Clinical Resource Guide: Nonopioid Analgesics

INTRODUCTION TO NONOPIOID ANALGESICS

Opioids are the most utilized analgesics for the management of pain in the palliative care and hospice settings. Available as immediate and sustained-release formulations, rapidly titratable (excluding methadone and transdermal fentanyl), low cost and accessibility of most commonly utilized agents, it is easy to understand why opioids would be a preferred starting point when managing pain in patients with a life-limiting illness. However, when pain is particularly difficult to manage, or opioid-induced side effects are impacting patient goals and/or quality of life, additional pharmacotherapeutic interventions should be considered. In addition to opioids, two other classes of medications are available to manage pain: **nonopioid analgesics** (acetaminophen, NSAIDs) and **adjuvant analgesics** (term used for medications originally brought to market for other reasons but found effective for the management of pain). This Pharmacist Corner was created to serve as a resource to hospice administrators and clinicians by providing guidance on the following:

Pharmacist Corner Objectives

1. Identify the role for acetaminophen in hospice agency pain management treatment plan
2. Understand the indications for nonopioid analgesics in the hospice setting.
3. Compare the safety and efficacy of available topical and systemic NSAIDs
4. Identify characteristics of nonopioid analgesics influencing prescribing decisions when developing a patient-specific
5. Determine appropriate dosing and monitoring strategies of NSAIDs prescribed for pain.

NONOPIOID ANALGESICS

Acetaminophen and NSAIDs comprise the class of medications referred to as nonopioid analgesics. While clinical evidence supporting the utilization of these agents in the hospice setting may be limited, there are many clinical scenarios in which a trial of a nonopioid analgesic is warranted to optimize a patient-specific pain need or to align with a goal of care.

Acetaminophen

The mechanism of action of acetaminophen is poorly understood. In theory, the analgesic effect may involve inhibition of prostaglandin formulation in the CNS. Unlike the NSAIDs, acetaminophen does not have anti-inflammatory properties. With a favorable side effect profile, acetaminophen may be a consideration for patients with mild-moderate pain and concern for opioid tolerability. However, there is limited evidence supporting specific conditions in which acetaminophen is the analgesic of choice. Additionally, there is little anticipated opioid-sparing benefit when acetaminophen prescribed for a patient receiving ≥ 60mg morphine or equivalent dose/day

Acetaminophen Considerations	
Starting dose and titration	325mg-650mg po every 4 hours prn pain
Patient with hx of hepatic dysfunction	50-75% daily dose reduction
Patient drinking > 2 oz liquor, 8 oz 2 beers,	2500mg/24 hours
Contraindications	APAP allergy, chronic alcohol use/abuse

Acetaminophen Dosing Recommendations				
Age Group	**Q4H Dose**	**Q6H Dose**	**Max Single Dose**	**Max Daily Dose**
Adults (>50kg)	650mg	1000mg	1000mg	4000mg in 24 hrs
<13 years old (<50kg)	12.5mg/kg	15mg/kg	15mg/kg (up to 750mg)	75mg/kg in 24hrs (up to 3750mg)

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs have analgesic, anti-inflammatory, and antipyretic effects. Evidence supports benefit as monotherapy and when used in combination with opioids, especially in the palliative care and hospice settings. NSAIDs may be of particular benefit in patients with bone pain or pain related to inflammatory lesions. However, limited efficacy has been demonstrated in patients with neuropathic pain.

Mechanism of Action

Analgesia is produced by inhibiting the enzyme cyclooxygenase (COX) in the periphery and the CNS, which results in decreased tissue concentration of central and peripheral prostaglandins via interruption of synthesis. There are two COX isoforms: COX-1 and COX-2. COX-1 is essential for the production of prostaglandins necessary for gastric and duodenal protection, enhanced GI mucosal blood flow and promotion of epithelial cell reproduction. COX-2 is necessary for the synthesis of prostaglandins that activate and sensitize nociceptors, increasing nerve impulse activity, but are not as prevalent throughout the entire body.

