### Program Name:
Managing Mild to Moderate Pain in Primary Care – Case Study Approach

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Introduction
A patient in pain is one of the most common clinical presentations seen in primary care. Although there are a vast number of conditions that cause mild to moderate pain, many of them can be effectively managed by over the counter (OTC) analgesics. Clinicians are encouraged to customize analgesic selection based on the patient’s pain, their underlying medical conditions and current medication regimen. This can allow for effective pain relief at the lowest risk of adverse effects and issues with the analgesic.

This program will introduce a structured approach to customizing analgesic selection for mild to moderate pain. We will apply this structure to four common cases seen in primary care and explore the issues associated with the painful conditions, as well as factors which may limit different selected analgesic options.

Learning Objectives
1. Review the use of different non-prescription analgesics for the management of several common acute pain conditions
2. Discuss the benefits and risks of using acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs) for mild to moderate pain
3. Explore the management of patients presenting with both pain and fever
4. Summarize the considerations when selecting analgesics in patients with underlying medical conditions

Pre/post-course Survey Questions
1. Please describe your current comfort level in the management of patients with mild-to-moderate pain? (1 not comfortable, 5 very comfortable)
2. Please describe your comfort level in the management of pain in patients with underlying medical conditions? (1 not comfortable, 5 very comfortable)
3. What do you feel are the barriers to the appropriate management of mild-to-moderate pain? (check all that apply)
   - Lack of effective options for the management of mild to moderate pain
   - Safety of using NSAIDs
   - Safety of using opioids
   - Safety of using acetaminophen
   - Lack of guidance on the management of pain for common acute conditions
   - Determining the best analgesic option to use for a patient with underlying medical conditions or other medications
4. How often do you ask patients about their current OTC analgesic use?
   - Every visit
   - Most visits
   - Some visits
   - Rarely
5. What is your current non-prescription analgesic of choice for musculoskeletal/joint pain in patients WITHOUT any underlying medical conditions?
   a) Acetaminophen
   b) Ibuprofen
   c) Naproxen sodium
   d) Acetaminophen with codeine
   e) Topical NSAIDs
   f) Other: __________________________

6. What is your current non-prescription analgesic of choice for musculoskeletal/joint pain in patients WITH significant underlying medical conditions?
   a) Acetaminophen
   b) Ibuprofen
   c) Naproxen sodium
   d) Acetaminophen with codeine
   e) Topical NSAIDs
   f) Other: __________________________

Post-Test

Agnes presents in your practice. She is experiencing mild to moderate pain and she would like your help in selecting a medication to help to reduce her pain.

Each of the questions feature what-if scenarios. Please answer the question based on the information presented in the specific question and do not assume that information from previous questions still apply.

1. What if Agnes had chronic kidney disease? Which of the following statements is TRUE?
   a. Acetaminophen has never been associated with a worsening of renal function in patients with chronic kidney disease
   b. Opioids should be avoided in most patients with chronic kidney disease
   c. Coxibs would be a safer choice than traditional NSAIDs as they have minimal effect on kidney function
   d. Patients with chronic kidney disease commonly have chronic pain

2. What if Agnes was asked the three questions in the lesson and she responded with the following:

<table>
<thead>
<tr>
<th>What medical conditions do you have?</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What medications do you currently take?</th>
<th>Hydrochlorothiazide 12.5 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candesartan 16 mg daily</td>
</tr>
<tr>
<td></td>
<td>Tiotropium soft-mist inhaler 5 mcg daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Can you tell me about your pain?</th>
<th>4 out of 10 on a numeric pain scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osteoarthritis pain in her hip</td>
</tr>
</tbody>
</table>
Which of the following would be the safest choice for her osteoarthritis (OA) pain?

a. Acetaminophen  
   b. Ibuprofen  
   c. Naproxen sodium  
   d. Glucosamine

3. What if Agnes had a sore muscle and would like to use a topical NSAID? Which of the following statements is TRUE?

   a. Topical NSAIDs are effective long-term medications for chronic pain
   b. Systemic absorption does not occur with topical NSAIDs
   c. Topical NSAIDs can be used with oral acetaminophen
   d. There are many commercially prepared topical NSAIDs in Canada

4. What if Agnes has a cardiovascular condition? Which of the following statements regarding NSAID/coxib use in cardiovascular patients is TRUE?

   a. Coxibs are safer than traditional NSAIDs for both cardiovascular and gastrointestinal complications
   b. Naproxen has a lower risk of cardiovascular and gastrointestinal complications
   c. Naproxen has not be associated with an increase in congestive heart failure risk
   d. NSAIDs can decrease the antihypertensive actions of beta-blockers

5. What if Agnes had hepatic dysfunction? Which of the following statements is TRUE?

   a. Acetaminophen is contraindicated in patient with hepatic dysfunction
   b. Intentional overdoses account for 80% of acetaminophen induced hepatotoxicity
   c. Taking a cytochrome P450 blocker can increase the risk of acetaminophen induced hepatotoxicity
   d. NSAID use can be problematic in patients with hepatic dysfunction

6. What if Agnes had acute mild to moderate musculoskeletal pain? Which of the following OTC analgesics would be indicated for this pain?

   a. Acetaminophen
   b. Ibuprofen
   c. Naproxen
   d. All of the above

7. What if Agnes was a child and had both pain and fever? Which of the following statements is TRUE?

   a. She should always be given an antipyretic if her temperature is > 39 °C
   b. If given ibuprofen, the recommended dose would be 5 mg/kg Q4H
   c. Codeine leads to unpredictable analgesic relief in pediatric patients
   d. The combination of acetaminophen and ibuprofen is associated with better outcomes than either drug given alone for fever
8. What if Agnes has mild to moderate pain associated with a tension-type headache? Which of the following drugs and doses would be recommended to manage the pain?
   a. Ibuprofen 400 mg
   b. Acetylsalicylic acid 500 mg
   c. Naproxen sodium 220 mg
   d. Acetaminophen 650 mg

9. What if Agnes wanted a medication for dysmenorrhea? Which of the following would be the most effective treatment option?
   a. Naproxen sodium 220 mg
   b. Acetaminophen 325 mg
   c. OTC menstrual formulation
   d. All of the above are equally effective

10. What if Agnes was recommended to take acetaminophen? Which of the following should she be counselled on?
    a. Never exceed the recommended dose of 4 grams per day
    b. Never take any other OTC products unless they verify it with her physician or pharmacist
    c. Explain that it could be taken as required or regularly to reduce her pain
    d. All of the above
Section 1 - Optimizing OTC Analgesic Selection

Optimizing OTC Analgesic Selection
Each patient with pain is unique. Although OTC analgesic can be used for most conditions with chronic pain, several factors can limit the use of these agents. When presented with a patient with mild to moderate pain, clinicians are encouraged to ask three open-ended questions:

- What medical conditions do you have?
- What medications do you currently take?
- Can you tell me about your pain?

Clinical Practice Tip
Many patients with mild to moderate pain will commonly self-select an OTC with little guidance from a healthcare professional. When patients are diagnosed with a new condition or start on a new medication, consider discussing if they should avoid specific OTC medications.

What medical conditions do you have?
There are a number of medical conditions that can impact the choice of analgesics. Each of these conditions can potentially limit some analgesic options. For many of these conditions, the use of a specific analgesic is not contraindicated but there could be safer options for the patient.

Kidney Disease
The prevalence of chronic kidney disease (CKD) during the period 2007–2009 was 12.5%, representing about 3 million Canadian adults. The estimated prevalence of stage 3–5 disease was 3.1% (0.73 million adults) and with albuminuria was 10.3% (2.4 million adults). Although the prevalence of CKD is high, the awareness of kidney dysfunction is low in adults with stage 3-5 kidney disease. Chronic kidney disease (CKD) can decrease the metabolism of many medications and different analgesics themselves may even further decrease kidney function.

