Dentistry and Basic Non-Opioid Prescribing in Pain

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Goals of Pain Management

- Decrease pain
- Increase function
- Utilize medications that limit unacceptable side effects, including addiction

Goals of This Presentation

- Gain knowledge of appropriate use of NSAIDs and acetaminophen for pain management in dentistry
- Improve insight into benefits and adverse effects of various NSAIDs
- Learn appropriate alternatives to opioid use for pain management

Opioids:
Use with Caution

- Use of opioids for the treatment of acute pain may be appropriate in dental practice
- Chronic use of opioids in dental practice is highly discouraged
- Patients may abuse and divert pain medications.
- Dentists must do whatever is possible to ensure the best care of patients with pain and minimize abuse and diversion
- As of January 1, 2019, Indiana dentists are required to use INSPECT to verify the prescription history of patients before prescribing opioids: http://www.in.gov/pla/inspect/

Risk for Overdose Up With Opioid Prescriptions After Dental Procedure

- Two analyses conducted to examine the correlation between opioid exposure (at least one initial prescription of opioids within three days of the procedure) and opioid overdose within 90 days of the procedure.
- 8,544,098 procedures among privately and publicly insured patients aged 13 to 64 years, and the family analysis included 3,461,469 procedures for privately insured patients in family plans
- 90-day risk for overdose was 5.8 versus 2.2 per 10,000 procedures when at least one initial opioid prescription did and did not occur
- 90-day risk for overdose in a family member was 1.7 versus 1.0 per 10,000 procedures

Chua K-P, Kenney B, et al. Dental Opioid Prescriptions and Overdose Risk in Patients and Their Families Am J of Prevent Med, April 29, 2021DOI:https://doi.org/10.1016/j.amepre.2021.02.008

Overprescribing of Opioids to Adults by Dentists in the U.S., 2011-2015

- Dentists prescribe 1 in 10 opioid prescriptions in the U.S
- A study of population-based sample of 542,958 U.S. commercial dental patient visits
- Appropriate prescribing was determined from the 2016 CDC guidelines for pain management based on a recommended 3 days' supply of opioid medication and anticipated post-procedural pain.
- 29% of prescribed opioids exceeded the recommended morphine equivalents for appropriate management of acute pain.
- 53% exceeded the recommended days' supply. Patients aged 18-34 years, men, patients residing in the Southern U.S., and those receiving oxycodone were most likely to have opioids prescribed inappropriately

Suda KJ, Zhou J et al, Overprescribing of Opioids to Adults by Dentists in the U.S., 2011-2015. Am J Prev Med. 2020 Apr;58(4):473-486

Is it time US dentistry ended its opioid dependence?

- 22.3% of US dental prescriptions were for opioids
- 0.6% of dental prescriptions for opioids in England
- NSAIDs accounted for most dental analgesic prescribing in the world
- NSAIDs and NSAID-acetaminophen combinations are as effective as or more effective than opioids for controlling dental pain and cause significantly fewer adverse effects
- Opioids are not needed for routine oral health care

Thornhill MH, Suda KJ et al, Is it time US dentistry ended its opioid dependence? J Am Dent Assoc. 2019 Oct;150(10):883-889

Nonsteroidal Anti-Inflammatory Drugs and Opioids in Postsurgical Dental Pain

- Postsurgical dental pain is mainly driven by inflammation
- Remarkable efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Opioids are inferior to NSAIDs as analgesics in postsurgical dental pain, produce a higher incidence of side effects in dental outpatients
- Unused opioids are also subject to misuse and diversion, and they may cause addiction
- 1- or 2-d course of opioids added to their NSAID regimen may be appropriate

Hersh EV, Moore PA et al, Nonsteroidal Anti-Inflammatory Drugs and Opioids in Postsurgical Dental Pain. J Dent Res. 2020 Apr 14:22034520914254.

NSAIDs-associated Mortality

- Literature reports 16,500 deaths annually as a result of NSAID-induced GI bleeding

  Data from the Arthritis, Rheumatism, and Aging Medical Information System, 1999

- An alterative estimate reports a smaller number of 3,200 deaths annually

  Cryer B. NSAID-associated deaths: the rise and fall of NSAID-associated GI mortality. Am J Gastroenterol. 2005;100(8):1694-1695

  Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther. 2004;11(1):17-25

- An overall mortality incidence rate of 48/1,000 person-years was reported for patients taking non-selective NSAIDs compared with 75/1,000 person-years with opioids

  Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968-1976

Risks of Short Versus Long Course of NSAIDs

- Risk of GI bleeding and cardiovascular problems starts almost immediately after a patient begins NSAID medication, and the risk is approximately equally high when used for short-term or long-term treatment

- Risk of kidney failure becomes higher the longer NSAIDs are used for pain management

Acetaminophen

- Use
  - For mild-to-moderate pain
  - Efficacy comparable to NSAIDs in some musculoskeletal conditions
  - Common combination drug (e.g., hydrocodone)
- Safety
  - Few adverse effects
  - Hepatic toxicity possible at high doses (> 4 g/d) or with chronic alcohol abuse
- Dosage
  - Up to 4 g/d in divided doses in acute use
  - Up to 3 g/d in divided doses in chronic use
  - Lower dose in elderly, dehydration, or liver disease

Acetaminophen

- A centrally acting analgesic that increases the pain threshold
- Mechanism of action is not known but may involve nitric oxide, NMDA, substance P, and antagonism of COX-2 and COX-3 enzymes

