Opioid Pharmacology

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Tri-Cities Pain Conference, 4/26/2024

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Disclosures

None

Objectives

1. Differentiate between the functions of full mu agonists, partial agonists and opioid antagonist
2. Classify key differences in pharmacology of commonly used opioids and compare their potency
3. Apply best practices for prescribing or managing outpatient opioid medications

Roadmap

Pharmacodynamics **Pharmacokinetics** **Put It Into Context** **Highlights**

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Pharmacodynamics - Where do they work?[1,2]

- Endogenous opioids found in central nervous system (CNS) and peripheral nervous system (PNS)
  - Afferent fibers carry signals to CNS, efferent fibers away from CNS
- 4 opioid receptors - **mu (μOR), kappa (κOR), delta (δOR), opioid-like receptor-1 (ORL-1)**
- Endogenous opioids - enkephalins, endorphins, dynorphins, endomorphins, nociceptin
- Most traditional opioids have primary analgesic activity at μOR

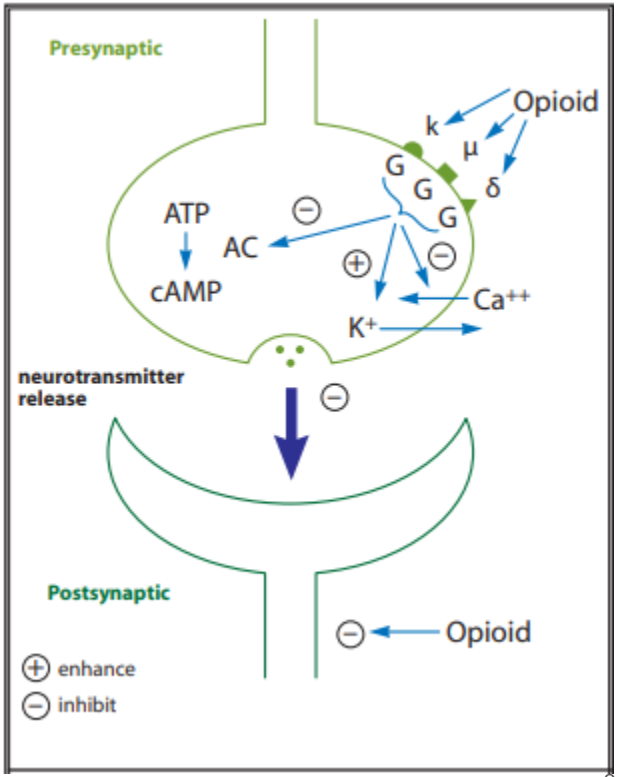
Endogenous Opioids[2]

- Endorphins - μOR and δOR
  - PNS - inhibit release of substance P, glutamate
  - CNS - inhibit release of GABA, increase dopamine release
- Enkephalins - δOR
  - CNS - facilitate dopamine release
  - Spinal cord - inhibit afferent nociceptive signals
- Dynorphins - κOR
  - Amygdala - reward/behavior pathway, anxiety
  - Increased during stress response
- Surgeries, acupuncture, exercise increase release of endorphins
  - Exogenous opioids reduce this effect

Pharmacodynamics - Unexpected Effects[9,10]

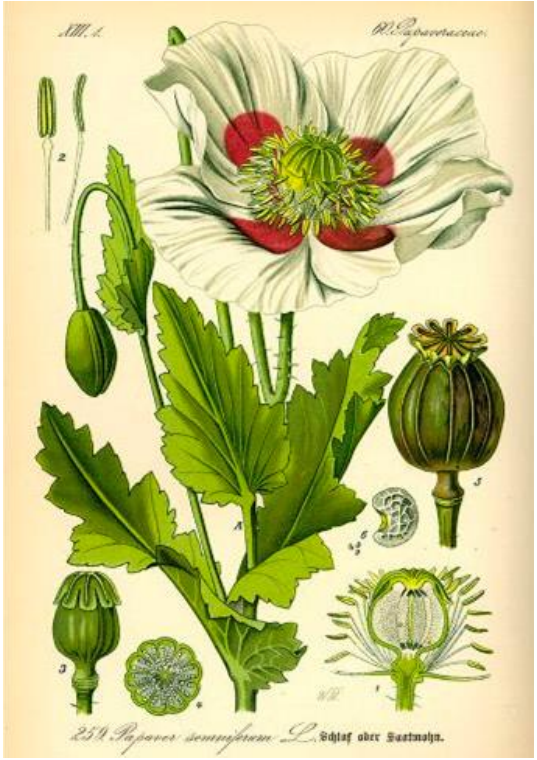
- Immune system - higher rate of infection in chronic opioid use
  - Inhibit NK cells, reduce cytokine production (IL-6, TNF), reduction in T cell proliferation
  - Endogenous opioids regulate immune system
- Opioid endocrinopathy
  - Decreased testosterone → decreased libido, reduced energy, ED
  - Decreased estrogen → decreased libido, reduced BMD, amenorrhea
- Pruritus
  - Mast cell degranulation - histamine mediated, tryptase
  - opioid receptor mediated - μOR involved in itch sensation, dynorphin/κOR reduce itch
- Constipation - μOR agonists decrease gastric motility

