Acute Pain

Musculoskeletal, Low Back, Post-Surgical

2020

Academic Detailing Service

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ABBREVIATIONS AND DEFINITIONS

ALBP	Acute low back pain
AE	Adverse event(s)
ACE-I	Angiotensin-converting-enzyme inhibitor(s)
AFib	Atrial Fibrillation
AHRQ	Agency for Healthcare Research and Quality
AKI	Acute Kidney Injury
APTC	Antiplatelet Trialists' Collaboration
ARB	Angiotensin II receptor blocker(s)
BP	Blood pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central nervous system
CNT	Coxib and Traditional NSAID Trialists'
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
Coxib	COX-2 inhibitor/COX-2 selective
CrCl	Creatinine clearance
CrI	Credible Interval
CV	Cardiovascular
CVD	Cardiovascular Disease
CVE	Cardiovascular event
DERP	Drug Effectiveness Review Project
FDA	Food & Drug Administration
GI	Gastrointestinal
HF	Heart Failure
HR	Heart rate
H2RA	Histamine 2 receptor antagonist/H2 blocker
HTN	Hypertension
MA	Meta-analysis
MCID	Minimal clinically important difference
MD	Mean difference
MI	Myocardial Infarction
MID	Minimal important difference
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNT	Number needed to treat *(is the number of people you need to treat to avoid one additional bad outcome OR benefit from a desirable outcome. For example, NNT 5 for a drug which reduces the risk of stroke means that for every 5 people treated, a stroke will be prevented in 1 person)*
NOS	Newcastle-Ottawa Scale

NSAID	Nonsteroidal anti-inflammatory drug(s)/non-selective/traditional
NSS	Not statistically significant
OA	Osteoarthritis
OR	Odds ratio
OTC	Over-the-counter
PPI	Proton Pump Inhibitor
PRICE	Protection, Rest, Ice, Compression, Elevation
RA	Rheumatoid arthritis
RCT	Randomized Controlled Trial(s)
RICE	Rest, Ice, Compression, Elevation
RR	Risk ratio/Relative risk *Note*: *The abbreviation RR is used to present outcomes of both relative risk (risk ratio) and rate ratio. Unless otherwise noted, RR refers to relative risk. In the NSAID risk section, RR is occasionally used to describe rate ratio (clearly identified where applicable).*
SCr	Serum creatinine
SD	Standard Deviation
SR	Systematic Review(s)
SS	Statistically significant
SMR	Skeletal muscle relaxant(s)
TCA	Tricyclic antidepressants
THC	Tetrahydrocannabinol
US	United States
UTI	Urinary tract infection
VAS	Visual analogue scale
WMD	Weighted mean difference

INTRODUCTION

There are many challenges with managing pain in the primary care setting. Depending on pain severity, many individuals may receive their first opioid prescription for acute pain. Opioid use and overdose deaths have been an ongoing concern in Nova Scotia. There were 59 reported opioid-related deaths in 2019.[12] This is an increase from 54 deaths in 2018, but a decrease from 63 in 2017.[12] As of June 2020, there have been 3 confirmed opioid-related deaths in Nova Scotia.[12] The Nova Scotia government developed the Nova Scotia Opioid Use and Overdose framework, in 2017, in response to the opioid crisis.[12,13] This framework outlines key focus areas for effectively responding to the opioid crisis, such as understanding the issue, prevention, harm reduction, treatment and prescribing practices as well as criminal justice and law enforcement.[13] As part of the harm reduction strategy, access to free naloxone kits is provided through the Nova Scotia Take Home Naloxone Program.[12] Over 13,400 naloxone kits have been dispensed since January 2016, with 141 reported opioid overdose reversals.[12]

The risk for acute to chronic opioid use is increased within the first few days of use, particularly with > 3-5 days opioid use.[4,5] The rate of long-term (≥ 1 year) opioid use for persons whose first episode of opioid therapy for 1 day, ≥8 days and ≥ 31 days was 6%, 14% and 30%, respectively.[5] High risk practices such as using long-acting opioid prescriptions for acute pain, concomitant opioid and benzodiazepine prescribing, and prescribing high opioid doses have led to increasing numbers of opioid overdoses.[6] Guidelines addressing opioid prescribing practice can foster practice change and improve patient care and safety.[6]

Pain is a multidimensional, complex interplay of biopsychosocial components.[1]

- *Acute pain (*typically presents for < 3 months) is a predicted physiologic response to an adverse stimulus caused by tissue damage often associated with trauma, surgery or acute illness. [1,2,3]

- *Chronic pain* (persisting beyond normal tissue healing time, usually > 3 months) is pathological with no apparent biological value or protective function.[1]

- *Pain Chronification (*the transition from acute to chronic pain) is a key focus area for primary care providers to identify patients at risk and prevent the transition.[1]

The purpose of this document is to provide primary care providers with some tools to help identify, assess and manage patients presenting with acute pain and communicate treatment goals effectively. There are many acute pain conditions, however, this document focuses on post-surgical, musculoskeletal and low back pain acute conditions.

PAIN CHRONIFICATION

Pain chronification is essentially the transition from acute to chronic pain.[1] It has been described as the process of transient pain progressing into persistent pain and involves pain processing change as a result of an imbalance between pain amplification and pain inhibition.[1] Genetic, environmental and biopsychosocial factors determine the risk, degree and time-course of chronification.[1] It is particularly common with trauma, low back pain and osteoarthritis.[1]

