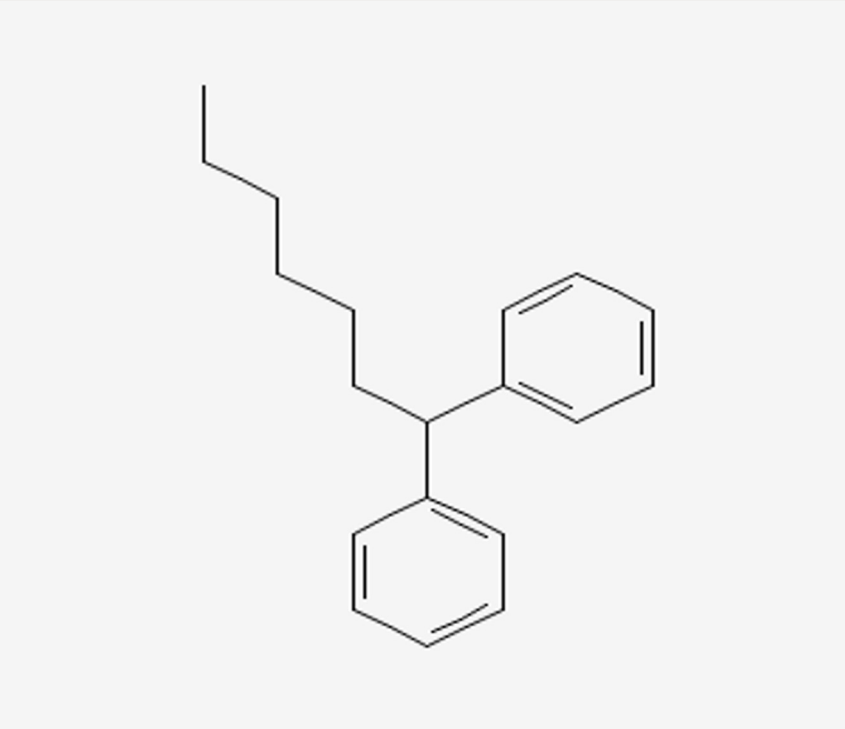
Lexi-Drugs/buprenorphine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
Christian Heidbreder, Paul J. Fudala, Mark K. Greenwald, History of the discovery, development, and FDA-approval of buprenorphine medications for the treatment of opioid use disorder, Drug and Alcohol Dependence Reports, Volume 6, 2023: 2772-7246
https://mms.mckesson.com/product/1148253/Rhodes-Pharmaceuticals-42858050203 accessed on August 12, 2023.

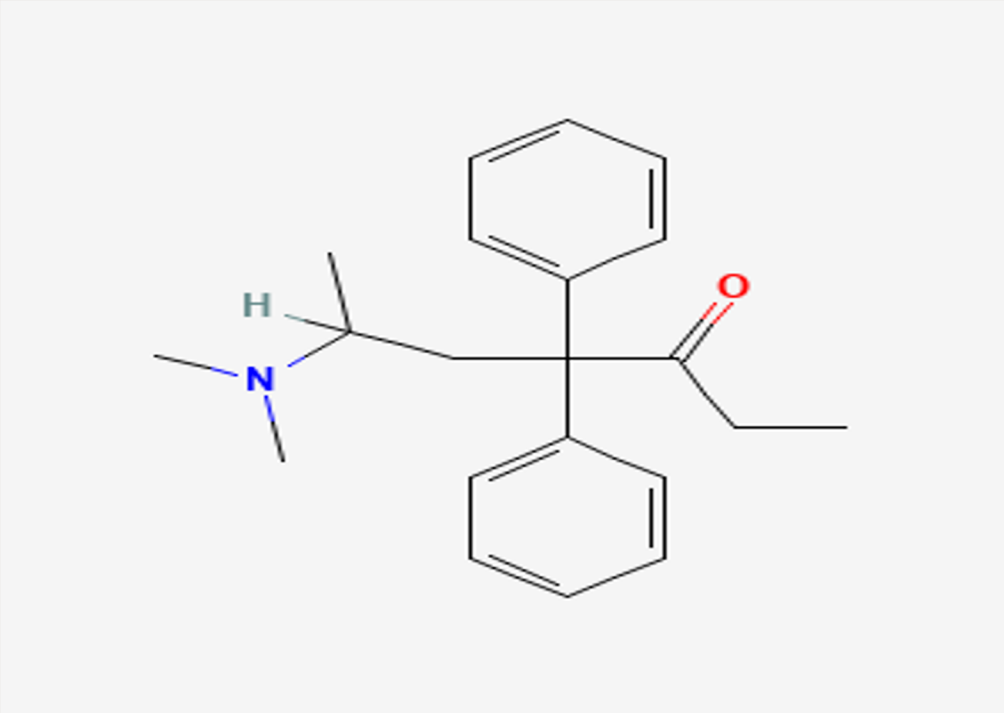
Buprenorphine

- Removal of X identifier:
  - + Previously, in order to prescribe buprenorphine for opioid use disorder (OUD) in the United States, clinicians had to apply for a federally required DATA Waiver (X-Waiver)
  - + January 2023, the Consolidated Appropriations Act of 2023 removed this requirement and allowed ALL clinicians with schedule III authority on their Drug Enforcement Administration registration to prescribe buprenorphine for OUD treatment if permitted by applicable state law
  - + Does not apply if using for pain
    - Pain would be off label use

Lexi-Drugs/buprenorphine. Lexicomp app. UpToDate Inc. Accessed August 6, 2023.
https://www.cbc.ca/news/canada/british-columbia/oat-coverage-british-columbia-1.6876365 accessed on August 12, 2023.