Clinical Practice Tip
The prevalence of pain in patients with pre-end stage renal disease can be as high as 70%. With most analgesics available for self-selection, it is crucial for all primary care clinicians to discuss the management of pain in patients with reduced renal function. By providing the patient with some analgesic selection options, clinicians can reduce the risk of further reducing renal function.

NSAIDs
All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with renal adverse effects. It is estimated that 1% to 5% of NSAID users may develop renal adverse effects. Both acute and chronic renal failure can be caused by NSAIDs.

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The acute form of these adverse effects are dose and duration dependent and are usually reversible upon NSAID discontinuation. The renal effects of NSAIDs are reviewed in Table 1. Current use (nearly every day for 30 days or longer) of any NSAID was reported by 2.5%, 2.5%, and 5.0% of the population with no, mild (eGFR ≥60 mL/min), and moderate (eGFR = 15-59 mL/min) to severe CKD (eGFR < 15mL/min). Among those with moderate to severe CKD who were currently using NSAIDs, 10.2% had a current NSAID prescription and 66.1% had used NSAIDs for 1 year or longer. Despite the potential renal effects of NSAID therapy in patients with kidney dysfunction, the use of these agents tends to be widespread in patients with chronic kidney disease (CKD).

Table 1 – Renal Effects of NSAIDs

<table>
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<th>Renal Effect</th>
<th>Description</th>
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<tbody>
<tr>
<td>Glomerular filtration rate</td>
<td>Glomerular filtration rate (GFR) is a reflection of damages to the renal system. NSAIDs have been associated with reductions in GFR.</td>
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<tr>
<td>Acute renal failure</td>
<td>This NSAID adverse effect tends to be dose and duration-dependent and reversible. NSAIDs are thought to produce renal failure through the inhibition of prostaglandin production, which leads to a decrease in renal blood flow and/or induction of interstitial nephritis. Concomitant administration of ACE inhibitors, angiotensin receptor blockers (ARBs) and diuretics increase the risk of developing acute renal failure.</td>
</tr>
<tr>
<td>Renal papillary necrosis</td>
<td>NSAIDs may induce this by decreasing the blood flow to papillae and intensifying hypoxia present in papillae.</td>
</tr>
<tr>
<td>Nephrotic syndrome with acute interstitial nephritis (AIN)</td>
<td>Inflammation in the spaces between kidney tubules is the underlying mechanism of developing acute interstitial nephritis. The incidence of AIN is rare. It occurs days after exposure and is reversible. Nephrotic syndrome presents with edema, oliguria, and foamy urine. Hematuria and proteinuria can also occur. Due to inhibition of cyclooxygenase, an increase in production of other arachidonic cascade products (e.g., leukotrienes) can be responsible for induction of nephrotic syndrome by NSAIDs.</td>
</tr>
<tr>
<td>Electrolyte and fluid retention</td>
<td>Sodium retention that occurs in 25% of patients exposed to NSAIDs causes edema and weight gain. All NSAIDs have been reported to cause peripheral edema. A significant number of studies have discussed the effect of both non-selective NSAIDs and COXIBs on sodium balance. Regardless of the COX-2 selectivity, NSAIDs have been associated with hyperkalemia.</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Chronic renal failure occurs when an assault, disease or toxins damage the kidneys resulting in inadequate removal of fluids and wastes. Although rare, NSAIDs cause chronic renal failure secondary to interstitial nephritis or papillary necrosis. It can be an end-stage disease.</td>
</tr>
<tr>
<td>Hypertension due to electrolyte retention</td>
<td>It is generally believed that NSAIDs increase blood pressure, especially in hypertensive patients. NSAIDs can increase blood pressure by several mechanisms including retention of salt and fluid.</td>
</tr>
</tbody>
</table>
Clinical Practice Tip
Consider recommending each patient with CKD have a medication review by a pharmacist at least once annually. This would screen for potential prescription and OTC medications that could be a concern with CKD. This could also help to identify patients with significant CKD who continue to use OTC NSAIDs such as ibuprofen or naproxen sodium.

Kidney Disease (continued)
Acetaminophen
When taken appropriately, acetaminophen is associated with significantly less renal concerns than NSAIDs. Acetaminophen in doses exceeding the recommended maximum of 4 grams per day have been associated with renal dysfunction.² It is important to remind patients with renal dysfunction to not exceed the recommended daily maximum (4g/day) and to not consume any additional OTC product without discussing it with their physician or pharmacist.

Immediate release opioids at low doses are generally considered safe in patients with chronic kidney disease.¹² Accumulation of active metabolites is possible with controlled-release morphine.² Controlled-release hydromorphone and buprenorphine may be better choices in patients with CKD.

Cardiovascular Disease
Cardiovascular disease and its risk factors are seen in patients every day in primary care. Clinicians must effectively manage these conditions and modifiable risk factors to reduce the risk of cardiovascular complications.

Pharmacotherapy for mild to moderate pain can also impact several cardiovascular risk factors and put the patient at risk of a cardiovascular event. Most of these negative effects with analgesics are due to NSAID therapy.

The Coxib and Traditional Trialists’ (CNT) Collaboration meta-analysis reviewed over 280 trials of NSAIDs versus placebo (n=124,513) and 474 trials of one NSAID versus another NSAID (n=229,296) to determine their effect on gastrointestinal and cardiovascular effects.⁵ Coxibs, diclofenac and possibly ibuprofen increase the vascular risk, whereas naproxen was associated with less vascular risk than other NSAIDs (Figure 1).⁵ All NSAIDs were associated with an increased risk of congestive heart failure (CHF).⁵
The FDA reviewed the data from the CNT meta-analysis and provided stricter cardiovascular warnings on all prescription NSAIDs (Table 2). Although naproxen was not shown to increase cardiovascular risk, the FDA did not exclude it from these new warnings, citing that the meta-analysis was not designed to demonstrate superior safety of one NSAID compared to another. Health Canada has also provided warnings regarding the diclofenac and ibuprofen and cardiovascular risk.

Table 2 – 2015 FDA Label Changes for all Prescription NSAIDs

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.
Cardiovascular Disease (continued)

NSAIDs also have been shown to mildly increase blood pressure. Compared to patients using acetaminophen, NSAID users had a 2 mmHg increase in systolic blood pressure. Coxib users had a 5 mmHg increase compared to acetaminophen. Patients currently using ACE inhibitors, ARBs or beta-blockers can experience a decrease in antihypertensive efficacy when combined with a NSAID.

Clinical Practice Tip
In patients with previously controlled blood pressure, who have had their blood pressure trending higher, consider screening them for both pain and NSAID use. In some patients, an increase in pain or the use of NSAIDs could be associated with the increase in blood pressure and this increase may be managed by controlling the pain and using a more appropriate analgesic.

Acetaminophen has not been shown to affect cardiovascular outcomes and can even be safely administered in the acute myocardial infarction setting. Opioids do not adversely affect cardiovascular risk factors and can normally be used in this patient population.

Opioids have not been associated with direct cardiovascular organ damage with appropriate use.

Hepatic Dysfunction
Hepatic failure and hepatic dysfunction with acetaminophen has become a concern for some healthcare professionals. This is an issue that primarily occurs during acetaminophen overdose.

Acetaminophen
More than 4,000 Canadian hospitalizations occur each year due to accidental or intentional acetaminophen overdose. Approximately 6% of these hospitalizations lead to severe liver injuries (e.g. acute liver failure). The vast majority of cases occurred in patients exceeding the daily maximum of 4 grams per day. Of the patients who exceed the maximal dose, approximately half were intentional (i.e. suicide) and the other half were unintentional. The unintentional overdose is a major concern for healthcare professionals.

Clinical Practice Tip
A key practice point is that approximately 5% of patients who use acetaminophen exceed the recommended daily maximum. For this reason, primary care clinicians should check on the dosing of their patients taking acetaminophen, stress the importance of not exceeding 4 g/day, and ensure they are not unknowingly taking other products containing acetaminophen (such as cough and cold medications).

Acetaminophen is the leading cause of acute liver failure (ALF) in the United States. One study found that in patients with acetaminophen-induced ALF, the median ingested dose was 24 grams, equivalent to 48 acetaminophen 500 mg tablets.