Receptor	Location	Effect [3,4]
μOR	Brain stem, thalamus	euphoria, supraspinal analgesia, sedation, respiratory depression, pruritus, anorexia, reduced gastric motility
κOR	Brain stem, spinal cord, limbic system	spinal analgesia, sedation, dysphoria, respiratory depression
δOR	Brain	analgesia, spinal analgesia, reduce gastric motility
OLR1	Spinal and supraspinal	antidepressant, analgesic effect



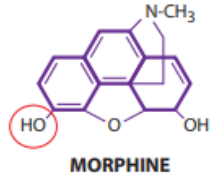
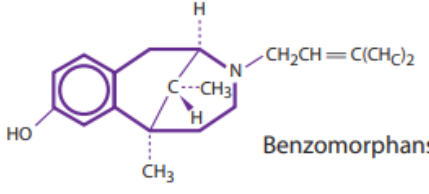
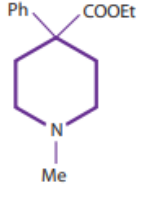
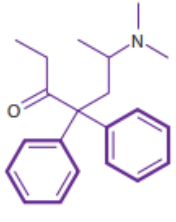
Mechanism of opioid receptor[3]

Classify Opiates per CDC



Naturally occurring - derived from opium poppy	morphine, codeine
Semi-synthetic - chemically derived from natural opiates	hydromorphone, hydrocodone, oxycodone, buprenorphine, heroin
Synthetic - synthesized in a laboratory	fentanyl, methadone, tramadol

https://museum.dea.gov/exhibits/online-exhibits/cannabis-coca-and-poppy-natures-addictive-plants/opium-poppy

 MORPHINE Phenanthrenes	**morphine, codeine, hydromorphone, oxycodone, oxymorphone, buprenorphine, nalbuphine, butorphanol**
 Benzomorphans	**pentazocine (discontinued)**
 Phenylpiperidines	**fentanyl, sufentanil, alfentanil, meperidine**
 Diphenylheptanes	**methadone, propoxyphene**

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Classify Opiates by Activity

Mu Agonist	morphine, codeine, oxycodone, hydrocodone, fentanyl, methadone
Partial Agonist	buprenorphine, butorphenol
Antagonist	naloxone, naltrexone, naloxegol (peripheral), methylnaltrexone (peripheral)

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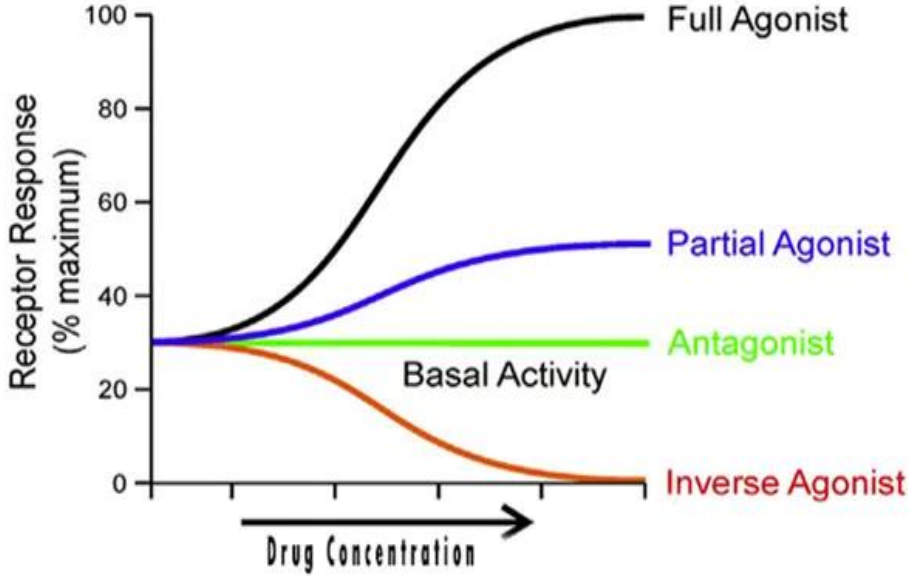
At The Receptor

