PAINWEEK®

Rational Polypharmacy

Thomas B. Gregory, PharmD, BCPS, CPE, FASPE

Disclosures

- Clinical advisory board: Daiichi Sankyo

Introduction

- Cox Health
  - Ambulatory Pain Clinic Pharmacy Specialist

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Learning Objectives

- Define rational polypharmacy as it pertains to the patient in pain
- Recognize the various pharmacological classes used in rational polypharmacy of pain management
- Distinguish between rational and irrational polypharmacy with respect to acute and chronic pain

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Current Situation

- States, counties and municipalities continue filing suits against opioid manufacturers, distributors, and providers[1]
- Centers for Medicaid and Medicare Services*, States and some pharmacies limiting opioid prescribing[2]
  - –Opioid naive patients
  - * Slated for 2019
- Shortages of opioids
  - –DEA mandated[3]
  - –Manufacturers[4]

1. https://www.nbcnewyork.com/news/local/NYC-Opioids-Heroin-Epidemic-Big-Pharma-Suit-470722263.html accessed 2.7.2018
2. https://www.cnn.com/2017/09/22/health/cvs-prescription-restrictions-opioids-bn/index.html accessed 2.7.2018
3. http://www.pharmacist.com/article/dea-mandates-reduction-opioid-manufacturing-2018 accessed 2.7.2018
4. https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-list?page=CurrentShortages accessed 2.7.20018

* https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Downloads/Advance2019Part2.pdf accessed 2.7.2018

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How does rational polypharmacy apply in today's opioid climate?

- Do more with less
  - –Synergistic combinations decreasing the amount of opioid needed for pain control
- Using nonopioids as first line therapy can minimize or even prevent the need for opioid medications on a chronic basis
- Many medications used in pain management are not on the 'drug shortage list' including
  - –NSAIDs
  - –SNRIs and TCAs
  - –Anticonvulsants

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Definitions

- Polypharmacy:
  The use of 2 or more drugs together,
  usually to treat a single condition or disease
- Synergy:
  The cooperative action of 2 or more stimuli or drugs
- Rational:
  Proceeding or derived from reason or based in reason
- Irrational:
  Not endowed with the faculty of reason

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Goals of Rational Polypharmacy

- Minimize adverse effects
  - –Lower doses of individual medications
  - –Opioid sparing effects
- Increase adherence to the prescribed regimen
- Using synergistic combinations of medications to achieve improved outcomes compared to the individual medications
- Increase efficacy by utilizing long acting and short acting preparations

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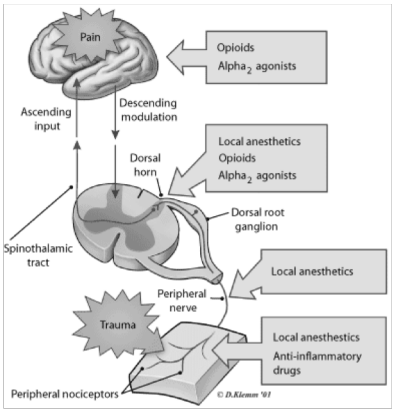
Hitting the Target(s)

- Stimulation of nociceptors causes signal transduction to the dorsal horn
  - –Transduction
- The spinothalamic tract transmits the signals to the brain where pain is first experienced
  - –Transmission and perception
- Descending pathways from the brain attempt to block the signal from the periphery
  - –Modulation



http://napaanesthesia.com/blog-pre-emptive-pain-management accessed January 30, 2018

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Medications Used in Pain Management

- Acetaminophen
- NSAIDs
- Opioids
- Antidepressants
- Anticonvulsants
- Local anesthetics
- Skeletal muscle relaxants

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Acetaminophen

- Mechanism of action is still not entirely known
  - –Thought to be a partial COX inhibitor
- March 2014 FDA mandates all prescription drug combination products containing acetaminophen cap the dose at 325 mg
- Maximum daily dose limits vary based on comorbidities and who you ask
  - –FDA vs Johnson and Johnson

http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm165107.htm accessed January 30, 2018
https://www.tylenol.com/safety-dosing/usage/dosage-for-adults accessed January 30, 2018