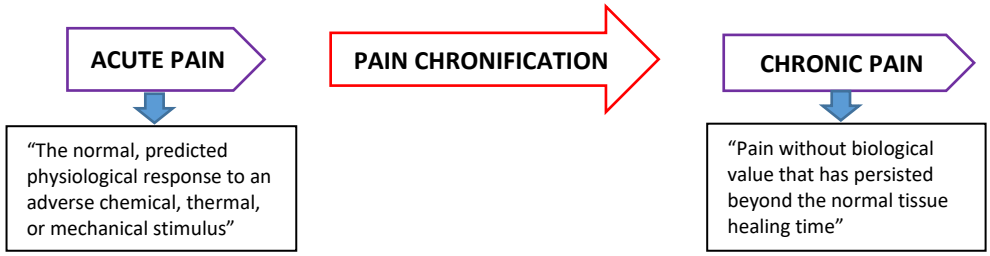

Figure 1: *Adapted from Morlion et al.[1]*

The transition from acute to chronic pain results from complex interactions between biological, psychological, and social factors.[1,7,14] Biological factors include central sensitization (pain amplification), gliopathy (neuroinflammation), nociceptive dysregulation and pain protective behaviours.[1,7,14] Psychosocial factors play a crucial role in pain chronification. More cumulative traumatic life events, higher levels of depression in the early stages of a new pain episode, and early beliefs that pain may be permanent, all contribute significantly to increased severity of subsequent pain and disability.[1] Early administration of a cognitive-behavior therapy (CBT) intervention which focuses on the psychological aspects of pain appears to be feasible for identifying patients at high risk of pain chronification.[1] Research in this area is currently limited but anticipated to better understand contributing factors, identify at-risk individuals and potentially lead to the development of novel therapeutic interventions.[1]

PREVENTING PAIN CHRONIFICATION

One goal of acute pain management is to prevent pain chronification. Preventative strategies include rapid, early identification and adequate treatment of acute pain or subacute pain, thereby preventing chronic pain.[1,7] Primary care providers have a crucial role to play in avoiding diagnostic and therapeutic delays.[1]

Patient assessment and management[1]

- Patient history and examination
- Immediate (preventative) treatment (reassurance, non-pharmacological and/or pharmacological interventions) **monotherapy often leads to insufficient therapeutic response; hence, wherever possible, it is important to identify the distinct factors causing acute pain and treat them properly via a multimodal therapeutic approach*
- Early treatment (days to weeks) should aim to build on previous management options and should consider psychosocial factors and interventions (*screen for yellow flags*)
- Late treatment (weeks to months)

IDENTIFYING PATIENTS AT RISK FOR DEVELOPING PAIN CHRONIFICATION[1,7]

Predictive Risk Factors	Modifiable Risk Factors
• **Patient demographics** (level of education, female gender, older age, poor health status) • **Epigenetics** (phenotypic trait variations which result from developmental and environmental cues) • **Acute pain characteristics** (intensity/severity, duration, cumulative trauma exposure) • **Psychological factors** (high baseline fear, anxiety, negative beliefs on chronic pain severity, depression, catastrophizing, pain vulnerability/resilience)	• High body mass index (BMI) ≥25 • Severe pre-operative pain • Higher incidence of post-operative complications • Presence of chronic pain in other areas of the body

***Table 1**: Adapted from McGreery et al.*[7]

Table 1. Main factors influencing the pain chronification process.

Positive factors	Negative factors
Social support (marriage/family)	Poor health status
High level of education	Type (e.g. neuropathic) and severity of pain
Coping strategies	Depression
Work satisfaction	Stress
Appropriate communication with HCPs	Litigation
Adequate self-recognition	Fear avoidance
	Perceived injustice
	Catastrophizing

Abbreviation. HCPs, health care professionals.

***Figure 2**: Morlion et al.*[1]

There are currently no simple, easy-to-use, evidence-based assessment tools or questionnaires for primary care providers, specifically relating to the transition from acute to chronic pain.[1] Development of such a tool could benefit primary care providers in early diagnosis of patients at risk of pain chronification.[1] As key influencers in the management of patients with acute pain, promoting awareness and knowledge of pain chronification and providing skills and training to primary care providers is vital in preventing pain chronification.[1]

YELLOW FLAGS 8-10

***Psychosocial risk factors** (yellow flags) for developing pain chronicity include:*

- ✓ Attitude, expectations, beliefs and behaviors (substance abuse, withdrawn/reduction in activities)
- ✓ Emotions: fear, catastrophizing, anxiety, irritability, anger, depression, stress
- ✓ Financial problems
- ✓ Job dissatisfaction
- ✓ Family problems, lack of support

Interventions to consider:

- ✓ Educate patient and family
- ✓ Referral to active rehab including CBT
- ✓ Assess for psychopathology and treat
- ✓ Follow-up regularly
- ✓ Refer if recovering slowly

COMMUNICATING WITH PATIENTS…

TALKING POINTS[11]

- ✓ Listen. Be open, curious and non-judgmental.
- ✓ Acknowledge and validate suffering. Reassure they are being cared for. (SAFE-ED)
- ✓ Manage risk and expectations.
- ✓ Recognize that the pain experience is influenced by many factors.
- ✓ Be more mindful of the habits and behaviors we give patients to manage their suffering.
- ✓ Address fears and help them address pain protective behaviors that could be driving pain.

SAFE-ED[11]

- ✓ Calm "Worst-case **S**cenario" thinking
- ✓ **A**ddress pain specific **F**ear's and pain protective behaviors
- ✓ **E**xam carefully for any new pathology or progression of a pre-existing disease
- ✓ Manage treatment **E**xpectations
- ✓ **D**ispense small quantities of short-acting, opioids over a short period of time

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ACUTE MUSCULOSKELETAL PAIN

SUMMARY STATEMENTS

- Acute pain typically presents for less than three months and is caused by trauma, surgery, or damage to tissues.[1,2]
- Acute non-low back-related musculoskeletal pain includes strains, sprains, dislocations, whiplash and contusions.[3]
- Sprains and strains are the most frequently reported acute musculoskeletal injury.[3]

QUESTION 1: WHAT IS THE EVIDENCE FOR THE EFFICACY AND SAFETY OF THE PHARMACOLOGICAL OPTIONS IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

