Objectives

- Review the basic and clinical pharmacology of NSAIDs related to their use as analgesics
- Recognize the potential risks from use of NSAIDs or acetaminophen and options to reduce those risks
- Discuss the rationale for use and various options available for adjuvant medications

Three-Step Analgesic Ladder (WHO Pain Relief ladder)

FDA Recommendations

- Patients should be offered evidence-based non-pharmacologic treatments:
  - Application of heat or cold, exercise, weight loss, or self-management programs
  - Topical NSAID or non-NSAID topical treatments
    - eg - capsaicin, methylsalicylate, topical anesthetics
- Oral NSAID regimens that minimize risk, using the lowest-risk agents - at the lowest effective dose - for shortest period of time.

Inflammatory Pain

Mediators induce hyperalgesia and ectopic activity in both injured and adjacent uninjured primary afferent nociceptors at the lesion site

The Role of Prostaglandins in Inflammation and Pain

Local Vasodilation
Hyperalgesia
Prostaglandins in the CNS

From periphery

PGs

Astrocytes / Microglial Cells

To brain

PGs reduce firing threshold of pre and post-synaptic pain neurons in the CNS – increase frequency of firing = “Hyperalgesia”

Inflammatory Pain

Quality
– Aching
– Throbbing
– Worse with movement

Clinical setting
– Postoperative
– Trauma
– Infection
– Arthritis

Physical findings
– Warm
– Red
– Swollen

Drug Management
NSAIDs
acetaminophen*
corticosteroids

* analgesic only

Sites of action for analgesics

Higher Centers
NSAIDs, opioids, acetaminophen

Spinal Cord
Opioids, NSAIDs acetaminophen?

Peripheral
NSAIDs

Inflammatory / nociceptive pain conditions

• RA
• OA
• Inflammatory arthritis, AS, psoriatic arthritis
• Acute gout
• Metastatic bone pain
• Muscle trauma
• Sprains, strains, contusions, bruises, overuse, etc
• Dysmenorrhea
• Headache (migraine?)
• Postoperative pain
• Ileus
• Renal colic

Pharmacology of NSAIDs

COX-1 vs COX-2

COX-1

PGE
PGD
PGF
TxA

COX-2

PGE
PGI
### Physiological Roles of COX-1 & COX-2

- **COX-1 (PGE$_2$)**
  - Gastric protection
  - Mucous secretion
  - Bicarbonate
  - Mucosal blood flow

- **COX-1&2 (PGE$_2$ & PGI$_2$)**
  - Afferent arteriole
  - Vasodilatation (↑GFR)
  - ↑ Na & H$_2$O excretion

- **COX-1&2 (TxA$_2$ & PGI$_2$)**
  - Vascular (COX-2 – PGI$_2$)
  - Vasodilatation
  - Inhibits platelet aggregation

### Pathophysiological Role
- COX-2 is “inducible” in proliferative states (inflammation, neoplasia, etc)
- COX-2 derived PGE and PGI play role in vasodilation, hyperalgesia, angiogenesis

### Common Pharmacological Effects
- Inhibit both COX1 & COX2
- Weak organic acids
- Highly protein bound (~ 96 – 99% to Albumen)
- Analgesic (CNS and peripheral effect)
- Antipyretic (CNS effect)
- Anti-inflammatory due mainly to PG inhibition
  - Low doses – central analgesia + antipyretic effect
  - High Doses – anti-inflammatory
- Same set of common side effects
- Differ only in potency, duration, selectivity for COX-1 or COX-2, cost

### Efficacy of NSAIDs
- Approx 60% of patients will respond to any NSAID
- Those who do not respond to one may well respond to another.
- Pain relief starts from the first dose, with full analgesic effects obtained within a week.
- May be “ceiling effect” for NSAIDs re: analgesia
- Anti-inflammatory effects may not be achieved for up to three weeks.
- Higher doses may correlate with greater anti-inflammatory effects

### NSAIDs Contraindications
- Hypersensitivity to ASA or other NSAIDs
- Uncontrolled heart failure
- Active gastric/duodenal/peptic ulcer
- Cerebrovascular bleeding
- Severe hepatic impairment
- Severe renal impairment (CrCl <30 mL/minute)
  - deteriorating renal disease; known hyperkalemia;
- Breast-feeding; pregnancy (third trimester)
- Coronary artery bypass graft (CABG) surgery