Björkman R, et al. *Pain*. 1994;57:259-264

NSAIDs: Beneficial Effects

- Analgesia
- Anti-inflammation
- Anti-pyresis
- Standard of care in acute pain
- Limited use in chronic pain

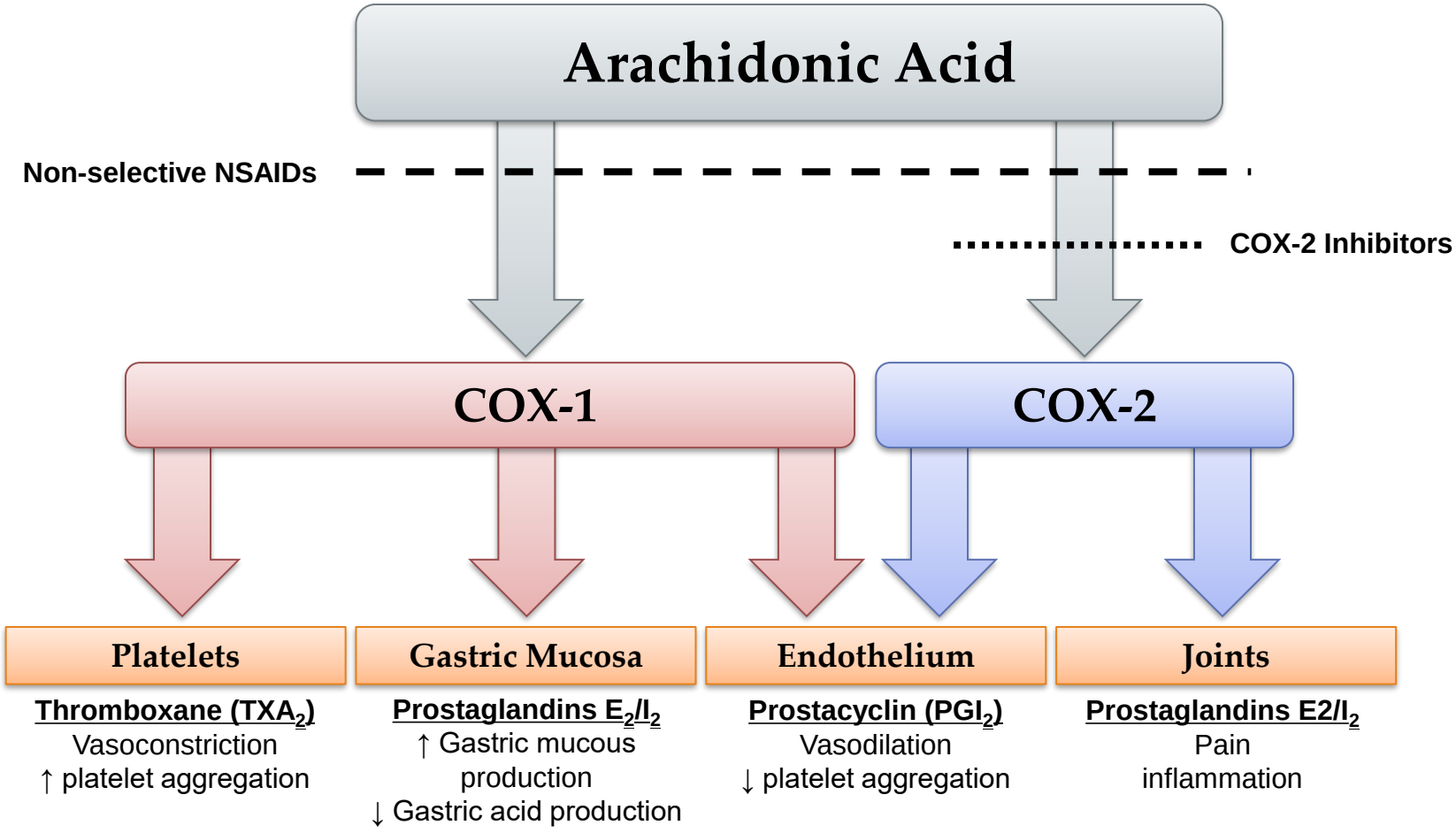
Classes of NSAIDs

- Propionic
  - Ibuprofen, naproxen, ketoprofen
- Acetic
  - Indomethacin, sulindac, tolmetin
- Salicylic (carboxylic)
  - ASA, sodium salicylate, salicylamide, diflunisal
- Anthranilic (enolic)
  - Phenylbutazone, piroxicam
- Pyrrolopyrroles
  - Ketorolac, etodolac
- COX-2 inhibitors
  - Celecoxib
  - Rofecoxib, valdecoxib—off the market

NSAIDs: The Biological Basis

- The analgesic, anti-inflammatory, and anti-pyretic properties of NSAIDs are mediated through their inhibition of COX enzymes
- NSAIDs have varying degrees of COX-1 and COX-2 selectivity
- Inhibition of COX-1 and COX-2 by NSAIDs is dose related

NSAID Mechanism of Action



Adapted from Atchinson J, et al. *J Manag Care Pharm.* 2013;19(9 Supp A): 1-19.