NSAID Side Effect Profile

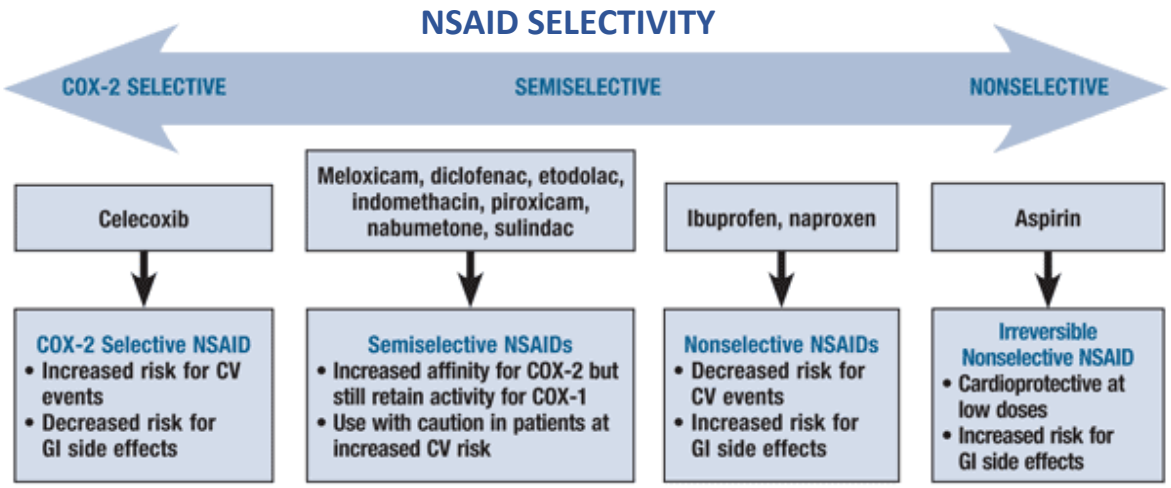
Gastrointestinal	• NSAIDs increase the risk of GI side effects, ranging form pain, nausea or gastric esophageal disease to ulceration and/or bleeding. • NSAIDs developed to more specifically inhibit the COX-2 enzyme have been shown to result in fewer GI side effects.
Renal	• Inhibition of COX-1 interferes with prostaglandin formation essential to maintaining kidney health. Use of nonselective NSAIDs can result in decreased renal clearance
Cardiovascular	• NSAIDs have the potential to produce cardiovascular toxicities, including fluid retention, increased risk for thrombotic event, and increased blood pressure.

NSAID Indications in the Hospice Setting

- Neoplasm-related pain with metastases to bone
- Neoplasm-related pain with metastases to liver
- Acute, inflammatory process(es)

NSAID Considerations

- Limited guidance regarding minimal effective NSAID dose, agent specific
- Creation of NSAID monitoring plan essential for safe and effective assessment of efficacy and tolerability
- General principle for NSAID dose titration: 5-7 days
- Contraindications include:
  - Older adults with heart failure
  - Uncontrolled blood pressure
  - CKD/AKI



Perry, Laura A. et al. Cardiovascular Risk Associated with NSAIDs and US Pharmacist March 19, 2014

NSAID	Starting Dose	Max Daily Dose	Analgesic ½ Life	Estimated Cost/Dose	Additional Notes
Ibuprofen	400mg po q4-6hrs	3200mg	~2 hours	*Tablets* 200mg = $0.02 400mg = $0.07 600mg = $0.12 800mg = $0.10 *Liquid (100mg/5ml)* 200mg/10ml = $0.25 400mg/20ml= $0.50 600mg/30ml= $0.75 800mg/40ml = $1.00	• COX nonselective • 50-75% renally excreted • Good option for incidental/ breakthrough pain due to versatility with dosing frequency
Naproxen	250mg po BID	1500mg	~12-17 hrs	*Tablets* 250mg = $0.21 500mg = $0.11	• COX nonselective • 95% renally excreted • Good option for stable pain; half-life significant longer than ibuprofen
Meloxicam	7.5mg po QPM	15mg	~15-22hrs	*Tablets* 7.5mg = $0.51 15mg = $0.43	• COX-2 semi-selective • Dosed once/day, ideal for long-term care setting or patient with limited support
Celecoxib	100mg po BID	400mg	~11hrs	*Tablets* 100mg = $0.20 200mg = $0.41	• COX-2 selective • Fewer anticipated GI & renal side effects

Contraindications to NSAID Therapy

- Active anticoagulation therapy
- Active or recent GI bleed
- Renal insufficiency
- Diagnosis of heart failure

Topical NSAIDS: Diclofenac

- If a contraindication to oral NSAID therapy exists, the topical route could be considered
- In a head-to-head trial, compared to oral diclofenac, topical diclofenac was found to have no statistically significant difference in
  - Pain
  - Physical function
  - Stiffness
- Due to limited systemic absorption, topical diclofenac is safe to trial in patients on anticoagulation therapy or with history of peptic ulcer disease.

Despite these findings, there is limited practicality of prescribing topical diclofenac formulation in the hospice setting due to need to apply 3-4 times/day for efficacy, increasing likelihood of noncompliance as well as increased cost medication formulation.

RECOMMENDATION SUMMARY

Medication	Therapy Considerations
Acetaminophen	• Analgesic option for patient with mild pain and/or persisting fever • Limited analgesic benefit when added to regimen containing opioid
NSAIDs Systemic • Ibuprofen • Naproxen • Meloxicam • Celecoxib Topical • Diclofenac	• Mild/moderate analgesia • Antipyretic • If inflammation thought to be contributing to pain experienced, **recommend trial of celecoxib** over ibuprofen, naproxen or meloxicam due to decreased prevalence of GI or renal side effects with use • Celecoxib available as generic, no longer cost prohibitive • Diclofenac gel available if patient with contraindication to system NSAID • Approximate therapy cost of 100g diclofenac 1% gel tube: $10-15

References

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