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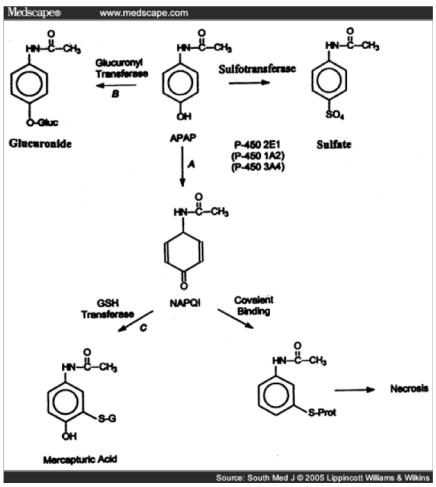
Acetaminophen (cont'd)

- Largest concern is unintentional overdoses
- Metabolism of acetaminophen by the liver is a saturable process
- Over the counter products and cumulative acetaminophen dosing



http://www.medscape.com/viewarticle/518631_3 accessed January 30, 2018

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Nonsteroidal Anti-Inflammatory Agents

- COX 1 more specific to the GI tract and renal homeostasis
- COX 2 more specific to inflammation and platelet aggregation
- Certain comorbidities limit the dosing on most NSAIDs
  - –Patients on anticoagulants
  - –Patients with renal dysfunction
  - –Pregnancy

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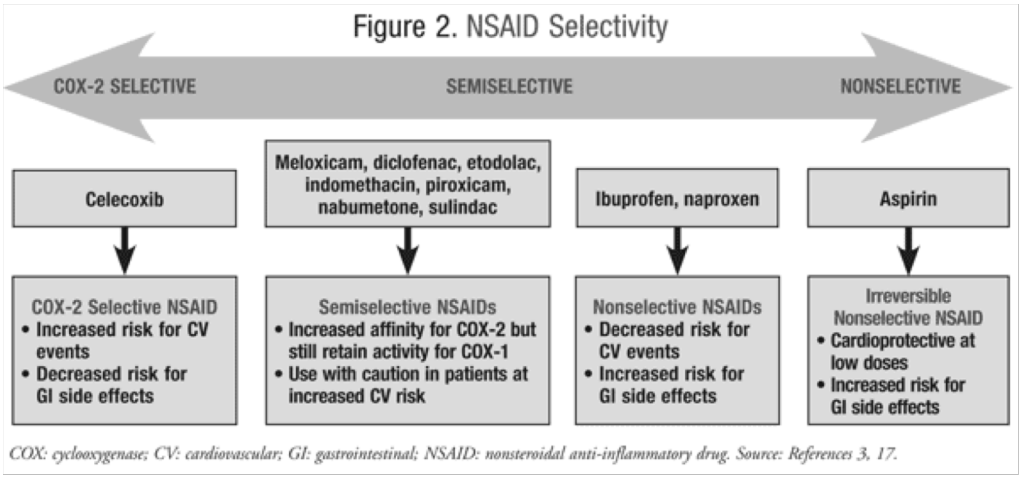
NSAIDs and COX Selectivity



https://www.uspharmacist.com/article/cardiovascular-risk-associated-with-nsaids-and-cox2-inhibitors accessed January 30, 2018

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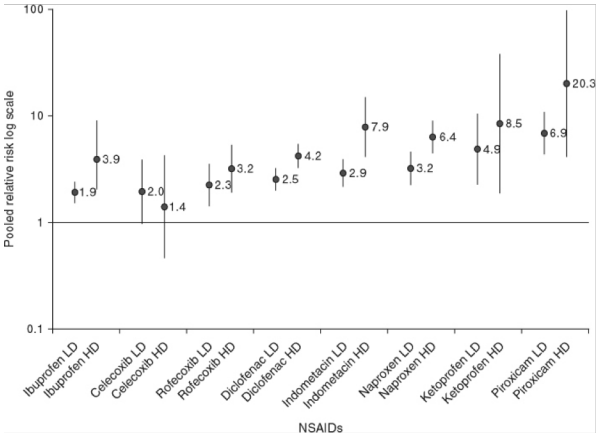
NSAIDs and GI Complications (GIC)