Diphenylheptane





National Center for Biotechnology Information. PubChem Compound Summary for CID 4095. Methadone. https://pubchem.ncbi.nlm.nih.gov/compound/Methadone. Accessed Aug. 6, 2023.
https://homework.study.com/explanation/draw-the-structure-of-the-compound-3-phenylheptane.html accessed on August 6, 2023.

Methadone (Dolophine/Methadose)

- Synthesized in Germany in the 1930s to solve the problem of opium shortage
  + Brought into the U.S. for the treatment of pain after World War II
- Termed “dollies” on the streets of NYC when used to help withdrawal
- MME: Methadone: Morphine: Based on methadone dose:
  + 0-20mg: 1:4
  + 20-40: 1:8
  + 40-60: 1:10
  + >60: 1:12
- MOA if different from opioids: NMDA receptor antagonism
- Onset of action: PO: 30 mins-1 hour
- Duration of action: 4-8 hours but will increase to 8-12 hours w/ repeat dosing

Green M, Kellogg S, Kreek MJ. Methadone: history, pharmacology, neurobiology, and use. Accessed at https://safe.menlosecurity.com/doc/docview/viewer/docN3819D17C45EB6ddfe6120ab5ac2f49e473b3b80bba5a38ad5a1841a6e45203f4a0d98659cb91 on 7/20/23.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
https://www.alamy.com/stock-photo-vintage-elixir-methadon-hydrochloride-methadone-bottle-usa-91467405.html accessed on August 12, 2023.

Methadone (Dolophine/Methadose)

- Metabolism:
  - **Substrate** of CYP2B6 (major/inactive), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major)
  - **Inhibits** CYP2D6 (weak)
- Moderate level of association between methadone and CYP2B6
  - **1* and **4* alleles increase methadone clearance
  - **6* and **18* cause decreased methadone clearance
- Limited to the pharmacokinetic dose-response in patients prescribed methadone for harm minimization in heroin addiction
- No current prescribing analgesic recommendation
- Promising area for future research

Green M, Kellogg S, Kreek MJ. Methadone: history, pharmacology, neurobiology, and use. Accessed at https://safe.menlosecurity.com/doc/docview/viewer/docN3819D17C45EB6ddfe6120ab5ac2f49e473b3b80bba5a38ad5a1841a6e45203f4a0d98659cb91 on 7/20/23.
Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

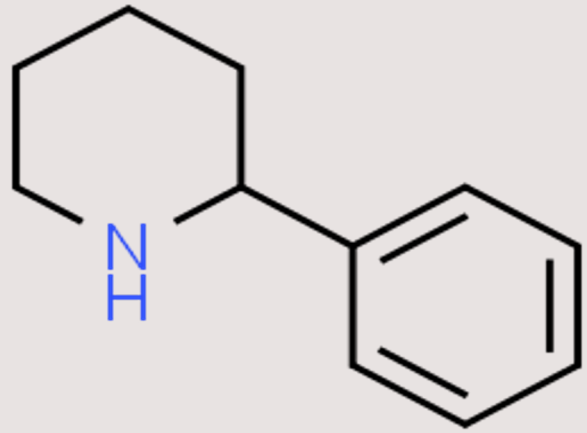
Methadone (Dolophine/Methadose)

- BBW:
  + QTc prolongation:
    - QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone
    - Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction
    - Closely monitor patients with risk factors for development of prolonged QT interval, a history of cardiac conduction abnormalities, and those taking medications affecting cardiac conduction for changes in cardiac rhythm during initiation and titration of methadone
  + Drug interactions:
    - Concomitant use of methadone with all CYP P450 3A4, 2B6, 2C19, 2C9, or 2D6 inhibitors may result in an increase in methadone plasma concentrations
    - Could cause potentially fatal respiratory depression
    - Discontinuation of concomitantly used CYP450 3A4, 2B6, 2C19, or 2C9 inducers may also result in an increase in methadone plasma concentration.
    - Consider dosage reduction with any changes of concomitant medications that can result in an increase in methadone levels

-Lexi-Drugs/methadone. Lexicomp app. UpToDate Inc. Accessed August 16, 2023

Phenylpiperidine

- Phenyl moiety directly attached to piperidine
- There are a variety of pharmacological effects associated with phenylpiperidines including morphine-like activity or other CNS effects
- Non-opioid phenylpiperidines include paroxetine



http://www.chemspider.com/Chemical-Structure.93072.html accessed on 7/20/23.