COX-1 Inhibitors

- Cyclooxygenase-1 is a “housekeeping” enzyme responsible for protective cellular functions within platelets, the stomach, and the kidneys

- COX-1 inhibitors can produce adverse effects associated with the inhibition of the COX-1 enzyme
  - These include increased bleeding time, ulcers, and impaired renal function

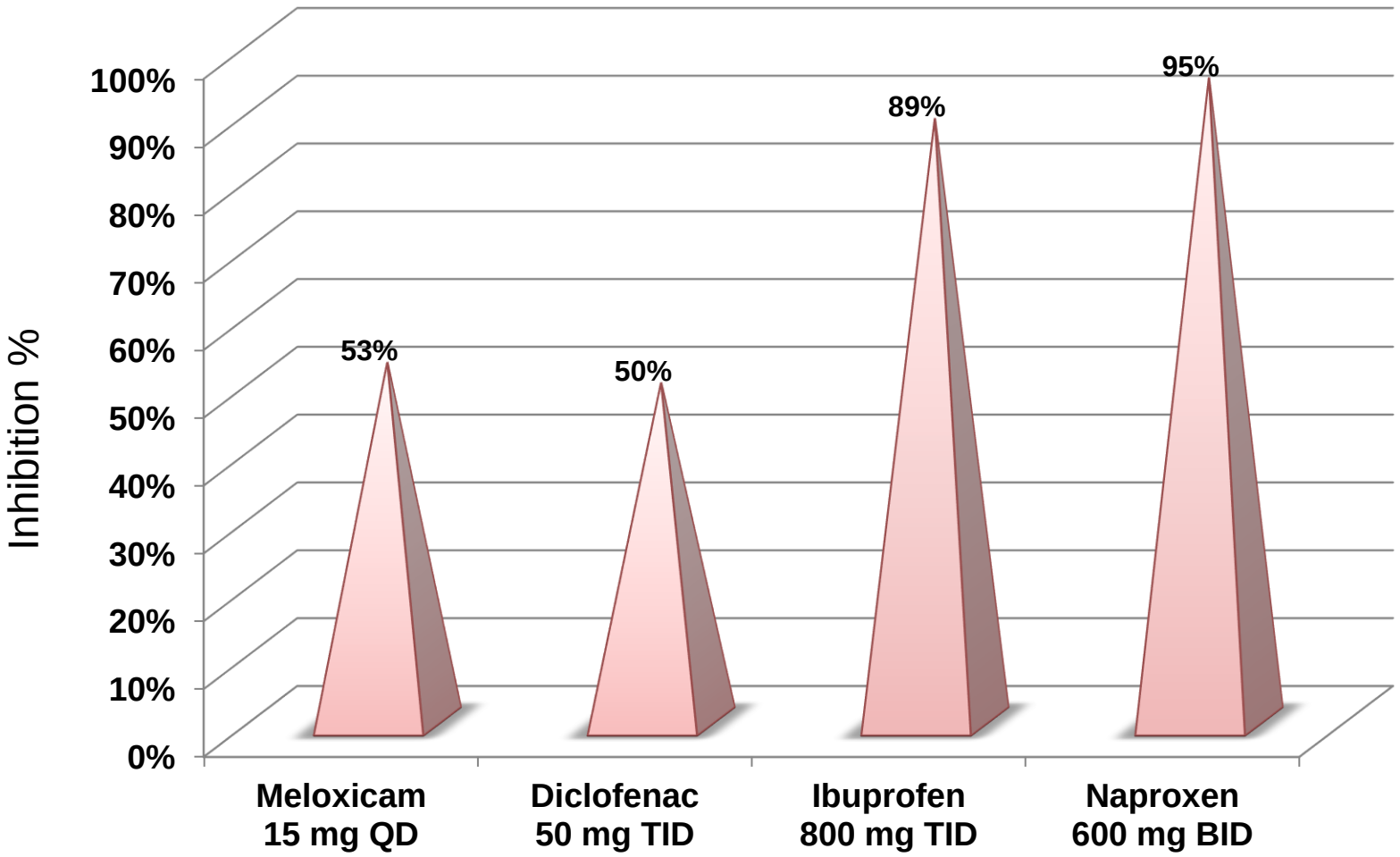
COX-2 Inhibitors

- Cyclooxygenase-2 is an enzyme that is responsible for the inflammatory response and mitogen activity (encouragement of cell division)
- COX-2 inhibitors can produce therapeutic effects associated with the inhibition of the COX-2 enzyme
  - Decreased pain and decreased inflammation
  - Prevention of multiple polyps in large intestine (polyposis)
- COX-2 inhibitors can produce adverse effects associated with the inhibition of the COX-2 enzyme
  - Heart attacks; strokes; and renal complications, including renal failure
- COX-2 inhibitors avoid many of the adverse effects associated with COX-1 inhibitors

