Starting and Switching Opioids

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Objectives

- Describe how initiating, titrating, and continuing opioid in patients with advanced cancer may be similar or different than for non-malignant pain.
- Describe how to select an opioid for starting opioid treatment in a patient with cancer
- Describe how to balance scheduled extended-release doses of opioids with immediate-release doses for breakthrough pain
- Describe how to switch from one opioid to another
- Describe how to respond to common adverse effects of opioids, including over-titration, constipation, and hyperalgesia

Decision Points

- Is the pain severe enough to warrant opioids?
- Consider alternative, non-opioid drugs unless the alternative:
  - Is contra-indicated (eg., ketorolac in patient with kidney disease, heart failure)
  - Is not working
  - Is not likely to work
- Which opioid should be used?
  - Typically, avoid pro-drugs and mixed agonist-antagonist drugs
  - Morphine is preferred unless renal dysfunction exists or known intolerance
  - Hydrocodone/APAP doses equivalent to morphine, but limited by APAP
  - Oxycodone is less affected by renal function

Concurrent Medications with Opioids

- SCHEDULED laxatives
  - Senna +/- DOSS
  - PEG (Miralax®) and others
- Non-opioid analgesic
  - Acetaminophen
  - NSAID if an inflammatory component
- Naloxone
  - Prescription needs to be normalized due to concerns with:
    - Accidental (or Intentional) use by non-patients
    - Drug interactions, dosing errors in patient

What are (Old) Starting Doses in Opioid-naive Adults?

Drug	Acute, new	MEDD
Morphine	7.5-15mg (1/2-1, 15mg tablet) PO every 4-6 hours PRN	90 mg 6x * 15mg
Hydrocodone (APAP)	5-10mg (1-2 5mg tablets) every 4-6 hours PRN	60 mg 6x * 10mg
Oxycodone	5-10mg (1-2 5mg tablets) every 4-6 hours PRN	90 mg 6x * 10mg * 3/2

What are Starting Doses in Opioid-naive Adults?

Drug	Acute, new	Max MEDD
Morphine	7.5-15mg (1/2-1 15mg tablets) PO every 6 hours PRN	60mg (4x 15mg)
Hydrocodone (APAP)	5-10mg (1-2 5mg tablets) every 6 hours PRN	40mg (4x 10mg)
Oxycodone	2.5-5mg (1/2-1x 5mg tablets) every 4-6 hours PRN	45mg (6x 5mg x 3/2)

CDC and WiMEB discourage starting MEDD >= 50mg/day

PRN vs Scheduled

- Injury / Trauma / Procedural pain we expect to improve over 2 weeks
- If pain is consistent:
  - Re-evaluate
- We often expect pain from advanced cancer to be consistent and likely to increase
  - These patients are more likely to get higher doses, and more scheduled doses.
- Other instances of non-malignant pain that are often helped by chronic opioids Re chronic pain from Ehlers-Danlos syndrome or from vaso-occlusive event residuals in patients with Sickle Cell disease.

Example: Adding Scheduled ER

- From an Rx of Morphine 15mg q2Hr PRN patient is averaging 90mg/day:

Change to: 30mg Morphine SR PO Q 12 hrs

7.5-15mg Morphine IR PO Q 2 hrs PRN (approximates 10-20% of 60mg/day)

Extended / Sustained Release Opioids

- Extended (ER) and Sustained Release (SR) Opioid formulations are just more convenient methods of providing opioids around the clock for patients who have a demonstrated, consistent benefit from their use for chronic pain.
  - Patient with chronic pain receiving scheduled opioids may use less opioid/d than one taking them PRN to beat down pain.
  - Adjuvant meds should be continued (Laxatives, APAP/NSAIDs, etc)
- Daily SR/ER dose is determined for patients with malignant pain:
  - Tally usual daily dose of IR formulation, ideally over several days.
  - Take 60-75% of the daily IR dose needs and convert to SR/ER dose/day
  - Provide 10-20% of the daily SR opioid dose EVERY 2-3 hours, AS NEEDED
    - Why dose PRNs every 2-3 hours in cancer patients with chronic pain?

Why every 2-3 hours vs 4-6 hours?