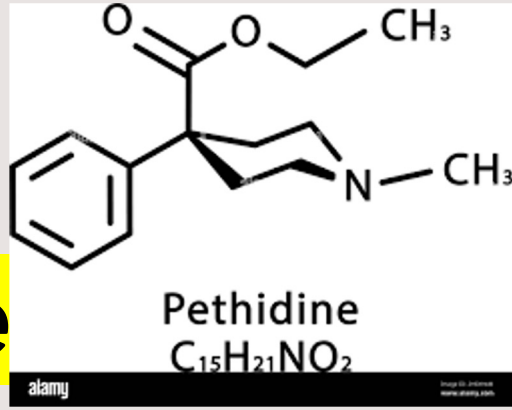
Sufentanil (Dsuvia)

- Approval date: 2018
- MME: Morphine: sufentanil: 5:1
- Onset of action: SL: ~30 mins
- Duration of action: SL: 3 hours
- Dose: SL tab: Initial: 30 mcg; may repeat every hour with a minimum of 1 hour between doses; max dose: 360 mcg/day; do not use for >72 hours
- Metabolism: Primarily hepatic & small intestine via demethylation & dealkylation
  + Dose adjustment
    - Renal: None
    - Hepatic: None
- Pearls
  + Expensive
  + Must be specially trained to administer

-Sufentanil: Drug information. Hudson, OH: Lexicomp, 1978-2023. http://online.lexi.com/. Updated date. Accessed 1/29/23
-Dsuvia, single applicator. McKesson. Accessed on https://mms.mckesson.com/product/1139888/AcelRx-Pharmaceuticals-Inc-61621043011 on 1/29/23.

Meperidine (pethidine) (Demerol)

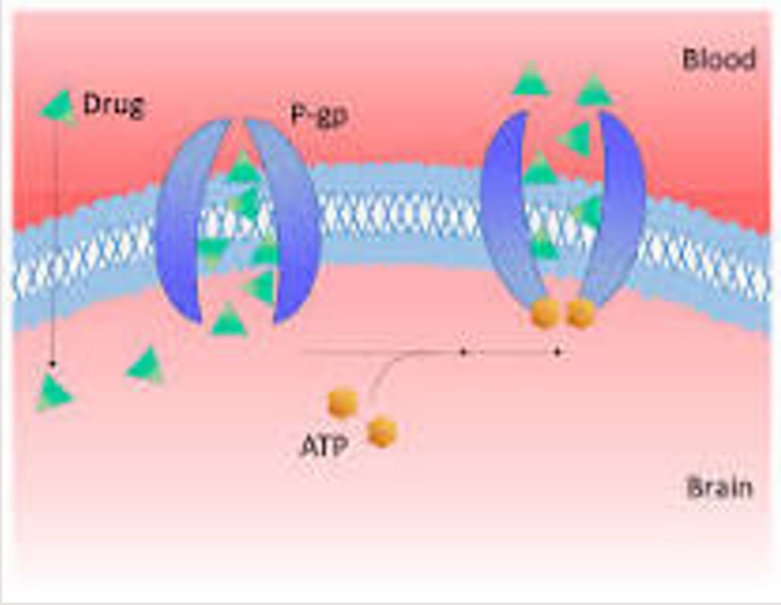
PO version no longer manufacture



- Synthesized in 1939
- MME: Morphine:meperidine-1:10
- Onset of action: 10-15 mins; peak effect 2 hours
- Metabolism: Hepatic; hydrolyzed to meperidinic acid (inactive) or undergoes N-demethylation to normeperidine (active; has $^{1}/_{2}$ the analgesic effect and 2 to 3 times the CNS effects of meperidine)
- Genomic issues: None
- BBW:
  + The concomitant use of meperidine with all cytochrome P450 3A4 inhibitors may result in an increase in meperidine plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in meperidine plasma concentration. Monitor patients receiving meperidine and any CYP3A4 inhibitor or inducer.
  + Concomitant use of meperidine with MAOIs can result in coma, severe respiratory depression, cyanosis, and hypotension. Use of meperidine with MAOIs within last 14 days is contraindicated.
- Clinical Pearls: Shivering treatment post surgical

Lexi-Drugs/meperidine. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
BATTERMAN RC, HIMMELSBACH CK. DEMEROL—A NEW SYNTHETIC ANALGESIC: A REVIEW OF ITS PRESENT STATUS AND COMPARISON WITH MORPHINE. *JAMA*. 1943;122(4):222–226. doi:10.1001/jama.1943.02840210014004

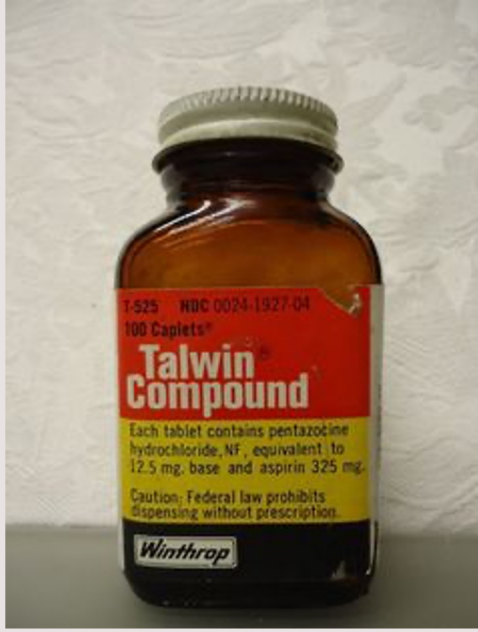
Benzomorphan



- Loperamide (Imodium)
  + Originally a Schedule V medication when FDA approved in 1977
  + Removed from schedule and made OTC in 1988
  + Therapeutic doses (<16mg/day)-No psychoactive effects
    - Limited by poor absorption (<2% bioavailability)
    - Substrate of CNS P-glycoprotein active efflux
  + Large doses (>70mg/day), 35 tabs of OTC Imodium-psychoactive effects
    - Overwhelm P-glycoprotein efflux
  + May cause QTc prolongation and torsades de pointes

https://missouripoisoncenter.org/loperamide-an-unexpected-drug-of-abuse/ accessed on August 9, 2023.
Antoniou T, Juurlink DN. Loperamide abuse. CMAJ. 2017 Jun 12;189(23):E803. doi: 10.1503/cmaj.161421. PMID: 28606977; PMCID: PMC5468105.