One study evaluated unintentional overdose to provide clinicians with some insight on the reason for patient overdose. These overdoses account for 48% of the cases of ALF. The characteristics of these patients are:
• 68% of the unintentional cases involved acetaminophen in combination with an opioid. These patients wanted more opioid for the management of their pain, and did not realize the potential of acetaminophen toxicity.

• 81% of the unintentional cases were using acetaminophen for pain.

Intentional overdose accounted for 44% of the cases of ALF. What is very encouraging is that the rate of acetaminophen overdose has been decreasing in recent years due to increased education, clinician consultation and awareness of the issue.¹⁴

The use of acetaminophen in the therapeutic dosing range does not seem to be strongly linked to the development of hepatic issues.¹⁵

Health Canada is in the process of reviewing acetaminophen use and has published a summary of safety review and a labeling guidance for acetaminophen.

**Hepatic Dysfunction (continued 1)**

In a review of over 40,000 patients taking prolonged therapeutic doses of acetaminophen, the risk of hepatic issues was very small.¹⁵ In the prospective trials involving 30,865 patients, there were 129 (0.4%) cases where aminotransferase levels (AST, ALT) were greater than the upper limit of normal but no cases of fulminant hepatic injury, liver transplantation, or death.¹⁵ In the retrospective studies involving 9,337 patients, 96 patients (1%) had ALT levels higher than the upper limit of normal, one patient (0.01%) underwent transplantation and six (0.06%) died.¹⁵ The authors found that 13.8% of patients in the retrospective trials were taking between 3.9-4 g per day and speculated the difference between the prospective and retrospective trials could be due to inadvertent overdose rather than true therapeutic dosing.¹⁵

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**Clinical Practice Tip**

The risk of hepatotoxicity is not equivalent in all patients. Patients with chronic alcohol use, liver disease, dehydration, taking certain medications (e.g. antiepileptics) may be at higher risk.

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To understand the risk of hepatotoxicity with acetaminophen, it is important to understand the mechanism of elimination of acetaminophen (Figure 2). The primary path of metabolism of acetaminophen is through conjugation (90-95% of dose).¹⁶ At therapeutic doses, this pathway is effective at eliminating acetaminophen.¹⁷ A very small amount of acetaminophen is metabolized through the cytochrome P450 enzyme system (5% of the dose) to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).¹⁷ This metabolite can induce hepatotoxicity. Fortunately, NAPQI is rapidly inactivated by conjugation with glutathione and is eliminated through renal excretion.¹⁷

The problem occurs when patients take toxic doses of acetaminophen. Ingesting above therapeutic doses lead to depletion of glutathione and thus can induce hepatotoxicity as NAPQI is not conjugated.¹⁷ The lowest dose of acetaminophen to cause hepatotoxicity is believed to be between 125 and 150 mg/kg.¹⁸ The threshold dose to cause hepatotoxicity is 10 to 15 g of acetaminophen for adults and 150 mg/kg for children.¹⁸
Figure 2 – Metabolism of Acetaminophen

Clinical Practice Tip
With the P450 pathway being the source of NAPQI, any medication that stimulates the P450 system can potentially increase the toxicity of acetaminophen. The most common drug interactions include the antiepileptic medications (e.g. carbamazepine, phenytoin) as they can increase the level of acetaminophen.

Patients taking these antiepileptic medications should be advised to take lower than the maximal daily dose of acetaminophen.
The bottom line is that acetaminophen is not contraindicated in patients with hepatic disease although many experts recommend that patients with significant hepatic dysfunction should: 16,19

- Take a maximum daily dose 2-3 grams per day if taking it for more than 14 days, but short-term use of acetaminophen at a dosing of 3-4 grams per day appears to be safe.

**Hepatic Dysfunction (continued 2)**

**NSAIDs**

NSAIDs as a class are largely metabolized by hepatic cytochrome P450 enzymes, and most are heavily protein bound (typically > 95%), usually to albumin. 19 Most patients with cirrhosis or significant hepatic dysfunction have both normal or reduced P450 enzyme activity and an impaired production of drug-binding hormone proteins. 19

NSAID-induced (and idiosyncratic) hepatotoxicity has also been well described. 16 However, in cirrhotic patients with portal hypertension, the greater concern with NSAID use is the associated renal impairment, in particular hepatorenal syndrome. 16 This condition is aggravated by NSAIDs due to the inhibition of prostaglandins, which leads to a profound decrease in renal perfusion, reduction in GFR, and marked sodium retention. 16

NSAIDs can cause mucosal bleeding in patients at increased risk of bleeding as a result of thrombocytopenia and coagulopathy associated with advanced liver disease. 16 This risk is even greater in patients with portal hypertension–related complications, such as esophageal/gastric varices and portal hypertensive gastropathy or gastric antral vascular ectasias. 16

The bottom line is that NSAIDs may be tolerated in patients with mild chronic liver disease, but they should be avoided in all patients with cirrhosis because of the increased risk of hepatorenal syndrome. 16

**Opioids**

Liver is the major site of biotransformation for most opioids; thus, the metabolism of these drugs may be affected in patients with hepatic insufficiency. 19 Opioids commonly contribute to the manifestations of hepatic encephalopathy, and should be avoided in patients with cirrhosis, especially in those with portal hypertension and encephalopathy. 19

The bottom line is that if opioids are required in patients with cirrhosis, they should be administered with a longer interval between doses and possibly lower doses with slow titration. 19 Regular monitoring should be done for signs of complications and they should be discontinued if they appear. 19

**Did you know?**

Codeine is a pro-drug with no analgesic activity. Its analgesia is due to its conversion to morphine via the cytochrome P450 enzymeCYP2D6 in liver. 19 Patients with reduced hepatic function and/or patients who lack the enzyme to convert codeine to morphine (CYP2D6) may experience less pain control when using codeine.
Gastrointestinal Conditions

It is estimated that close to 10% of the US adult population has peptic ulcer disease. An endoscopy analysis of chronic NSAID users found that 37% of chronic NSAID users had significant GI lesions and 24% had ulcers. Epidemiology data found that NSAID use was associated with a four-fold increase in upper GI tract bleeding or perforation. Coxib therapy is associated with a lower risk of GI bleeding compared to traditional NSAIDs.

Guidelines recommend non-selective NSAIDs in patients with average GI risk (< 70 years of age; no prior upper GI event; no drugs of issue). Patients with GI risk factors should consider co-therapy with a proton pump inhibitor or misoprostol to reduce the risk of GI bleeding, but neither completely eliminate the risk.

Acetaminophen and opioids are less likely to lead to GI irritation and are safer options than NSAIDs in patients with peptic ulcer disease.

Are you Taking any Medications?

In addition to a patient’s medical conditions, there are several medications that can be a concern with common analgesics used for mild to moderate pain (Table 3).

Table 3 – Medications which could be a concern with common analgesics

<table>
<thead>
<tr>
<th>Concern</th>
<th>Potential drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Risk of Bleeding with NSAIDs</td>
<td>• Some Selective-Serotonin Reuptake Inhibitors (SSRI)</td>
</tr>
<tr>
<td></td>
<td>• Some tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>• Acetylsalicylic acid (ASA)</td>
</tr>
<tr>
<td></td>
<td>• Corticosteroid</td>
</tr>
<tr>
<td></td>
<td>• Warfarin</td>
</tr>
<tr>
<td></td>
<td>• Novel Oral Anticoagulants (NOAC)</td>
</tr>
<tr>
<td></td>
<td>• Ginkgo biloba</td>
</tr>
<tr>
<td></td>
<td>• Other medications containing NSAID (e.g. cold medication)</td>
</tr>
<tr>
<td>Decreased antihypertensive efficacy with NSAIDs</td>
<td>• Angiotensin converting enzyme (ACE) inhibitors</td>
</tr>
<tr>
<td></td>
<td>• Angiotensin II receptor blockers (ARB)</td>
</tr>
<tr>
<td></td>
<td>• Diuretic</td>
</tr>
<tr>
<td></td>
<td>• Beta-blocker</td>
</tr>
<tr>
<td>Increased drug levels with NSAIDs</td>
<td>• Lithium</td>
</tr>
<tr>
<td></td>
<td>• Methotrexate†</td>
</tr>
<tr>
<td>Increased Risk of Acetaminophen Toxicity</td>
<td>• Epilepsy medications (e.g. carbamazepine)</td>
</tr>
<tr>
<td></td>
<td>• Other P450 enzyme inducers (e.g. isoniazid, rifampin)</td>
</tr>
<tr>
<td></td>
<td>• Alcohol</td>
</tr>
</tbody>
</table>

† - This is only relevant with high dose methotrexate as used in oncology (not relevant with low dose weekly methotrexate as used in rheumatology).
Can you Tell me about your Pain Symptoms?
Before recommending any product for pain, clinicians should assess the patient’s pain (Table 4) by completing a pain history. The clinician can determine if analgesics are the best choice or if further investigation (e.g. imaging) is required.