COX-2 Inhibitors

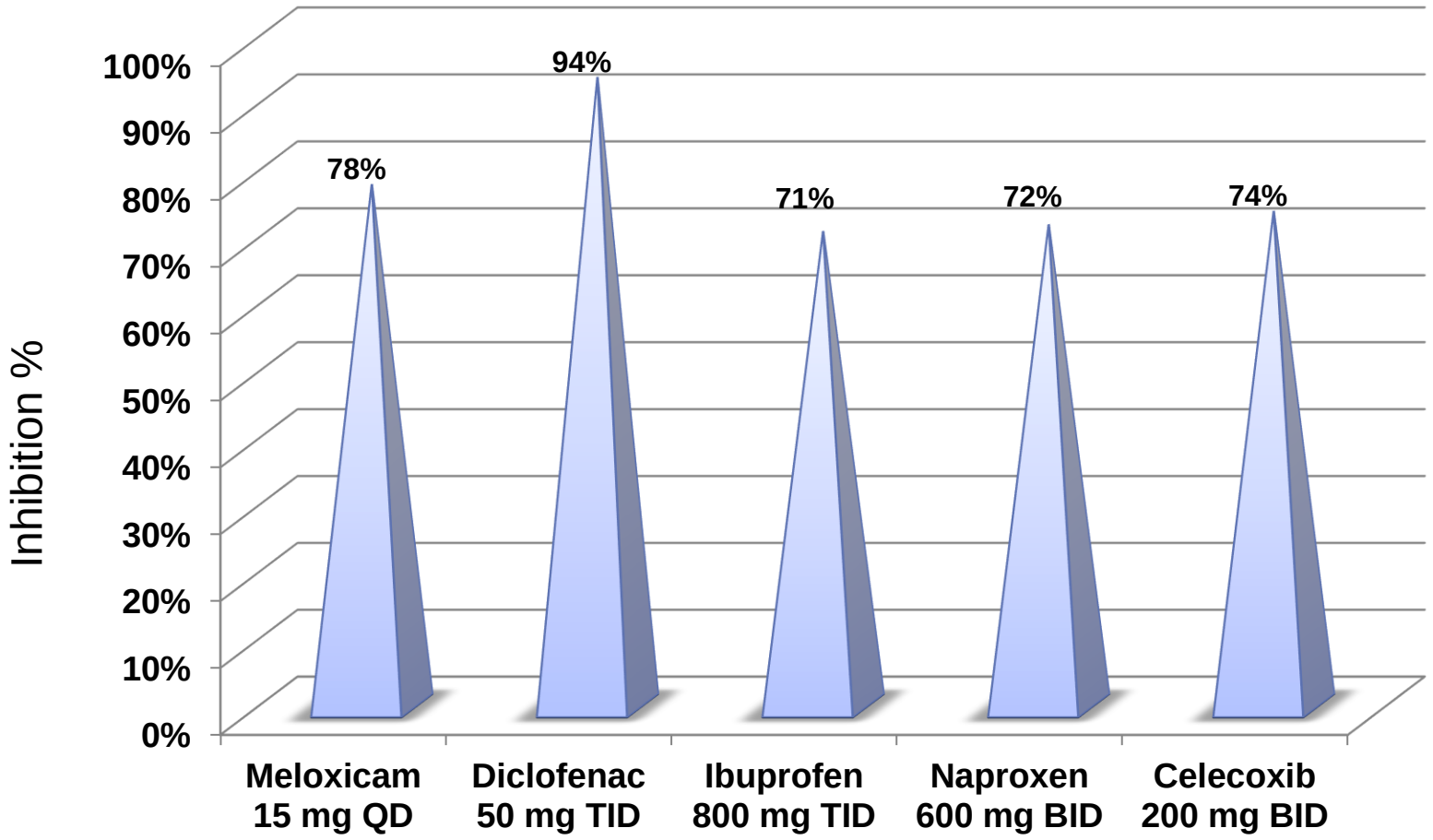
- Lack of inhibition of platelet aggregation
  - Protection from longer bleeding times
- Lack of effect on gastric mucosa
  - Protection from ulcers and GI bleeds
  - Combination with even low-dose aspirin (ASA) reduces this protection

Levels of COX-1 Inhibition



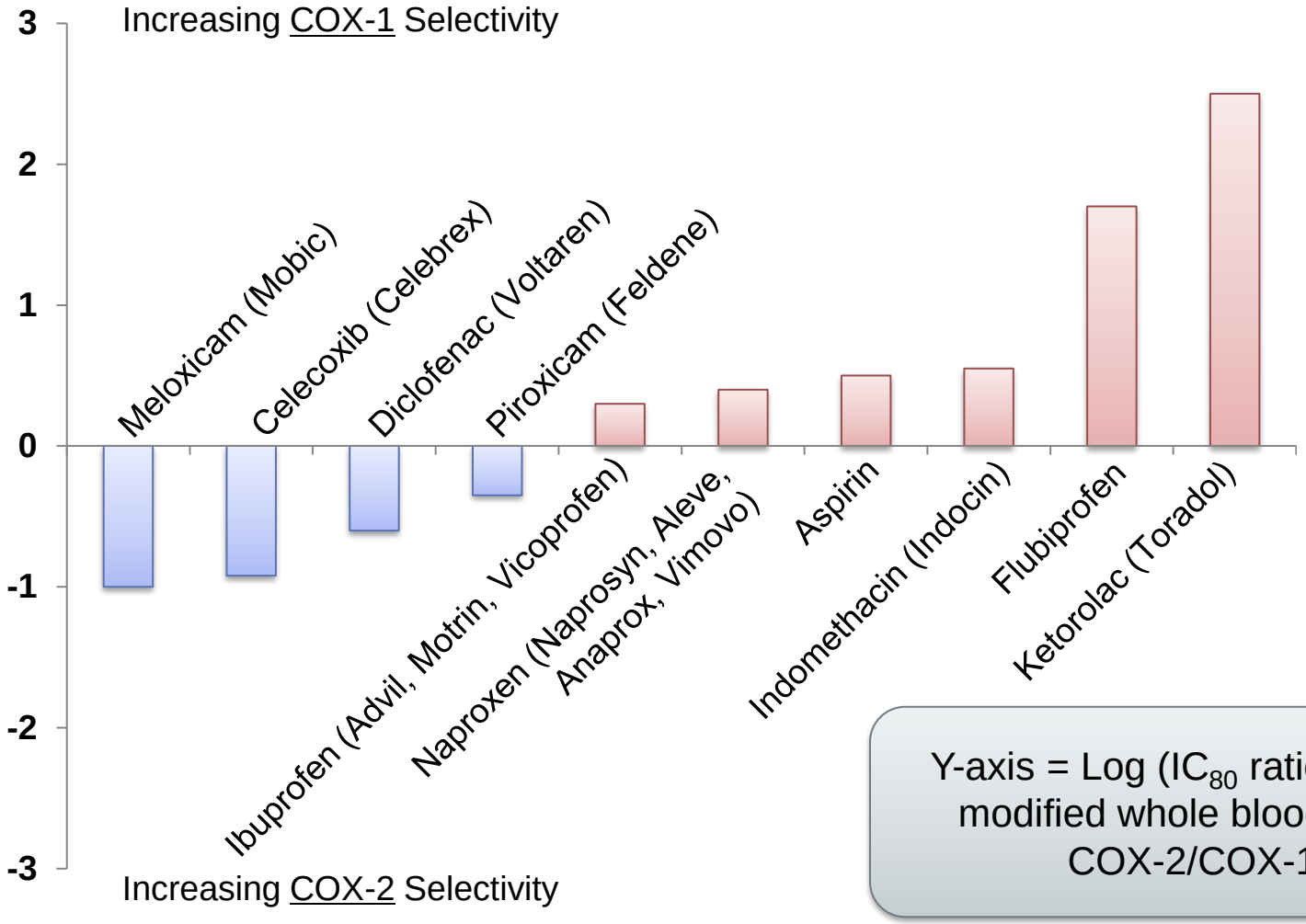
Reference: Van Hecken A, et al. *J Clin Pharmacol*. 2000;40(10):1109-1120.