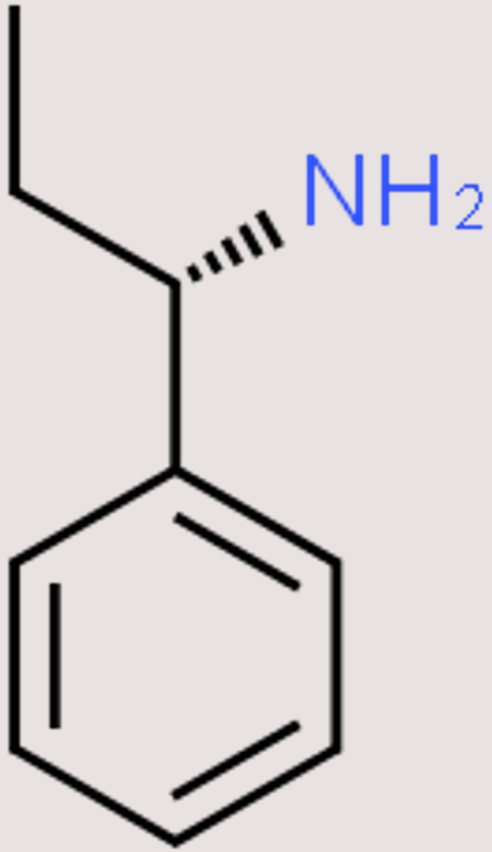
Pentazocine/naloxone (Talwin NX) Abuse Deterrent Form



- FDA approved in 1967
  - Abused in the 1970s by adding tripelennamine (antihistamine) *Ts and blues*
- MME: Morphine:pentazocine-1:3
- Dose:
  - 1 tablet (pentazocine 50 mg/naloxone 0.5 mg) every 3 to 4 hours as needed; may increase to 2 tablets (pentazocine 100 mg/naloxone 1 mg) based on response and tolerability. Maximum daily dose: 12 tablets (pentazocine 600 mg/naloxone 6 mg) per day
- Onset of action: 15-30 mins
- Metabolism:
  - Hepatic via oxidative and glucuronide conjugation pathways; extensive first-pass effect
- Genomic issues: None
- BBW if different from other opioids: none
- Clinical Pearls: Naloxone added to reduce ability to crush and inject

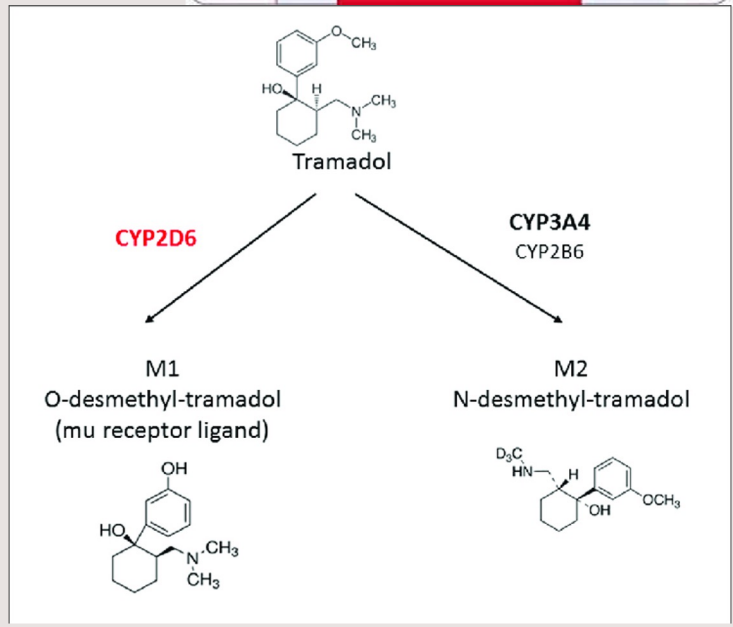
Lexi-Drugs/pentacozine. Lexicomp app. UpToDate Inc. Accessed August 10, 2023.
Showalter CV. T's and blues. Abuse of pentazocine and tripelennamine. JAMA. 1980 Sep 12;244(11):1224-5. doi: 10.1001/jama.244.11.1224. PMID: 7411785.
https://www.pinterest.com/janroaldr/ineedanursemedicine-drugs-vintage/ accessed on August 12, 2023.

Phenylpropylamine derivatives



(-)-1-Phenylpropylamine | C9H13N | ChemSpider accessed on August 6, 2023.

Tramadol/ER (Ultram,Ultram ER, ConZip, Qdolo)



- Synthetic 4-phenyl-piperidine analog of codeine
- MME: Morphine: Tramadol: 1:10
- MOA different from opioids:
  - SNRI which also modifies the ascending pain pathway
- Onset: <1 hour: peak effect: 2-3 hours
- Metabolism: Extensively by 3A4 & 2D6 with 1 active metabolite (O-desmethyltramadol (M1))
  - Important since the active metabolite has a longer $T_{1/2}$
- Adverse effects different than other opioids: seizures, serotonin syndrome
- Genomic issues:
  - CYP 2D6 PM: 20% higher concentration of tramadol
  - CYP 2D6 PM: 40% lower concentration of active metabolite (M1)

Lexi-Drugs/Tramadol. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
Ultram Prescribing Information: Drugs.com. https://www.drugs.com/pro/ultram.html accessed on 7/31/2023.
Kizilbash A, Ngô-Minh CT. Review of extended-release formulations of Tramadol for the management of chronic non-cancer pain: focus on marketed formulations. J Pain Res. 2014 Mar 24;7:149-61. doi: 10.2147/JPR.S49502. PMID: 24711710; PMCID: PMC3968086.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.

