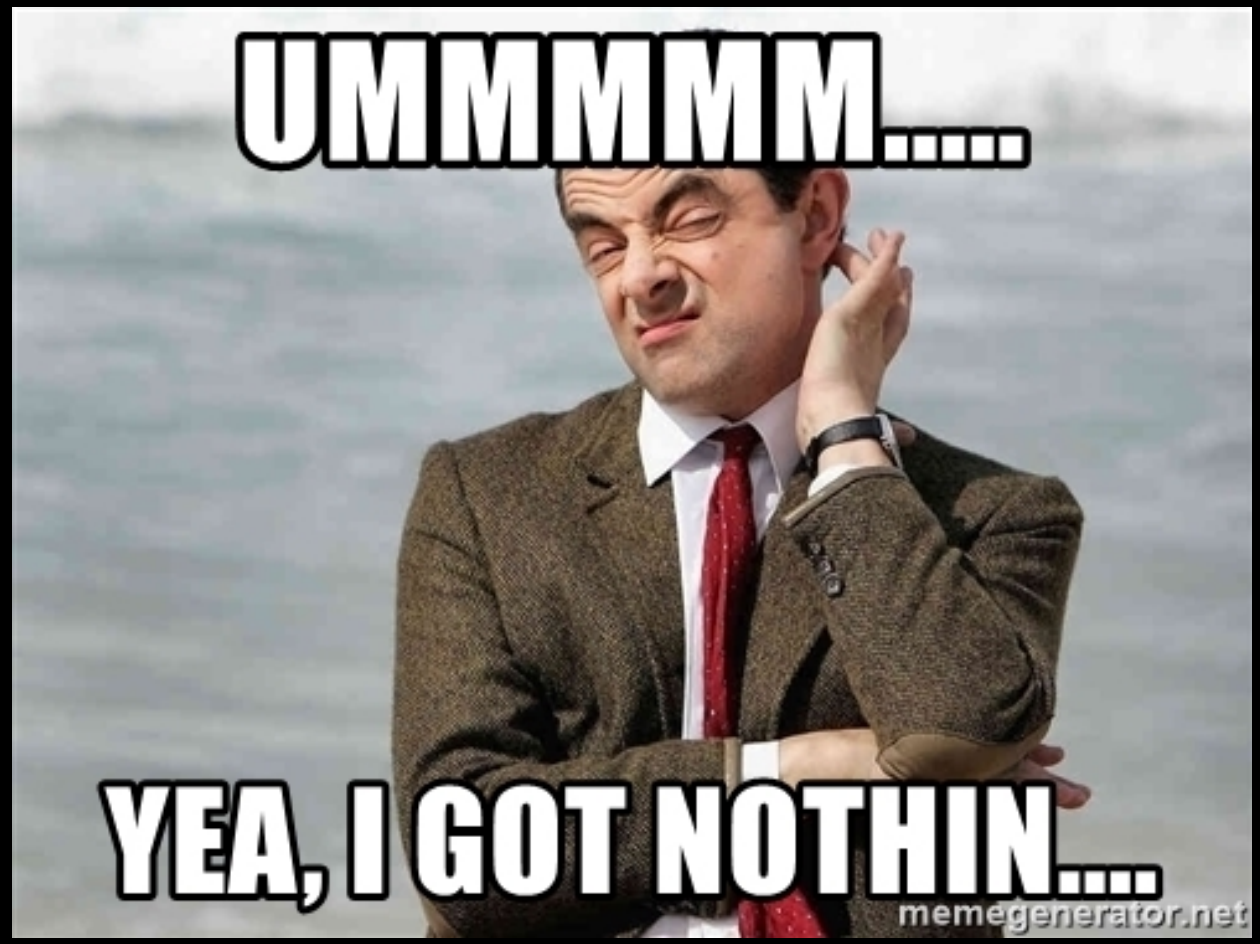
PAINWEEK®

Pain Therapeutics

Alexandra L. McPherson, PharmD, MPH

Disclosures

- Nothing to disclose



Learning Objectives

- Recall the various pharmacological classes of medications used in pain management
- Predict which patient populations would be at risk for adverse drug events based on co-morbidities and known medication effects
- Review current guidelines related to the management of pain

Definitions

- **Pain** is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
- **Nociceptive pain** arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- **Neuropathic pain** is caused by a lesion or disease of the somatosensory nervous system

Definitions, cont.

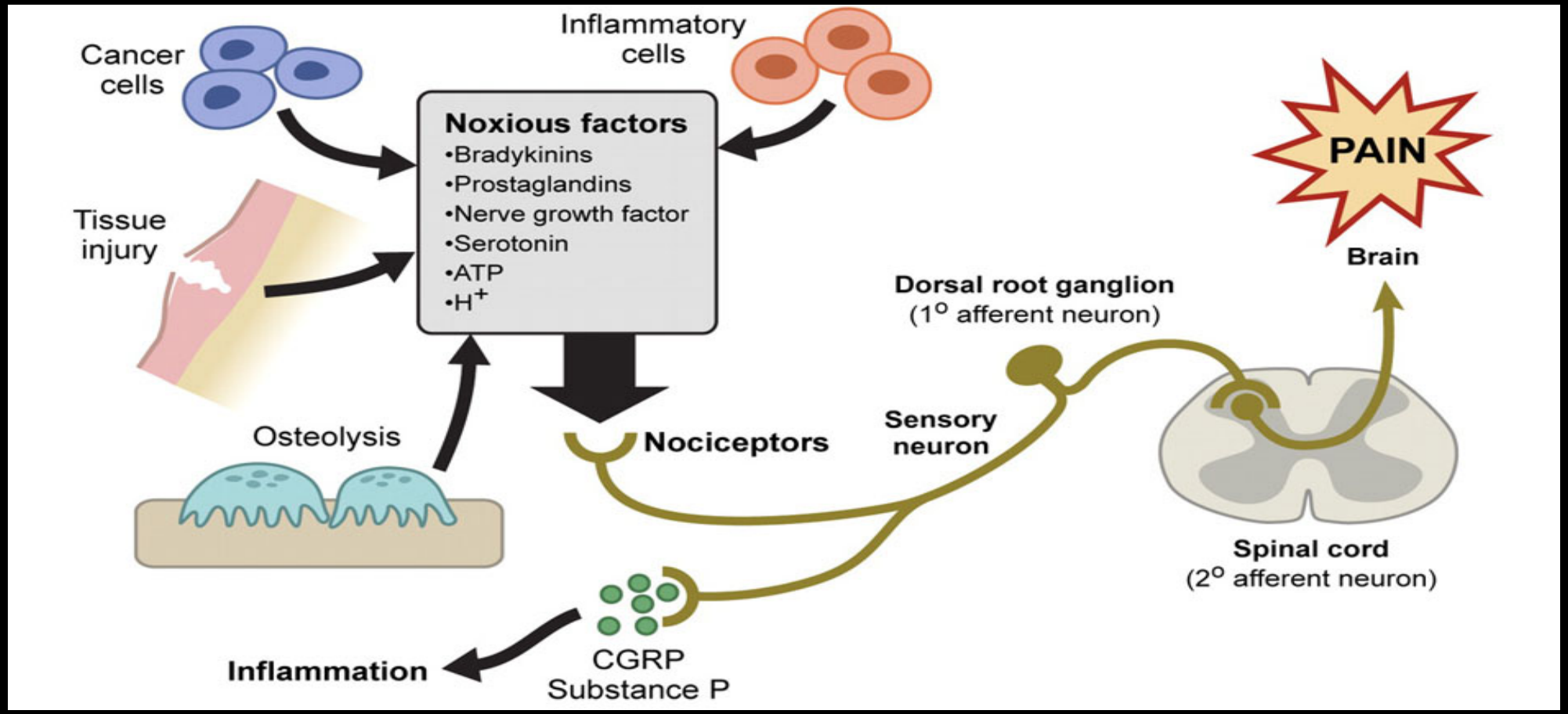
- **Acute pain** is provoked by a specific disease or injury, serves a useful biologic purpose, is associated with skeletal muscle spasm and sympathetic nervous system activation, and is self-limited
- **Chronic pain** outlasts the normal time of healing, if associated with a disease or injury
  - May arise from psychological states, serves no biologic purpose, and has no recognizable end-point
  - May be considered a separate disease state

https://www.ncbi.nlm.nih.gov/pubmed/1875958

Pain Path

- Stimulation o
  the dorsal ho
  - Transductio
- The spinotha
  where pain is
  - Transmissio
- Descending
  signal from th
  - Modulation

Pain Pathway, cont.



https://synapse.koreamed.org/DOIx.php?id=10.5124/jkma.2008.51.12.1139&vmode=PUBREADER

Pain Assessment

- Multiple validated pain assessment scales available
  - Most common being 0-10
- The scale used should be based on the patient characteristics
  - Age
  - Verbal ability
  - Cognitive ability
- The same assessment scale used should be used consistently and documented


There are 3 levels of pain:
Pain, excruciating pain, and
stepping on a Lego.
yourecards
someecards.com

Non-Pharmacologic Treatment or Therapy

- Temperature therapy (Heat/cool)
- Massage
- Physical therapy
- Transcutaneous electrical nerve stimulation (TENS) unit
- Spinal cord stimulator
- Relaxation
- Guided imagery
- Music therapy
- Biofeedback
- Meditation, self-hypnosis
- Acupuncture, acupressure
- Distraction

https://www.drugs.com/cg/non-pharmacological-pain-management-therapies-for-adults.html

Medication Classes

- Acetaminophen
- NSAIDs
- Opioids
- Antidepressants
- Anticonvulsants
- Local anesthetics
- Skeletal muscle relaxants
- Capsaicin
- Cannabinoids
- Miscellaneous agents

Acetaminophen

- Mechanism of action is still not entirely known
  - Thought to be a partial COX inhibitor
- In 2014 FDA mandated all Rx combination products containing acetaminophen cap dose at 325 mg
- Maximum daily dose limits vary based on co-morbidities and who you ask
  - FDA → 4000 mg
  - Johnson and Johnson → 3000 mg