### NSAID Side Effects
- Gastrointestinal (dyspepsia, peptic ulcers, GI bleeding)
- Cardiovascular (MI, stroke, HTN, HF)
- Renal (acute renal injury, Na* / fluid retention)

#### Less Common
- Hepatic
- CNS (confusion, vertigo, tinnitus)

#### Low likelihood (in adults)
- Allergy / Bronchospasm (esp in asthma)
- Reye’s syndrome (ASA only)
- Rash

### Relative selectivity of common NSAIDs

### NSAIDs Contraindications
**GI Risk**
- Relative risk for GI bleed or perforation increases ~4X in pts who use NSAIDs vs those who don’t
- Risk factors include:
  - Age over 65
  - History of GI bleed or ulcer
  - Concurrent use of drugs that increase the risk of GI adverse events – K+ or Fe++ salts, bisphosphonates, tetracycline, etc
  - Heavy smoking or alcohol use
  - High doses / prolonged use
  - Select NSAIDs
  - Serious co-morbidity

**Cardiovascular Risk**
- Risks
  - Hypertension, heart failure, MI, stroke, death (to varying degrees) **even in healthy people.**
- Proposed Mechanisms
  - NSAID-associated HF - due to increased peripheral vascular resistance and reduced renal perfusion caused by PG inhibition.
  - MI / Stroke – imbalance between platelet thromboxane A2 (vasoconstriction produced by COX-1) and vascular endothelium produced PGI2 (prostacyclin produced by COX-2)
  - NSAIDs that are the safest from a CV standpoint tend to have higher GI toxicity and vice versa.

**Increased Risk of MI / Stroke**
- Low-dose AA- inhibits platelet COX-1 (irreversible)
- COX-2 Inhibition – Reduces antiplatelet PGI2 in endothelium
- No decrease in platelet TxA2 synthesis

**Nephrotoxicity**
- Risk factors for acute kidney injury include:
  - Older age, diabetes, renal insufficiency, HF
  - NSAIDs can increase blood pressure, cause fluid retention, and worsen renal function in above
  - Patients with HTN, NSAID use ≥3 months (~30%) more likely to develop CKD vs nonusers
  - In high-risk patient (including those taking an ACEI, ARB, or diuretic), check serum creatinine and K+ weekly for several weeks
  - Monitor renal function
  - Avoid NSAIDs with t½ > 12 hours (ie., ketorolac, nabumetone, naproxen, meloxicam or piroxicam)

**Nephrotoxicity**
- Mechanism
  - NSAIDs reduce blood flow to the glomerulus by inhibiting production of vasodilating prostaglandins

**Balancing the Risk of all NSAIDs**
- NSAID medication selection should consider both the individual patient's GI and CV risk profile
Reducing GI Risk

- Lowest dose that provides benefit
- Shortest amount of time
- Use of gastroprotective drugs:
  - PPIs, Misoprostol
  - H2 Blockers (high dose)
  - Long term PPI use risky in elders
- Remember to DC PPIs

Reducing Cardiovascular Risk

- For patients with CV disease or risk factors for ischemic heart disease
- Consider acetaminophen, aspirin or other salicylates, tramadol, IR opioids (short-term) before moving to an NSAID
- Consider adding aspirin 81 mg and a proton pump inhibitor in patients with increased CV risk
- Monitor renal function and blood pressure. Watch for edema and GI toxicity
- Post MI - there does not seem to be a safe time frame for using an NSAID

Cardiovascular Risk

NSAIDs increase cardiovascular risk in those with and without a history of known cardiovascular disease

- Both selective & nonselective NSAID use associated with increased risk of CV events such as ischemic CV disease and heart failure.
- This effect all in drugs seems to be both dose and time dependent.
- Low dose NSAIDs:
  - Ibuprofen ≤ 1200 mg daily
  - Diclofenac ≤ 100 mg daily
  - Naproxen ≤ 500 mg daily
  - Celecoxib ≤ 200 mg daily