- **Agonist** - binds receptor causing downstream effect on the neuron
- **Partial Agonist** - bind at receptor but cause less downstream effect
- **Antagonist** - binds at the receptor, but does not cause any downstream effect on the neuron, reversing the effect of the agonist



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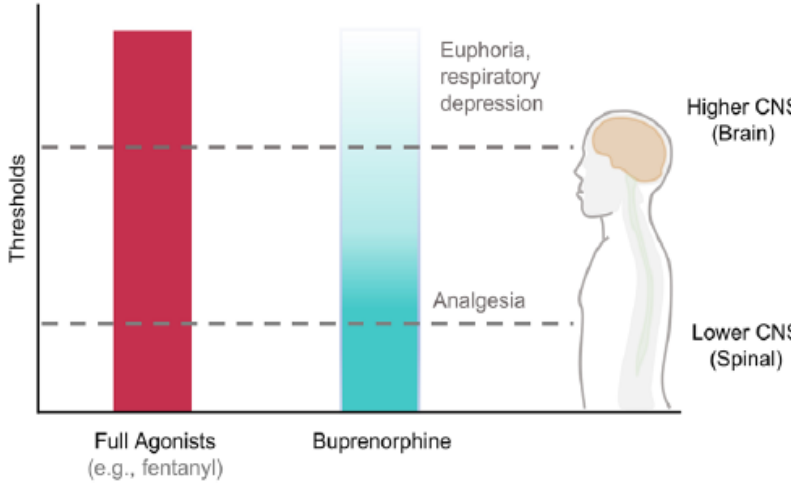
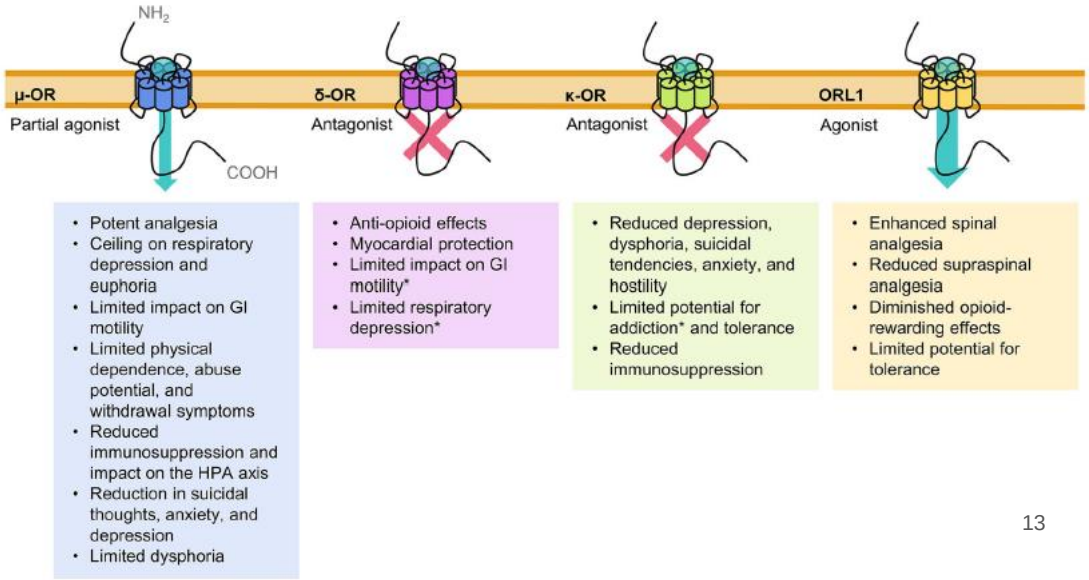
https://pharmaeducation.net/agonist-partial-agonist-antagonist-inverse-agonist/

