

## Pharmacologic Management of Pain

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## Types of Pain

### Nociceptive

- Somatic
  - Easy to localize
  - Sharp, throbbing
  - persistent
- Visceral
  - Hard to localize
  - Difficult to describe
  - Comes in waves

### Neuropathic

- Burning, tingling, shooting
- Intermittent
- Radiating pain

## Objectives

- Identify types of pain and options for pharmacologic treatment based on a systematic patient assessment.
- Discuss the pharmacology of adjuvant analgesics.
- Determine opioid dose on initiation, titration, and conversion.

## Case #1

- SM is a 23 yo female with relapsed AML diagnosed in Nov 2010. She is s/p 7+3 induction chemotherapy and HiDAC consolidation x2. She has developed severe pain in her bilateral hands and feet.
- Describes pain as burning, tingling and numbness

## **Pain Assessment**

- **O – Onset**
- **P – provoking or palliating features**
- **Q – quality of pain**
- **R – radiation (from where to where)**
- **S – severity (intensity and effect on function)**
- **T – temporal pattern/course**

## **Pain Assessment Expanded**

- **Severity**
  - What is pain now?
  - Worst in last 24 hours?
  - Best in 24 hours?
  - On avg?
  - Pain prior to prn?
  - Pain at peak of prn?
  - How long does prn last?

## **Patient Assessment**

- **O – Onset**
  - Since chemotherapy
- **P – provoking or palliating features**
  - Anything that touches feet or hands, even lightly hurts
- **Q – quality of pain**
  - Burning, tingling, and numbness
- **R – radiation (from where to where)**
  - Stays in hands and bottoms of feet
- **S – severity**
  - 8/10, not able to walk
- **T – temporal pattern/course**
  - Constant

## **Neuropathic Pain - Treatment**

- **Anticonvulsants**
- **Antidepressants**
- **Lidocaine**
- **Ketamine**
- **Opioids**
  - Particularly methadone

## Gabapentin (Neurontin®) vs. Pregabalin (Lyrica®)

### Similarities

- Mechanism of action
- Pharmacokinetics
  - Renal excretion

### Differences

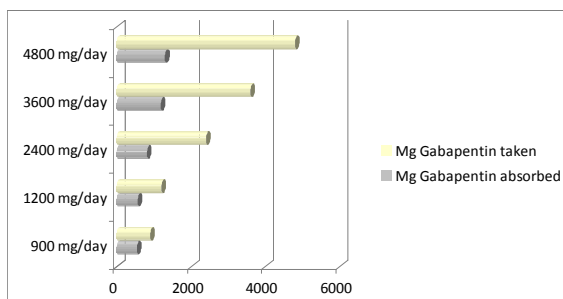
- Pharmacokinetics
  - Absorption
  - Dosing
- Side effects
- Easier to titrate pregabalin
- Gabapentin is generic

Bockbrader HN. Clin Pharmacokinet. 2010;49:661-9.

## Tricyclic Antidepressants

- Mechanism of action:
  - Inhibits reuptake of norepinephrine and serotonin
  - Sodium channel antagonist
- Tertiary amines
  - Amitriptyline, doxepin, imipramine
- Secondary Amines
  - Desipramine, nortriptyline

## Gabapentin absorption



Pregabalin [Lyrica] Product Info 2009  
Gabapentin [Neurontin] Product Info 2010

## TCA Comparison: Major differences

- Serotonin (5HT) vs. Norepinephrine
  - Amitriptyline (Elavil®) primarily 5HT
  - Desipramine (Norpramine®) primarily NE
- Na channel effects
  - Desipramine strong antagonist

### **TCA Comparison: Major differences**

- **Anticholinergic effects**
  - Amitriptyline (Elavil®) most
  - Desipramine (Norpramine®) and Nortriptyline (Pamelor®) least
- Doxepin (Sinequan®) and Imipramine (Tofranil®) strong antihistamines