- T_{max} for most IR opioid formulations is within 1-2 hours
- T1/2 for most common opioids is ~ 3 hours
- If pain is not relieved after 2 hours, why is the next PRN dose delayed for 2-4 hours?
  - For acute pain (eg, s/p trauma, procedure) we expect the pain to resolve
  - For chronic cancer pain we do not expect this, and more frequent PRN IR dosing (Q2-3hrs) is usual

Dangerous Practices

- If a patient is <u>not yet opioid tolerant:</u>
  - DO NOT start an opioid basal infusion (use Patient Controlled Analgesia instead)
  - DO NOT place a patient on long acting oral opioids
  - DO NOT place a fentanyl patch

- Use PRN, immediate-release or IV boluses to determine the consistency and magnitude of opioid needs first.

FDA Opioid Tolerance Definition

- Patients who are taking, for 1 week or longer, at least:
  - 60 mg oral morphine (hydrocodone)/day
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 µg transdermal fentanyl/hour
  - 25 mg oral oxymorphone/day; or
  - An equianalgesic dose of any other opioid.

Titrating Dose Up

- Tally the daily use of SR & IR opioids over several days
- Take 60-75% of the daily opioid dose and make this the daily SR dose
  - Include new Rx for breakthrough: 10 – 20% of the new daily SR dose
- Higher jumps (up to 100%) may be needed for very poorly controlled pain
  - Do not increase daily opioid dose by > 100% (2x)
- If dose escalations do not improve the pain (or in some cases make it worse), suspect hyperalgesia, and switch to a different opioid

Example: Escalating Dose - 1

- Pancreatic cancer Pt: Pain score remains 6-8
- 30 mg Oxycodone ER every 8 hours (= 90mg)
- 10-20 mg Oxycodone IR every 2 hours PRN, using **150 mg IR over 24 hours**
- Thus, 240 mg/day (90 + 150)
  - **Choose 60mg SR q8 = 180mg, although 240mg/day possible**

Example: Escalating Dose - 2

- Thus, 240 mg/day (90 + 150)
  - **Choose 60mg SR q8 = 180mg, although 240mg/day possible**
- Oxycodone ER 60 mg every 8 hours
- Oxycodone IR 20-40 mg every 2 hours PRN
  - Approximates 10-20% of daily 180mg SR dose

What if your SR dose is too low?

- Suppose the morphine SR + IR use has been 240-260mg/day
- You decide to recommend a morphine SR dose of 60mg PO every 8 hours.
  - 180mg morphine SR/day, or 75% of SR + IR total
- IR morphine dose (10 – 20% of daily SR) is 15-30mg every 2-3hours
  - (Morphine comes in 15mg tablets)
- How much morphine could they receive from the IR doses per day?
  - 12 doses x 30mg = 360mg of POTENTIAL rescue doses
  - EMPHASIZE in your patient instruction that these IR doses are PRN.

Hyperalgesia

- A perception of pain that is worse than expected, often due to CNS sensitization
- Allodynia is the perception of pain when none is expected
  - eg., stroke of a feather is painful
- Some opioid metabolites (especially of morphine and hydromorphone) are thought to cause chemical hyperalgesia
- Ketamine (IV or PO) may be helpful in reversing hyperalgesia, but usually an opioid rotation (switch) is performed

Switching Opioids

- Determine Morphine Equivalent Daily Dose (MEDD) of drug(s) from which the patient is to be changed
- Use equianalgesic table to find equivalent daily dose of new opioid
- Apply a 25-33% empiric reduction to account for unknown, incomplete cross-tolerance
  - 25-33% range allows for available products
  - Empiric reduction not applied moving to fentanyl patch

Equianalgesic Tables

Drug	IV/SC (mg/d)	Oral (mg/d)	Topical (patch)
Morphine	10	30	
Oxycodone	-	20-30	
Hydromorphone	1.5	7.5	
Hydrocodone	-	30	
Tramadol	100	120	
Methadone	5	7.5	
Fentanyl	0.1 mg	-	15 mcg/hr

McPherson ML. Demystifying Opioid Conversion Calculations, 1st ed. ASHP, Bethesda, 2010.