Tramadol Pharmacogenomics (2D6)

- Ultra metabolizer
  - Increased conversion to M1 leading to increased risk of toxicity (e.g. nausea, vomiting, constipation, respiratory depression, confusion, and urinary retention) (serotonin syndrome)
  - Avoid use due to potential for toxicity; use alternative non-codeine opioid
- Normal metabolizer
  - Normal conversion to M1
  - Use label-recommended dosing
- Intermediate metabolizer
  - Reduced conversion to M1 leading to reduced analgesia
  - May use label-recommended dosing, if less efficacious, use alternative non-codeine opioid
- Poor metabolizer
  - Greatly reduced conversion to M1 leading to reduced analgesia
  - Avoid use due to lack of efficacy; use alternative non-codeine opioid

Wong AK, Somogyi AA, Rubio J, Philip J. The Role of Pharmacogenomics in Opioid Prescribing. Curr Treat Options Oncol. 2022 Oct;23(10):1353-1369. doi: 10.1007/s11864-022-01010-x. Epub 2022 Aug 24. PMID: 36001223; PMCID: PMC9526685.

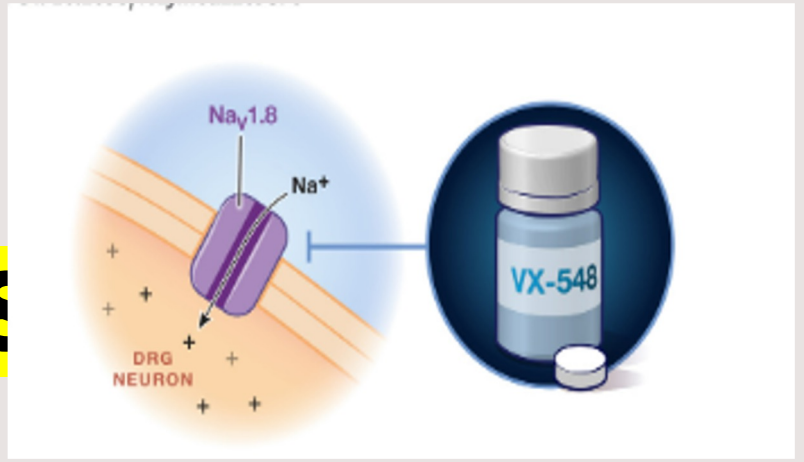
Tapentadol (Nucynta)

- Discovered in the late 1980s. Approved in 2008
- MME: morphine: tapentadol- 1:2.5
- MOA different from opioids:
  + SNRI which also modifies the ascending pain pathway
  + Stronger NE reuptake inhibition, weaker Se reuptake inhibition
- Onset of action: 30 mins
- Adverse effects: Constipation less common that oxycodone
- Genomic issues: No CYP interactions
- Abuse: Lower than other CII medication (oxymorphone, oxycodone, morphine, fentanyl) but higher than tramadol

Lexi-Drugs/Tapentadol. Lexicomp app. UpToDate Inc. Accessed July 31, 2023.
https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf accessed on 7/31/2023.
Chang EJ, Choi EJ, Kim KH. Tapentadol: Can It Kill Two Birds with One Stone without Breaking Windows? Korean J Pain. 2016 Jul;29(3):153-7. doi: 10.3344/kjp.2016.29.3.153. Epub 2016 Jul 1. PMID: 27413479; PMCID: PMC4942642.
RapidDetox by Waismann Metho. https://www.rapiddetox.com/rapid-opiate-detox/nucynta-addiction-rapid-detox/ accessed on 7/31/2023.

New Drug Class

Selective Inhibition of $Na_V1.8$



- Still in Clinical Trials (Phase III)
- Voltage-gated sodium channel $Na_V1.8$ is a therapeutic target for pain because of:
  - Role in transmitting nociceptive signals and selective expression in peripheral nociceptive neurons of the dorsal-root ganglia
  - $Na_V1.8$ is a sodium ion channel subtype that in humans is encoded by *SCN10A*
  - Role of $Na_V1.8$ in pain transmission is a function in normal sensory physiologic response
- Pathologic states arising from mutations in *SCN10A* animal models, and pharmacologic effects of $Na_V1.8$-modulating agents
- Hypothesis:
  - Selective inhibition of $Na_V1.8$ would provide effective pain relief without the risks associated with opioid treatments
  - Similar to local anesthetics

Jones J, Correll DJ, Lechner SM, Jazic I, Miao X, et al. Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain. N Engl J Med 2023; 389:393-405