### **Somatic Pain: Treatment Options**

- **Non-steroidal Anti-inflammatory Drugs (NSAIDs)**
- **Acetaminophen (Tylenol®)**
- **Opioids**

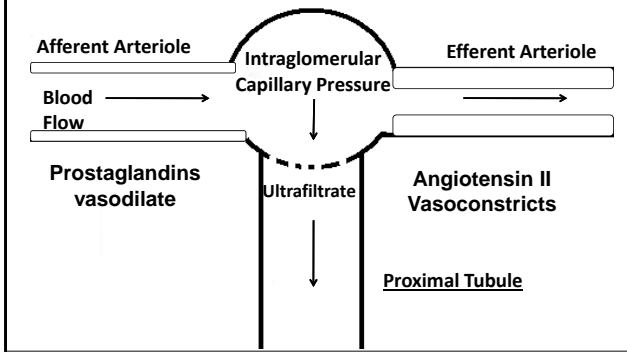
### **TCAs Precautions**

- **Significant cardiac disease**
- **Anticholinergic**
- **Suicide risk**

### **NSAIDs**

- **MOA: Inhibits cyclooxygenase (COX), leading to decreased prostaglandins and inflammation**
- **Examples**
  - Ibuprofen (Motrin®)
  - Naproxen (Naprosyn®, Aleve®)
  - Meloxicam (Mobic®)
- **Caution in patients with renal disease, bleeding disorders, or h/o GI bleed**

## Autoregulation of Renal Blood Flow

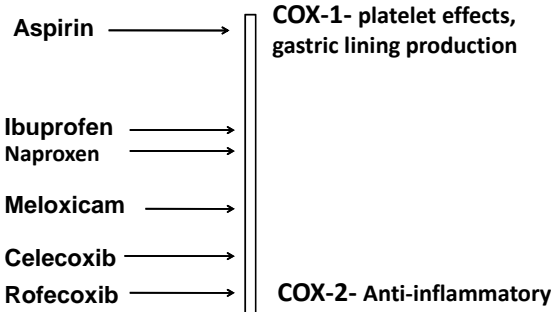


## COX-2 Inhibitors

- Celecoxib (Celebrex®)
  - Less gastrointestinal irritation
  - Less risk of bleed
  - Use with aspirin negates benefits

Weideman RA. Gastroenterology. 2004 Nov;127(5):1322-8.

## COX-1 vs COX-2



Wong SL. Adv Pharmacol. 2010;60:61-83

## WHO Analgesic Ladder

- Step 1:
  - Non-opioid ± Adjuvant
- Step 2:
  - Opioid for mild-moderate pain, ± Non-opioid, ± Adjuvant
- Step 3:
  - Opioid for moderate - severe pain, ± Non-opioid, ± Adjuvant

<http://www.who.int/cancer/palliative/painladder/en/>

## Opioid Analgesic Classes

### Phenanthrenes

- Morphine
- Codeine
- Hydromorphone
- Oxycodone
- Hydrocodone

### Phenylheptanones

- Methadone
- Propoxyphene

### Phenylpiperidines

- Meperidine
- Fentanyl

## Opioids: Major Differences

- Mechanism of action
  - Tramadol (Ultram®)
    - SNRI
  - Tapentadol (Nucynta®)
    - SNRI
  - Methadone
    - NMDA antagonist

## Opioids: Precautions

- Constipation
- CNS effects
- Myoclonic jerking / seizures
- Nausea / vomiting
- Pruritus
- Respiratory depression
- Addiction/ Abuse/ Diversion

## Opioids: Major Differences

- Dosage forms
  - Sustained release vs. Immediate release
  - Combined with acetaminophen
  - Transdermal
  - Buccal
  - Sublingual
  - Parenteral

## Opioids: Major Differences

- **Metabolism**
  - Cyp2D6
  - Cyp3A4
  - Glucuronidation
- **Active and toxic metabolites**
  - **Neurotoxicity: Morphine> hydromorphone> oxycodone>> methadone/ fentanyl**
- **Potency/ Equianalgesic doses**

Smith HS. Mayo Clin Proc 2009;84:613-24.