Levels of COX-2 Inhibition[1,2]



References: 1. Van Hecken A, et al. *J Clin Pharmacol*. 2000;40(10):1109-1120. 2. Hinz B, et al. *Arthritis Rheum*. 2006;54(1):282–291.

Degree of COX Selectivity Among Common NSAIDs



Y-axis = Log (IC_{80} ratio, human modified whole blood assay COX-2/COX-1)

Adapted from Warner TD, et al. *Proc Natl Acad Sci U S A.* 1999;96(13):7563-7568, and from Atchinson J, et al. *J Manag Care Pharm.* 2013;19(9 Supp A): 1-19

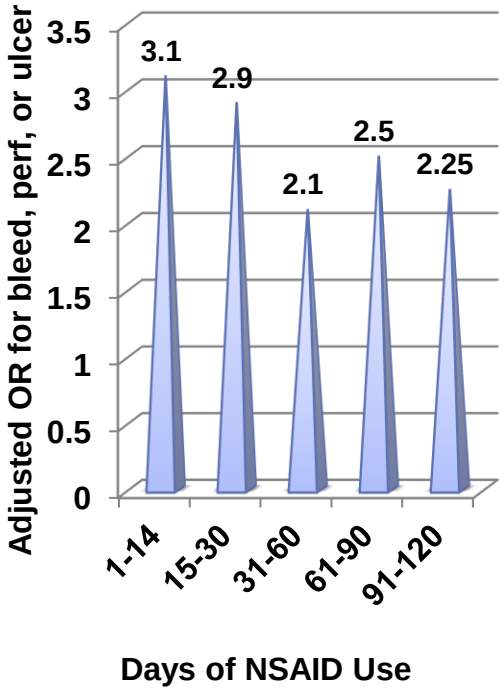
Other Actions of NSAIDs

- Blockade of voltage-dependent Na++ channels
- Positive allosteric modulation of K- channels (hyperpolarization and keeping them opened)

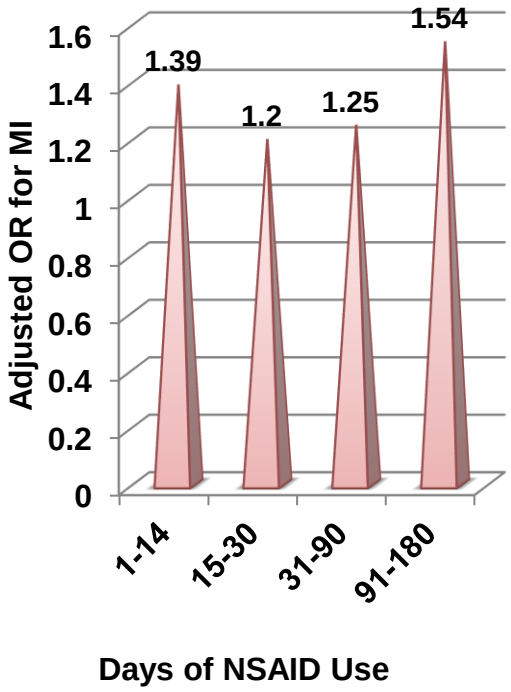
Note: Both mechanisms are associated with peripheral anesthetic effects, mirroring lidocaine action