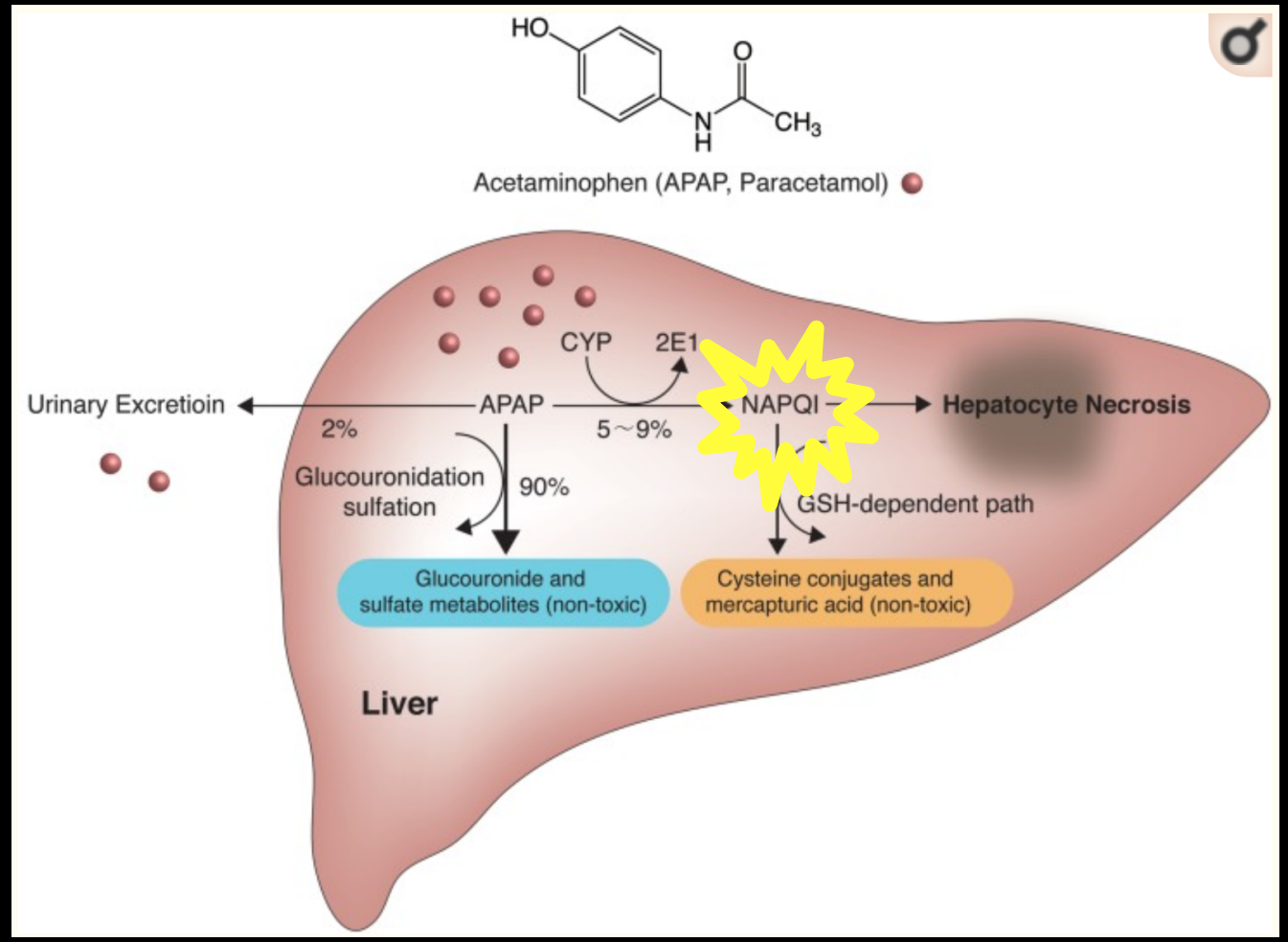
Analgesic
Antipyretic

Anti
Pain
Anti
Pyretic

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

Acetaminophen

- 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.xiahepublishing.com/2310-8819/ArticleFullText.aspx?sid=2&id=10.14218%2FJCTH.2015.00052

Acetaminophen

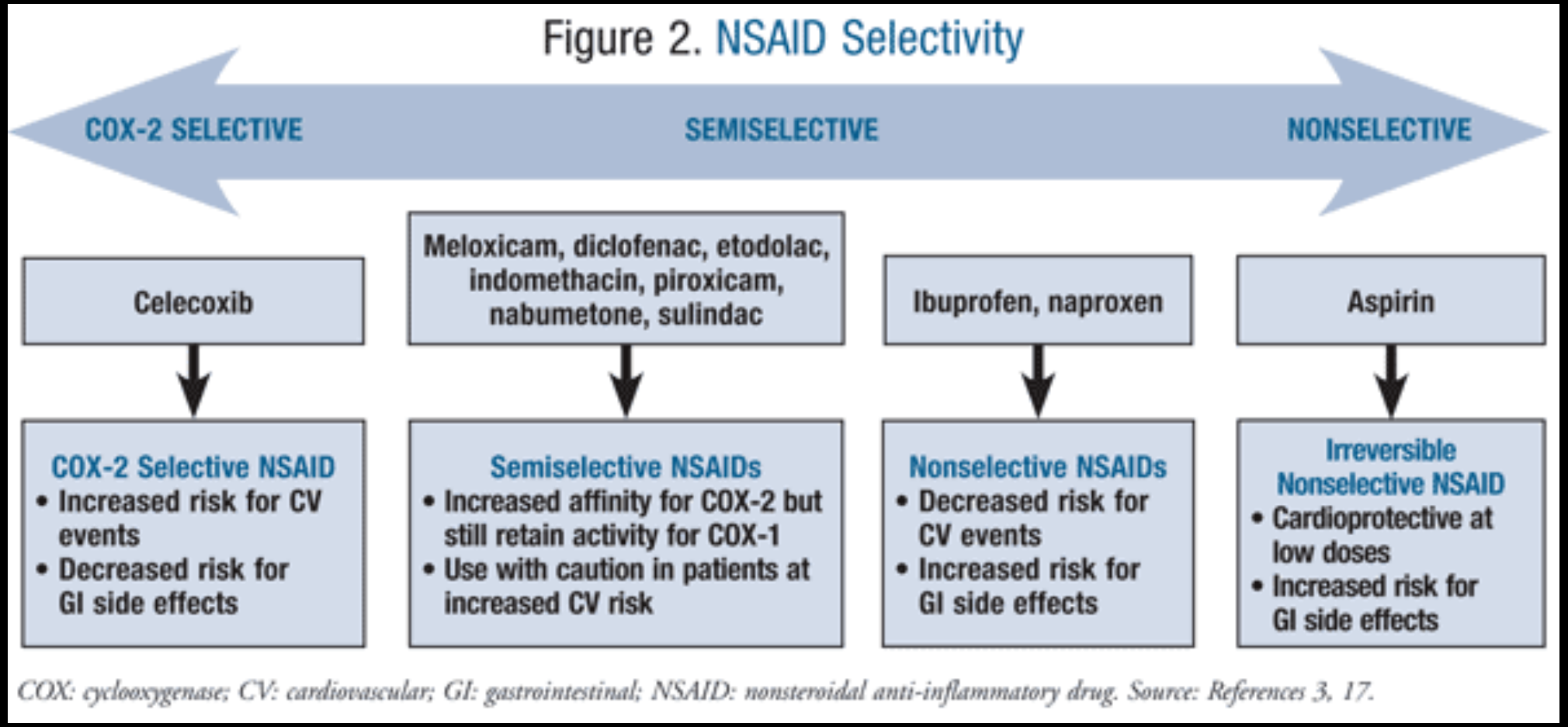
- Preferred in the following patient populations:
  - Elderly
  - History of peptic ulcer disease, GI bleed
  - Patients taking warfarin
    - Recommend limiting acetaminophen dose to ≤ 2 g **weekly**
- Labeled acetaminophen dosing varies by formulation
  - Do not exceed 4 grams daily; consider all drugs
- Use caution/avoid with liver disease, chronic alcohol use

Non-Steroidal Anti-Inflammatory Drugs

- NSAIDs inhibit COX or prostaglandin synthase (PGHS)
  - Impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin & thromboxanes
- COX-1 more specific to the GI tract & renal homeostasis
- COX-2 more specific to inflammation

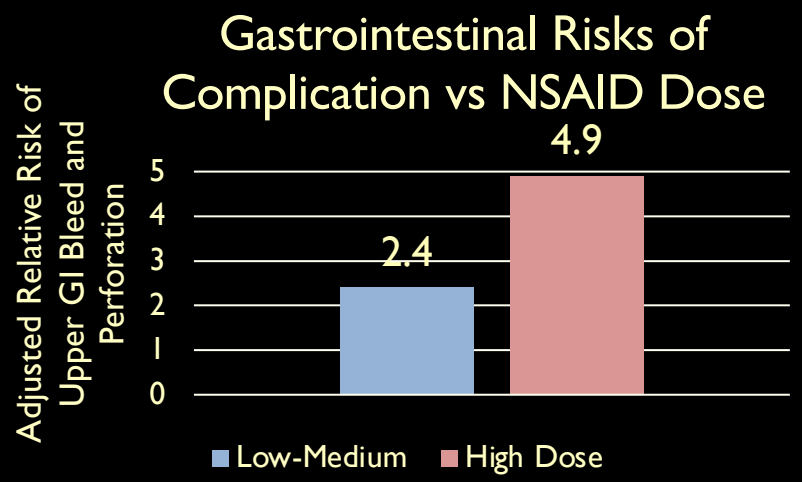
Analgesic
Antipyretic
Anti-inflammatory
Antiplatelet

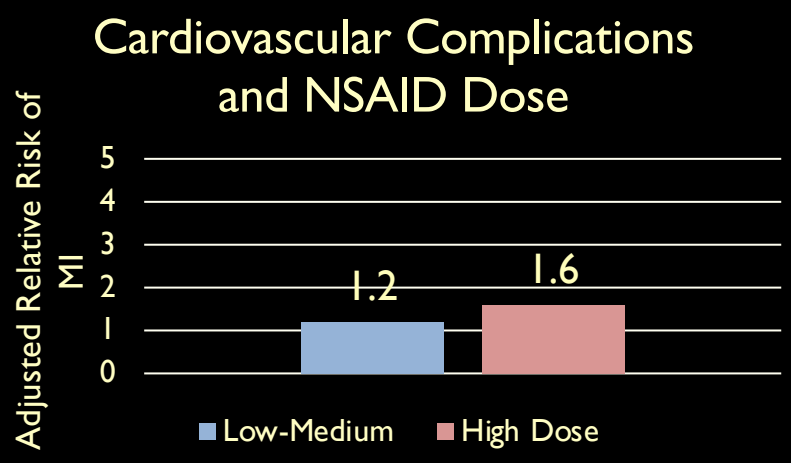
NSAIDs and COX Selectivity

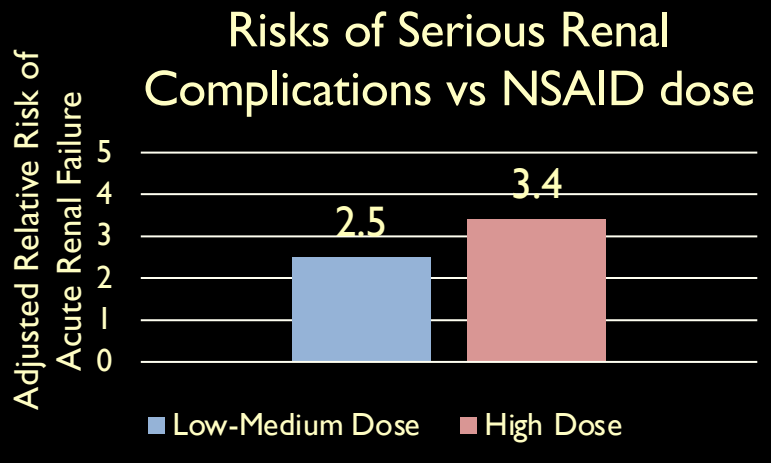


https://www.uspharmacist.com/article/cardiovascular-risk-associated-with-nsaids-and-cox2-inhibitors

GI, CV, Renal Risk vs NSAID Dose







Cut offs for "low-medium"

Celecoxib 200 mg Meloxicam 7.5 mg
Diclofenac 100 mg Naproxen 750 mg
Ibuprofen 1200 mg Ketorolac 30 mg
Indomethacin 75 mg