Table 4 – Components of Pain Assessment

| Pain description | • Pain location and quality  
|                  | • Aggravating and alleviating factors  
|                  | • Timing and duration  
|                  | • Pain relief and functional goals  
|                  | • Intensity  
| Cause of pain    | • Could the cause of pain be treated?  
| Tools to assess level of impairment | • Acute pain  
|                  |   o Visual analog scale (VAS)  
|                  |   o Numeric rating schedule  
|                  | • Chronic pain  
|                  |   o Brief pain inventory (BPI)  

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Section 2 – Selecting Analgesics for Specific Patient Cases

Patient Case #1 – Acute Muscle and Joint Pain

Thomas (35 years old) presents today to ask if you can help him with his joint and muscle pain.

He has been experiencing pain almost every day since he started a new construction job approximately 3 weeks ago.

He has been having issues with his knees and neck and this has been impacting both his work and home life.

His only medical condition is major depressive disorder, which was diagnosed approximately 1 year ago. He currently takes citalopram 20 mg daily.

You ask what he has been taking for the pain and he mentions he was using ibuprofen 400 mg three times daily. He was complaining about the pain, so a co-worker recommended that he add naproxen sodium 220 mg three times a day to help for additional pain relief. This is working but he is finding the combination to be causing GI discomfort.

Through your assessment, he mentions that his pain with the ibuprofen is approximately a 4-5 on a scale from 1 to 10 with 0 being no pain and 10 being the worse pain he has ever felt. He says the pain is starting to affect his sleep and making it somewhat uncomfortable for him to sleep.

He wants to know if you can recommend a product for his pain.

What would you recommend?

Based on the case presented, which of the following do you feel is the best option for Thomas?

a) Acetaminophen
b) Ibuprofen OTC
c) Naproxen OTC
d) Prescription traditional NSAID
e) Topical NSAID
f) Coxib
g) Opioids

Test your Current Knowledge

1. Which of the following medications increase the risk of upper GI problems when combined with a NSAID?
   a. Citalopram
b. Dabigatran  
c. ASA  
d. All of the above

2. Which of the following statements is TRUE?  
a. Combination of two low-doses of NSAIDs is safe and offers more pain relief than just one NSAID  
b. Topical NSAIDs are indicated to manage chronic knee pain  
c. The safe and effective dose of acetaminophen is 4000 mg per day  
d. All of the above

Asking the Three Assessment Questions
The clinician asks Thomas the three questions regarding his condition (Table 5).

<table>
<thead>
<tr>
<th>Table 5 – Thomas’ Answers to the Three Assessment Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What medical conditions do you have?</strong></td>
</tr>
<tr>
<td>• Depression for approximately 1 year</td>
</tr>
<tr>
<td><strong>What medications do you currently take?</strong></td>
</tr>
<tr>
<td>• Citalopram 20 mg daily</td>
</tr>
<tr>
<td>• Ibuprofen 400 mg TID</td>
</tr>
<tr>
<td>• Naproxen Sodium 220 mg TID</td>
</tr>
<tr>
<td><strong>Can you tell me about your pain?</strong></td>
</tr>
<tr>
<td>• 4-5 out of 10 on a numeric pain scale</td>
</tr>
<tr>
<td>• Started after beginning a new construction job</td>
</tr>
<tr>
<td>• Has sore knees and neck</td>
</tr>
</tbody>
</table>

Choosing the Analgesic
Thomas is experiencing acute pain due to the increase in physical activity associated with his new construction employment. This is leading to moderate pain in his neck and knees. He is managing his pain with a combination of two OTC NSAIDs and this is providing him pain relief but leading to an increase in gastrointestinal upset.

Clinical Practice Tip
As both ibuprofen and naproxen sodium are available OTC, some patients will use the combination assuming the ibuprofen is for one pain condition and the naproxen is for another. When presented with a patient using OTC products for pain, it is important for clinicians to assess all analgesics being used, as some patients may not report using 2 or even 3 OTC analgesic products.

Acetaminophen or NSAIDs
For acute mild to moderate pain, both acetaminophen and NSAIDs are commonly used. Both of these medications can reduce the pain experienced by a patient with acute muscle or joint pain. Table 6 provides a quick summary of acetaminophen and NSAIDs.
Table 6 – Acetaminophen, Ibuprofen and Naproxen Sodium for Acute Pain

| Acetaminophen |  • Standard dose is 325-1000 mg Q6H PRN (maximum dose 4 grams per day)  
|  • Compared to full dose NSAIDs acetaminophen has:  
| o Less adverse effects  
| o Less drug interactions  
| o Does not have anti-inflammatory action  
| NSAIDs |  • Ibuprofen  
| o OTC recommended dose 200-400 mg every 6 to 8 hours (maximum of 1200 mg per day)  
| o Prescription recommend dose 1200 mg daily in divided doses (maximum 2400 mg per day)  
|  • Naproxen sodium  
| o OTC - 220 mg every 8 to 12 hours (maximum 440 mg per day)  
| o Prescription - 375-550 mg BID PRN (maximum 1375 mg per day)  
|  • Full single doses of most NSAIDs provide more effective analgesia than full doses of ASA or acetaminophen  
|  • Each NSAID and coxib – comparable results for pain and function improvement  
|  • More adverse effects compared to acetaminophen: (Section 1)  
| o Gastrointestinal  
| o Renal  
| o Hematological  
| o Cardiovascular  
| Adverse effects can occur with therapeutic doses  

Clinical Practice Tip

All NSAIDs at equivalent doses have similar effects for improving both pain and function. Approximately 70% to 80% of patients will respond to a specific agent. If a patient does not respond to one NSAID, switching to another NSAID may be effective in improving pain and function.

Ask the Expert Question

There is clinician confusion on the recommend daily maximum dose of acetaminophen. Could you comment on what you normally recommend for patients and why you are comfortable with that dose?

Acetaminophen or NSAIDs (continued)

Looking at Thomas’ case, he currently is taking two NSAIDs for pain and a SSRI for the management of depression. This dramatically increases the risk of an upper GI clinical event with NSAIDs. Although GI events are most commonly seen with chronic use, the patient is already experiencing GI discomfort, thus a change in his regimen is likely warranted.

Table 7 – Risk factors Associated with Upper GI Clinical Events with NSAIDs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60–75 years</td>
<td>2.0–5.5</td>
</tr>
<tr>
<td>History of upper GI symptoms</td>
<td>1.2–5.3</td>
</tr>
</tbody>
</table>
Topical NSAIDs

Topical NSAIDs are increasingly being used throughout the world. These products are typically used for short-term use for localized muscle or joint pain. A Cochrane Collaboration review found that the number needed to treat (NNT) for 50% acute pain relief was 4.5 (3.9-5.3) for 6 to 14 days. They found that topical diclofenac, ibuprofen, ketoprofen and piroxicam to be essentially equivalent, although only topical diclofenac is commercially available in Canada.