Partial Agonism (Buprenorphine)[11]

- Buprenorphine is a partial μOR agonist, κOR and δOR antagonist
  - Blocks full agonist at binding site - very strong binding affinity
  - Ceiling effect for respiratory depression
  - Dose dependent analgesia





Pharmacokinetics (PK)

Absorption

Distribution

Metabolism

Excretion

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Absorption

- Oral
  - Immediate release vs extended release formulation
- Transmucosal
  - Buccal buprenorphine, fentanyl lollipop
  - Avoids first pass metabolism
- Transdermal
  - Fentanyl and buprenorphine
  - Highly lipophilic

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Distribution

- Central compartment / intravascular vs peripheral compartment / extravascular
- Quick onset of fentanyl (vs morphine) related to lipophilicity and non-ionized
  - Quickly distributes into CNS, crosses blood brain barrier
  - Heroin also more lipophilic than morphine - “rush” and “high”
- Lipophilicity also allows fentanyl and methadone to accumulate in fat
  - Impact on urine drug screening[16]

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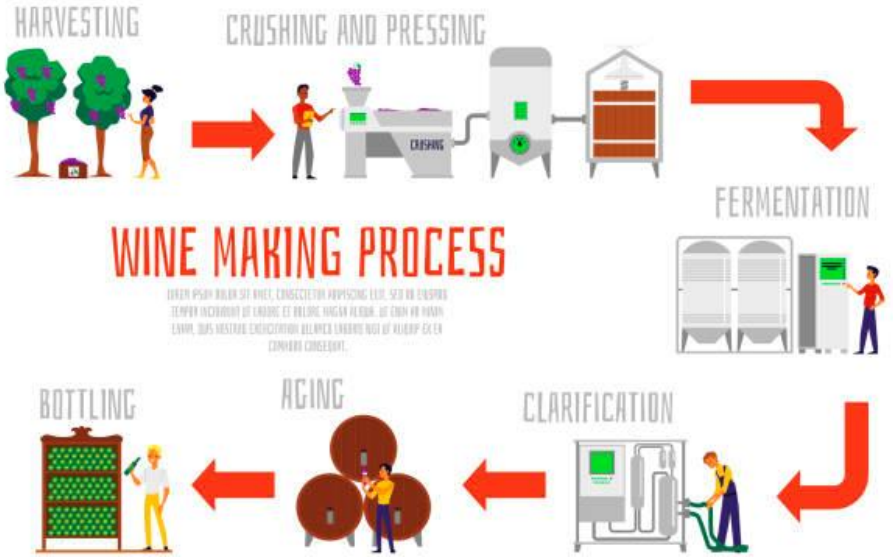
Metabolism[12]

- Cytochrome P450 (CYP450) system in the liver
  - Primarily 3A4 and 2D6 for opioids
  - 2D6 has genetic polymorphism
  - Prodrug and drug clearance considerations
- Glucuronidation via UGT enzymes → promotes renal clearance
  - Generally renders drug inactive *except* morphine
  - Active metabolites undergo glucuronidation to become inactive

Prodrugs

Parent drug weakly active

- Hydrocodone
- Codeine
- Tramadol



Slowing metabolism prevents transition to the primary opioid agonist

Increasing metabolism increases exposure to active metabolite

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istockphoto.com credit: sabelskaya

Hepatic Considerations

Case of codeine and tramadol[6]

- Codeine active metabolite = morphine
- Tramadol metabolite = O-desmethyltramadol, 6x more potent
- CYP2D6 poor metabolizers (5-10% of population) = no analgesic effect
- CYP2D6 ultra metabolizers (1-2% of population) = higher risk of adverse effects

CYP3A4 and 2D6[12]

we'll come back to this

Enzyme	Opioid	Metabolite
CYP3A4	Codeine	Inactive metabolite - norcodeine
	Oxycodone	Inactive metabolite - noroxycodone
	Hydrocodone	Inactive metabolite - norhydrocodone
	Fentanyl	Inactive metabolite - norfentanyl
	Tramadol	Inactive metabolite
	Buprenorphine	Active metabolite - norbuprenorphine
CYP2D6	Codeine	Morphine
	Oxycodone	Oxymorphone (~10%)
	Hydrocodone	Hydromorphone
	Tramadol	Active metabolite