Summary – ACC, AHA, and ACR

- Discourage use of all NSAIDs in patients with chronic heart failure
- Recommend against use of NSAIDs, particularly COX-2 inhibitors, in patients with established CV disease
- Recommend NSAIDs be avoided in patients taking aspirin for cardioprotective benefit
- If treatment becomes necessary in ASA patient, ibuprofen should be avoided (insufficient data to assess other NSAIDs)
- If the patient is at moderate to high risk of a potential cardiovascular event and treatment becomes necessary then initial management should be attempted initially with acetaminophen rather than naproxen

NSAID / Aspirin Interaction

- Competition between some NSAIDs and ASA for binding to COX-1 in platelet
- Appears ibuprofen worst culprit
- Recommended:
  - Avoid ibuprofen or take immediate release aspirin 1-2 hrs before
  - may not be possible to avoid the interaction if ibuprofen is taken more than once daily.
  - Avoid enteric-coated ASA if using NSAIDs
  - Also use IR NSAIDs
  - Naproxen may be a better choice with ASA
  - Little is known about other NSAIDs and ASA platelet interactions

Safety Comparison of NSAIDs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COX-2 Selectivity</th>
<th>GI RISK</th>
<th>CV RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>High</td>
<td>Low</td>
<td>Moderate to High</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Etodolac</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate to High</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Low</td>
<td>Moderate to High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Low</td>
<td>High</td>
<td>Data not available</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Moderate</td>
<td>Low</td>
<td>Data not available</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Low</td>
<td>Moderate</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Unavailable</td>
<td>Low</td>
<td>Data not available</td>
</tr>
</tbody>
</table>
Summary Recommendations

<table>
<thead>
<tr>
<th>Low GI risk</th>
<th>Moderate GI risk</th>
<th>High GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV risk</td>
<td>Celecoxib or other low-GI risk NSAID (see previous table)</td>
<td>1. Celecoxib alone</td>
</tr>
<tr>
<td></td>
<td>2. Other NSAID plus PPI (misoprostol, or 2X-dose H2-blocker (second line)</td>
<td>2. Celecoxib plus PPI (or misoprostol)</td>
</tr>
<tr>
<td>High CV risk</td>
<td>Naproxen* or low-dose celecoxib (if on aspirin, naproxen plus GI protection)</td>
<td>1. Naproxen* PPI, misoprostol or 2X-dose H2-blocker</td>
</tr>
</tbody>
</table>

* Limit to 500 mg BID

---

Topical NSAIDs for acute musculoskeletal pain in adults: Cochrane Review June 2015

- Review of 61 studies of topical NSAID
  - Good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral NSAIDs.
  - Gel formulations of diclofenac, ibuprofen, ketoprofen, and some diclofenac patches, provided best effects. (NNT < 4)
  - Topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success (≥ 50% pain relief) v. topical placebo (moderate or high quality data)
  - Local skin reactions are most common - generally mild and transient

---

Topical NSAIDs

- Peak plasma concentration 0.2 – 8% of concentrations observed with oral dosing
- Tissue concentrations (∴., meniscus, tendon sheath) from 4 - 100 times greater than that observed from oral dosing
  - Tmax about 10x longer vs PO ranging from 2.2 – 23 hrs.
  - With multiple topical doses, steady state is achieved within 2–5 days, and C_{max} is about 2.5 times higher than C_{max} following a single topical dose
  - Still carry FDA same warning regarding all NSAIDs??!!

---

Another thing to consider - NSAID Clearance

- CYP2C9 metabolizes many NSAIDS
  - celecoxib, ibuprofen, naproxen, diclofenac, meloxicam, piroxicam
  - Inhibitors of CYP2C9 may increase risk of NSAID-related SEs.
    - Fluconazole, voriconazole, metronidazole, amiodarone, cotrimoxazole
  - Especially in genetically poor metabolizers- 3 – 16% caucasian

---

Acetaminophen – Possible Mechanism(s)

1. Enhances endocannabinoids
2. Inhibition of COX (1, 2 or 37)
3. TRPV1 agonist / desensitizer
**Acetaminophen – Possible Mechanism(s)**

Example: Spinal cord. Descending NA input (antinociceptive) from the brainstem usually under inhibitory control by GABA.