Note: 2mg/day oral morphine -> 1mcg/hr patch

Opioid Conversion Guidelines

- Conversion from IV/SC to PO dose of same drug can use table directly
- Conversion from one opioid to another typically includes a 25-33% empiric reduction
- Opioid analgesic (and risk) equivalents are typically presented in morphine equivalents
- MEDD to Fentanyl conversion is conservative

Drug	IV/SC (mg)	Oral (mg)	Topical (patch)
Morphine	10	30	
Oxycodone	-	20-30	
Hydromorphone	1.5	7.5	
Hydrocodone	-	30	
Tramadol	100	120	
Methadone	5	7.5	
Fentanyl	0.1 mg	-	2 MEDD = 1 mcg/hr

Opioid Conversion Example

- Consider a patient on 5mg/hr of morphine IV who is confused and experiencing myoclonic jerking.
  - Scr has increased, and eGFR has decreased to 35 mL/min
  - You recommend converting to fentanyl:
- 5mg/hr * 100mcg fentanyl / 10 mg morphine =

  50mg/hr fentanyl

  Because we are changing from one drug to another, decrease the initial fentanyl rate by 25-33% to 35mcg/hr

  Include order for PRN RN boluses of 35mcg fentanyl IV every 20 minutes

Opioid Conversion Example

- Dang…"fentanyl is on shortage, could we try hydromorphone?"
- 5mg/hr morphine * $\frac{\text{1.5 mg hydromorphone IV}}{\text{10 mg morphine IV}}$

  = 0.75 mg hydromorphone/hour

  Because we are changing from one drug to another, decrease the initial hydromorphone rate by 25-33% to 0.5 mg/hr

  Include order for RN boluses of 0.5mg IV hydromorphone every 20 minutes for pain

Methadone

- A useful opioid analgesic, but is more difficult to use because it demonstrates:
  - Widely variable kinetics – conversions between drugs are complex
  - Long $t_{1/2}$: Slow to reach therapeutic plateau (1-2 wks), and slow to be eliminated
  - Multiple drug interactions (CYP3A4/5, CYP2B6)
  - Can prolong the QTc (increase the risk of torsades de pointes, fatal arrhythmia)
    - Typically not started if QTc is >470 msec

Methadone

- The half-life of most opioids is about 3 hours, but for methadone and buprenorphine it is 1-3 DAYS
  - Steady state is achieved for most oral opioids within 1-2 DAYS
  - Steady state is achieved for a new regimen of methadone or buprenorphine after 1-2 WEEKS

New McPherson Method

Total Daily Dose Oral Morphine Equivalent (MEDD, MME, OME)	Conversion Ratio to Oral Methadone
0 – 60 mg	2 – 5 mg oral methadone daily
60 – 199 mg AND < 65 years old	10mg MEDD : 1 mg Oral Methadone
≥ 200 mg OR ≥ 65 years old	20mg MEDD : 1 mg Oral Methadone

Do not exceed **30**-40mg oral methadone per day as starting dose, REGARDLESS of previous opioid MEDD.

Reduce calculated oral methadone dose by 25-30% if patient is receiving a known enzyme inhibitor (CYP2B6 or CYP3A4)

Methadone TO Morphine

- VERY LITTLE information on this
- DO NOT use 1:10 ratio (or higher)
- Recommendation:

1:3 ratio to be conservative

eg. From 15mg Q8H methadone go to 45mg q8H extended release morphine

Patient-controlled Analgesia (PCA)

- In opioid-naïve patient start at:
  - Morphine 0.5 – 1 mg with an q12-15 min lockout
  - Hydromorphone 0.1 – 0.2 mg with an q12-15 min lockout
  - Fentanyl 10mcg with an q8-10 min lockout
- All of these opioids can also be given Subcutaneously at a 1:1 ratio to the IV dose. Lockouts need to be longer for SC.

Patient-controlled Analgesia - 2

- **Basal infusions are usually not indicated without preexisting, chronic opioid needs**
  - If used, the basal rate is based upon prior opioid use:

120mg oral morphine/24hr = 40mg IV Morphine/24hr = 1.6mg/hr infusion

- **Patient boluses:** 50-100% of basal rate: 0.8-1.6mg Q12min
- **RN bolus**: 100-200% of basal rate: 1.6 – 3.2mg Q12-60min