- Meta-analysis of GIC from individual NSAIDs
- GIC included ulceration, perforation, obstruction, and bleeding
- All COX nonspecific NSAIDs increase in risk of GIC when taken on a daily basis

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Individual NSAIDs and Upper Gastrointestinal Complications. Drug Safety 2012; 35(12): 1127-1146

Nonsteroidal Anti-Inflammatory Drugs

- Topical vs systemic NSAIDs
  - –Patch, cream, lotion, etc
    - •Range in application frequency from twice to 4 times daily
  - –Topical can provide NSAID relief at the site of inflammation without the systemic side effects
  - –Cost can be a limiting factor
  - –Still carry a black box warning on the labeling for cardiovascular complications

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Glucocorticoids

- Mechanism of action leads to a decrease in production of heat shock proteins intracellularly leading to a decrease inflammation
- Multiple routes of administration
  - –Oral
  - –Parenteral
    - •IV
    - •IM depot
    - •Intraarticular

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Glucocorticoids (cont'd)

- Caution should be exercised in patients with the following conditions
  - –Diabetes
  - –Psychiatric history
  - –Heart failure
  - –Adrenal suppression
    - •Taper needed when therapy exceeds 10 to 14 days
  - –Immunocompromised

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Opioids

- Opioids work on multiple receptors within the CNS
  - –Analgesia and adverse effects are derived from mostly Mu receptors
- There is no ceiling dose for analgesia however as doses increase the incidence of adverse effects increases
- CDC (2016) and VA/DoD (2017) guidelines outlining the use of opioids in chronic pain have been published

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Opioids (cont'd)

- Agonists vs partial agonists vs antagonists
  - –Morphine, fentanyl, methadone, etc
  - –Buprenorphine, nalbuphine, butorphanol
  - –Naloxone and naltrexone
- Awareness of other nonpain combination products
  - –Naltrexone-bupropion for weight loss

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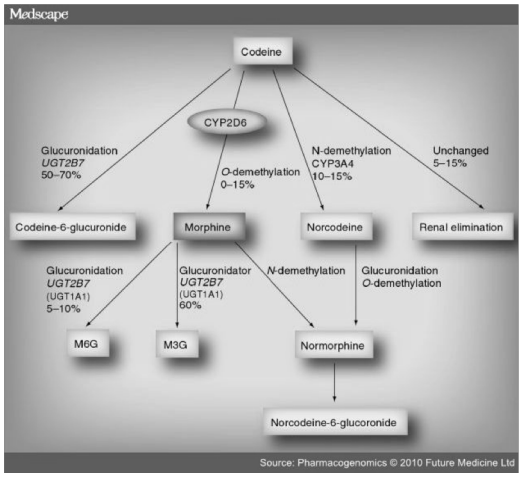
Opioid Metabolism



- Metabolic pathways can become saturated leading to metabolism by other pathways
  - –Codeine
  - –Oxycodone
    - •2D6 → noroxycodone
    - •3A → oxymorphone

http://www.medscape.com/viewarticle/723131_2 accessed January 30, 2018

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Opioids

- Accounted for 8.45% of medication related fatalities in 2015
- Populations at greater risk for experiencing adverse effects
  - –Patients with sleep apnea and sleep disordered breathing
  - –Pregnancy
  - –Hepatic or renal dysfunction
  - –Age greater than 65
  - –Mental health or substance use disorders
  - –Nonfatal overdose history

2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clinical Toxicology 2016; 54 (10): 924-1009
CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR 2016; 65(1): 1-49

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Immediate Release (IR) vs Extended Release (ER)