New Drug Class

Selective Inhibition of $Na_V1.8$

- Two phase 2 trials involving participants with acute pain after abdominoplasty or bunionectomy
- In the abdominoplasty trial, participants were randomly assigned in a 1:1:1:1 ratio to receive one of the following over a 48-hour period
  - 100-mg oral loading dose of VX-548, followed by a 50-mg maintenance dose every 12 hours (the high-dose group)
  - 60-mg loading dose of VX-548, followed by a 30-mg maintenance dose every 12 hours (the middle-dose group)
  - Hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours)
  - PO placebo every 6 hours.
- In the bunionectomy trial, participants were randomly assigned in a 2:2:1:2:2 ratio to receive one of the following over a 48-hour treatment period:
  - 100-mg oral loading dose of VX-548, followed by a 50-mg maintenance dose every 12 hours (the high-dose group)
  - 60-mg loading dose of VX-548, followed by a 30-mg maintenance dose every 12 hours (the middle-dose group)
  - 20-mg loading dose of VX-548, followed by a 10-mg maintenance dose every 12 hours (low-dose group)
  - PO 5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours
  - PO placebo every 6 hours

Jones J, Correll DJ, Lechner SM, Jazic I, Miao X, et al. Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain. N Engl J Med 2023; 389:393-405

New Drug Class

Selective Inhibition of $Na_V1.8$

- Primary end point was the time-weighted sum of the pain-intensity difference (SPID) over the 48-hour period (SPID48)
  - Derived from the score on the Numeric Pain Rating Scale (range, 0 to 10; higher scores indicate greater pain) at 19 time points after the first dose of VX-548 or placebo
  - Main analysis compared each dose of VX-548 with placebo: not powered to compare to opioid
- Enrollees
  - 303 participants in the abdominoplasty trial
  - 274 in the bunionectomy trial
  - Least-squares mean difference between the high-dose VX-548 and placebo groups in the time-weighted SPID48 was 37.8 (95% confidence interval [CI], 9.2 to 66.4) after abdominoplasty and 36.8 (95% CI, 4.6 to 69.0) after bunionectomy
  - Both trials, participants who received low dose of VX-548 had results like placebo
  - Headache and constipation were common adverse events with VX-548

Jones J, Correll DJ, Lechner SM, Jazic I, Miao X, et al. Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain. N Engl J Med 2023; 389:393-405

Opioid-Induced Pruritis

- Variety of opioids were identified as evoking
- Incidence depends on the opioid used and mode of administration
- Occurs in approximately 2–10% of patients administered oral opioids
  + Incidence increased when opioids are administered epidurally or intraspinally
    - Highest incidence (up to 100%) is associated with intrathecal morphine
  + Incidence increases with increasing doses of opioids
  + Parturients are most susceptible
  + Facial areas innervated by the trigeminal nerve are mostly affected
    - Due to the high concentration of opioid receptors in the spinal nucleus of the trigeminal nerve
    - Typically, patients scratch the nose, perinasal area and upper part of the face
    - Generalized pruritus has also been reported

Reich A, Stander S, Szepietowski C. Drug Induced Pruritis: A Review. Acta Derm Venereol 2009; 89 236-244.

Opioid-Induced Pruritis

- Postulated mechanism:
  + Centrally mediated process via μ-opioid receptors
  + Modulation by the serotoninergic pathway and involvement of prostaglandins or histamine may also be important
  + Stimulation of opioid receptors in the skin by opioids cannot be excluded
  + Medullary dorsal horn may be a critical site for the action of opioids in producing pruritus
    - In Simians, morphine injected unilaterally into this region causes ipsilateral facial scratching

Reich A, Stander S, Szepietowski C. Drug Induced Pruritis: A Review. Acta Derm Venereol 2009; 89 236-244.

Opioid-Induced Pruritis

- Considered easy to treat but no treatment modalities are fully satisfactory
- Opioid antagonists may have a role in the prevention of opioid-induced pruritus
  + BUT: Both naloxone and naltrexone decrease analgesia, especially at higher doses
- Nalbuphine (a 40 mg IV bolus) prevented pruritus without increasing pain but:
  + Treatment was associated with increased drowsiness
  + Ineffective in the treatment of postoperative opioid-induced pruritus in pediatric patients
- 5-HT3 receptor antagonists (ondansetron, dolasetron) remain controversial-mixed results
- Preoperative gabapentin prevents pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anesthesia
- Antihistamines, droperidol, propofol, alizapride, tenoxicam and diclofenac have been tried with various success
- Possible pruritus prevention by reduction in opioid dose by combining with other meds, (sufentanil w/ bupivacaine)
  + Such combination offers satisfactory analgesia with a very low incidence of pruritus

Reich A, Stander S, Szepietowski C. Drug Induced Pruritis: A Review. Acta Derm Venereol 2009; 89 236-244.

Opioid-Induced Constipation

- American Gastroenterological Association published guidelines in 2019
- The Rome IV definition for OIC is the following:
  + new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:

    (1) straining during more than 25% of defecations

    (2) lumpy or hard stools more than 25% of defecations

    (3) sensation of incomplete evacuation more than 25% of defecations

    (4) sensation of anorectal obstruction/blockage more than 25% of defecations

    (5) manual maneuvers to facilitate more 25% of defecations (eg digital evacuation, support of the pelvic floor)

    (6) fewer than 3 spontaneous bowel movements per week

Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.