QUESTION 1a: WHAT IS THE EVIDENCE FOR TOPICAL ANALGESICS IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

- A 2017 Cochrane review of 13 SRs with MAs evaluated topical analgesics for acute musculoskeletal conditions. The review found that topical NSAIDs had the greatest evidence of efficacy for acute musculoskeletal pain (primarily sprains and strains) with moderate or high-quality evidence.[4]
  - The NNT to achieve at least a 50% pain relief on pain scales *over 1 week* with topical NSAIDs compared to placebo were as follows:[4]
    - Diclofenac Emulgel: NNT 1.8 (95% CI 1.5 to 2.1)
    - Ketoprofen gel: NNT 2.5 (95% CI 2.0 to 3.4)
  - There was no increased risk of AEs or withdrawal with topical NSAIDs compared to placebo in the treatment of acute pain (strains and sprains).[4]
    - Withdrawals, all topical NSAIDs: RR 1.0 (0.7 to 1.7)
    - AEs, all topical NSAIDs: RR 1.0 (0.7 to 1.3)
  - There was limited evidence of efficacy for topical salicylates, herbal remedies and ibuprofen gels/creams (very low-low quality and very sparse data).[4]

- A 2017 CADTH rapid response review of topical NSAIDs for acute musculoskeletal pain was undertaken based on the research question "what is the comparative clinical effectiveness of topical NSAIDs versus opioids for the treatment of acute musculoskeletal pain?"[6]
  - No direct evidence regarding the comparative effectiveness of topical NSAIDs versus opioids could be identified. [6]

- A 2020 NMA of RCTs evaluated the comparative effectiveness of various outpatient treatments for acute pain from non–low back, musculoskeletal injuries.[7]
  - The NMA found a reduction of pain with topical NSAIDs compared to placebo as reported on a 10 cm Visual Analogue Scale (VAS), both within 2 hours of

treatment and during 1-7 days of treatment. [7] Additionally, topical NSAIDs improved physical function as reported on the VAS 10 cm function scale.[7]
    - 2 hours of treatment: WMD −1.02 (95% CI −1.64 to −0.39)
    - 1-7 days of treatment: WMD -1.08 (95% CI -1.40 to -0.75)
    - Physical function: WMD 1.66 (95% CI 1.16 to 2.16)
- Topical NSAIDs plus menthol gel also improved pain at less than 2 hours
- All of these outcomes met the minimally important difference (MID).[7]
    - The MID was defined as a reduction of at least 1 cm on the 10 cm VAS pain scale and an increase in 1 on the 10 cm VAS function scale.[7]
- Topical NSAIDs had a significantly greater improvement in physical function compared to oral NSAIDs (MD -0.73; 95% CI -1.69 to – 0.17), the difference did not meet the MID.
- The odds of experiencing a GI, neurological or dermatological AE with a topical NSAID was not significantly different compared to placebo.[7]

➢ The amount of topical NSAID application and the extent of systemic absorption varies with different products and the size of the pain area (see table on page 21 for commercially available products in Canada).

QUESTION 1b: WHAT IS THE EVIDENCE FOR <u>ORAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), ACETAMINOPHEN AND OPIOIDs</u> USED IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

➢ <u>A 2020 Cochrane review</u> evaluated the benefits and harms of oral NSAIDs compared to other oral analgesics in patients with acute soft tissue injury.[12]
NSAIDs vs. acetaminophen:
- There were no differences between an NSAID and acetaminophen for pain at < 24 hours, 1-3 days, or ≥ 7 days. There were no differences in return to function by or after day 7.[12]
- NSAIDs had a slight increased risk of GI AE compared to acetaminophen (RR 1.34, 95% CI 0.97 to 1.86); however, the 95% CI included the possibility of no difference or a very small increase for acetaminophen. There was no significant difference in neurological AE.[12]

NSAIDs vs. opioids:
- There was no difference in pain at < 24 hours with NSAID versus an opioid.[12]
- NSAIDs improved pain on VAS scales significantly more than an opioid at 4 days (MD -6.50 mm on 100 mm VAS, 95% CI -9.31, -3.69) and at 7 days (MD – 6.5 mm on a 100 mm VAS, 95% CI -9.31 to -3.69).[12]
    - The differences did not reach the MCID of 13 mm on a 100 mm VAS.[12]
- There were fewer GI and neurological AE with an NSAID compared to an opioid; (RR 0.48, 95% CI 0.36 to 0.62) and (RR 0.40, 95% CI 0.30 to 0.53), respectively.[12]

NSAIDs vs. combination analgesics (acetaminophen + codeine or dextropropxyphene):

- There were no differences between treatment arms for pain at days 1-3 or at 7 days.[12]
- There were no significant differences in GI and neurological AE.[12]

- A 2019 SR evaluated the effectiveness of acetaminophen compared to other analgesics in the treatment of pain in acute musculoskeletal injuries.[13]
  - The SR found no differences in the effectiveness of acetaminophen compared to NSAIDs or a combination of acetaminophen + NSAID.[13]
  - This evidence, however, was considered of low quality due to a high risk of bias in two of the included studies.[13]

- A 2019 RCT showed that a single dose of acetaminophen 1000 mg was no different in reducing pain at 60 minutes compared to a combination of acetaminophen 1000 mg + ibuprofen 400 mg + codeine 60 mg, in adult patients with acute closed limb or trunk injury presenting to the emergency department.[14] More AEs were observed in the combination versus the acetaminophen group (NNH 7, 95% CI 4 to 50).[14]

- The 2020 NMA that assessed the comparative effectiveness of various outpatient treatments in the management of non-low back, musculoskeletal injuries (i.e. sprains, strains and whiplash) concluded that of the oral therapies studied, NSAIDs and acetaminophen (± diclofenac) had the greatest benefit to harm ratio.[7] This was rated as moderate to high certainty evidence.[7]

- ***Other considerations with opioids in the treatment of acute musculoskeletal pain***
  - A 2020 SR of observational studies found an association between prolonged opioid use in patients with a greater physical co-morbidity, older age, and past or present substance use disorder. Low certainty evidence showed that prolonged opioid use was associated with prescriptions lasting more than 7 days and with higher morphine milligram equivalents/day.[15]

QUESTION 1c: WHAT IS THE EVIDENCE FOR SKELETAL MUSCLE RELAXANTS (SMRs) IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

- The evidence for skeletal muscle relaxants in acute musculoskeletal pain treatment is primarily for acute low back pain. Please refer to the acute low back pain section.