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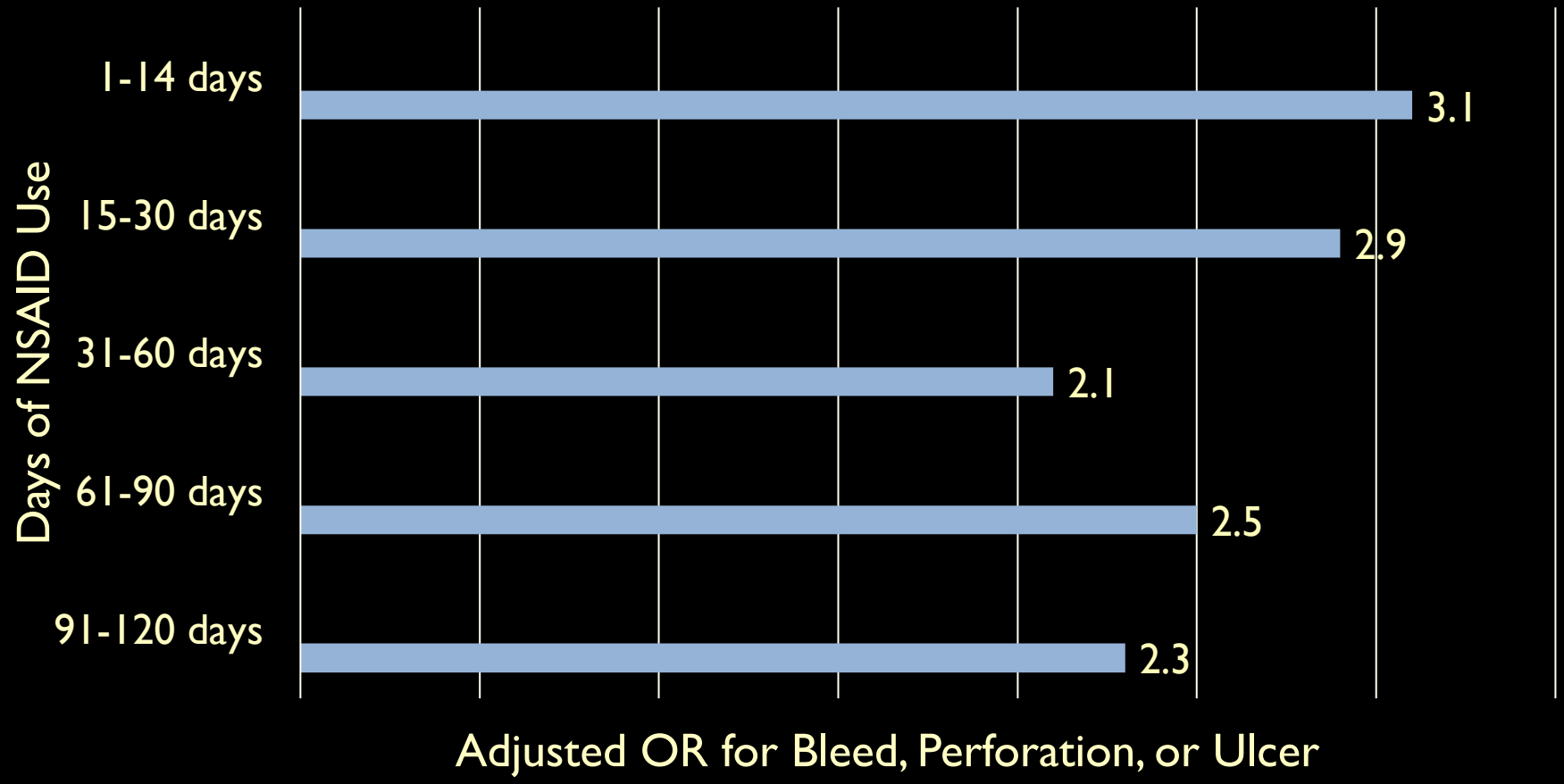
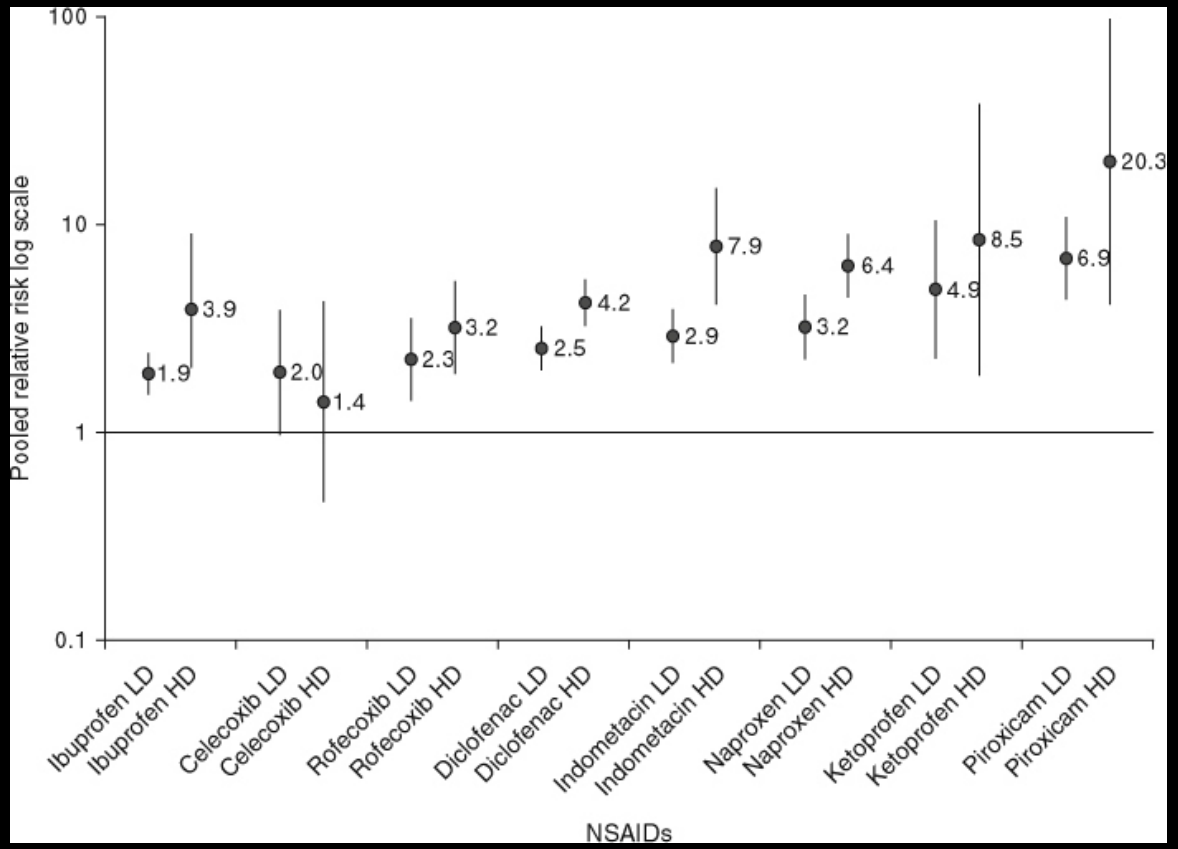
Garcia Rodriguez LA, et al. Epidemiology. 2001;12:570-576
Garcia Rodriguez LA, et al. J Am Coll Cardiol. 2008;52:1628-1636
Huerta C, et al. Am J Kidney Dis. 2005;45:531-539

Risk of GI Bleed, Perforation, or Ulcer vs. Time



Helin-Salmivaara A, et al. Scand J Gastroenterol. 2007;42:923-932

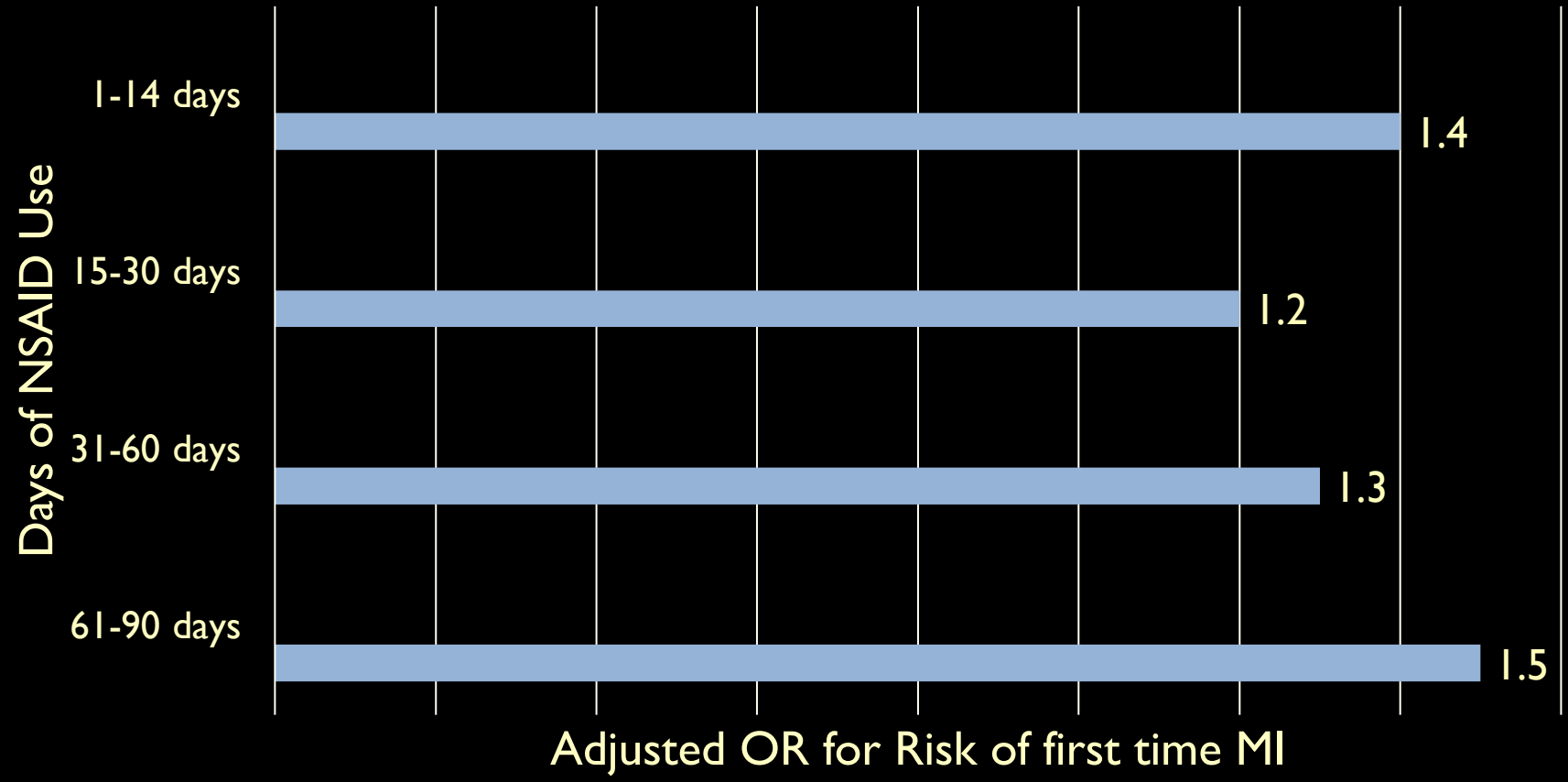
NSAIDs and GI Complications (GIC)



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

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714137/

Risk of First Time MI vs. Time



Helin-Salmivaara A, et al. Eur Heart J. 2006;27:1657-1663

Aspirin and NSAIDs

- Aspirin's cardiovascular protection can be inhibited by the use of ibuprofen
  - Doses between 2 and 12 hours before aspirin administration demonstrated prevention of aspirin binding to platelets
  - Doses given 2 hours after aspirin did not have this interaction
- Indomethacin may have this same interaction
- Other NSAIDs may have this interaction but data are conflicting

http://www.pharmacytimes.com/publications/issue/2013/may2013/antiplatelet-effects-of-aspirin-which-nsaids-interact

Topical vs. Systemic NSAIDs

- Patch, cream, lotion, gel etc.
  - Application frequency ranges from 2-4 times daily
- Topicals can provide relief at the site of inflammation without the systemic side effects
- Topical NSAIDs still contain the black box warning regarding serious cardiovascular and GI events
- Cost can be a limiting factor