Topical NSAIDs are tolerated very well with localized reactions being the most common adverse effect. Currently topical diclofenac gel is indicated for short-term use for localized muscle or joint pain. Topical NSAIDs are only indicated for acute pain and for up to 7 days of use.

Clinical Practice Tip

Topical NSAIDs are a viable option for acute localized muscle or joint pain. Key considerations with topical NSAIDs:

- Systemic absorption of the NSAID can occur when applied to a large area of the skin
- They are only indicated for short-term use
- The combination with oral NSAIDs is contraindicated

Discussion Forum

When do you consider topical NSAIDs for your patients and what has your experience been with this class of analgesics?

Combination of Acetaminophen and a NSAID

With NSAIDs and acetaminophen having different mechanisms of action, some clinicians have used their combination to provide more pain relief than either drug alone. This is also done as an opioid sparing strategy.

Although commonly done in practice, there is little data to support the use of this combination in many types of pain. There were two systematic reviews published regarding the use of the NSAID/acetaminophen combination (Table 8).

<table>
<thead>
<tr>
<th>Topical NSAIDs</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>4.5 (3.9-5.3)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td></td>
</tr>
</tbody>
</table>

Table 8 – Combination Therapy with Acetaminophen and a NSAID

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**Acute post-operative pain**
- Systematic review of literature
- 17/20 studies found the combination more effective than acetaminophen alone
- 9/14 studies found combination more effective than NSAID alone
- There was no evidence of an increased incidence of side effects with combined treatment compared to a single analgesic
- **Conclusion:** A combination of acetaminophen and NSAIDs provided superior analgesia than either agent administered alone.

**Dental Extraction**
- Ibuprofen/acetaminophen combination may offer better analgesia, with fewer untoward effects than many opioid-containing combinations

---

**Clinical Practice Tip**
The combination acetaminophen with a NSAID could be considered in patients with pain that is unresponsive to a single treatment and the clinician wishes to avoid the use of opioids.

---

**Ask the Expert Question**
What are your key concerns when using acetaminophen and NSAIDs with mild to moderate pain?

**Opioids**
Codeine and tramadol are opioids commonly used for the treatment of mild to moderate pain. The advantage of opioids is that they do not have any long-term effects on major organ systems (with the exception of hypogonadism).

The vast majority (80%) of patients will experience at least one GI or CNS related adverse effect. The risk of misuse/abuse is also a concern with opioid therapy.

**Codeine is not active until it is converted to morphine** by the cytochrome P450 system (CYP2D6). In patients with low levels of CYP2D6 or who are taking medications which block this enzyme, may experience very little pain relief from codeine therapy. Approximately 10% of the population do not have sufficient CYP 2D6 and have poor relief with codeine. 2-5% are rapid metabolizers and are at higher risk of adverse effects.

The combination of acetaminophen and ibuprofen was found to offer the same amount of pain relief to acetaminophen/codeine. Codeine as a single agent is not reliable for the treatment of acute pain in adults.

Tramadol is commonly used for the treatment of mild to moderate pain. A Cochrane Collaboration evaluating its use in osteoarthritis concluded that tramadol or tramadol/acetaminophen decreases pain intensity, produces symptom relief and improves function, but these benefits are small. Although some authors do not recommend tramadol as a first-line analgesic in acute pain, it may be a reasonable analgesic for some patients. Depending on the formulation, the maximum daily dose of tramadol is 300-400 mg per day.

**Discussion Forum**
When do you consider an opioid therapy for a patient with moderate pain? Do you normally recommend an opioid in combination with a NSAID?
Revisit our Patient Case – Thomas

Thomas is currently using two NSAIDs for his pain and taking SSRI therapy. Both of these are independent risk factors for upper GI issues. He is also currently experiencing some GI discomfort.

Based on his current presentation, Thomas would be a candidate for acetaminophen, a topical NSAID, or opioid therapy. Acetaminophen may help to reduce his pain and cause less issues with his GI system. A topical NSAID could be considered if his pain is localized. Opioids could also be considered to provide additional pain relief.

Each of these options are considered, and Thomas would prefer to avoid opioids as he needs to be alert when working in construction. He won’t be able to stop working to apply the topical NSAID. He would prefer to try acetaminophen regularly and if required he will add one of the OTC NSAIDs for additional pain relief.

Patient Case #2 – Pediatric Pain and Fever

Ashley (5 years old) present today with a case of otitis media. She has left ear pain and a temperature of 37.8°C for the last 24 hours.

Her mother is very concerned and brought her in to receive an antibiotic.

She has no underlying medical conditions and is not currently taking any medications.

She has a moderate level of pain with it occasionally becoming intense.

What would you recommend?

Based on the case presented, which of the following do you feel is the best option for Ashley?

a) Consider antibiotic therapy
b) Recommend acetaminophen
c) Recommend ibuprofen
d) Recommend alternating acetaminophen and ibuprofen

Test your Knowledge

1. Which of the followings statements regarding the management of otitis media is TRUE?
   a. All patients should have watchful waiting for the first 48 hours after symptom presentation
   b. 10-days is the standard course of antibiotic therapy for acute otitis media
   c. Acetaminophen or ibuprofen should be used to manage comfort level and not most cases of fever
   d. Amoxicillin/clavulanate is first-line therapy in Canada due to increasing resistance patterns
2. Which one of the following statements regarding opioids in pediatrics is TRUE?
   a. Codeine is not a reliable analgesic in children
   b. Approximately 10% of children have weak CYP2D6 activity and are unresponsive to morphine
   c. Opioids offer significantly greater analgesia than ibuprofen for acute pain
   d. All of the above

**Asking the Three Assessment Questions**
The clinician asks Ashley’s mother the three questions regarding his condition (Table 9).

<table>
<thead>
<tr>
<th>Table 9 – Ashley’s Answers to the Three Assessment Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What medical conditions do you have?</strong></td>
</tr>
<tr>
<td><strong>What medications do you currently take?</strong></td>
</tr>
</tbody>
</table>
| **Can you tell me about your pain?** | • Unilateral left ear pain  
• Mother says the pain is moderate but can become intense |

**Managing Otitis Media**
In February 2016, the Canadian Paediatric Society (CPS) updated their position statement on the management of acute otitis media in children 6 months of age and older. A complete review on the management of otitis media is beyond the scope of this lesson. Table 10 reviews some of the key points from the CPS position statement.

<table>
<thead>
<tr>
<th>Table 10 – Summary of the CPS Position Statement on Otitis Media</th>
</tr>
</thead>
</table>
| **Symptoms** | • Nonspecific and, by themselves, are insufficient to diagnose acute otitis media (AOM)  
• Systemic symptoms, such as difficulty sleeping or decreased playfulness as well as irritability and fever, are common in respiratory viral infections and not diagnostic for otitis media  
• Symptoms such as ear tugging or ear pain (otalgia), while often helpful in verbal children, may also indicate myringitis due to a viral infection or Eustachian tube dysfunction with decreased hearing  
• Using symptoms only, could over-diagnose or under-diagnose cases of AOM |
| **Diagnostic criteria** | • Characterized by acute onset of symptoms (eg, otalgia or suspected otalgia) with middle ear fluid and significant inflammation of the middle ear.  
• The presence of a middle ear effusion (MEE) is a necessary minimal diagnostic criterion for AOM |
| **Recommended treatment for a child with perforated tympanic membrane with purulent drainage** | • Criteria:  
  o Children > 6 months of age  
  o Who are generally healthy  
  o Acute onset of illness |
<table>
<thead>
<tr>
<th>Recommended treatment for a child with middle ear effusion and a bulging tympanic membrane (Mildly ill)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria:</strong></td>
</tr>
<tr>
<td>- Children &gt; 6 months of age</td>
</tr>
<tr>
<td>- Who are generally healthy</td>
</tr>
<tr>
<td>- Acute onset of illness</td>
</tr>
<tr>
<td>- ± fever</td>
</tr>
<tr>
<td>- Suspected acute otitis media</td>
</tr>
</tbody>
</table>