Cannabinoids modulate activity by reducing GABA release freeing NA neurons to more freely release NE in Dorsal horn and ganglia – net result – attenuation of incoming pain signals.

**Is acetaminophen effective?**

Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials

*BMJ 2015;350:h1225*

- High quality evidence that "Tylenol" ineffective in treating low back pain or disability.
- Found evidence that acetaminophen quadruples risk of having abnormal LFT
  - but clinical significance of that finding unclear
- Studies of pain from knee and hip arthritis found small but clinically insignificant short-term pain-relief effect for acetaminophen compared with a placebo.

**Acetaminophen Toxicity**

Why is FDA limiting the maximum strength of acetaminophen in oral prescription products?

- By limiting the maximum amount of acetaminophen in oral prescription products to 325 mg per tablet, capsule, or other dosage unit, patients will be less likely to overdose on acetaminophen if they mistakenly take too many doses of acetaminophen-containing products.
- Under new dosage limit, HCPs can direct patients to take 1 or 2 tablets (etc) of a prescription product containing 325 mg of acetaminophen up to 6 times a day (12 dosage units) and still not exceed the maximum daily dose of acetaminophen (4000 mg).

**Adjuvant Agents**

- Defined as drugs with other indications that may be analgesic / antinociceptive in specific circumstances
- Not really classified as “analgesic”
- Many used in "neuropathic pain" conditions
  - However – most, if not all, chronic pain conditions have an neuropathic component

**Adjuvant agents**

- Multi-purpose analgesics???
  - Neuropathic pain
  - Musculoskeletal pain
  - Cancer pain
  - Headache
  - Typically not effective for acute pain !!!
  - Lower doses may be effective compared to their primary indications
  - Used alone or in combinations with other analgesics
  - Good potential for synergy
Adjuvant Medication Classes

- Antidepressants
  - TCA, SSRIs, SNRIs
- Antiepileptics
- Local anesthetics
- Topicals
  - Muscle relaxants
  - Corticosteroids

Antidepressants and Descending Pathways

The Role of Antidepressants

Antidepressants
• Pain reduction independent of antidepressant effect
• Benefit (if effective) will often occur earlier (days–few weeks) vs antidepressant action (4 – 8 weeks)
• Analgesic effect has been classically attributed primarily to inhibition of reuptake of NE >> 5HT
  – Involvement of 5HT varies with the type of pain
• Serotonin elevation appears to be the primary mechanism for acute analgesic effects of class??
• Norepinephrine elevation plays more critical role in chronic pain states

Tricyclic Antidepressants (TCAs)

Amitriptyline, Nortriptyline, others

Multiple Mechanisms:
1. Block reuptake of NE & 5HT
2. NMDA receptor antagonism
3. Blockade of voltage gated Na⁺ channels
4. Neuromodulatory effect on opioid systems
5. alpha-adrenergic blockade

Tricyclic Antidepressants (off-label)

Potential Advantages
- Low dose – less side effects
- Sedation may be helpful in some cases
- Both 2nd and 3rd TCAs effective – multiple choices

Adverse effects
- Anticholinergic
- Sedation
- Orthostatic hypotension
- Weight gain
- QRS, QTc prolongation

Amitriptyline
25 - 50 mg qhs; may increase as tolerated to 150 mg daily
Nortriptyline
10 - 25 mg qhs; increase as tolerated (q3d) up to 150 mg daily
SNRIs - All Block reuptake of both NE and 5HT
May not be as effective as TCAs ??
- Duloxetine (neuropathy, musculoskeletal pain)
  Range 30 – 60 mg once daily
- Milnacipran (approved for fibromyalgia)
- Levomilnacipran (not labelled for pain)
- Venlafaxine (not labelled for pain)
Common Side effects:
- dizziness, nausea, dry mouth, sweating, tiredness, insomnia, anxiety, constipation, difficulty urinating, headache, loss of appetite, loss of libido, anorgasmia
- Caution - Serotonin syndrome (interactions)