Opioid-Induced Constipation

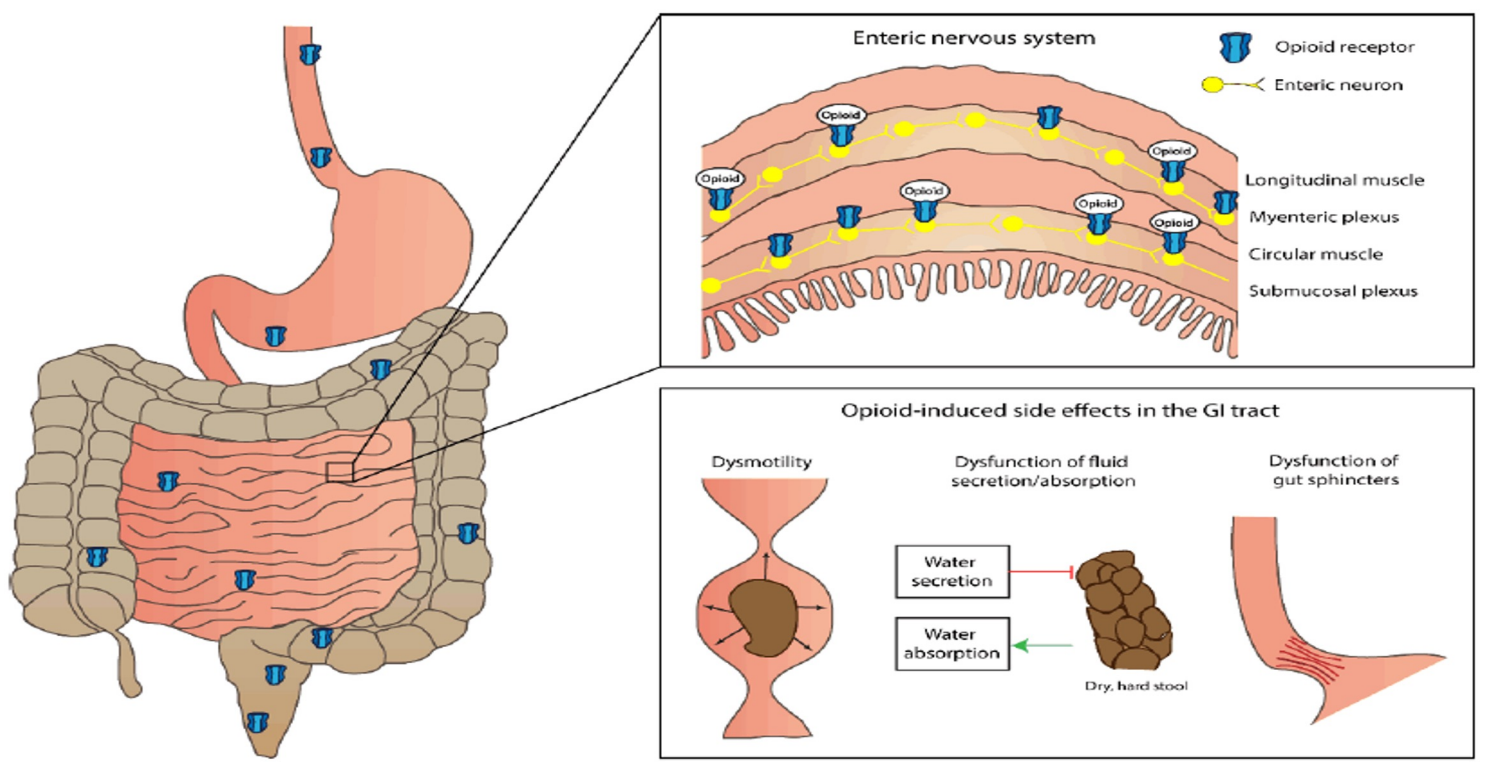


FIGURE 2. Illustration of the anatomical location of the myenteric and submucosal plexuses in the gut wall, and how opioid receptor activation in the enteric nervous system leads to three predominant adverse effects: (i) gut dysmotility, (ii) dysfunction of fluid secretion/absorption and (iii) gut sphincter dysfunction.

Hyldahl S, Gronlund D, Drewes AM, Brock, C. The patient burden of opioid induced bowel dysfunction. Clinical Practice (2018) Volume 15, Issue 4.

Opioid-Induced Constipation

- 1st line recommendation: Traditional Laxative
  + Osmotic: Draw water into intestine to hydrate and soften stool
    - PEG (Miralax)$$
    - Lactulose (Kristalose)$
    - Magnesium citrate (Citroma)$
    - Magnesium hydroxide (Milk of Magnesia)$
  + Stimulant: Irritate sensory nerve endings to stimulate colonic motility and reduce colonic water absorption
    - Bisacodyl (Dulcolax)$
    - Sodium picosulfate(Clenpiq/Prepopik): not available OTC
    - Senna (Ex-Lax, Senokot)$

Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.

Opioid-Induced Constipation

- 1st line recommendation: Traditional Laxative
  + Detergent/surfactant/stool softener: Allow water and lipids to penetrate the stool to hydrate and soften fecal material, but not move it along.
    - Docusate (Colace)$
  + Lubricant: Lubricate the lining of the gut to facilitate defecation
    - Mineral oil$

Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.

Opioid-Induced Constipation

- 2nd line recommendation: PAMORA (Peripherally Acting Mu Opioid Receptor Antagonists)
  + MOA: Block mu-opioid receptors in the gut, thereby effectively restoring the function of the enteric nervous system
    - Naldemidine (Symproic)$$$$
    - Naloxegol (Movantik)$$$$
    - Methylnaltrexone (Relistor)-$$$$$$----oral and SQ options
  + All agents recommended for laxative refractory OIC only

Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.