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Morphine

- Parent drug goes through glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)
  - 10-15% turned into M6G → analgesic activity
  - 55% turned into M3G → not active at opioid receptor, toxicity?
- No major drug interactions
- Renal implications

Methadone Complex PK[15]

- R- and S- enantiomers
  - R active at μOR, both active at NMDA receptors and SNRI
- High bioavailability, highly protein bound, lipophilic with large volume of distribution, extensively metabolized
  - Long ½ life related to distribution out of peripheral tissue
  - Analgesia only lasts 6-8hr, in plasma at sub analgesic levels beyond that
- CYP enzymes involved: 2B6 (major), 3A4, 2C19, 2C9, 2D6, 3A5
  - 2B6 highly polymorphic
  - 2B6 inducer (efavirenz, rifampin, carbamazepine), inhibitor (vori, tenofovir)
- Severe cirrhosis can ↑ bioavailability and ↓ CYP metabolism

Important Drug Interactions[14]

Mechanism	Opioid	Common Offender
CYP3A4 Inhibitor	Oxycodone, codeine, fentanyl, methadone, buprenorphine	Ritonavir, cobicistat, azole antifungals (itraconazole > fluconazole), diltiazem/verapamil (moderate)
CYP3A4 Inducer	Oxycodone, codeine, fentanyl, methadone	Rifampin, carbamazepine, phenytoin, primidone (moderate)
CYP2D6 Inhibitor	Codeine, tramadol, hydrocodone	Paroxetine, fluoxetine, bupropion, duloxetine (moderate)
Respiratory depression	All opioid agonists Including buprenorphine	Benzodiazepines, alcohol, CNS depressants
Serotonin syndrome	Tramadol, methadone	SSRIs, SNRIs, trazodone, TCAs, MAOIs

Case Context #1

48yo F on chronic oxycodone for psoriatic arthritis and osteoarthritis. She has been working on tapering, but current dose is stalled at 80mg using oxycodone 10mg IR tablets prn. PMH includes DM, HTN, depression, and BMI>45. She is pending bariatric surgery, but tests positive for COVID requiring surgery to be delayed. She gets Rx for Paxlovid™ from urgent care.

On follow up, 7 days into COVID course which is her last day of Paxlovid™, she notes that she is finally down to only oxycodone 40-50mg per day and is feeling well from pain perspective.

Paxlovid™ Interaction

Ritonavir as a boosting agent

- Major 3A4 interaction

Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.

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Paxlovid [Package Insert]. Pfizer Laboratories Inc; 2023.

Case Context #2

71yo F with rheumatoid arthritis, OA, HTN and hypothyroidism on chronic opioids with MED >200mg daily which was increased after an acute wrist fracture related to osteoporosis. Her RA is well managed on sulfasalazine. She asks Rheumatologist if there's anything else to help manage her pain as she wants to reduce opioid dosage.

Rheumatologist advises she can try duloxetine 30mg daily, increase to 60mg as tolerated. She is not on any other SSRI or anti-depressants.

Which of the following opioids would potentially interact with the addition of duloxetine?

A. Morphine
B. Hydromorphone
C. Hydrocodone
D. Oxycodone
E. Tramadol

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A. Morphine
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E. Tramadol

Food for thought: which antidepressant would have a stronger drug interaction with hydrocodone/tramadol?

If someone is on one of those antidepressants, which opioid would be preferred for acute pain Rx?