Topical Diclofenac Available OTC

NSAIDs

- Use at the **lowest possible dose** for the **shortest possible duration**
- Labeled NSAID dosing varies by formulation
- Use caution/avoid in the following patient populations:
  - GI disorders/bleeding
  - Cardiovascular disease, heart failure, or a history of stroke
  - Renal impairment
  - Asthma

Corticosteroids

- Several mechanisms of action
  - Prostaglandin inhibition, cell membrane stabilization, sodium channel blockade, inhibition of osteoclastic activity
- Multiple routes of administration
  - Oral
  - Parenteral
    - IV
    - IM depot
    - Intra-articular

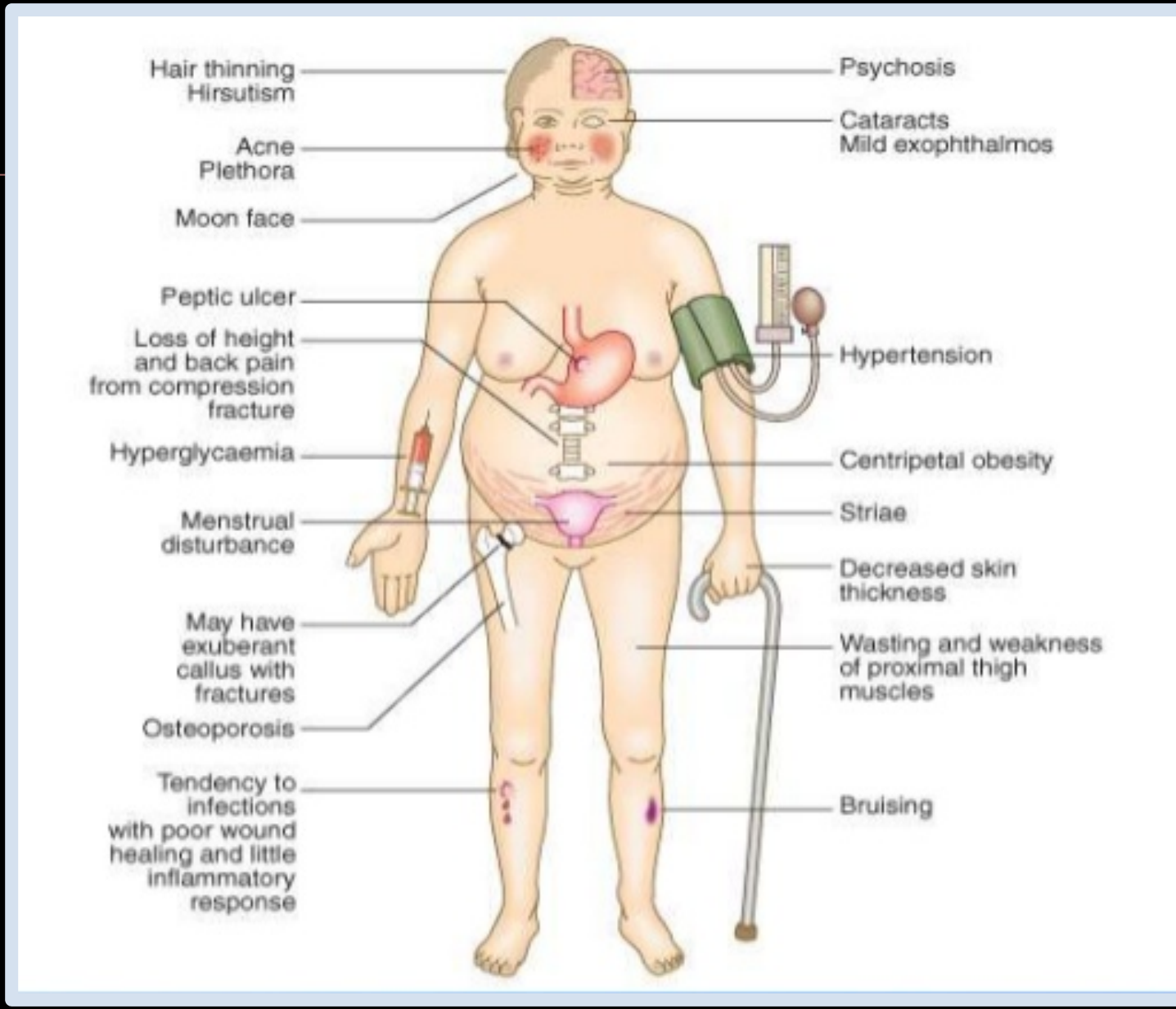
Corticosteroids

Corticosteroid Conversion Chart				
Glucocorticoid	Approximate Equivalent Dose (mg)	Relative Anti-Inflammatory (Glucocorticoid) Potency	Relative Mineralocorticoid (Salt Retaining) Potency	Biological Half-Life (Hours)
Short-Acting				
Cortisone	25	0.8	0.8	8 - 12
Hydrocortisone	20	1.0	1.0	8 - 12
Intermediate-Acting				
Methylprednisolone	4	5	0.5	18 - 36
Prednisolone	5	4	0.8	18 - 36
Prednisone	5	4	0.8	18 - 36
Long-Acting				
Dexamethasone	0.75	25	0.0	36 - 54

Meikle AW et al. Potency and Duration of Action of Glucocorticoids. AM J of Med. 1977. 63 (2);200 - 207. PMID: 888843

Corticosteroids

Adverse effects associated with steroid use



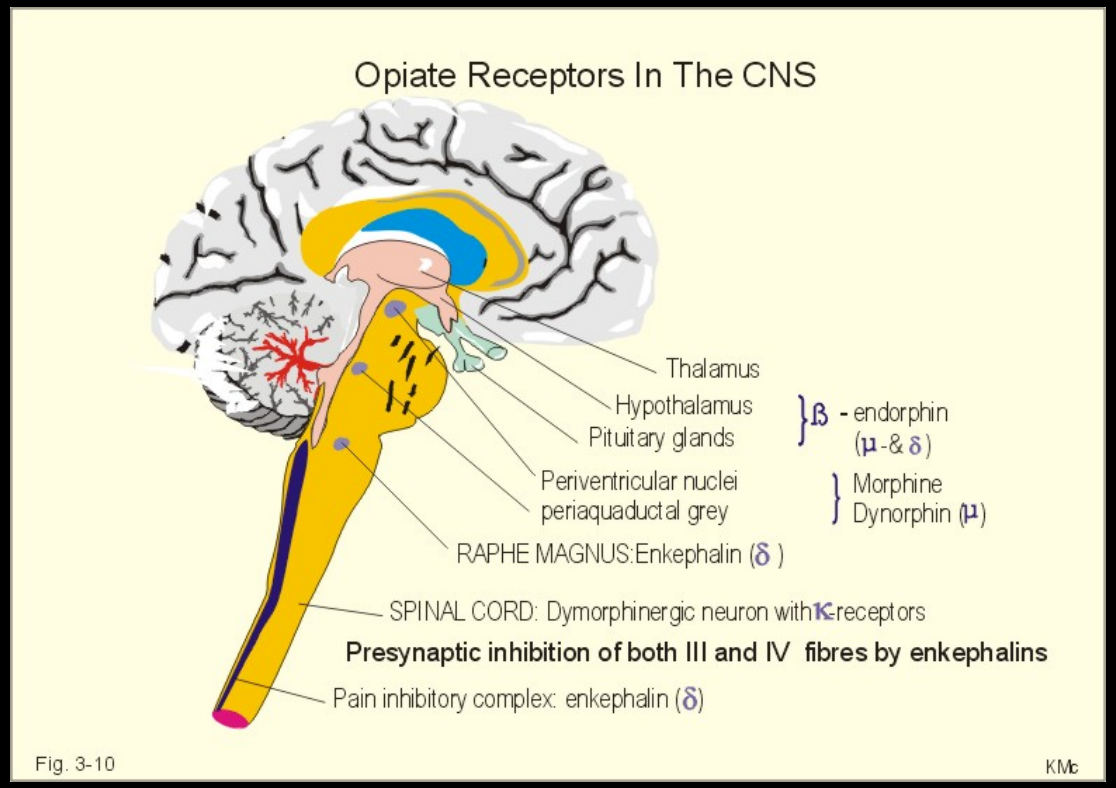
Corticosteroids

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

Opioids

- Opioids work on multiple receptors within the CNS
- For pure opioid agonists, there is no ceiling dose for analgesia however as doses increase the incidence of adverse effects increases
- CDC (2016) and VA/DoD (2017) guideline published outlining the use of opioids in chronic pain

Opioid Receptors

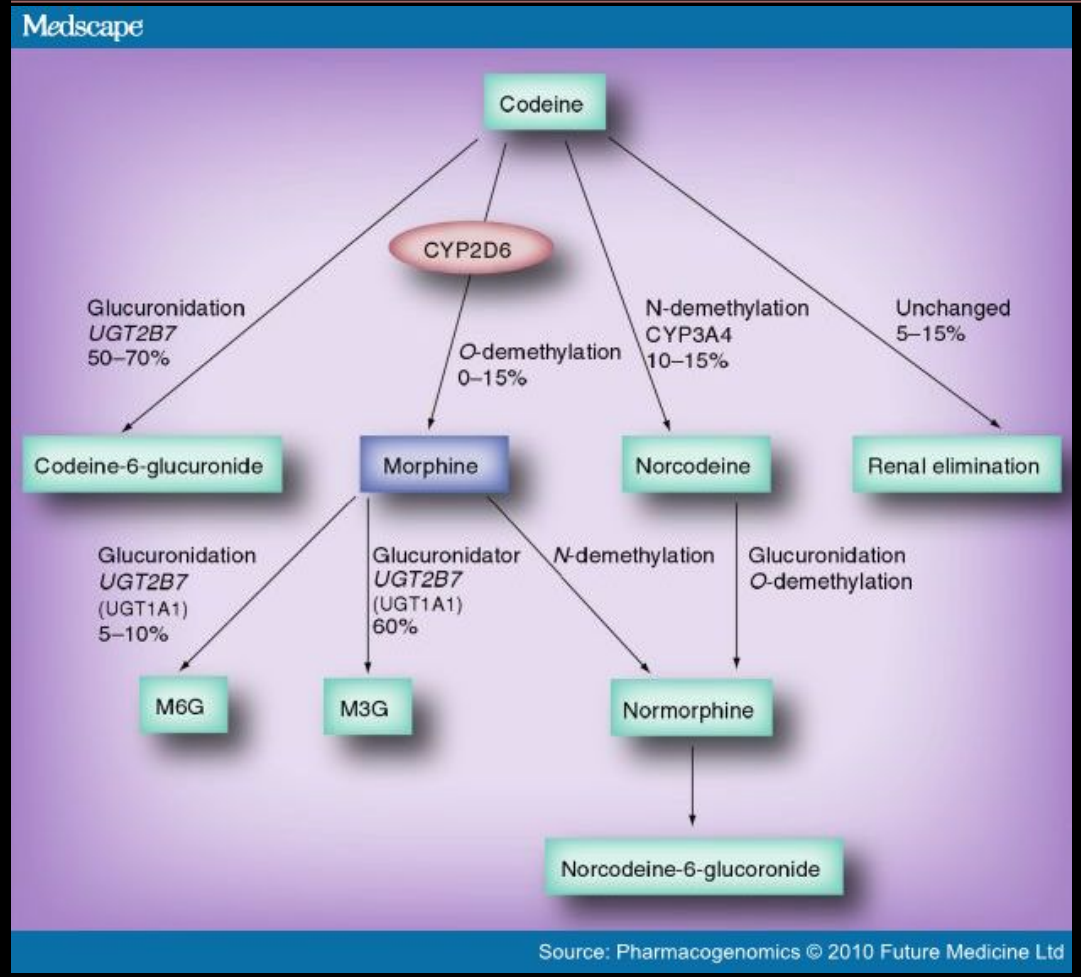


- Mu, kappa, delta and zeta receptors are known
  - Analgesia from all but zeta
- Different subtypes of receptors exist and exert different clinical effects
  - Mu-1 - analgesia
  - Mu-2 - respiratory depression