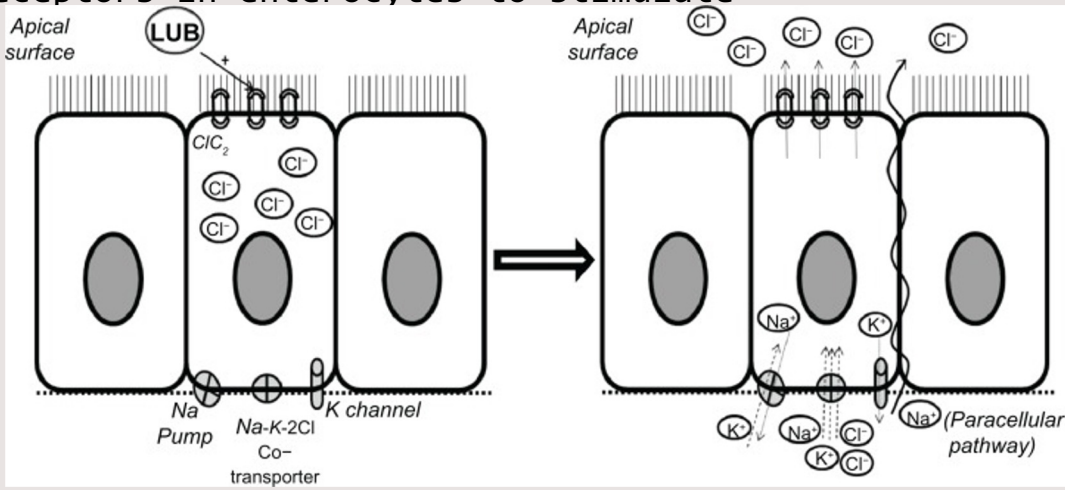
Opioid-Induced Constipation

- 3rd line: Intestinal Secretagogues

  + Lubiprostone (Amitiza)$$$

    - MOA: Act on chloride channels or guanylate cyclase receptors in enterocytes to stimulate fluid secretion into the intestinal lumen

- No recommendation for use per AGA guidelines



-Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.
-https://www.researchgate.net/figure/Summary-of-the-mechanism-of-action-of-lubiprostone-Notes-Chloride-channels-2-present_fig1_235729580 accessed on August 16, 2023.

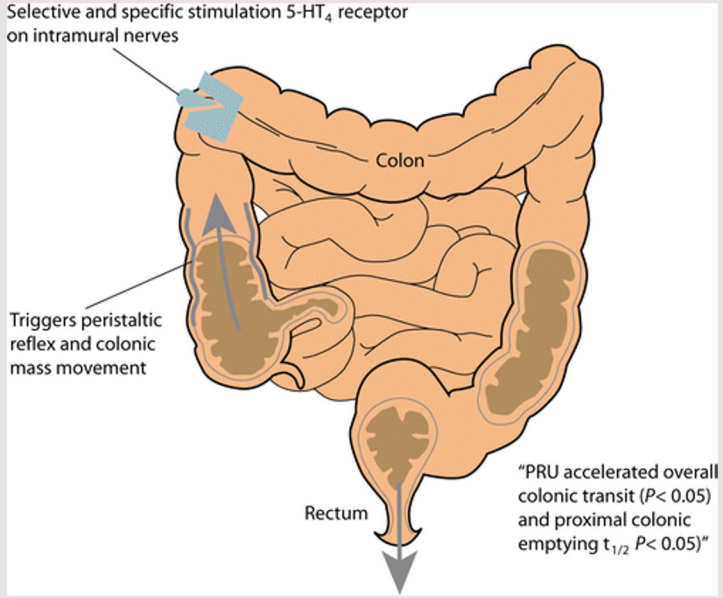
Opioid-Induced Constipation

- 4th line: Selective 5-HT agonists

  + Prucalopride (Motegrity) $$$$

    - MOA: Activate 5-HT4 receptor (agonist), leading to increased colonic motility and accelerated transit
    - Indication: Chronic idiopathic constipation

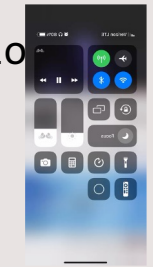
- No recommendation for use per AGA guidelines



-Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology 2019;156:218–226.
-The use of Resolor (prucalopride) for chronic constipation in women British Journal of Nursing. Accessed at https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.magonlinelibrary.com%2Fdoi%2F10.12968%2Fbjon.2012.21.16.982&psig=AOvVaw06OpnnVy0XPNOGYQ_zKa0L&ust=1692291300378000&source=images&cd=vfe&opi=89978449&ved=0CA8QjhxqFwoTCIDo4sLS4YADFQAAAAAdAAAAABBh on August 16, 2023.

In Memoriam

- Kadian (Morphine ER) NB/Morphabond ER (Mophine ER) NB/Arymo ER (Morphine ER)
- Exalgo ER (Hydromorphone ER) NB
- Darvon/Darvocet (Propoxyphene/APAP): All forms
- Opana (name brand) abuse deterrent
- Vicodin/Lorcet/Lorcet Plus/Norco/Vicoprofen(NB)/Alor/Bancap HC/Kwelcof/Histinex HC/ Vidone/Zamicet/Zohydro ER (hydrocodone ER) NB
- Demerol (meperidine)
- Percodan (oxycodone/ASA)/Tylox/Taxadone/Oxyfast/Xolox/Narvox/Perlo



Questions