- **Mildly ill** |
  - No rigors, responding to antipyretics, able to sleep, < 39°C without antipyretics or < 48 hours of illness |
  - Watchful waiting for 24 to 48 hours with analgesia |
  - If no improvement or clinical worsening treat with antimicrobials (10 days for 6 months to 2 years and 5 days if ≥ 2 years) |

- **Moderately ill** |
  - Irritable, difficulty sleeping, poor response to antipyretics, severe otalgia OR ≥ 39°C OR > 48 hours of symptoms |
  - Treat with antimicrobials: 10 days if 6 months to 2 years, 5 days if ≥ 2 years |

<table>
<thead>
<tr>
<th>Recommended treatment for a child without middle ear effusion OR non-bulging or mildly erythematous tympanic membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider viral etiology such as RSV or influenza</strong></td>
</tr>
<tr>
<td><strong>Reassess in 24 to 48 hours</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five days of antimicrobial treatment with oral amoxicillin has been shown to be at least as effective as 10 days of therapy in most children ≥ 2 years of age with uncomplicated disease</td>
</tr>
<tr>
<td>Ten days of oral antimicrobial treatment courses are appropriate for children &lt; 2 years of age, for children with recurrent AOM or otitis media associated with a perforated TM, and for cases where initial therapy failed.</td>
</tr>
</tbody>
</table>

- **First-line (no penicillin allergy)** |
  - Amoxicillin – 75 mg/kg/day–90 mg/kg/day divided twice per day as capsules or suspension; OR |
  - Amoxicillin – 45 mg/kg/day–60 mg/kg/day divided three times per day as capsules or suspension |

- **First-line (if non-life threatening penicillin allergy)** |
  - Cefuroxime-axetil – 30 mg/kg/day divided twice or three times per day as tablets or suspension |
  - Ceftriaxone – 50 mg/kg intramuscularly (or intravenously) daily for three days |

- **If initial therapy fails (ie, no symptomatic improvement after two to three days):** |
  - Amoxicillin-clavulanate for a child weighing ≤35 kg, 45 mg/kg/day–60 mg/kg/day divided three times a day for 10 days. Specify 400 mg/5 mL suspension of 7:1
formulation.
- Amoxicillin-clavulanate for a child weighing >35 kg, 500 mg tablets orally three times a day for 10 days.

AOM – Acute otitis media, TM – tympanic membrane

Analgesic and Antipyretic Use in Pediatrics

The American Academy of Pediatrics (AAP) published a statement in 2011 on fever and antipyretic use in children. This statement provides some clear guidance for clinicians and parents on the management of pain and fever in children (Table 11). The key message from this statement is that treatment of fever is not required and clinicians should promote as needed antipyretic use only to make the child more comfortable.

When recommending acetaminophen or ibuprofen, it is important that they are dose appropriately. Table 12 summarizes key points regarding dosing of these drugs in children.

<table>
<thead>
<tr>
<th>Table 11 – Summary Points of AAP’s Statement on Fever and Antipyretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fever does not endanger the child and may actually help</td>
</tr>
<tr>
<td>• Goal of treatment is to increase comfort &amp; well-being</td>
</tr>
<tr>
<td>• Treatment is not about normalizing temperature</td>
</tr>
<tr>
<td>• Use antipyretics as needed for comfort versus around-the-clock</td>
</tr>
<tr>
<td>• Antipyretics do not prevent febrile seizures</td>
</tr>
<tr>
<td>• Acetaminophen and ibuprofen are effective</td>
</tr>
<tr>
<td>• Ibuprofen may decrease fever more</td>
</tr>
</tbody>
</table>

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### Table 12 – Pediatric Analgesic/Antipyretic Information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acetaminophen</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in temperature °C</td>
<td>1 – 2</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Time of onset, hour</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Time to peak effect, hour</td>
<td>3 – 4</td>
<td>3 – 4</td>
</tr>
<tr>
<td>Duration of effect, hour</td>
<td>4 – 6</td>
<td>6 – 8</td>
</tr>
<tr>
<td>Dose</td>
<td>10 - 15 mg/kg Q4H</td>
<td>10 mg/kg Q6H</td>
</tr>
<tr>
<td>Maximum daily dose</td>
<td>5 doses per 24 hours</td>
<td>4 doses per 24 hours</td>
</tr>
</tbody>
</table>

**Discussion Forum**

Do you regularly recommend parents to treat fever with antipyretics and will you reduce their use after reading this section?

**Health Literacy and Pediatric Dosing**

When recommending pediatric medications, it is important to clearly review the dosing instructions. *One review found that approximately 40% of parents provide inappropriate doses of pediatric medications.* They found that 16.7% of doses are given by parents with a non-standardized measuring device (e.g. teaspoon or tablespoon) and this significantly increases the odds of making a dosing error.

Clinicians should make no assumptions and review the dosing with the parent to ensure a clear understanding of how the medication is to be used.

**Clinical Practice Tip**

Consider asking parents how they give their medications to their child. Many times this can quickly identify inappropriate dosing and allow the clinician to intervene to ensure the child is dosed correctly.

**Ask the expert**

How often would you recommend primary care clinicians to actively screen patients regarding OTC medication use?

**Combination of Ibuprofen and Acetaminophen in Pediatrics**

A common practice recommended by healthcare professionals is for parents to use a combination of ibuprofen and acetaminophen to help manage pain and fever in children. *A Cochrane Collaboration review was conducted* on the use of this combination for febrile children. They concluded:

- Some evidence that the combination is more effective at decreasing fever
- No evidence that the combination improves outcomes

It is important to remind parents that the treatment of fever is for comfort and not for a specific temperature. The use of two agents could also increase the risk of inappropriate dosing for the child.

*One study reviewed the use of the combination* for the management of acute pain post-tonsillectomy. This trial found that the combination was more effective for analgesia than either drug alone. This combination could be considered for acute pediatric pain in an opioid sparing strategy.
Clinical Practice Tip
Prior to considering the combination of acetaminophen and ibuprofen, it is important to verify the weight of the child. Many times, appropriately dosing based on the child’s weight (not the age) can be effective and not require multiple agents.

Discussion Forum
What has been your experience with using the combination of acetaminophen and ibuprofen in pediatric patients with fever or pain?

Opioids in Pediatrics
Opioids can be considered for moderate to severe pain in pediatric patients. Codeine was traditionally used in children requiring more analgesia than provided by acetaminophen or ibuprofen. Codeine is no longer recommended for use in children for several reasons. One study found that 47% of children have weak CYP2D6 activity and thus cannot convert codeine to morphine and received little or no therapeutic benefit. Some children are rapid metabolizers at CYP2D6 and therefore are at higher risk of toxicity with codeine use. Codeine provided less reliable analgesia compared to morphine.

Some studies have evaluated opioids in comparison to ibuprofen for acute pain. Ibuprofen was found to be equivalent to acetaminophen/codeine for pediatric arm fracture pain and resulted in better improvements in function and less adverse effects. Other trials have compared ibuprofen to morphine for pediatric post-fracture pain and extremity injuries and found that ibuprofen offered equivalent pain reduction with lower adverse effects.

Clinical Practice Tip
For the most part, the role of opioids in the treatment of acute pediatric pain is limited. Before considering opioids in this population, the clinician may wish to try ibuprofen monotherapy or combination of acetaminophen/ibuprofen.

Revisit our Patient – Ashley
Ashley’s mother is encouraged to watchful wait for 24-48 hours before considering antibiotic therapy for her otitis media. She is told that Ashley should be reassessed in 48-72 hours if the otitis media does not improve or if it clinically worsens.

The mother is encouraged to use either ibuprofen or acetaminophen to make Ashley comfortable. Either drug is to be used only as needed and is not dosed around the clock. Education is provided surrounding the fact that fever is not harmful to Ashley and it does not have to be treated.