Opioids

- Agonists vs. partial agonists vs. antagonists
  - Morphine, fentanyl, methadone etc.
  - Buprenorphine, nalbuphine, butorphanol
  - Naloxone and naltrexone
- Awareness of other non-pain product's active ingredients
  - Naltrexone-bupropion for weight loss
  - Naltrexone injectable suspension for alcohol dependence

Opioid Metabolism



- Metabolic pathways can become saturated leading to metabolism by other pathways
  - Codeine
  - Oxycodone
    - 2D6 → nor-oxycodone
    - 3A → oxymorphone

http://www.medscape.com/viewarticle/723131_2

Opioids and Risk Factors

- ~70% of drug overdose deaths involved an opioid (2018)
- 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
  - Non-fatal overdose history

https://www.cdc.gov/mmwr/volumes/69/wr/mm6911a4.htm

Naloxone

- Designed to rapidly reverse opioid overdose
- Available as intranasal and intramuscular injections
  - Intranasal 2 mg or 4 mg individual spray dosage forms
  - Intramuscular available as 2 mg/ 0.4 ml single dose auto injector
  - To be administered to anyone with suspected opioid overdose
  - Many states allow for protocol dispensing from a pharmacy without a prescription

https://www.cdc.gov/media/modules/dpk/2016/dpk-pod/rr6501e1er-ebook.pdf

Immediate Release (IR) vs. Extended Release (ER) opioids

- Initial therapy should include the use of IR formulations
- ER preparations are appropriate for patients that…
  - Routinely use IR preparation with relief of pain
  - Are not experiencing adverse effects which decrease QOL
  - 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 guidelines

Opioid Rotation

- Converting a patient from one opioid to another
- There is evidence in cancer patients where rotation can be beneficial
- There are some retrospective trials that looked at opioid rotation in non-cancer pain patients but not enough to make a recommendation

SELECTED EQUIVALENCIES

	Equianalgesic Equivalence (mg)	
OPIOID	PARENTERAL	ORAL
Morphine	10	25
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Oxycodone	10 *(not in US)*	20
Oxymorphone	1	10

http://americanpainsociety.org/uploads/education/guidelines/chronic-opioid-therapy-cncp.pdf
McPherson ML. Demystifying opioid conversion calculations. 2018.

Incomplete Cross-Tolerance

- Results from the differences in pharmacokinetics and pharmacodynamics between opioids
- The use of dose conversion charts should be utilized whenever transitioning a patient from one opioid to another
- Accounting for incomplete cross-tolerance should be done to prevent acute overdose of the new opioid
- Caution MUST be exercised if converting to or from methadone

Opioid Conversion

- Convert opioid total daily dose to equivalent oral morphine dose
- Account for incomplete cross-tolerance
  - Decrease by 25-50% for patients experiencing adequate pain control
  - Decrease by 0-25% for patients experiencing diminished pain control on current opioid
- Convert to the new opioid and adjust dosing based on available formulations
- Monitor for pain control and adverse effects after the conversion

Conversion to Methadone

- Methadone has a variable $t_{1/2}$
  - Between 7 to 59 hours
- Multiple conversion charts exist in the literature
- EXTREME caution should be exercised when converting a patient to methadone from another opioid

Table 1. Comparison of Proposed Morphine To Methadone Conversion Parameters

Ripamonti et al, 1998						
Morphine dose (mg/d)	30-90		91-300		301+	
Morphine:Methadone EDR	3.70:1		7.75:1		12.25:1	
Ayonrinde et al, 2000						
Morphine dose (mg/d)	<100	101-300	301-600	601-800	801-1,000	>1,001
Morphine:Methadone EDR	3:1	5:1	10:1	12:1	15:1	20:1
Mercadante et al, 2001						
Morphine dose (mg/d)	30-90		91-300		301+	
Morphine:Methadone EDR	4:1		8:1		12:1	
Fudin, 2012						

$$Methadone\ (mg) = \frac{x}{21} \times \left\{ 5.7 - 3 \times \sin\left(\frac{90}{\left(\frac{110}{x}\right)^{5} + 1} \right) - \sin\left(\frac{90}{\left(\frac{320}{x}\right)^{7} + 1} \right) \right\}$$

x = morphine (mg)
Based on references 15-17, 19.
EDR, equianalgesic dose ratio

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https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=DA0A54C6-8B53-4774-8C40-E615AC8D804D&type=display
Practical Pain Management. 2012; Sept:46-51.

DOSING METHADONE IN ADVANCED ILLNESS

- Methadone is a very useful opioid, but requires close attention to detail in dosing and follow-up.
- Evaluate patient's risk status (e.g., QTc prolongation), prognosis, history of medication adherence, interacting medications, pain history.
- ***Opioid-naïve patients***: 2-5 mg oral methadone total daily dose (or, up to 7.5 mg per day if appropriate). Consider interacting medications.
- ***Opioid-tolerant patients***: Convert patient's current opioid regimen to oral morphine equivalents (see reserve side).

Recommended dosing is as follows:

Total Daily Dose Oral Morphine Equivalent (OME)	Conversion Ratio to Oral Methadone
0-60 mg	Follow opioid-naïve dosing (above)
60-199 OME *and* < 65 years old	10 mg OME : 1 mg oral methadone
> 200 mg OME *and/or* > 65 years old	20 mg OME : 1 mg oral methadone

ADDITIONAL GUIDANCE:

- Do not increase dose before 5-7 days.
- Do not increase total daily oral methadone dose by more than 5 mg/day (can increase by up to 10 mg/day once total daily oral methadone dose is 30-40 mg/day)
- When converting to oral methadone, do not exceed 30-40 mg oral methadone per day as starting dose, regardless of previous opioid dose.
- Reduce calculated oral methadone dose by 25-30% if patient receiving known enzyme inhibitor.
- Assess patient daily for 5-14 days after methadone initiation and adjustment.
- References: *palliative@umaryland.edu*

This is not a substitute for clinical judgment, particularly with complex comorbidities and high morphine equivalents.

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410-706-PALL (7255) | *graduate.umaryland.edu/palliative*

McPherson ML, et al. J Pain Symptom Manage 2019;57(3):635-645.e4.

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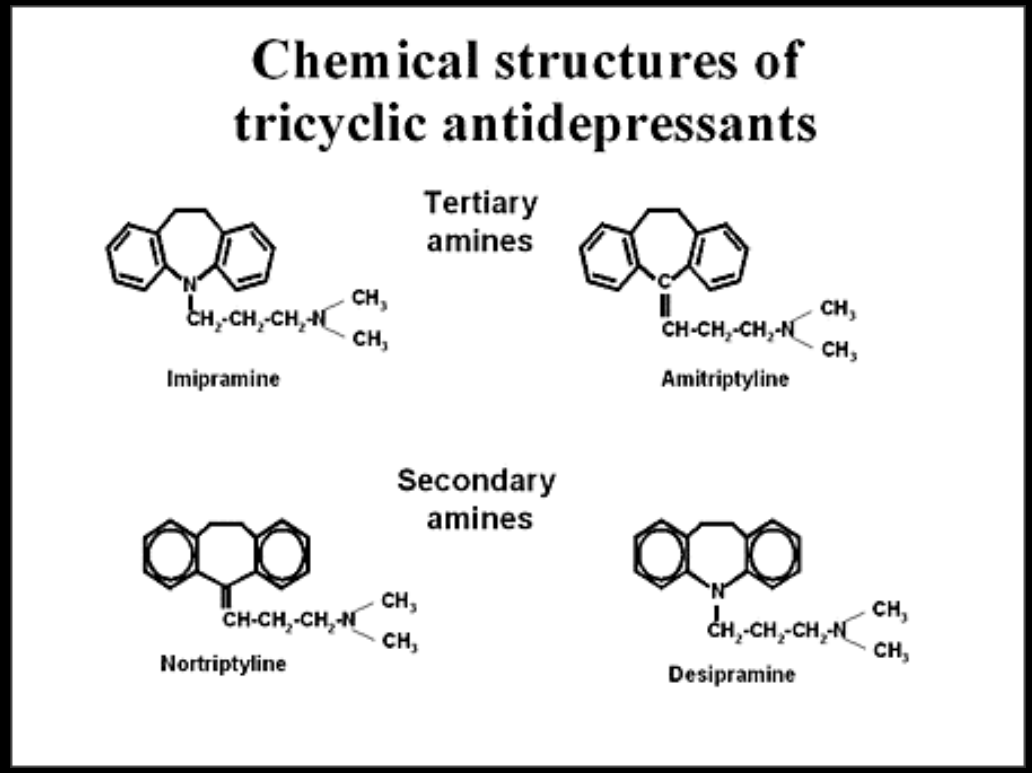
Tricyclic Antidepressants (TCAs)

- 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
  - >65 years old

Anticholinergic Properties Among TCAs

- Tertiary amines are associated with more of the anticholinergic side effects compared to secondary amines
- Anticholinergic side effects include
  - Sedation
  - Dry mouth/ urinary retention
  - Postural hypotension
  - Arrhythmias or seizures



http://www.fpnotebook.com/Psych/Pharm/TrcyclcAntdprsnt.htm
http://www.medscape.org/viewarticle/413110_3

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- 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

SSRIs and Neuropathic Pain

- Cochrane review in 2007 reviewed the literature regarding
  - Tricyclic antidepressants (TCAs)
  - Select serotonin reuptake inhibitors (SSRIs)
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
- TCAs and venlafaxine have data which support their use in neuropathic pain
- There is limited evidence to suggest SSRIs are effective in managing neuropathic pain
  - They were better tolerated compared to TCAs relating primarily to side effect profile

http://www.cochrane.org/CD005454/SYMPT_antidepressants-for-treating-neuropathic-pain

SSRIs and Chronic Pain

- 36 trials included in a review of SSRIs in the management of chronic pain
  - Reviewed data on nine SSRIs including citalopram, fluoxetine and others
- 25 of the studies reported significant effect regarding chronic pain outcomes
  - Only 2 of those trials had low risk of bias
- SSRIs may have some effect on chronic pain however more robust clinical trials are needed in order to make a recommendation for their use for chronic pain

https://www.hindawi.com/journals/prm/2016/2020915/

Anticonvulsants

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

Anticonvulsants

- For gabapentin and pregabalin only - reasonably good second tier evidence for efficacy in painful diabetic neuropathy and post-herpetic neuralgia
- There was little evidence and no judgement could be made about efficacy for valproic acid
- Low quality evidence was likely to be subject to a number of biases overestimating efficacy for carbamazepine
- Reasonable quality evidence exists indicating little or no effect for lamotrigine, oxcarbazepine, topiramate

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010567.pub2/epdf

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 injection
  - IV
- Patches are indicated for the management of post herpetic neuralgia

Local Anesthetics, cont.