- Initial therapy should include the use of IR formulations
- ER preparations are appropriate for patients
  1. That routinely use the IR preparation with relief of pain
  2. That are not experiencing adverse effects which decrease quality of life
  3. That are on stable doses of IR preparations and have been for an appropriate time frame
- IR and ER preparation use should be re-evaluated for safety and efficacy periodically or per state guideline

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Opioid Rotation and Cross Tolerance

- There is evidence in cancer patients where rotation can be beneficial
- There are some retrospective trials which have looked at opioid rotation in noncancer pain patients but not enough to make a recommendation
- Incomplete cross tolerance is the difference in pharmacokinetics and pharmacodynamics of opioids
- The use of dose conversion charts should be utilized whenever transitioning a patient from one opioid to another

APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. 2009

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Tricyclic Antidepressants (TCA)

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake and inhibition of sodium channel action potentials
- The antidepressant effects and the neuropathic pain analgesia are independent
  - –Higher dosing and longer treatment time needed for antidepressant effects
- Caution should be exercised in patients
  - –With cardiac arrhythmias
  - –Over the age of 65

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Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake
- Dosing is generally higher for treating neuropathic pain compared to treating depression
- Withdrawal syndromes can occur if patients are taken off SNRI therapy abruptly
  - –Anxiety, irritability, headache, paresthesia, nervousness
- Caution should be exercised in patients with liver dysfunction, uncontrolled hypertension, or moderate cardiovascular disease

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Antiepileptics

- The primary antiepileptics used in pain management work on calcium channels
  - –Gabapentin
  - –Pregabalin
- Other antiepileptics have had mixed results regarding neuropathic pain
  - –Valproic acid
  - –Phenytoin
- Carbamazepine for trigeminal neuralgia

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Local Anesthetics

- Mechanism of action is through membrane stabilization of sodium channels preventing depolarization and signal transduction
- Acute uses for local anesthesia (procedures, etc)
  - –Topical application
    - •Cream, ointment, patch, etc
  - –Intradermal injections
  - –Nerve blocks
- Patches are indicated for the management of postherpetic neuralgia

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Skeletal Muscle Relaxants

- Multiple medications are included in this general taxonomy
  - –Certain agents approved for spasticity
    - •Baclofen and tizanidine
- Others stand out for reasons other than their indication
  - –Cyclobenzaprine and orphenadrine regarding their anticholinergic effects
  - –Chlorzoxazone and potential for hepatotoxicity
  - –Carisopradol and meprobamate and potential for abuse

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Rational Polypharmacy in Pain Management

- Using multiple medications to use the lowest effective doses of each
  - –Decreasing the potential for adverse effects
- Dual purposing medications
  - –Dexamethasone for chemo induced nausea and bone pain in a cancer patient

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Nonrational Polypharmacy

- Utilizing 2 medications in the same family for the same condition
  - –Ibuprofen and naproxen
  - –Morphine immediate release and oxycodone immediate release
- Adding a medication that may be contraindicated based on the patients other comorbidities
  - –Methadone use in a patient with a history of QTc prolongation
  - –Tramadol or use in a patient with underlying seizure history
  - –Meperidine use in a patient with renal dysfunction

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Effects of Aging on PK/PD

- Advanced age leads to physiologic changes which can impact pharmacokinetics (PK)
  - –Decreased total body water and lean muscle mass
  - –Increased adipose tissue
- Potential for harmful drug interactions
  - –Initiation of methadone in a patient recently taken off fluoxetine
- Pharmacodynamic (PD) changes
  - –Increased risk of sedation from CNS depressants (opioids)

Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications Br J Clin Pharmacol. 2004 Jan; 57(1): 6–14.