QUESTION 1d: WHAT DO CLINICAL PRACTICE GUIDELINES RECOMMEND FOR THE PHARMACOLOGIC MANAGEMENT OF ACUTE MUSCULOSKELETAL PAIN?

- The most recent guideline for the treatment of acute pain from non-low back, musculoskeletal injuries are the 2020 American College of Physicians and American Academy of Family Physician Guidelines.[16]
    - This guideline is based on the 2020 NMA of various outpatient treatments used in the management of acute pain from non–low back, musculoskeletal injuries and the SR of observational trials on the predictors of prolonged opioid use.[7,15]
    - **The guideline recommends that topical NSAIDs (± menthol) be used as first line treatment for pain reduction and function improvement.[14] The guidelines also recommend NSAIDs for pain reduction and function improvement and acetaminophen for pain reduction.[16]**
        - Topical NSAIDs had the greatest net benefit, followed by oral NSAIDs and acetaminophen with or without diclofenac. Effects of these agents on pain were modest (around 1 cm on a 10-cm visual analogue scale, approximating the minimal important difference).[7]
    - **The guidelines recommend *against* opioids (including tramadol) for acute musculoskeletal injury pain treatment due to lack of a benefit greater than NSAIDs and increased harms (GI and neurological).[18]**
        - No opioids achieved benefit greater than that of NSAIDs but caused the most harm.[7]
        - There is an association between prolonged opioid use and greater physical co-morbidity, age, and past or present substance use disorder. Prolonged opioid use is associated with prescriptions lasting > 7 days and with higher morphine equivalents/day. [15]

QUESTION 2: IS THERE EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

Musculoskeletal pain from sprains, strains, or whiplash

- Using the results of the 2020 NMA, the ACP and AAFP guidelines recommend that acute pain from non-low back, musculoskeletal injuries may be treated with specific acupressure to reduce pain and improve physical function or with transcutaneous electrical nerve stimulation to reduce pain (Grade: conditional recommendation; low certainty evidence).[16]

Musculoskeletal pain from ankle sprains

- Evidence-based guidelines from 2018 on ankle sprains treatment recommend:
    - Functional support (4-6 weeks) over immobilization improve self-reported function and prevent recurrence.[18] Ankle braces were reported to have greater efficacy compared to other forms of support (level 2). [18]

  - A short period of immobilization with plaster cast or rigid support may reduce pain or edema. Immobilization should be for a maximum of 10 days after which functional treatment should be started (level 2).[18]
- Exercise through exercise therapy programs (± RICE therapy) is also recommended post ankle sprain to aid joint function recovery (level 1).[18]
  - A majority of trials evaluating exercise programs have found they are associated with a quicker time to recovery and enhanced outcomes (level 1). A few trials contradict these findings, concluding that there is no added benefit of supervised exercise therapy when added to conventional treatment alone (usually various components of PRICE; protection, rest, ice, compression, elevation).[18]
  - There is no evidence that RICE alone, or cryotherapy, or compression therapy alone has any positive influence on pain, swelling or patient function.[18]

➢ CADTH published two Rapid Response Reports in 2020, one evaluating exercise therapy and the other evaluating functional supports in *ankle sprains*.[19,20]

Exercise Therapy:

- Evidence in this review found overall there were no significant differences in the effectiveness between exercise interventions compared with usual care (PRICE) nor between different programs. Future well-controlled studies are needed to determine the effectiveness of different types of exercise programs with specific content and volume that is optimally suited for the general population, competitive sport medicine settings, or populations of different grades of ankle injury.[19]

External Supports:

- Based on the available evidence there is insufficient information to support use of a particular type of external support in the treatment of ankle sprains.[20]

Prescriber Resources and Patient Information

Prescriber Resources	Patient Information
➢ Clinical Practice Guidelines (The Orthopaedic Trauma Association Musculoskeletal Pain Take Force): https://journals.lww.com/jorthotrauma/Pages/articleviewer.aspx?year=2019&issue=05000&article=00011&type=Fulltext ➢ Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline: https://bjsm.bmj.com/content/52/15/956 ➢ Musculoskeletal Strains and Sprains - Guidelines for Prescribing NSAIDs: https://medsask.usask.ca/musculoskeletal-strains-and-sprains---guidelines-for-prescribing-nsaids.php *(NOTE-requires subscription)* ➢ Musculoskeletal Pain Algorithm (For Pharmacists): https://medsask.usask.ca/documents/musculoskeletal_algorithm.pdf ➢ Pain Relief Toolkit: https://www.aaos.org/PainReliefToolkit/?ssopc=1	➢ Information on Sprains and Strains: https://medlineplus.gov/sprainsandstrains.html ➢ Information on non-steroidal anti-inflammatory drugs (NSAIDs): https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/NSAIDs

BACKGROUND

- Acute pain typically presents for less than three months and is caused by trauma, surgery, or damage to tissues.[1-2]
- Acute non-low back-related musculoskeletal pain includes strains, sprains, dislocations, contusions and whiplash. Sprains and strains are the most frequently reported acute musculoskeletal injury.[3]
- Acute musculoskeletal pain management includes pharmacological (topical, oral) and non-pharmacological options. The evidence is primarily from MAs and/or SRs and RCTs and for sprains and strains.