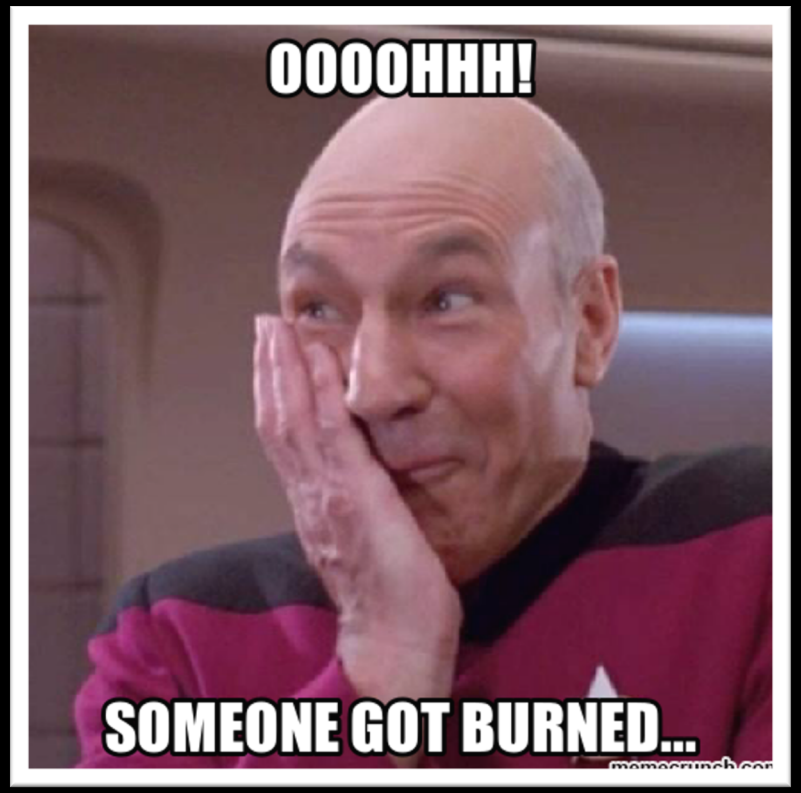
- Ester and amide sub families of local anesthetics
  - Esters include chloroprocaine and procaine
  - Amides include bupivacaine, lidocaine and others
- Allergies are possible to the ester types secondary to the metabolic by-product para-amino-benzoic acid (PABA)
  - Amide type local anesthetics do not metabolize to a PABA moiety
- Adverse events can effect CNS, CV and hematologic systems
  - Local anesthetics can be proarrhythmogenic, especially bupivacaine, if given parenterally

https://www.ncbi.nlm.nih.gov/pubmed/8826570 \

Skeletal Muscle Relaxants

- Multiple medications are included in this general taxonomy
  - Certain agents approved for muscle spasticity
    - Baclofen through activity on GABA
    - Tizanidine through activity on alpha-2
- Others stand out for reasons other than their indication
  - Cyclobenzaprine and orphenadrine regarding their anti-cholinergic effects
  - Chlorzoxazone and potential for hepatotoxicity
  - Carisoprodol and meprobamate and potential for abuse

Capsaicin



- Mechanism of action is though stimulation of the TRPV1 receptor in order to deplete substance P release from the periphery
- Indications include:
  - Neuropathic pain associated with post-herpetic neuralgia
  - Arthritis and musculoskeletal pain
- Topical formulations and an 8% Rx patch are available
  - The patch requires significant resources as it is applied in-office every three months
- Localized irritation is the most common side effect

Ketamine

- Mechanism of action
  - NMDA receptor antagonist
  - Weak mu opioid receptor agonist (potentiates effect of opioids)
  - Potentiates the effects of GABA
- Multiple available routes of administration
  - IV, IM, SQ, PO, rectal, intranasal, topical, etc.
- Consider ketamine for:
  - Escalating pain, hyperalgesia, allodynia, intolerable side effects to opioids, opioid non-responsiveness, depression, PTSD

Miscellaneous Agents

- Ziconotide
  - Synthetic conopeptide binding to N-type calcium channels in primary afferent neurons
- Botulinum Toxin A
  - Indication for migraine
- Cannabinoids

Putting it all together

Type of pain	How patient's describe it	Analgesics
Nociceptive somatic pain	• May be sharp or dull, often aching in nature • Familiar pain (e.g., toothache) • May be exacerbated by movement (incident pain) • Well localized and consistent with underlying lesion • Examples: metastatic bone pain, postsurgical pain, musculoskeletal pain, arthritis pain	Responds well to primary analgesics such as NSAIDs and opioids
Nociceptive visceral pain	• Arises from distention of a hollow organ • Usually poorly localized, deep, squeezing and crampy • Often associated with autonomic sensations such as N/V, diaphoresis • May be referred (heart pain to shoulder or jaw; gallbladder pain to scapula; pancreas pain to back) • Examples: pancreatic CA, intestinal obstruction, intraperitoneal mets	Responds well to primary analgesics such as opioids, possibly non-opioids
Neuropathic pain	• Patient struggle to describe it; it's unfamiliar • They use words such as burning, electrical, numb • Innocuous stimuli may bring on pain (allodynia) • Patients may complain of paroxysms of electrical sensation (lancinating or lightning pains) • Examples: trigeminal neuralgia, postherpetic neuralgia, PDN	Adjuvant agents such as anticonvulsants, antidepressants are primary intervention

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
- 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.

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.

Ethnicity and Genetic Effects on Pharmacokinetics (PK)

- Differences among ethnic groups in drug-metabolizing enzymes and drug transporter proteins could potentially result in variability in PK
- Races identified as having various allelic frequencies include
  - Asian
  - African
  - Middle Eastern
  - European
- Patients sensitive to multiple medications may benefit from genetic screening

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

Ethnicity and Genetic Effects on Pharmacokinetics, cont.

- CYP enzymes and medications metabolized
  - 1A for amitriptyline, cyclobenzaprine
  - 2D6 for tramadol, oxycodone and duloxetine
  - 3A for venlafaxine, buprenorphine, fentanyl

Table 1. Metabolizer Status and Selected CYP2D6 Genotypes

Metabolizer Status	Examples of Allele Combinations
Ultra-rapid (UM)	CYP2D6*1/*1XN, CYP2D6*1/*2XN
Extensive (EM)	CYP2D6*1/*1, CYP2D6*2/*3
Intermediate (IM)	CYP2D6*4/*10, CYP2D6*9/*10
Poor (PM)	CYP2D6*3/*6, CYP2D6*19/*38

** Denotes allele number. 1 is usually normal version of allele. Each individual has at least 2 copies for a gene, in multiple combinations. XN denotes more than two copies of alleles.*
Source: Reference 4.

For assistance with interpretation of genetic testing results:
https://www.pharmgkb.org/

https://www.uspharmacist.com/article/pharmacogenetic-testing-and-opioids

Pain Management Guidelines

PAINWEEK®

Acute or Subacute Low Back Pain

- **Acetaminophen** – No difference compared to placebo at 4 weeks
- **NSAIDs** – Small improvement compared to placebo
  - Specific NSAIDs showed no difference in pain control or improvement in function
- **Skeletal muscle relaxants** – Small improvement in short-term pain control compared to placebo
  - Inconsistent findings on the combination of skeletal muscle relaxants and NSAIDs compared to NSAIDs alone
- **Corticosteroids** – No difference in pain or function after single IM injection or 5-day course of oral steroid compared to placebo

Ann Intern Med.2017;166:514-530

Chronic Low Back Pain

- **NSAIDs** – Small to moderate evidence of improvements in pain with no difference in functionality compared to placebo
- **Opioids** – Moderate evidence of improvements in pain for strong opioids compared to placebo
  - No clear difference between IR vs. ER in terms of pain or functionality
- **Skeletal muscle relaxants** – Insufficient evidence regarding use but no difference in any outcome compared to placebo

Ann Intern Med.2017;166:514-530

Chronic Low Back Pain, cont.

- **Antidepressants** – No difference between TCAs or for most SNRIs compared to placebo with respect to function
  - Duloxetine was associated with a small improvement in pain intensity and function compared to placebo
- No sufficient evidence regarding the use of acetaminophen, corticosteroids or anticonvulsants regarding pain relief or improvement in functionality

Ann Intern Med.2017;166:514-530

VA/DoD CPG: Diagnosis and Treatment of Low Back Pain

	Recommendation	Strength of Evidence
Acute Low Back Pain	For patients with acute or chronic low back pain, we recommend **treating with NSAIDs** with consideration of patient-specific risks.	Strong For
	For patients with acute low back pain or acute exacerbations of chronic low back pain, we suggest offering a **non-benzodiazepine muscle relaxant for short-term use**.	Weak For
	For patients with acute or chronic low back pain with or without radiculopathy, we recommend **against the use of systemic corticosteroids** (oral or IM injection).	Strong Against
	For patients with acute low back pain or acute exacerbations of chronic low back pain, there is **insufficient evidence** to recommend for or against the use of **time-limited opioid therapy**	N/A
	For patients with acute or chronic low back pain, there is **insufficient evidence** to recommend for or against the use of time-limited (<7 days) **acetaminophen** therapy	N/A
	For the treatment of acute or chronic low back pain, including patients with both radicular and non-radicular low back pain, there is **insufficient evidence** to recommend for or against the use of **antiepileptics i**ncluding gabapentin and pregabalin.	N/A

Pangarkar SS, et al. J Gen Intern Med 2019;34(11):2620-9.

VA/DoD CPG: Diagnosis and Treatment of Low Back Pain

	Recommendation	Strength of Evidence
Chronic Low Back Pain	For patients with acute or chronic low back pain, we recommend treating with **NSAIDs** with consideration of patient-specific risks.	Strong For
	For patients with chronic low back pain, we suggest **offering an exercise program**, which may include Pilates, yoga, and tai chi.	Weak For
	For patients with chronic low back pain, we suggest offering **acupuncture**.	Weak For
	For patients with chronic low back pain, we suggest offering treatment with **duloxetine**, with consideration of patient-specific risks.	Weak For
	For patients with chronic low back pain, we suggest **against offering a non-benzodiazepine muscle relaxant.**	Weak Against
	For patients with acute or chronic low back pain with or without radiculopathy, we recommend **against the use of systemic corticosteroids** (oral or intramuscular injection).	Strong Against
	For patients with chronic low back pain, we recommend **against the chronic use of oral acetaminophen.**	Strong Against

Pangarkar SS, et al. J Gen Intern Med 2019;34(11):2620-9.

Case #1

- 38 year old male with chronic low back pain from traumatic injury sustained five years ago. Had a significant GI bleed six months ago from overuse of NSAIDS requiring multiple transfusions.
- Current medications include:
  - pregabalin 150 mg po bid
  - oxycodone IR 30 mg po Q6H PRN, average 3 doses per day
  - fentanyl 2 x 100 mcg/hr patch changed Q48H
- Pain is 6/10 (baseline) but today's complaint is about lack of energy, feeling of hopelessness and decrease in social activities.
- What would be the best option based on current guidelines?

Case #1, cont.

A. Cyclobenzaprine 10 mg po bid PRN spasm
B. Increase oxycodone to 45 mg po Q6H PRN
C. Initiate duloxetine and titrate up as tolerated
D. Start scheduled piroxicam 20 mg po daily

Case #1, cont.

A. Cyclobenzaprine 10 mg po bid prn spasm
B. Increase oxycodone to 45 mg po q 6 hrs
C. Initiate duloxetine and titrate up as tolerated
D. Start scheduled piroxicam 20 mg po daily

Chronic Pain of Cancer Survivors

- Clinicians may prescribe the following systemic non-opioid analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications, including serious drug-drug interactions exist:
  - NSAIDs
  - Acetaminophen
  - Antidepressants
    - Duloxetine
  - Anticonvulsants
    - Gabapentin
    - Pregabalin

Paice JA, et al. J Clin Oncol 2016;34: 3325-3345

Chronic Pain of Cancer Survivors, cont.

- Clinicians may prescribe topical analgesics for the management of chronic pain
- Corticosteroids are **not** recommended for long-term use in cancer survivors solely to relieve chronic pain
  - Specifically looked at high doses of corticosteroids for 8 weeks
- Clinicians should assess the risk of adverse effects of pharmacologic therapies, including non-opioids, adjuvant analgesics, and other agents used for pain management

Paice JA, et al. J Clin Oncol 2016;34: 3325-3345

Chronic Pain of Cancer Survivors, cont.