The clinician reviews the dosing based on Ashley’s weight (Table 12) and reviews the dosing in mL and frequency to administer the drug.
Patient Case # 3 – Dysmenorrhea and Tension Headache

Krystal (24 years-old) presents today complaining of a headache and dysmenorrhea. She describes the headache as a diffuse pain occurring on both sides of her head and feeling like there is tight band around her head.

She explains that she commonly experiences a headache 2 to 3 days premenstrually with pelvic discomfort.

She is currently taking:
- Oral contraceptive tablet daily
- L-thyroxine 0.1 mg daily

She would ideally like to use on medication to help to manage both types of pain.

What would you recommend?

Based on the case presented, which of the following do you feel is the best option for Krystal?

a) Acetaminophen
b) Ibuprofen OTC
c) Naproxen OTC
d) Prescription traditional NSAID
e) Topical NSAID
f) Coxib
g) Opioid

Test your Current Knowledge

1. Which of the following statements regarding dysmenorrhea is TRUE?
   - a. Dysmenorrhea occurs in approximately 75% of women
   - b. Pain normally starts within hours of menstruation
   - c. Acetaminophen and NSAIDs are equally effective for dysmenorrhea
   - d. Clinicians should recommend OTC menstrual pain products due to their superior efficacy

2. Which of the following symptoms is more common with tension headache than migraines?
   - a. Light sensitivity
   - b. Interference with daily activity
   - c. Nausea
   - d. Bilateral headache
Asking the Three Assessment Questions

The clinician asks Krystal the three questions regarding his condition (Table 13).

<table>
<thead>
<tr>
<th>Table 13 – Krystal’s Answers to the Three Assessment Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What medical conditions do you have?</strong></td>
</tr>
<tr>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td><strong>What medications do you currently take?</strong></td>
</tr>
<tr>
<td>• Oral contraceptive</td>
</tr>
<tr>
<td>• L-thyroxine</td>
</tr>
<tr>
<td><strong>Can you tell me about your pain?</strong></td>
</tr>
<tr>
<td>• Tension headache with bilateral pain</td>
</tr>
<tr>
<td>• Dysmenorrhea</td>
</tr>
<tr>
<td>• Both occur 2 - 3 days premenstrually</td>
</tr>
</tbody>
</table>

Dysmenorrhea

Dysmenorrhea refers to the occurrence of painful menstrual cramps of uterine origin, usually developing within hours of the start of menstruation and peaking as the flow becomes heaviest during the first day or two of the cycle. Pain is usually centred in the suprapubic area but may radiate to the back of the legs or lower back, and may be accompanied by other symptoms such as nausea, diarrhea, headache and light headedness.

Dysmenorrhea is thought to occur in up to 90% of women. It is classified as either primary or secondary dysmenorrhea. Primary dysmenorrhea is defined as recurrent, crampy pain occurring with menses in the absence of identifiable pelvic pathology. Secondary dysmenorrhea is menstrual pain associated with underlying pelvic pathology such as endometriosis. The diagnosis and management of dysmenorrhea is reviewed in the Society of Obstetricians and Gynaecologists of Canada’s (SOGC) primary dysmenorrhea consensus guideline.

Risk factors for dysmenorrhea are reviewed in Table 14.

<table>
<thead>
<tr>
<th>Table 14 – Risk Factors for Primary Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age – More pronounced in adolescents than in older women</td>
</tr>
<tr>
<td>• Early menarche</td>
</tr>
<tr>
<td>• Heavy and increase duration of menstrual flow</td>
</tr>
<tr>
<td>• Family history</td>
</tr>
<tr>
<td>• Smoking</td>
</tr>
<tr>
<td>• Irregular menstrual cycles</td>
</tr>
<tr>
<td>• Lower socioeconomic groups</td>
</tr>
</tbody>
</table>

Clinical Practice Tip

Primary dysmenorrhea can be managed through the use of analgesics. Secondary dysmenorrhea is due to an underlying pathology. Clinicians should suspect a secondary cause (e.g. endometriosis, pelvic inflammatory disease, chronic pelvic pain) with an onset in older women and no history of dysmenorrhea.
Management of Primary Dysmenorrhea

A Cochrane Collaboration review evaluated the treatment of primary dysmenorrhea. This review evaluated 80 randomized controlled trials evaluating different treatment options. The authors concluded that:

- NSAIDs were more effective for dysmenorrhea pain relief compared to acetaminophen
- No evidence to support superiority of any individual NSAID
- No evidence that coxibs are more effective or better tolerated for dysmenorrhea

The bottom line of the review is any NSAID including OTC ibuprofen and naproxen sodium will offer the patient significant dysmenorrhea pain relief.

Clinical Practice Tip

Many of the OTC products marketed for the management of dysmenorrhea contain acetaminophen and a variety of other ingredients. These 'PMS' or 'menstrual' formulations are likely to be less effective and more costly than OTC ibuprofen or naproxen sodium.

Discussion Forum

Which analgesic do you most commonly recommend for dysmenorrhea and why?

Managing Tension-Type Headache

In August 2015, Canadian guidelines were published on the management of headache in primary care. They estimate the lifetime prevalence of headache is 66%. Tension-type headache has the highest prevalence with a prevalence of 46% to 78%. The economic effects of headache are also substantial. It is estimated that headache accounts for 20% of work absences.

The guidelines provide an algorithm to help with the diagnosis of the different headache types. Table 15 provides some of the different symptoms for both tension-type and migraine headaches. The management of migraines is beyond the scope of this lesson, but is reviewed in detail in the Canadian guideline document.

<table>
<thead>
<tr>
<th>Table 15 – Common Symptoms for Tension-Type and Migraine Headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine</strong></td>
</tr>
<tr>
<td>Headache with ≥ 2 of:</td>
</tr>
<tr>
<td>- Nausea</td>
</tr>
<tr>
<td>- Light sensitivity</td>
</tr>
<tr>
<td>- Interference with activities</td>
</tr>
<tr>
<td><strong>NOTE:</strong></td>
</tr>
<tr>
<td>- Consider migraine diagnosis for recurring “sinus” headache</td>
</tr>
</tbody>
</table>
Clinical Practice Tip
When presented with a patient with recurrent headaches, it is important to assess their current management of headaches. Some of these patients could be experiencing medication-overuse headache.49 This type of headache should be considered in:49

- Ergots, triptans, combination analgesics, or codeine or other opioids ≥ 10 days/month OR
- Acetaminophen or NSAIDs ≥ 15 days/month

The most effective measure is gradual or abrupt withdrawal of the analgesic (NOTE long-term use of opioids should be gradually tapered).

Management of Tension-Type Headache
Tension-type headache can be effectively managed with OTC analgesics. Table 16 reviews the recommended analgesics for the management of tension-type headache.

<table>
<thead>
<tr>
<th>Medication for Acute Headache</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
</tr>
<tr>
<td>Acetylsalicylic acid (ASA)</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>500-550 mg</td>
</tr>
<tr>
<td>(OTC version contains 200-220 mg/tablet)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

Ask the Expert
What education would you recommend clinicians provide to patients taking a NSAID?

Revisit our Patient Case- Krystal
Krystal is experiencing dysmenorrhea and tension-type headaches 2 to 3 days premenstrually. She has no contraindications or concerns with her medications.

The use of an OTC or prescription NSAID would likely reduce both the dysmenorrhea and headache pain. She could be presented with the options of OTC ibuprofen or naproxen sodium and allowed to select the product she would like to try.

It is important that she be counselled on how to use the NSAID appropriately and how to minimize potential adverse effects.
Patient Case #4 – Complicated Patient Case

John (67 years-old) is in today to discuss his osteoarthritis pain. He has been suffering from knee and hip pain for the last few years.

The pain has intensified over the last 3 months and it is starting to impact his mobility. He was told by a friend that naproxen sodium would be a great choice as it lasts for 12 hours and provides excellent pain relief.

John takes 7 different medications for diabetes, blood pressure and dyslipidemia.

He thought he would try some glucosamine with the naproxen as he heard it helps for his type of pain.

When asked, his pain is 3 out of 10 on a numeric pain scale. On bad days it increases to 5 out of 10.