Excretion[7, 13]

- Metabolites are generally renally cleared (active or inactive)
- Some portion of active parent drug may be renally cleared as well
- Dialysis - methadone and fentanyl are not dialyzable
  - Fentanyl highly protein bound, lipid soluble
  - Methadone is mostly metabolized and parent drug isn't dialyzed
  - Tramadol, hydromorphone, oxycodone likely dialyzable based on chemical characteristics → may need post-HD dose

Renal Considerations[7]

Toxic, active metabolites can accumulate in poor renal function

- Morphine metabolites morphine-3-glucuronide (inactive) and morphine-6-glucuronide (potent, active)
- Meperidine metabolite normeperidine is neuroexcitatory, seizures

Agents with active metabolites will effectively have longer half-life in CKD

- Avoid ER formulations - higher risk of accumulation

Renal Considerations[7,8,13]

- Relatively safer (pharmacokinetically) opioids in CKD
  - **buprenorphine** - CKD does not change PK
  - **methadone** - not renally cleared nor active metabolites
  - **fentanyl** - some impact by CKD, but relatively safe short term
- Altered PK in CKD
  - **hydromorphone** - active metabolites can accumulate
  - **hydrocodone** - active metabolites can accumulate
  - **oxycodone** - higher peak concentrations and longer $T_{1/2}$
  - **tramadol** - active metabolites and longer $T_{1/2}$

Case Context #3

68yo F with HTN, DM2, HF and chronic back pain.

Meds: losartan 100mg daily, metoprolol ER 100mg daily, furosemide 20mg BID, semaglutide 1mg weekly, empagliflozin 10mg daily, morphine ER 30mg BID

She is admitted with altered mental status and found to have AKI. Her ARB and SGLT2i was held and diuretic dose was reduced.

What is appropriate management of morphine?

A. Hold all opioids
B. Transition to transdermal fentanyl (50mcg/hr)
C. Transition to acetaminophen-codeine (120mg/day)
D. Switch ER morphine to immediate release hydromorphone (8-10mg/day)
E. Switch ER morphine to immediate release morphine (60mg/day)

What is appropriate management of morphine?

A. Hold all opioids
    - Induce withdrawal
B. Transition to transdermal fentanyl (50mcg/hr)
    - higher MED (120) than her baseline Rx
C. Transition to acetaminophen-codeine (120mg/day)
    - just as high risk
D. Switch ER morphine to IR hydromorphone (8-10mg/day)
    - reasonable choice, start with lower MED (40) than baseline
E. Switch ER morphine to immediate release morphine (60mg/day)
    - just as high risk

Case Context #4

70yo M with HTN, DM2, chronic pain and progressing CKD. In the last year, eGFR has fallen from 40-45 to 25-30mL/min/1.73m2

His chronic pain has been managed on oxycodone 5-10mg TID for the last 2 years. He previously tried morphine which caused itching, hydrocodone which was not as effective as oxycodone, and was transitioned from oxycodone ER to IR 2 years ago when eGFR fell below 60.

What is appropriate management of chronic opioid given reduced renal function in the last 1 year?

A. Initiate opioid taper by 10-15% of total daily dose as tolerated
B. Transition to buprenorphine 10mcg/hr patch every 7 days
C. Transition to methadone 10mg daily
D. Switch to oxycodone ER to reduce risk of accumulation in CKD

What is appropriate management of chronic opioid given reduced renal function in the last 1 year?

A. Initiate opioid taper by 10-15% of total daily dose as tolerated
    - reasonable option, CKD is causing higher peaks and longer $T_{1/2}$
B. Transition to buprenorphine 10mcg/hr patch every 7 days
    - reasonable option, safer opioid in CKD
C. Transition to methadone 10mg daily
    - CKD-wise safer choice, but has additional risks making it less desirable
D. Switch to oxycodone ER to reduce risk of accumulation in CKD
    - ER formulation likely higher risk

Relative Potency

- Compare opioids using morphine equivalent dose (MED)
  - Consider drug interactions with old and new opioid
  - ex: switch from hydromorphone to oxycodone but also on 3A4 inhibitor
- Buprenorphine = a partial agonist does not have MED conversion
  - Package insert of buccal and transdermal form for conversion
- Methadone = no consensus, non linear
  - Use conversion factors as guidelines, monitor closely
- MED calculators available
  - Oregon Pain Guidance
  - Washington Agency Medical Directors' Group
  - 2022 CDC Chronic Pain Guideline[17]

Highlights

- Partial agonist does **not** mean only partial analgesia
- A lot of (pharmacokinetic) drug interactions to consider → morphine, hydromorphone, oxymorphone have the least to worry about
- Pharmacogenomic differences in opioid response → ability to metabolize via 2D6 into active drug, methadone metabolism via 2B6
- Avoid morphine and codeine in renal disease, buprenorphine has good role here

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Questions?

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