Adverse Events with NSAIDs

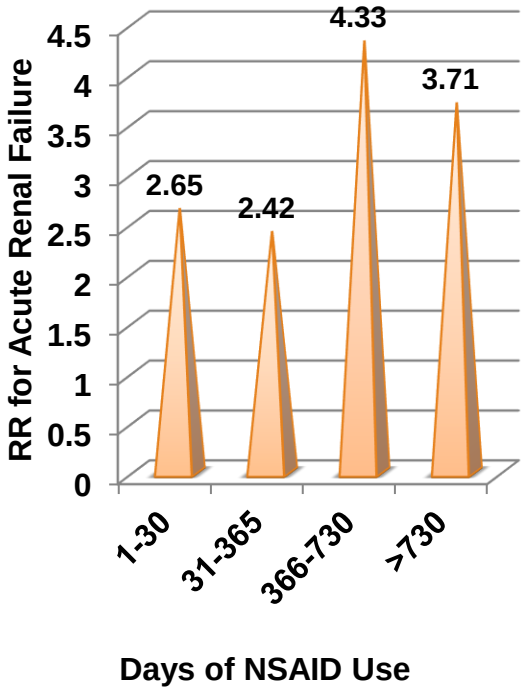
Gastrointestinal [1]



Cardiovascular[2]



Renal[3]



References: 1. Helin-Salmivaara A, et al. *Scand J Gastroenterol.* 2007;42(8):923-932. 2. Helin-Salmivaara A, et al. *Eur Heart J.* 2006;27(14):1657-1663. 3. Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.
Graphs adapted from Helin-Salmivaara A, et al, 2007, Helin-Salmivaara A, et al, 2006, and Huerta C, et al. 2005.

Basics of Risk

- Odds ratios were used in the previous slide to indicate the risks of having various adverse events with NSAIDs over time
- These odds ratios provide *estimates* of relative risks of adverse events with NSAIDs
- Relative risk is the ratio obtained by dividing the risk of an adverse event among those taking a medication by the risk of an adverse event among those not taking a medication

Reference: James R Miller, DDS, MSD, PhD, personal communication, August 2015

Basics of Risk

- Understanding the concepts of risk, relative risk (or odds ratio, as an estimate of relative risk), as well as excess risk form the foundation for understanding adverse effects associated with NSAIDs

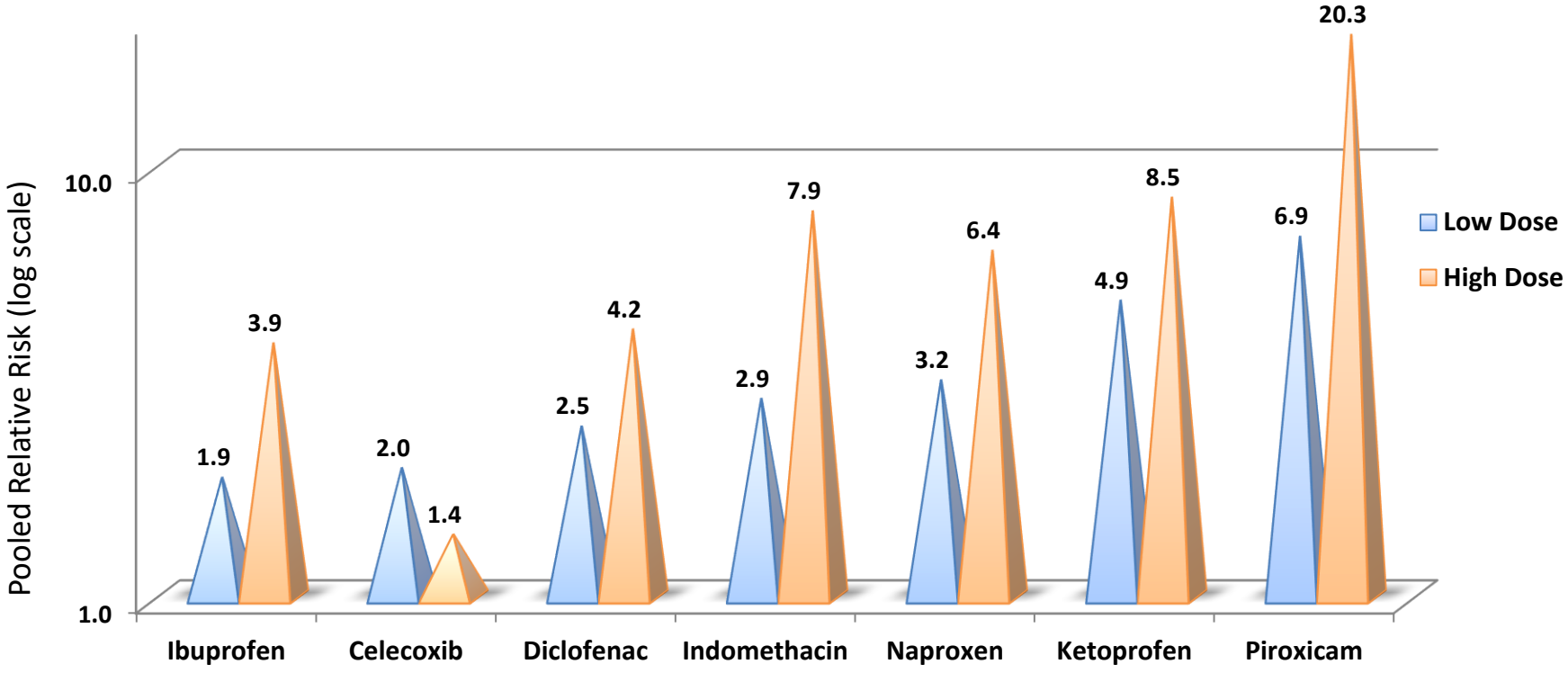
- Addendum B contains more information about these concepts for those who are interested
  - For this course, Addendum B is *optional* material

NSAIDs Adverse Effects and Time Considerations

- Not related to time:
  - GI events: Odds ratios for GI events remain about the same over time
  - CV events: Odds ratios for CV events remain about the same over time
- Possibly related to time:
  - Renal events: Odds ratios for renal events appear to increase over time

GI Risk of Individual NSAIDs by Dose

- In a recent systematic review of observational studies, the risk of NSAID-induced GI events (perforations, ulcers, bleeds) was generally shown to be dose related.