### Opioids: Initial doses in opioid-naïve patients

Morphine (MSIR®, Roxanol®)	PO: 5-15 mg IV/SQ: 2-6 mg
Hydromorphone (Dilaudid®)	PO: 2-4 mg IV/SQ: 0.2-0.6 mg
Oxycodone (Oxy IR®, Roxicodone)	PO: 5-15 mg
Hydrocodone (Vicodin®)	PO: 5-10 mg
Oxymorphone (Opana®)	PO: 2.5 mg

## Opioids: Initiation

- **Acute and/or breakthrough pain**
  - Use IR opioids prn not extended-release formulations
- **Interval based on peak effect**
  - Point at which patient gets most pain control and highest risk for toxicity (i.e. sedation, respiratory depression)
  - In general, peak effect:
    - PO = 1 hour
    - SC = 30 min
    - IV = 15 min (except Fentanyl = 6 min)

## Opioids: Titration

- **Individualize dose by gradual escalation until adequate analgesia**
  - No therapeutic ceiling unless side effects
- **If pain is poorly controlled and no side effects, can safely increase using % rule:**
  - Increase by 25-50% for moderate pain
  - Increase by 50-100% for severe pain

## Opioids: dosing for scheduled opioids

- Use scheduled opioids if:
  - adequate relief with prn meds, but pt needs frequent prn meds
  - persistent/chronic pain
- Options for scheduled opioids:
  - Immediate release opioid ATC (around the clock)
  - Sustained release opioid formulations
  - Continuous infusion of IV opioids
- Dosing based on:
  - 50-100% of total 24hr total OME (oral morphine equivalents) in divided doses

## Chronic Pain Regimen

- Example
  - Morphine ER 60 mg po q8h and Morphine 15-30 mg po q1h prn
  - Fentanyl 50 mcg TD q72h and Morphine 15 mg po q1h prn

## Opioids: PRN/Breakthrough for opioid-tolerant patient

- 10-20% of scheduled daily dose
  - Helps overcome tolerance
  - Often need more than anticipated for acute on chronic pain

Equianalgesic Conversion of Opioids\*

Drug	SQ/IV Dose	Oral Dose
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	-----	20
Oxymorphone	-----	10
Hydrocodone <sup>^</sup>	-----	30
Fentanyl	0.1 mg (100 mcg)	Not established





## Example conversion to Fentanyl

- Home Regimen:
  - Morphine SR (MSContin®) 60mg PO q8
  - Oxycodone/APAP (Percocet®) 10/325mg 2 tabs q4prn (uses 4 tabs daily)
- Morphine PO 220 mg/day = Fentanyl 50 – 75 mcg/hr patch q72h\*

## Example Conversion to Methadone

- Home Regimen:
  - Morphine SR (MSContin®) 60mg PO q8
  - Oxycodone/APAP (Percocet®) 10/325mg 2 tabs q4prn (uses 4 tablets daily)
- Morphine mg/day
  - $\frac{\text{Methadone 8 mg PO}}{\text{Morphine 1mg PO}} = \frac{\text{Methadone X mg PO IV}}{\text{Morphine 220 mg PO}}$
- Methadone 15 – 27.5 mg PO per day\*

Table 2: Equianalgesic Conversion to Methadone\*

<u>Oral Morphine Equivalent</u>	<u>Morphine: Methadone Ratio</u>
< 90 mg/day	4:1
90 - 300 mg/day	8:1
> 300 mg/day**	12:1
Oral methadone: IV methadone ratio= 2:1	

Ripamonti C. J Clin Oncol 1998;16:3216-21

## Summary

- Multiple pharmacologic treatment options for pain management.
- Systematic assessment important for drug selection.
- Many differences within classes of analgesics.