QUESTION 1: WHAT IS THE EVIDENCE FOR THE EFFICACY AND SAFETY OF THE PHARMACOLOGICAL OPTIONS IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

QUESTION 1a: WHAT IS THE EVIDENCE FOR <u>TOPICAL ANALGESICS</u> IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

- <u>A 2017 Cochrane review</u> evaluated 13 SRs with MAs that assessed the efficacy and safety of topical analgesics applied to intact skin for the treatment of acute and chronic pain in adults. The 13 SRs with MAs were previous Cochrane reviews of DB, RCTs.[4]
  - The interventions for acute pain were topical NSAIDs and rubefacients (salicylates).[6] Comparators were placebo or active comparators if available.[4] Although salicylates are chemically related to NSAIDs, when used topically they exert their pain relieving effect primarily through skin irritation and were thus labeled as rubefacients in this Cochrane overview.[4]
  - The acute pain conditions that were evaluated were strains and sprains.[4]
  - The primary outcome in the review was a 50% reduction in pain as reported by participants on pain assessment scales.[4]
  - *Over one week*, topical NSAIDs were more effective than placebo in the treatment of acute pain. The following topical products had the best quality evidence (moderate or high-quality):[4]
    - Diclofenac Emulgel: NNT 1.8 (95% CI 1.5 to 2.1) (2 studies, N=314)
    - Ketoprofen gel: NNT 2.5 (95% CI 2.0 to 3.4) (5 studies, N=348)
    - Diclofenac other plaster (i.e., excluding Flector plaster): NNT 3.2 (95% CI 2.6 to 4.2) (3 studies, N=474)
    - Piroxicam: NNT 4.4 (95% CI 3.2 to 6.9) (3 studies, N=522)
    - Diclofenac Flector plaster: NNT 4.7 (95% CI 3.7 to 6.5) (4 studies, N=1030)
  - There was limited evidence of efficacy for topical salicylates, herbal remedies and ibuprofen gels/creams (very low-low quality and very sparse data).[4]

- The strengths and dosages of topical NSAIDs applied in the various Cochrane Reviews were as follows:[5]

Diclofenac Emulgel (2 studies)	1% 2.32%	~2 g of product (up to 4 times a day) was applied (92-138 mg/day of diclofenac as diethylamine salt)
Ketoprofen gel (5 studies)	2.5%	5 cm, 5 g, or 7.5 g quantities applied twice a day (~100-375 mg/day of ketoprofen)
Diclofenac other plaster (3 studies)	1% (2 studies)	applied once daily 180 mg epolamine salt, 140 mg NA salt/day
	Unknown (1 study)	applied bid (280 mg Na salt/day)
Piroxicam (3 studies)	0.5%	1 study 5mg, 2 studies 1 g applied 3-4 times per day (15-20 mg piroxicam/day)
Diclofenac Flector Plaster (4 studies)	1%	applied 1-2 times per day (180-360 mg epolamine salt, 140-280 mg Na salt/day)

- There was no increased risk of AEs or withdrawals with topical NSAIDs compared to placebo when used for acute pain (strains and sprains).[4]
    - Withdrawals, all topical NSAIDs: RR 1.0 (95% CI 0.7 to 1.7)
    - AEs, all topical NSAIDs: RR 1.0 (95% CI 0.7 to 1.3)[4]

➢ A 2017 CADTH Rapid Response review of topical NSAIDs for acute musculoskeletal pain was undertaken based on the research question "what is the comparative clinical effectiveness of topical NSAIDs versus opioids for the treatment of acute musculoskeletal pain?."[6]

- No direct evidence regarding the comparative effectiveness of topical NSAIDs versus opioids could be identified.[6]

➢ A 2020 NMA assessed the comparative effectiveness of various outpatient treatments in the management of non-low back musculoskeletal injuries (primarily sprains, strains and whiplash).[7] The NMA concluded that topical NSAIDs had the best benefit–harm ratio for patients with acute pain from non–low back musculoskeletal injuries.

- The NMA included RCTs that evaluated currently available outpatient pain relief interventions for acute pain (pain < 4 weeks in duration, or defined as acute).[7]
- The investigators converted measures of pain intensity and function to a standardized 10 cm Visual Analogue Scale (VAS). The minimally important difference (MID) was defined as a reduction of at least 1 cm for the 10 cm VAS for pain scale and an increase of at least 1 cm on the 10 cm VAS for function scale.[7]
- The NMA found a reduction of pain with topical NSAIDs compared to placebo both within 2 hours and during 1-7 days of treatment (moderate quality evidence).[7] Topical NSAIDs improved physical function as reported on the VAS function scale (moderate quality evidence). Topical NSAIDs plus menthol gel also improved pain at less than 2 hours.[7]
    - All of these outcomes met the minimally important difference (MID).[7]
- Topical NSAIDs had a significantly greater improvement in physical function compared to oral NSAIDs (MD -0.73; 95% CI -1.69 to – 0.17), the difference did not meet the MID.

- The odds of experiencing a GI, neurological or dermatological AE with a topical NSAID was not significantly different compared to placebo. [7]

Table 1. Results of the NMA by Busse et al. (2020) for topical treatments compared to placebo. [7]

	Pain relief within 2 hours: MD	Pain relief 1-7 days: MD (95% CI)	Physical Function: MD (95% CI)	GI-Related AEs: OR (95% CI)	Neurological AEs: OR (95% CI)	Dermatological AEs: OR (95% CI)
Topical NSAID vs. placebo						
	−1.02 cm (−1.64 to −0.39)	**−1.08 cm (−1.40 to −0.75)**	**1.66 cm (1.16 to 2.16)**	1.14 (0.65 to 2.01)	1.18 (0.51 to 2.74)	0.78 (0.52 to 1.15)
Topical NSAID + Menthol gel vs. placebo						
	−1.68 cm (−0.27 to −3.09)	−0.89 cm (−2.33 to 0.54)	-	2.35 (0.04 to 124.85)	1.22 (0.02 to 69.98)	0.53 (0.05 to 6.29)
Menthol gel vs. placebo						
	-	**−1.14 cm (−2.28 to 0.00)**	0.70 cm (−0.61 to 2.02)	-	-	1.00 (0.11 to 8.91)

Results are the WMD on a scale or 0-10, or ORs and associated 95% CI between the intervention and placebo from the NMA. For pain relief, scores range from 0 to 10 cm; lower is better (MID = 1 cm). For physical function, scores range from 0 to 10 cm; higher is better (MID =1 cm). An OR greater than 1 for adverse events indicates that the treatment is associated with a higher likelihood of harms compared with placebo. Bolded results are statistically significant.