Castellsague J, et al. *Drug Saf*. 2012;35(12):1127-1146.
Graph adapted from Castellsague J, et al. 2012.

Note: The meta-analysis in Appendix B indicates that the RRs for diclofenac are likely less than in this slide, more in line with celecoxib (Dr. James R. Miller)

NSAIDs Adverse Effects that are Dose-Related

- GI events (upper GI)
  - Odds ratio (OR), which estimates relative risk (RR):

    x2.4 in low/medium dose

    x4.5 in high dose
- MI events (myocardial infarction is one type of CV event)
  - Odds ratio (OR), which estimates relative risk (RR):

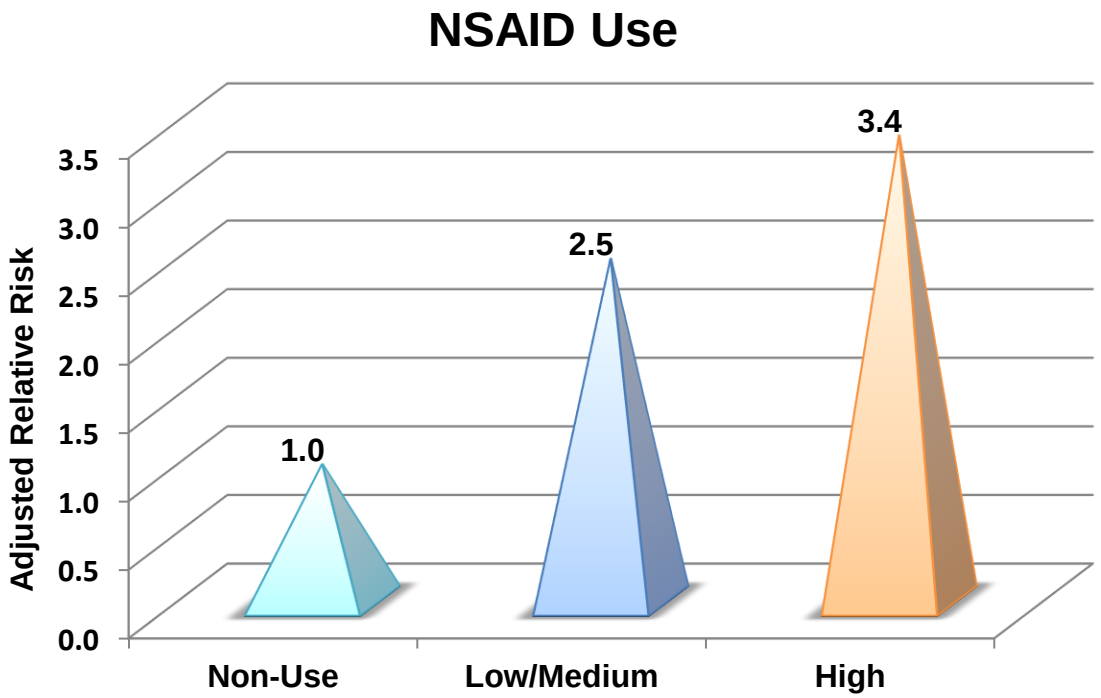
    x1.2 in low dose

    X1.6 in high dose

Note: From these data, a GI event appears to be more dose-related than a MI event (Dr. James R. Miller)

The Risk of NSAID-Associated Acute Renal Failure (ARF) May Be Dose Related

The Lower the Dose, the Lower the Risk



Reference: Huerta C, et al. *Am J Kidney Dis.* 2005;45(3):531-539.
Graph adapted from Huerta C, et al. 2005.

NSAIDs and Hypertension

No effect	ASA, sulindac (Clinoril)
Mild elevation	Celecoxib (Celebrex)
Intermediate elevation	Ibuprofen (Advil)
Significant elevation	Indomethacin, piroxicam (Feldene), naproxen (Naprosyn, Aleve)

J Clin Hypertens. 2000;2:319-323.

NSAIDs Adverse Effects

GI

- 60 – 80% of gastrointestinal bleeds are silent

CV

- NSAIDs have an FDA class warning that includes a risk for CV adverse effects
- Among NSAIDs, naproxen is generally considered the safest NSAID for patients at risk for cardiovascular adverse effects

Additional Adverse Effects

- Mental—Irritability, anxiety, psychosis
- Menstrual disturbance
- Hemolytic anemia (induces antibodies to Rh antigen)

Common but Frequently Overlooked NSAIDs Adverse Effects

- Fluid retention and edema
- Exfoliative dermatitis, Stevens-Johnson Syndrome, and epidermal necrolysis
- Headache
- Dizziness
- Hot flashes
- Syncope

NSAIDs and Pregnancy

Important Notes

- Caution should be exercised in prescribing NSAIDs during the 1st and 2nd trimesters
- **NSAIDs contraindicated in the 3rd trimester**

NSAIDs: Drug Interactions

Classes of drugs that can potentially interact with NSAIDS:

- Angiotensin converting enzyme inhibitors (ACE inhibitors)
- Anticoagulants
- Angiotensin receptor blockers (ARBs)
- Beta-blockers
- Lithium
- Loop diuretics
- SSRIs

Historical Approaches to Mitigate NSAID Risk[1-4]

Enteric Coating	Pro-Drug (ex: nabumetone)	NSAIDs + Gastro-protective Agents	COX-2 Inhibitors	Topical NSAIDs
Potentially reduce upper GI events but do not protect against lower GI, CV, or renal events			May reduce GI events but potential to increase CV and renal risks	Localized delivery but may have limited utility depending on location of pain

Lowering the Dose While Offering Efficacy Offers a Promising Approach

References: 1. Castellsague J, et al. *Drug Saf*. 2012;35(12):1127-1146 2. García Rodríguez LA, et al. *J Am Coll Cardiol.* 2008;52(20):1628-1636. 3. Zhang J, et al. *JAMA*. 2006;296(13):1619-1632. 4. RTI Cost Effectiveness Report. Iroko Pharmaceuticals, LLC.

Strategies for Mitigating Risk

Avoid Using NSAIDs in High-Risk Patients

Avoid in high-risk patients such as the elderly and those with congestive heart failure, coronary artery disease, hypertension, renal insufficiency, and cirrhosis of the liver

Strategies for Mitigating Risk

Use Minimum Dose Necessary

- Need IC 50-80 to block pain
- Diclofenac 75mg BID = 99% COX-2 inhibition

Strategies for Mitigating Risk

NSAIDs with Shorter T-1/2 Are Safer

A shorter half-life is generally associated with a decreased risk of GI adverse effects

Short T-1/2

- 2h Diclofenac (Voltaren)
- 2-6h Ketorolac (Toradol)
- 3-4h Ibuprofen (Advil, Motrin)

Long T-1/2

- 12-17h Naproxen (Aleve, Naprosyn, etc.)
- 15-20h Meloxicam (Mobic)
- 50h Piroxicam (Feldene)

Note: In addition to half-life, the risk associated with a particular NSAID can be influenced by its dosage, its duration of use, and its relative selectivity for the COX-1 versus COX-2 enzymes

Strategies for Mitigating Risk

Be Cautious Combining Medications

- Combo of NSAIDs and ASA significantly increases GI risks (need 2h break in between doses of NSAID and ASA)
- Avoid drug interactions by knowing potential interactions and taking a good history of medications

July 2015

- FDA strengthens its warning about Motrin, Advil, and Aleve
- The over-the-counter drugs can cause serious side effects that can occur as early as the first few weeks of using the temporary pain relievers, the agency said
- “There is no period of use shown to be without risk,” Dr. Judy Racoosin, deputy director of FDA’s Division of Anesthesia, Analgesia and Addiction Products, said in a statement
- People who have cardiovascular disease, particularly those who recently had a heart attack or cardiac bypass surgery, are at the greatest risk

*Note: Among patients with cardiovascular disease, **naproxen** is considered the safest NSAID*

Reference: *Lydia Wheeler “The Hill” 07/10/15 10:37 AM EDT

Suggested NSAIDs

For patients with high blood pressure

- Preferred use of sulindac, celecoxib
- Avoid naproxen, ibuprofen, indomethacin, piroxicam

Suggested NSAIDs

For patients with vascular risk (MI, strokes)

- Preferred use of naproxen
- Avoid ibuprofen, diclofenac, celecoxib

Suggested NSAIDs

For patients with GI, kidney, or bleeding problems

- Preferred use of meloxicam, diclofenac, celecoxib
- Avoid ketorolac, indomethacin, ibuprofen, naproxen, ketoprofen, piroxicam

Ibuprofen is found to be safest for Chinese kidney patients

- Effect of the 9 oral NSAIDs on kidney function examined in a retrospective cohort of 1,982,488 Chinese individuals in Hong Kong aged 18 years or older with an eGFR higher than 60
- 71% increased risk of incident eGFR less than 60%, 93% increased risk of an eGFR decline of 30% or greater, and 88% increased risk of the composite of either outcome compared with no NSAID use
- Ibuprofen was the safest NSAID, conferring a significant 12% increased risk of incident eGFR less than 60, 32% increased risk of an eGFR decline of 30% or greater, and 34% increased risk of the composite outcome.

Wan EYF, Yu YET, Chan L, et al. Comparative risks of nonsteroidal anti-inflammatory drugs on CKD. Clin J Am Soc Nephrol. Published online April 28, 2021. doi:10.2215/CJN.18501120

Use of NSAIDs in Pregnancy

Do not use NSAIDS in 3d trimester of pregnancy

New Options

- As of April 2020, an IV formulation of meloxicam is available for treatment of moderate to severe pain
- Marketed under brand name Anjesto
- 30mg IV push over 15 sec
- May be done daily for 5-7 days
- Due to high affinity to COX-2 receptor meloxicam is not associated with prolonged bleeding time

New Options

- On May 5, 2020, The Food and Drug Administration (FDA) has approved Elyxyb (Dr. Reddy's Laboratories), an oral solution formulation of celecoxib, for the acute treatment of migraine with or without aura in adults.
- **Off label** use in pain, including dental pain
- Supplied as a clear, colorless oral solution that contains 25mg of celecoxib per mL (120mg/4.8mL). The maximum dosage in a 24-hour period is 120mg.
- Formulated using a self-micro emulsifying drug delivery system that improves solubility and bioavailability of the drug leading to better absorption.
- Demonstrated a rapid onset of action