- Clinicians may follow specific state regulations that allow access to medical cannabis or cannabinoids for patients with chronic pain after a consideration of the potential benefits and risks of the available formulations
- Clinicians may prescribe a trial of opioids in carefully selected cancer survivors with chronic pain who do not respond to more conservative management and who continue to experience pain-related distress or functional impairment

Paice JA, et al. J Clin Oncol 2016;34: 3325-3345

Opioid Prescribing for Chronic Pain (CDC)

- Non-pharmacologic and non-opioids are preferred for chronic pain and to consider opioids only if benefits outweigh risks
- Before initiating opioid therapy clinicians should help establish realistic treatment goals for pain and function and consider how to discontinue opioid if risks outweigh benefits
- Reassess risks and benefits of opioids with the patient while on opioids

JAMA. 2016;315(15):1624-1645

Opioid Prescribing for Chronic Pain, cont.

- When starting patients on opioids, immediate release should be prescribed instead of extended release
  - Methadone and transdermal fentanyl should not be considered at this point in treatment
- When starting opioids, clinicians should prescribe the lowest effective dose
  - Reassess evidence of benefit and compare to risk if increasing beyond 50 MME
  - Avoid increasing or carefully justify a decision to titrate above 90 MME

MME = morphine milligram equivalents

JAMA. 2016;315(15):1624-1645

Opioid Prescribing for Chronic Pain, cont.

- When opioids are prescribed for ACUTE pain, the lowest dose of immediate release opioid should be used and the duration should rarely be more than 7 days
- Reevaluation of the patient at 1 to 4 weeks after initiation or dose changes and then every 3 months, and if risks outweigh benefits tapering down and potential discontinuation of opioids should be considered

JAMA. 2016;315(15):1624-1645

Opioid Prescribing for Chronic Pain, cont.

- Before initiation of and periodically thereafter, risk factors for opioid-related harms should be reviewed
  - Consider offering naloxone rescue therapy for patients at high risk for overdose including 50 MME
- Review your states prescription drug monitoring program (PDMP) at initiation and periodically at least every three months
  - Avoid dismissing patients based solely on PDMP results

MME = morphine milligram equivalence
JAMA. 2016;315(15):1624-1645

Opioid Prescribing for Chronic Pain, cont.

- Monitor urine drug testing (UDT) before and periodically throughout long-term opioid therapy
  - Avoid dismissing patients based solely on UDT results
- Clinicians should avoid prescribing pain medication and benzodiazepines whenever possible
- Offer or arrange access for patients with substance use disorders to methadone or buprenorphine combined with behavioral therapies

MME = morphine milligram equivalence
JAMA. 2016;315(15):1624-1645

VA Chronic Opioids in Chronic Pain

- We recommend alternatives to opioid therapy such as self management strategies and other non-pharmacological treatments
  - When pharmacologic therapies are used, we recommend non-opioids over opioids
  - We recommend against initiation of long-term opioid therapy for chronic pain
- If prescribing opioid therapy for patients with chronic pain, we recommend a short duration

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies, assessment for opioid use disorder, and consideration for tapering when risks exceed benefits
- We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder
  - For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- We recommend against the concurrent use of benzodiazepines and opioids
  - For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate
- We recommend against long-term opioid therapy for patients < 30 years of age secondary to higher risk of opioid use disorder and overdose
  - For patients < 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies
- We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every 3 months
- If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits
- As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain
- We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy
- We recommend tapering to reduced dose or discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Chronic Opioids in Chronic Pain, cont.

- We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics
- We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior
- We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder

https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

VA Opioids in Acute Pain

- We recommend alternatives to opioids for mild-to-moderate acute pain
- We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain
  - If take-home opioids are prescribed, we recommend that IR opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated

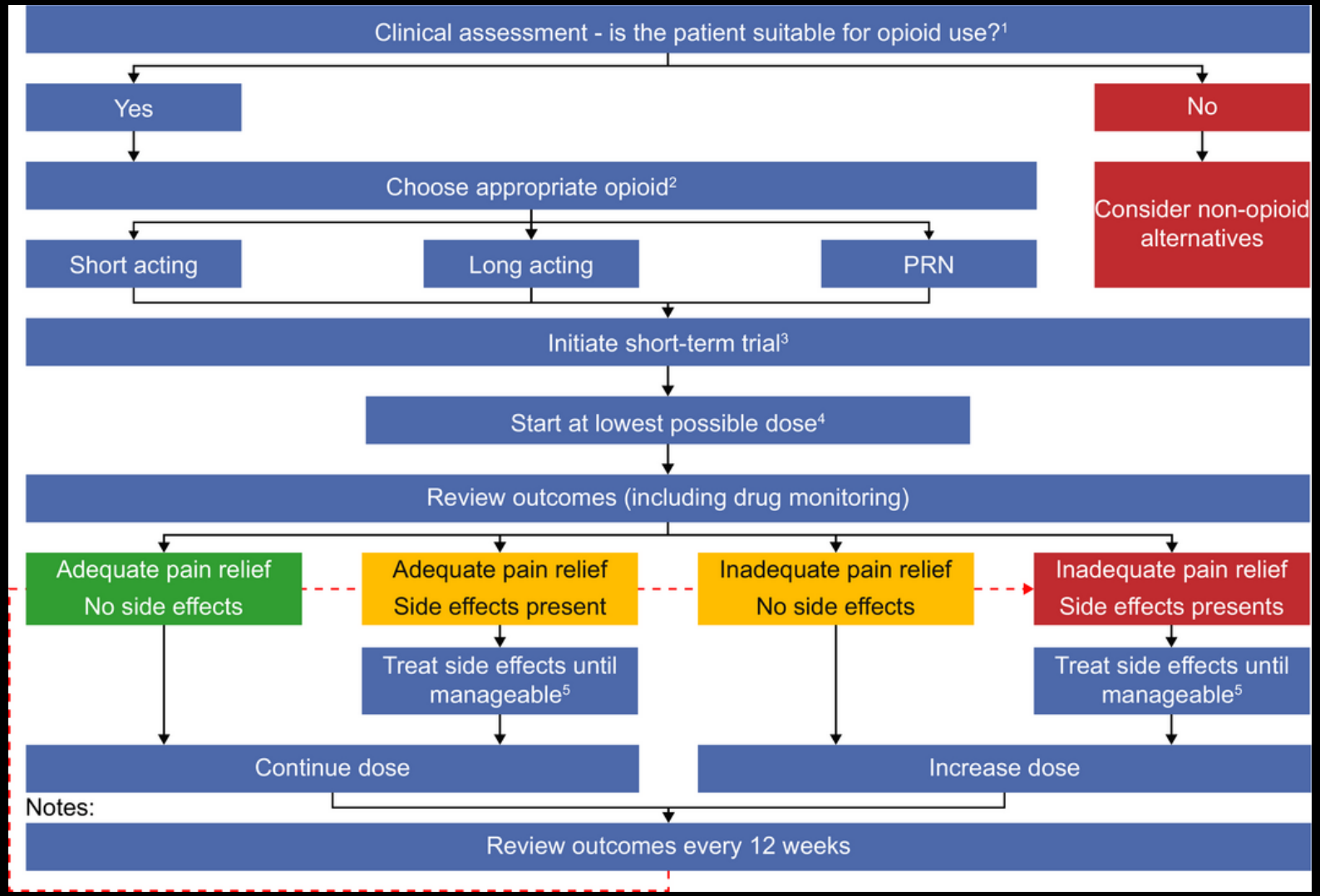
https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf

Federation of State Medical Boards

- Patient evaluation and risk stratification
- Development of treatment plan and goal
- Use of informed consent and treatment agreements
- Initiating an opioid trial
- Monitoring and adapting of the opioid trial
- Periodic and unannounced drug testing
- Consultation and referrals
- Discontinuation of opioid therapy
- Medical record documentation
- Compliance with controlled substance laws and regulations

https://www.fsmb.org/Media/Default/PDF/Advocacy/Opioid%20Guidelines%20As%20Adopted%20April%202017_FINAL.pdf

European Pain Federation Position Paper on Appropriate Opioid Use in Chronic Pain Management



European Journal of Pain
Volume 21, Issue 1, pages 3-19, 19 DEC 2016 DOI: 10.1002/ejp.970
http://onlinelibrary.wiley.com/doi/10.1002/ejp.970/full#ejp970-fig-0002

PAINWEEK

Neuropathic Pain in Adults

Strong recommendation for use	Total daily dose and dosing regimen	Recommendation
Gabapentin IR	1200-3600 mg in three divided daily doses	First line
Gabapentin ER	1200-3600 mg in two divided daily doses	First line
Pregabalin	300-600 mg in two divided daily doses	First line
Duloxetine[a] or Venlafaxine[b]	a. 60-120 mg daily b. 150-225 mg daily (extended release)	First line
TCAs	25-150 mg either one or two divided daily doses	First line

Lancet Neurol 2015; 162–73

Diabetic Neuropathy

- Consider either pregabalin or duloxetine as the initial approach in the symptomatic treatment of neuropathic pain in diabetes
- Although used off-label, TCAs are also effective for neuropathic pain in diabetes but should be used with caution given the higher risk of serious side effects

http://care.diabetesjournals.org/content/40/1/136.full-text.pdf

Diabetic Neuropathy, cont.

- Gabapentin may also be used as an effective initial approach, taking into account patients' socioeconomic status, comorbidities, and potential drug interactions
- Given the high risks of addiction and other complications, the use of opioids, including tapentadol or tramadol, is not recommended as first or second-line agents for treating the pain associated with distal symmetric polyneuropathy

http://care.diabetesjournals.org/content/40/1/136.full-text.pdf

Methadone Initial Dosing

- Patients with intermittent chronic pain requiring only ‘as needed’ opioids or have a history of medication non-compliance are NOT good candidates for methadone
- Initiate therapy at a low dose, under 15 mg per day in divided doses
- Increase doses no more frequently than once per week
- Daily dose increases should not exceed 5 to 10 mg per week
- Assess the patients risk for QTc prolongation and reassess QTc after dose changes. Decrease dose or discontinue therapy if QTc > 470 ms (men) or 480 ms (women).

Methadone Initial Dosing, cont.

- Do not prescribe for patients with known sleep disordered breathing or are non-compliant with their respiratory assistive devices
- Evaluate other respiratory depressant risk factors related to the use of sedatives with methadone
- Communicate to the patient the importance of not using methadone more often than prescribed even if their pain is not controlled
- Use IR opioids during methadone titrations if the initial dose of methadone is not adequate to manage the pain

Case #2

- 59-year-old female with chronic pain secondary to cervical post-laminectomy syndrome.
- She has tried multiple opioids including morphine, oxycodone and fentanyl and failed to achieve a return to her activities of daily living. She is currently using an average of 100 mg oral hydromorphone daily.
- Methadone is brought up during her discussion with you today. What are some things that must be carefully considered before initiating methadone?

Case #2, cont.

A. Review all medications, including over the counter products and complimentary or alternative medications for drug interactions
B. Obtain a baseline ECG since she has none on file
C. Use published conversion charts in order to safely calculate her initial dose of methadone
D. All of the above

Case #2, cont.

A. Review all medications, including over the counter products and complimentary or alternative medications for drug interactions
B. Obtain a baseline ECG since she has none on file
C. Use published conversion charts in order to safely calculate her initial dose of methadone
D. **All of the above**

Post-Operative Pain

- Pre-operative and peri-operative patient and caregiver education regarding post-operative pain management planning – managing expectations!
- Assessment and reassessment of post-operative pain
- The use of multimodal therapy
  - Physical modalities
  - Cognitive behavioral therapy (CBT)

J Pain 2016;17(2):131-157.