- Application and systemic absorption of topical NSAIDs commercially available in Canada:
  - The amount of topical NSAID application varies based on the product and the size of the pain area. Systemic absorption of topical NSAIDs also depends on the product, pain area, and amount of applied product (see *Table 2*).
  - Apply to intact skin and do not cover with occlusive dressings.[8]

Table 2. Application and systemic absorption of topical NSAIDs commercially available in Canada.

Topical NSAID	Topical Application	Systemic Absorption	OTC in Canada
Diclofenac diethylamine 1.16%, 2.32% w/w (Voltaren Emulgel 1.16% w/w, Voltaren Emulgel Extra Strength 2.32% w/w)	Apply TID-QID[8] 2-4 g (1 g = 2 cm) gel per 400-800 cm^2 area[16]	• Overall low systemic absorption[16] • 6% absorption of 2.5 g of 1.16% gel on 500 cm^2 skin versus tablet formulation[16]	Yes
Diclofenac sodium 1.5% w/w (Pennsaid)	50 drops per knee (OA), 3 times a day, or 40 drops per knee, 4 times a day[9]	• Single application (1 mL) to knee: mean plasma C_{max} = 9.7 ± 4.7 ng/mL after 24-48 hours (T_{max}) in 6 volunteers. Mean total urinary recovery = 3.68% diclofenac sodium[17] • 40 drops (one knee) or 80 drop (two knees) 4 times a day x 84 days = mean 8.95 ± 9.17 ng/mL plasma diclofenac sodium (20 patients).[17] • Note: mean C_{max} of oral 50 mg enteric-coated diclofenac sodium on an empty stomach = 1500 ng/mL after ~ 2 hours[17]	No

- In addition to commercially available products, diclofenac can be compounded in up to 10% strengths and in combination with other products (i.e. menthol, PLO gel) by community pharmacies in Canada.[10]
    - **No relevant literature on compounded diclofenac for topical anti-inflammatory treatment was identified in a CADTH rapid review.[11]**

- The Canadian product monograph of Voltaren Emulgel lists the concomitant use of this product with oral NSAIDs as a contraindication.[8]

Clinical Expert Opinion: Topical and oral NSAIDs are *sometimes* combined (off-label) if benefits outweigh the risks, with appropriate monitoring. This combination should take into account patient specific risk factors for NSAID toxicity (CV, GI, and renal risks).

QUESTION 1b: WHAT IS THE EVIDENCE FOR <u>ORAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), ACETAMINOPHEN AND OPIOIDs</u> USED IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

- <u>A 2020 Cochrane review</u> evaluated the benefits and harms of oral NSAIDs compared to other oral analgesics in patients with acute soft tissue injury (20 RCTs or quasi-randomized trials, N=3305).[12]
    - Acute soft tissue injury was defined as a sprain, strain or contusion (hematoma) of a joint, ligament, tendon or muscle that occurred <48 hours before study inclusion. [12]
    - The primary outcome of the review was pain (reported on VAS scales).[12] VAS scores were standardized to a 100 mm scale and the minimum clinically important difference (MCID) was defined as 13 mm. Secondary efficacy outcomes were swelling, function, AEs, and early re-injury. [12]
    - AEs at any time during or within 90 days of the study start date were included. [12] Gastrointestinal (GI) AEs were defined as nausea, vomiting, dyspepsia, abdominal pain, peptic ulcer disease, gastrointestinal bleeding, hepatic dysfunction, diarrhea, constipation and other, if reported. Neurological adverse effects were drowsiness or somnolence, dizziness or vertigo, headache, paresthesia, seizure, others if reported.[12]

NSAIDs vs. acetaminophen

- Evaluations comparing NSAIDs (ibuprofen, naproxen, diclofenac or indomethacin) with acetaminophen found no differences between them for the following efficacy outcomes: [12]
    - Pain at < 24 hours (6 studies, N=1178, I^2 = 0%; high certainty evidence)
    - Pain at days 1-3 (6 studies, N=1232, I^2 = 0%; high certainty evidence)
    - Pain at ≥ 7 days (4 studies, N=467, I^2=63%; low certainty evidence)

- Return to function ≥ day 7 (3 studies, N=386, I2 = 0%; low certainty evidence).

- The review found that NSAIDs may have a slight increased risk of GI AE compared with acetaminophen (RR 1.34, 95% CI 0.97 to 1.86, 10 studies, N=1504, I^2=0%);[12]
  - The 95% CI included the possibility of no difference or a very small increase for acetaminophen. [12]
- There was low-certainty evidence of no significant difference in neurological AE between NSAIDs and acetaminophen (9 studies, N=1679, I^2=0%).[12]

NSAIDs vs. opioids

- Evaluations compared NSAIDs (naproxen, ibuprofen, valdecoxib) with an opioid (dextropropoxyphene, dihydrocodeine, codeine, tramadol).[12]
- There were no differences between an NSAID and an opioid for improvement in pain at < 24 hours (4 studies, N=1058, I^2 = 0%; moderate certainty evidence).[12]
- NSAIDs were statistically superior to opioids in improving pain on VAS scales at day 4 (MD -6.50 mm, 95% CI -9.31, -3.69) and at day 7 (MD – 6.5 mm, 95% CI -9.31 to -3.69).[12]
  - The differences between the groups did not reach the MCID of 13 mm. These outcomes were from 1 RCT (N=706) and were classified as low quality evidence.[12]
- There was moderate-certainty evidence of fewer GI AE with NSAIDs compared with an opioid (RR 0.48, 95% CI 0.36 to 0.62, 5 studies, N=1151, I^2=55%). NSAIDs were less likely to result in neurological AE compared with an opioid (RR 0.40, 95% CI 0.30 to 0.53, 5 studies, N=1151, I^2=0%).[12]

NSAIDs versus combination analgesics (acetaminophen + opioid):