Notes on Antidepressants for Pain
In a number of studies comparing antidepressants for neuropathic pain – effectiveness ranks:
- TCA (NNT = 2-3) > SNRI (NNT = 4-5) > SSRI (NNT = 7+)
- Duloxetine cleared partially by CYP1A2 – smokers (tobacco / cannabis) have higher levels of 1A2 and clear duloxetine almost 2x faster than non-smokers.
- Remember – all antidepressants regardless of use have boxed warning regarding increased risk of suicidal ideation

Antiepileptics & pain
• Periphery / CNS – hyperalgesic state = increased frequency of 1st afferent firing (Na+ flux)
• Certain antiepileptics block central (and peripheral) voltage-dependent Na+ channels
  - carbamazepine
  - phenytoin
  - valproate
  - topiramate
  - lamotrigine
- All off-label for neuropathic pain
Also reduce release/action of excitatory neurotransmitter glutamate

Antiepileptics & pain
• Voltage-gated calcium channels on presynaptic pain neurons in spinal cord regulate release of excitatory neurotransmitters – glutamate, substance P, etc.
Ca++ entry necessary for vesicle fusion and release of neurotransmitters
Gabapentin and Pregabalin block subunit of those channels
- Decrease ascending afferent activity
- May also enhance descending pathways

Comparing Gabapentin and Pregabalin

<table>
<thead>
<tr>
<th></th>
<th>GABAPENTIN</th>
<th>PREGABALIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Onset, Peak (Tmax)</td>
<td>1-3 hr</td>
<td>~ 25 min</td>
</tr>
<tr>
<td>3 – 4 hrs</td>
<td>1 hr</td>
<td></td>
</tr>
<tr>
<td>Bioavailability (AUC)</td>
<td>35 – 55%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>- dose-dependent</td>
<td>- dose-independent</td>
<td></td>
</tr>
<tr>
<td>- decreases at higher doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Plasma concentrations</td>
<td>Non-linear / unpredictable</td>
<td>Linear / predictable</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>&gt; week</td>
<td>1 – 2 days</td>
</tr>
<tr>
<td>Hepatic</td>
<td>No metabolism</td>
<td>No metabolism</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>Adjust at CrCl &lt; 60ml/min</td>
<td>Adjust at CrCl &lt; 60</td>
</tr>
<tr>
<td>Controlled</td>
<td>No</td>
<td>Schedule V</td>
</tr>
</tbody>
</table>

Notes on Gabapentin & Pregabalin
• 2° benefits for pain pts - may help with anxiety / sleep
• Side Effects: dizziness - fatigue – somnolence - weight gain - drowsiness - peripheral edema – cognitive effects
• Gabapentin approved for postherpetic neuralgia only - all other pain-related uses are off-label
  - available as generic & as extended-release (Gralise)
• Pregabalin approved for neuropathic pain (associated with diabetes & spinal cord injury), postherpetic neuralgia, fibromyalgia
  - Pregabalin generics ? – will be a lag between generics approved for treating epilepsy and for treatment of peripheral and central neuropathic pain – based on "second medical use patent"
Topicals - Capsaicin
- OTC topical creams and ointments commonly used for treating arthritis and other painful conditions contain low concentrations (typically .025 to .075%)
- Stimulates TRPV1 receptors (heat and pain nociceptors)
- Causes metabolic depletion of neuropeptides (substance P)
  – also desensitizes nociceptors (against thermal, mechanical & chemical stimuli)
- Applied 4-5 times a day for days - weeks
- Compliance may be a problem
- Side effects
  • pain at the site of application

Topicals - Lidocaine Patch
- 5% lidocaine in a non-woven polyester patch
- Local anesthetic effect – blocks Na⁺ channels
- Binds more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in neurons that are rapidly firing – i.e., pain fibers firing at higher frequency
- More effective on small unmyelinated axons (e.g. those carrying nociceptive impulses – C-fibers) and

Topicals - Lidocaine Patch
- Lidoderm:
  - Approved for postherpetic neuralgia
  - Up to 3 patches may be applied in a single application.
  - Patch(es) may remain in place for up to 12 hours in any 24-hour period.
- LidoPatch:
  - Approved for localized pain
  - May remain in place for up to 12 hrs in any 24-hr period.
  - No more than 1 patch should be used in 24-hr period.

Questions?

Thank you for attending.

Alan

aagins@gotpharm.com