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Gender Effects on Pharmacokinetics

- Multiple pharmacokinetic differences between the sexes
  - –Males have increased BMI and total body water
  - –Females have increased adipose tissue
    - •Pregnancy can alter this even further
- Metabolism is also affected by gender
  - –Greater activity of CYP1A and UDP transferase in males
  - –Greater activity of CYP2D6, CYP3A in females

Sex Differences in Pharmacokinetics and Pharmacodynamics. Clin Pharmacokinet. 2009; 48(3): 143–157.

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Ethnicity and Genetic Effects on Pharmacokinetics

- Variations in the genes which code for pharmacokinetic and pharmacodynamic targets
  - –CYP enzyme activity
  - –Drug transport proteins
- Allelic variants can range from increased activity to absence of activity
  - –Many of the CYP enzymes which metabolize opioids, anticonvulsants and antidepressants can be affected

The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies Clinical pharmacology & Therapeutics 84: 3: 2008.

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Rationalizing Acute or Chronic Nociceptive Pain

- NSAIDs +/- acetaminophen
- Opioids in addition to the above
  - –AVOIDING opioids with minimal efficacy and increased safety concerns
    - Codeine
      - –Weak opioid activity
    - Meperidine
      - –Increased risk of seizures from metabolite

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Rationalizing Acute Nociceptive Pain

- Local anesthetics before minor procedures
- Muscle relaxants for short durations and only as needed
- Tricyclic and SNRI antidepressants and antiepileptics unlikely to be of benefit

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Rationalizing Neuropathic Pain

- Scheduled use of tricyclic or SNRI antidepressants at appropriate doses
- Use of antiepileptics at appropriate doses
  - –Opioids may be used in combination with the use of an antiepileptic
  - –Topical local anesthetics such as patches and creams with the above

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Rationalizing Neuropathic Pain (cont'd)

- NSAIDs and acetaminophen are unlikely to alleviate neuropathic pain
- Corticosteroids may have a place in treatment on a case by case basis
- Muscle relaxants are controversial in terms of efficacy

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Success Stories in Rational Polypharmacy

- Postoperative pain management
  - –Ketorolac can lead to a decrease in opioid consumption between 25% to 45% in the postoperative setting
  - –The use of epidural continuous infusions or intrathecal local anesthetics lead to a decrease in pain scores and lead to a return of bowel function postcolorectal surgery

Postoperative Pain Control Clin Colon Rectal Surg. 2013 Sep; 26(3): 191–196.

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Success Stories in Rational Polypharmacy (cont'd)

- Acute traumatic injury
  - –Parenteral opioids should be administered first and extended release opioids should be avoided in this setting
  - –Use of local anesthetics for regional analgesia for procedures to augment/prevent opioid use

Pain management in trauma: A review study. J Inj Violence Res. 2016 Jul; 8(2): 89–98

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Success Stories in Rational Polypharmacy (cont'd)

- Lidocaine patch and gabapentin in polyneuropathy[1]
  - –Significant improvements in brief pain inventory scores after 2 weeks of treatment
- Gabapentin and morphine for diabetic neuropathy[2]
  - –The combination of morphine and gabapentin decreased the pain score of the participants GREATER than either morphine or gabapentin alone

1. Lidocaine patch 5% with systemic analgesics such as gabapentin: a rational polypharmacy approach for the treatment of chronic pain. Pain Med 2003 Dec;4(4):321-30.
2. Morphine, Gabapentin, or Their Combination for Neuropathic Pain N Engl J Med 2005; 352:1324-1334

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Success Stories in Rational Polypharmacy (cont'd)

- Fibromyalgia
  - –Pain and depression consider the use of duloxetine or milnacipran
  - –Pain and insomnia consider the use of pregabalin or nortriptyline

https://www.practicalpainmanagement.com/pain/myofascial/fibromyalgia/part-2-fibromyalgia-practical-approaches-diagnosis-treatment accessed January 30, 2018

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Conclusion

- Pain management typically involves more than one modality in order to manage it; medications are not an exception to this
- Safety must take into consideration patient specific factors which will change over time
- Certain combinations can put patients at risk for adverse effects but having a complete picture of a patients medications can help prevent this

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