- Two trials compared diflusinal or naproxen to acetaminophen plus dextropropoxyphene and 2 trials compared diflusinal to acetaminophen plus codeine.[12]
- There were no significant differences between treatment arms for pain at days 1-3 (2 studies, N=149, I^2=0%) and pain at 7 days (2 studies, N=138, I^2=0%)
- There was no significant difference in GI and neurological AE (3 trials, N=141, I^2=0%).[12]
- The evidence for all reported outcomes was very low certainty. This was primarily due to the low number of participants and the associated imprecision. The review authors reported very little confidence in the effect estimates.[12]

- A 2019 SR (7 RCTs, N=2100) evaluated the effectiveness of acetaminophen compared with other analgesics in adult patients with acute minor musculoskeletal injuries (sprains, strains, contusions). The SR found no significant differences between acetaminophen and NSAIDs (ibuprofen, indomethacin, diclofenac) or the combination of both acetaminophen and NSAIDs in the treatment of acute pain as reported as changes in VAS pain scales at ≤ 24 hour or > 24 hours.[13]

- Acetaminophen dosages were 500 mg TID or 1000 mg QID for 3-10 days in most studies. The extended release formulation was used in one study (1300 mg TID for 9 days).[13]
- Studies with combination products all used 1000 mg acetaminophen QID for 3 days.
- Ibuprofen was dosed at 400 mg TID, diclofenac at 25-50 mg TID or 75 mg BID, and indomethacin at 25 mg TID.[13]
- A total of 830 AEs were reported in 6 RCTs, with no serious events reported.[13] Authors of the review point out that most studies did not have standardized measures for AE occurrence.[13] In one study, patients on acetaminophen had more AEs than those taking diclofenac or the combination.[13] However, patients were also concomitantly on PPI therapy in this study.[13]
- This evidence was considered of low quality due to a high risk of bias in two of the included studies.[13]

- A 2019 RCT (N=118) showed that a single dose of acetaminophen 1 g was no different in reducing pain at 60 minutes compared to a combination of acetaminophen 1 g + ibuprofen 400 mg + codeine 60 mg, in adult patients with acute closed limb or trunk injury presenting to the emergency department.[14]
  - The type of injury was primarily sprain, fracture, or contusion.
  - Pain was assessed at 60 minutes and 120 minutes; however, the study was underpowered for analyses at 120 minutes due to a high drop-out rate (almost half of the study participants).[14]
  - More AEs were observed in the combination versus the acetaminophen group (NNH 7, 95% CI 4 to 50 for any AE).[7] AEs listed in the study were drowsiness, dizziness, or lightheadedness, nausea or vomiting, and other.[7] AEs were considered mild.[14]

- The 2020 NMA that assessed the comparative effectiveness of various outpatient treatments in the management of non-low back, musculoskeletal injuries concluded that of the oral therapies studied, NSAIDs and acetaminophen (± diclofenac) had the greatest benefit to harm ratio, rated as moderate to high certainty of evidence (see Table 3 for comparisons with placebo).[7]

Table 3. NMA (Busse et al., 2020) results for select oral therapies vs. placebo.[7]

Pain relief within 2 hours: MD (95% CI)	Pain relief 1-7 days: MD (95% CI)	Physical Function: MD (95% CI)	GI-Related AEs: OR (95% CI)	Neurological AEs: OR (95% CI)	Dermatological AEs: OR (95% CI)
Oral NSAID vs. placebo					
−0.93 cm (−1.49 to −0.37)	**−0.99 cm (−1.46 to −0.52)**	**0.73 cm (0.17 to 1.30)**	**1.77 (1.33 to 2.35)**	1.02 (0.65 to 1.59)	1.33 (0.43 to 4.09)
Acetaminophen vs. placebo					
-1.03 cm (−1.82 to −0.24)	**−1.07 cm (−1.89 to −0.24)**	0.90 cm (−0.27 to 2.61)	0.50 (0.06 to 4.38)	-	-
Acetaminophen + Diclofenac vs. placebo					
−1.11 cm (−2.00 to −0.21)	−1.09 cm (−2.20 to 0.01)	-	-	-	-
Acetaminophen + Ibuprofen vs. placebo					
−0.70 cm (−1.62 to 0.22)	−1.18 cm (−2.74 to 0.38)	-	-	-	-
Acetaminophen + Ibuprofen + Codeine vs. placebo					
−1.36 cm (−2.49 to −0.23)	-	-	-	-	-
Acetaminophen + Opioid* vs. placebo					
−0.52 cm (−1.47 to 0.43)	**−1.71 cm (−2.97 to −0.46)**	-	**5.63 (2.84 to 11.16)**	**3.53 (1.92 to 6.49)**	-
Acetaminophen + Ibuprofen + Oxycodone vs. placebo					
−0.94 cm (−2.27 to 0.38)	-	-	-	-	-
Fentanyl vs. placebo					
−3.52 cm (−4.99 to −2.04)	-	-	**59.38 (6.21 to 567.71)**	**5.73 (1.20 to 27.47)**	-
Tramadol vs. placebo					
0.95 cm (−0.80 to 2.70)	-	-	5.98 (0.33 to 108.25)	**6.72 (1.24 to 36.39)**	-
***effect estimate for pain relief 1-7 days is from direct comparison than network estimate.**					

Results are the WMD on a scale or 0-10, or ORs and associated 95% CI between the intervention and placebo from the NMA. For pain relief, scores range from 0 to 10 cm; lower is better (MID = 1 cm). For physical function, scores range from 0 to 10 cm; higher is better (MID =1 cm). An OR greater than 1 for adverse events indicates that the treatment is associated with a higher likelihood of harms compared with placebo. Bolded results are statistically significant.