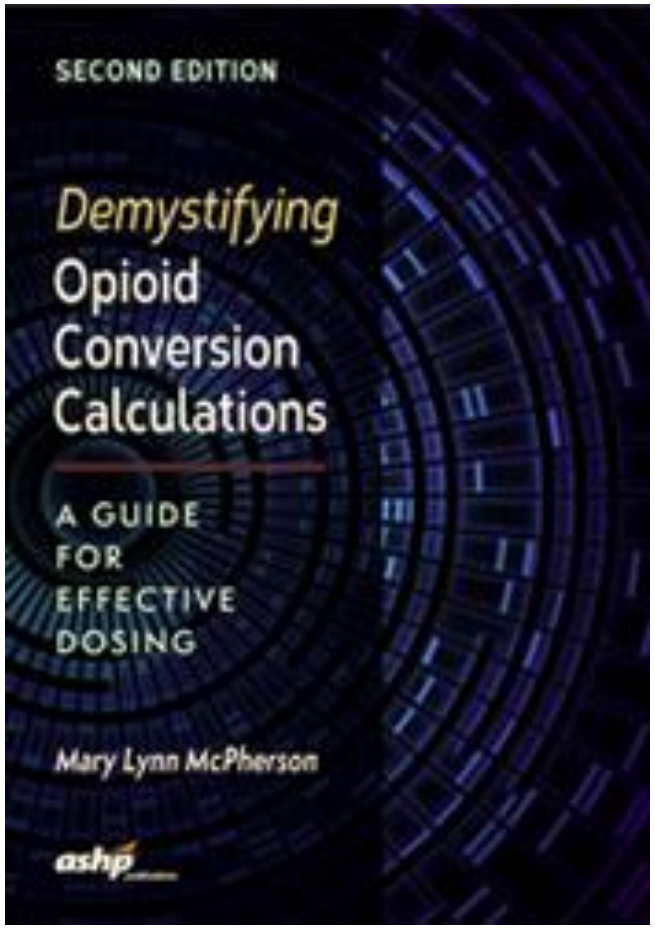
Monitor for Side Effects

- PREVENT constipation with SCHEDULED:
  - Senna-docusate
  - PEG
- Use PRN laxatives for treating constipation
  - Bisacodyl (tablets or suppository)
  - Magnesium Citrate
  - Naloxegol (PO) or methylnaltrexone (SC) (peripheral opioid antagonists)($$)
- Ask about breathing, fatigue, sleep changes, itching, other side effects

How do you discontinue opioids?

- Pregnant women and patients with cardiac angina should not experience opioid withdrawal
- A “therapeutic taper” is technically different than “a withdrawal”
  - Only “X” licensed prescribers can initiate an opioid withdrawal
- Opioids are tapered at about 10% of the original dose/week
  - Week 1: 90% of original dose Week 2: 81% of original dose
  - Week 3: 73% Week 4: 66% Week 5: 60% Week 6: 54%, etc.
  - Slow down taper if symptoms of withdrawal are poorly controlled.
- Adjuvant meds:
  - Clonidine 0.05-0.1 mg TID PRN for agitation
  - Loperamide for diarrhea; Diclomine for abdominal cramping
  - Gabapentin for insomnia / anxiety

Resource for Opioid Conversions



Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, 2nd Ed.
By Mary Lynn McPherson, PharmD, MA, MDE, BCPS, CPE
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Appropriate Use of Drugs of Abuse
Pharmacy 640 (Spring)

Course Introduction and Mechanics Introduction: Principles/Biological Basis of Substance Use Disorders
Opioids: Selecting, starting, switching, and tapering Optimal treatment of patients with chronic, malignant pain
Optimal treatment of patients with acute pain (trauma, procedural, etc) Optimal treatment of patients with chronic, non-malignant pain
Opioids for Pain: Treatment Cases
Management of opioid use disorders
Pharmacology of cocaine, amphetamines, and other stimulants Pharmacology of alcohol, benzodiazepines, inhalants, GHB, GBL, BD
Management of alcohol, or benzodiazepine use disorders Management of cocaine, stimulant use disorders
Management of Opioid Toxicity Management of Multiple or Unknown Exposure Cases
Cannabis / Cannabinoids (Benefits and Adverse effects of THC, CBD, and dosing methods)
Impaired Providers
Misuse of Prescription and OTC Drugs Substance misuse by special populations (g., athletes, students)
Dissociatives (PCP/Ketamine/Dextromethorphan) Hallucinogens/Psychedelics/Entactogens (2 hours) Cathinones (“Bath Salts”)
PDMP and UDT Case Presentations