Post-Operative Pain, cont.

- Systemic pharmacologic therapy
- Local or topical pharmacologic therapy
- Peripheral regional anesthesia
- Neuraxial therapy
- Policies and procedures regarding post-operative pain
- Transitioning to outpatient care

J Pain 2016;17(2):131-157.

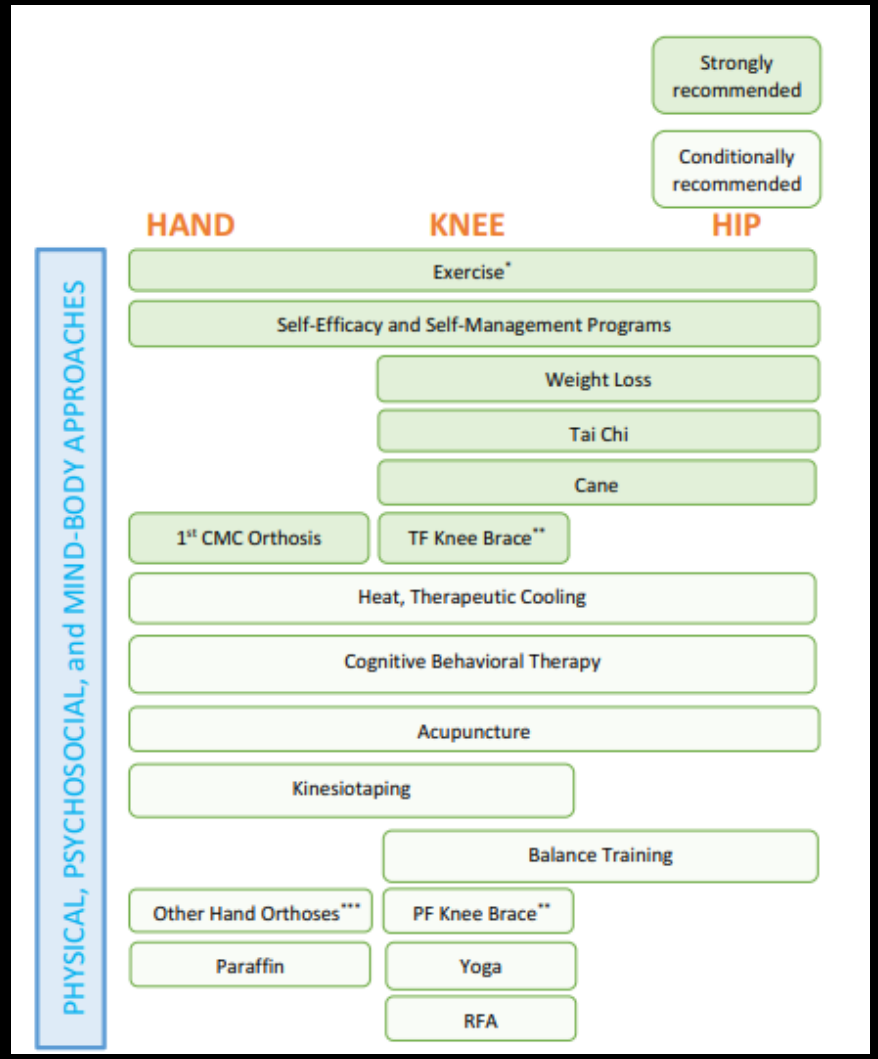
Post-Operative Pain, cont.

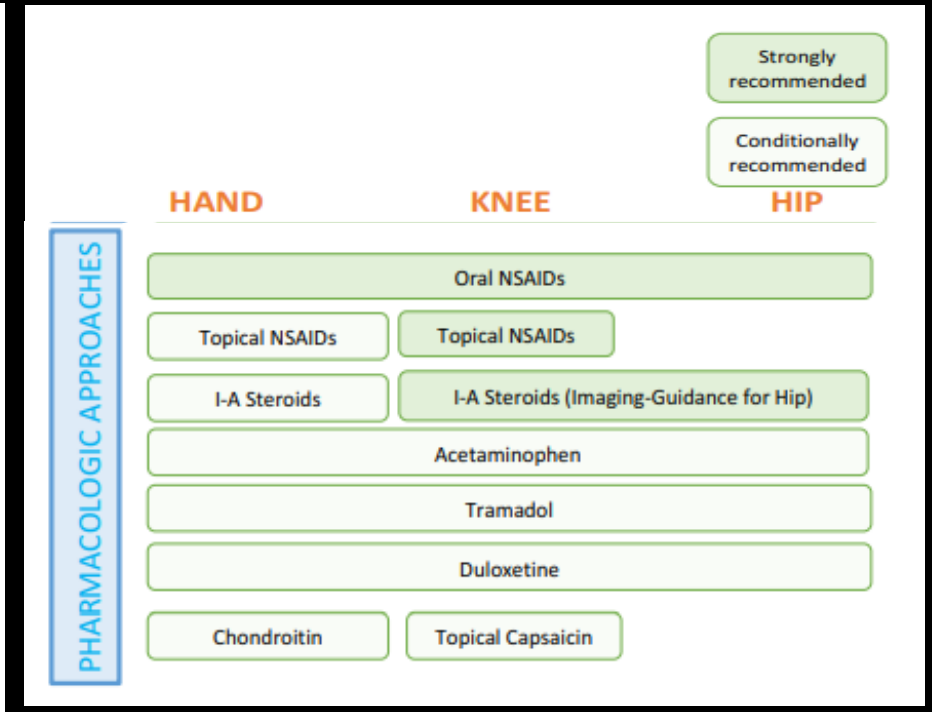
Table 3. Options for Components of Multimodal Therapy for Commonly Performed Surgeries

Type of Surgery	Systemic Pharmacologic Therapy	Local, Intra-articular or Topical Techniques*	Regional Anesthetic Techniques*	Neuraxial Anesthetic Techniques*	Nonpharmacologic Therapies†
Thoracotomy	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ i.v. ketamine¶		Paravertebral block	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Open laparotomy	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ i.v. ketamine¶ i.v. lidocaine	Local anesthetic at incision i.v. lidocaine infusion	Transversus abdominis plane block	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Total hip replacement	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ i.v. ketamine¶	Intra-articular local anesthetic and/or opioid	Site-specific regional anesthetic technique with local anesthetic	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Total knee replacement	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ i.v. ketamine¶	Intra-articular local anesthetic and/or opioid	Site-specific regional anesthetic technique with local anesthetic	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Spinal fusion	Opioids‡	Local anesthetic at incision		Epidural with local anesthetic (with	Cognitive modalities

J Pain 2016;17(2):131-157.

2019 ACR/AF Guideline for Management of OA of the Hand, Hip, and Knee





Osteoarthritis of the Hip

- Moderate strength evidence supports that the practitioner could use risk assessment tools to assist in predicting adverse events, assessing surgical risks and educating patients with symptomatic OA of the hip undergoing total hip arthroplasty
- Moderate strength evidence supports that obese patients with symptomatic OA of the hip, when compared to non-obese patients, may achieve lower absolute outcome scores but a similar level of patient satisfaction and relative improvement in pain and function after total hip arthroplasty

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Hip, cont.

- Strong evidence supports that NSAIDs improve short-term pain, function, or both in patients with symptomatic OA of the hip
- Moderate strength evidence does not support the use of glucosamine sulfate because it did not perform better than placebo for improving function, reducing stiffness and decreasing pain for patients with symptomatic OA of the hip

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Hip, cont.

- Strong evidence supports the use of intra-articular corticosteroids to improve function and reduce pain in the short-term for patients with symptomatic OA of the hip
- Strong evidence does not support the use of intra-articular hyaluronic acid because it does not perform better than placebo for function, stiffness, and pain in patients with symptomatic OA of the hip

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Hip, cont.

- Strong evidence supports the use of physical therapy as a treatment to improve function and reduce pain for patients with OA of the hip and mild to moderate symptoms
- Moderate evidence supports the use of post-operative physical therapy because it could improve early function to a greater extent than no physical therapy management for patients with symptomatic OA of the hip who have undergone total hip arthroplasty

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Knee

- Recommend that patients with symptomatic OA of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines
- Suggest weight loss for patients with symptomatic OA of the knee and a BMI ≥ 25
- Cannot recommend using acupuncture in patients with symptomatic OA of the knee

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Knee, cont.

- We cannot recommend using glucosamine and chondroitin for patients with symptomatic OA of the knee
- We recommend oral or topical NSAIDs or tramadol for patients with symptomatic OA of the knee
- We are unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic OA of the knee

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Osteoarthritis of the Knee, cont.

- We are unable to recommend for or against the use of intra-articular corticosteroids for patients with symptomatic OA of the knee
- We cannot recommend using hyaluronic acid for patients with symptomatic OA of the knee

https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/OA%20Hip%20CPG_3.13.17.pdf

Case #3

- 66-year-old male with chronic arthritis pain in bilateral knees but is not an appropriate candidate for knee arthroplasty
- Current medications include:
  - morphine ER 60 mg Q8H
  - oxycodone 15 mg Q4H prn severe pain, uses average of 3 doses daily
  - phenytoin (takes for seizures)
- For the past month he has been using all of his PRN and scheduled opioids. He states the pill burden is affecting his quality of life and he would like to be converted to a single opioid. Other pertinent medical history includes stage 4 heart failure and CABG.
- What options are appropriate for better pain control?

Case #3, cont.

A. Convert morphine ER to oxycodone ER 80 mg Q 12 hours and continue the oxycodone 15 mg PRN as ordered
B. Start diclofenac 100 mg po twice daily
C. Bilateral knee intra-articular injections with triamcinolone 10 mg
D. Start tramadol 100 mg every 4 hours scheduled in addition to current opioids

Case #3, cont.

A. **Convert morphine ER to oxycodone ER 80 mg Q 12 hours and continue the oxycodone 15 mg PRN as ordered**
B. Start diclofenac 100 mg po twice a day
C. Bilateral knee intra-articular injections with triamcinolone 10 mg
D. Start tramadol 100 mg every 4 hours scheduled in addition to current opioids

Acute Pain

- Acetaminophen is first line due to its safety and overall cost
- NSAIDs have similar analgesic activity, the decision should be made on the safety profile
- Opioid combinations should be considered for patients in which acetaminophen or NSAIDs were trialed but not effective in managing pain
- Opioids alone should be reserved for patients not experiencing appropriate pain control with the opioid combination products

Am Fam Physician. 2013 ; 87(11) :766 -77

Acute Pain

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Acetaminophen is the first-line treatment for most mild to moderate acute pain.	A	8, 18
Ibuprofen and naproxen (Naprosyn) are good, first-line NSAIDs for mild to moderate acute pain based on effectiveness, adverse effect profile, cost, and over-the-counter availability.	A	12, 13
Cyclooxygenase-2 selective NSAIDs are second-line medications for mild to moderate pain based on their similar effectiveness to nonselective NSAIDs and greater costs.	A	13
Celecoxib (Celebrex) alone and an NSAID plus a proton pump inhibitor have the same probability of causing gastrointestinal complications in those at high risk.	B	26, 27
Full opioid agonists may be used if opioids combined with acetaminophen or NSAIDs are insufficient to control moderate to severe pain.	A	14, 15, 31
Tramadol (Ultram) is less effective than hydrocodone/acetaminophen and is a second-line medication for the treatment of moderate to severe pain.	B	16, 39

NSAID = nonsteroidal anti-inflammatory drug.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Am Fam Physician. 2013 ; 87(11) :766 -77

Conclusions

- Pain patients have multiple evidence-based options regarding the pharmacologic management of pain
- Patient-specific physiology or pathology should be considered before and during medication therapy for pain patients
- Applying principles of rational pharmacotherapy can mitigate or even prevent some adverse effects

References

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