What would you recommend?
Based on the case presented, which of the following do you feel is the best option for John?

a) Acetaminophen  
b) Ibuprofen OTC  
c) Naproxen OTC  
d) Prescription traditional NSAID  
e) Topical NSAID  
f) Coxib  
g) Opioid

Test your Current Knowledge
1. Which of the following agents is safest in patients with cardiovascular disease?
   a. Ibuprofen  
b. Naproxen sodium  
c. Acetaminophen  
d. All of the above

2. What is the daily maximum dose of acetaminophen which can be used in an elderly patient?
   a. 2.6 grams per day  
b. 3 grams per day  
c. 4 grams per day  
d. 5 grams per day
Asking the Three Assessment Questions

The clinician asks John the three questions regarding his condition (Table 17).

**Table 17 – John’s Answers to the Three Assessment Questions**

| What medical conditions do you have? | Previous myocardial infarction (MI) 8 years before
|                                       | Type 2 diabetes
|                                       | Stage 3 chronic kidney disease (CKD)
|                                       | High blood pressure
|                                       | Dyslipidemia
| What medications do you currently take? | Metformin 500 mg BID
|                                           | Gliclazide MR 90 mg daily
|                                           | Perindopril 4 mg daily
|                                           | ASA 81 mg
|                                           | Atorvastatin 20 mg daily
|                                           | Bisoprolol 5 mg daily
| Can you tell me about your pain? | Pain and stiffness in hips and knees due to osteoarthritis

Management of Osteoarthritis

The American College of Rheumatology (ACR) published guidelines in 2012 for the management of hand, hip and knee osteoarthritis. Table 18 reviews the recommended pharmacological management of knee and hip osteoarthritis.

There are several treatment options which can help to reduce this patient’s osteoarthritis (OA) pain. Clinicians must tailor the treatment to meet the needs of the individual patient.

**Table 18 – ACR Recommended Management of Knee and Hip Osteoarthritis**

<table>
<thead>
<tr>
<th>Knee osteoarthritis</th>
<th>Hip osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended:</strong></td>
<td><strong>Recommended:</strong></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Oral NSAIDs</td>
<td>Oral NSAIDs</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Intraarticular corticosteroid injections</td>
</tr>
<tr>
<td>Intraarticular corticosteroid injections</td>
<td></td>
</tr>
<tr>
<td><strong>Patients should not use:</strong></td>
<td><strong>Patients should not use:</strong></td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Chondroitin sulfate</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Glucosamine</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>Glucosamine</td>
</tr>
</tbody>
</table>

The Challenges of Complicated Patients

Many of the patients seen in primary care have significant health conditions and complicated drug regimens. Cardiovascular, renal, hepatic and gastrointestinal disease can have a major impact on the selection of analgesic.
Our patient John has had a previous myocardial infarction, has hypertension, dyslipidemia, type 2 diabetes and chronic kidney disease. He has a complicated drug regimen and currently takes an ACE inhibitor, ASA and a beta-blocker. These three drugs are impacted by the use of NSAID therapy (Table 3).

**Balancing Risk versus Benefit**

In a patient such as John, the use of NSAIDs could increase his blood pressure and the combination with ASA could place him at elevated risk of an upper GI complication. NSAIDs are also associated with negative effects on renal function.

Acetaminophen would be an appropriate first-choice for John based on the current ACR guidelines. It does not cause any significant drug interactions with his current drug regimen and is not an issue with his diabetes, cardiovascular or renal disease. Adverse effects of acetaminophen are uncommon, even in elderly patients.

Opioids could be used to help the patient’s pain. Opioids do not cause any direct cardiovascular organ damage and low-dose hydromorphone or buprenorphine would generally be considered safe in a patient with chronic kidney disease. This patient has mild to moderate pain and likely would not require opioids to manage his condition. Also, many elderly patients are more susceptible to opioid-related adverse effects.

**Discussion Forum**

Which medical conditions do you feel most limit the choice of analgesics in an elderly patient?

**Clinical Practice Tip**

This patient has diabetes and reduced renal function. The Canadian Diabetes Association provides a [sick day medication list](#). These medications should be held in patients with diabetes who are ill and unable to maintain fluid intake. These drugs can be remembered by the acronym SADMANS:

- S sulfonylureas
- A ACE-inhibitors
- D diuretics, direct renin inhibitors
- M metformin
- A angiotensin receptor blockers
- N non-steroidal anti-inflammatory
- S SGLT2 inhibitors

**Acetaminophen**

Acetaminophen would likely be the best choice for the patient in the case due to the lack of significant renal, GI or cardiovascular issues with its use. Table 19 has the dosage recommendations for acetaminophen.
Clinical Practice Tip
Although acetaminophen is safe when used at its therapeutic dose, unintentional overdose can occur when patients combine OTC and prescription products with acetaminophen. It is important to stress to patients who are using any acetaminophen containing product to not use any additional OTC products unless they have verified it is safe with their pharmacist or physician.

<table>
<thead>
<tr>
<th>Table 19 – Key Counselling Points on Acetaminophen$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend specific products</td>
</tr>
<tr>
<td>o 325 mg caplets and tablets</td>
</tr>
<tr>
<td>o 650 extended release tablets (arthritis formulation contains 325 mg immediate release and 325 mg extended release)</td>
</tr>
<tr>
<td>Recommend the proper dosing</td>
</tr>
<tr>
<td>o 500 – 1,000 mg q4 – 6h prn (max 4 g total/ 24 h)—regular, extra-strength</td>
</tr>
<tr>
<td>o Acetaminophen can be taken regularly or as required for pain relief</td>
</tr>
<tr>
<td>Stress the maximum dosage</td>
</tr>
<tr>
<td>o Clinicians should stress that the patient not take any more acetaminophen than what is recommended on the label</td>
</tr>
</tbody>
</table>

Ask the Expert
What education would you recommend clinicians provide to patients taking acetaminophen?

Ask the Expert
What are the 4 to 5 key points you would like every primary care clinician to remember when recommending analgesics for mild to moderate pain?
Revisit our Case – John

With John’s multiple health issues, acetaminophen is the best choice for his mild to moderate osteoarthritic pain.

The clinician provides the patient with the different format options and reviews the dosage, and stresses that he not exceed the 4 grams per day maximum.

He is also counselled to adjust the dose of acetaminophen to help to control his pain as he may not require the full 4 grams per day. He is discouraged to use of glucosamine due to the ACR guideline statement. John is also reminded that he should never take any OTC, vitamin or herbal products without first checking with his pharmacist or physician in order to avoid further unintentional doses of acetaminophen or drug interactions with his medications.

Resources

- Brief pain inventory (BPI)
- FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes
- Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks
- Pain Assessment Scales
- Management of acute otitis media in children six months of age and older
- Primary Dysmenorrhea Consensus Guideline
- Guideline for primary care management of headache in adults
- American College of Rheumatology

Key Learning Points

- It is important to customize the analgesic selection for mild to moderate pain based on the patient, their medical conditions, their current medication regimen and the type of pain they are experiencing
- Consider asking the three assessment questions as they can help to further tailor the treatment:
  - What medical conditions do you have?
  - What medications do you currently take?
  - Can you tell me about your pain?
- NSAIDs are effective analgesics but must be used cautiously in patients with underlying medical conditions
- Acetaminophen is a product with minimal adverse effects and drug interactions but can become hepatotoxic if taken in excess of 4 grams per day
• There is acetaminophen in many OTC and prescription products. It is important to caution patients using acetaminophen to not to use any OTC products without verifying with their pharmacist or physician
• Pediatric dosing of analgesics is a common source of error. Clinicians must stress proper dosing of all medications given to children
• Actively engage patients with mild to moderate pain as clinician recommendations can help to provide the most effective and safe analgesic

Discussion Forum
1. With all the issues identified in this lesson, will this change your analgesic recommendations?
2. Where would you like more information to help with your management of pain?
3. Are there any other patient or disease factors that you use to help customize the choice of analgesic for a patient?
References