Additional considerations with opioids in the treatment of acute musculoskeletal pain:

- A 2020 SR of 13 observational studies (N=13 263 393) evaluated the risk factors associated with prolonged opioid use in adults after an initial prescription in acute musculoskeletal injuries that are managed in an outpatient setting.[15]
  - The prevalence of prolonged opioid use after an initial prescription for an acute musculoskeletal injury was 27% in high-risk populations (defined as patients receiving disability benefits, Veterans Affairs claimants, or those with comorbid substance use disorder) compared to 6% in the general population.[15]
    - Past or present substance use disorder was significantly associated with prolonged opioid use (low-certainty evidence grading):[15]
      - OR 3.14 [CI, 1.79 to 5.52]; ARI 10.5% [CI, 4.2% to 19.8%])
    - Older age in adults and greater physical comorbidity were also significantly associated with prolonged opioid use (moderate certainty evidence):[15]
      - Older age in adults: OR for every 10-year increase in age 1.20 [CI, 1.12 to 1.27]; ARI 1.1% [CI, 0.7% to 1.5%]

        - Greater physical comorbidity: OR 1.16 [CI, 1.02 to 1.31]; ARI 0.9% [CI, 0.1% to 1.7%]
    - Four **prescribing factors** were identified by several studies as associated with increased risk of prolonged opioid use (low certainty evidence):[15]
        - Prescribing opioids > 7 days
        - Higher morphine milligram equivalent dose
        - Long-acting versus short-acting opioids
        - > 1 refill in the first month
    - The authors of the SR recommend *restricting opioid prescriptions for acute musculoskeletal injuries to < 7 days, using lower doses, and not prescribing opioids in those with past or current substance use disorders to reduce prolonged opioid use.*[15]

QUESTION 1c: WHAT IS THE EVIDENCE FOR SKELETAL MUSCLE RELAXANTS IN ACUTE MUSCULOSKELETAL PAIN TREATMENT?

- The evidence for skeletal muscle relaxants in acute musculoskeletal pain treatment is primarily for acute low back pain. Please refer to the acute low back pain section.

QUESTION 1d: WHAT DO CLINICAL PRACTICE GUIDELINES RECOMMEND FOR THE PHARMACOLOGIC MANAGEMENT OF ACUTE MUSCULOSKELETAL PAIN?

- The 2020 American College of Physicians and American Academy of Family Physician Guidelines (ACP and AAFP) on the non-pharmacological and pharmacological management of acute pain from *non-low* back, musculoskeletal injuries recommend:[16]
    - Topical NSAIDs (± menthol) be used as first line treatment for pain reduction and function improvement (Grade: strong recommendation; moderate-certainty evidence). [16] The guidelines also recommend NSAIDs for pain reduction and function improvement and acetaminophen for pain reduction (Grade: conditional recommendation moderate certainty evidence).[16]
        - **Topical NSAIDs had the greatest net benefit, followed by oral NSAIDs and acetaminophen with or without diclofenac. Effects of these agents on pain were modest (around 1 cm on a 10-cm visual analogue scale, approximating the minimal important difference).[7]**
    - The guidelines recommend *against* opioids (including tramadol) for acute musculoskeletal injury pain treatment due to lack of a benefit greater than NSAIDs and increased harms (GI and neurological) (Grade: conditional recommendation, low certainty evidence).[16]
        - No opioid achieved benefit greater than that of NSAIDs, and opioids caused the most harm.[7]
        - Moderate certainty evidence showed an association between prolonged opioid use and greater physical co-morbidity, age, and past or present

substance use disorder. Low certainty evidence showed that prolonged opioid use was associated with prescriptions lasting more than 7 days and with higher morphine milligram equivalents/day.[15]

- This guideline is based on the 2020 NMA of various outpatient treatments used in the management of acute pain from non–low back, musculoskeletal injuries and the SR on the predictors of prolonged opioid use.[7,15]

- The 2019 Orthopedic Trauma Association Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury list NSAIDs and acetaminophen for the treatment of minor non-operative injury (e.g. sprain).[17]
  - Acetaminophen 1000 mg every 8 hours, then as needed, or NSAIDs as needed are recommended.[17]
  - Tramadol 50 mg is also listed but only if required.[17] The guidelines suggest a maximum of two prescriptions (20 tablets and 10 tablets, respectively) of tramadol 50 mg, 1 tablet every 6 hours as needed.[17]
  - The guidelines do not outline where the recommendation for tramadol comes from; however, they do comment on the lack of evidence on opiate comparisons for efficacy and safety in acute musculoskeletal injury pain treatment.[17]

- The 2018 evidence-based guidelines on the diagnosis, treatment, and prevention of ankle sprains only recommend NSAIDs as pharmacological therapy for reducing pain and swelling.[18]
  - The guidelines state that NSAIDs result in less pain in the short term (< 14 days) without significantly increasing the risk of AE compared with placebo (level 1 evidence).[18]
  - The guidelines state that acetaminophen seems to be associated with similar efficacy for pain, swelling, and range of motion compared to NSAIDs (level 1 evidence). However, the guidelines do not make specific recommendation for acetaminophen therapy.[18]
  - The guidelines also state that opioids may be equally effective as NSAIDs for pain relief but are associated with significantly more AE (level 2 evidence).[18]

QUESTION 2: IS THERE EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS IN THE TREATMENT OF ACUTE MUSCULOSKELETAL PAIN?

Musculoskeletal pain from sprains, strains, or whiplash

- The 2020 NMA that assessed the comparative effectiveness of various outpatient treatments in the management of non-low back, musculoskeletal injuries evaluated several non-pharmacological interventions including exercise, joint manipulation, both specific and non-specific acupressure, mobilization, transcutaneous electrical nerve stimulation, massage and supervised rehabilitation.[7]

- Transcutaneous electrical nerve stimulation, joint manipulation, and specific acupressure improved pain at 2 hours compared to placebo (low certainty evidence).[7]
- Transcutaneous electrical nerve stimulation and specific acupressure provided pain relief over 1 week compared to placebo without risk for gastrointestinal, neurologic, or dermatologic adverse events (low-certainty evidence).[7] Specific acupressure also improved physical function.[7]
- There were no differences between other nonpharmacological interventions and placebo for any outcome.[7]
- Most control participants had substantial pain relief by 1 to 7 days.[7]

Using the results of the 2020 NMA, the ACP and AAFP guidelines recommend that acute pain from non-low back, musculoskeletal injuries may be treated with specific acupressure to reduce pain and improve physical function or with transcutaneous electrical nerve stimulation to reduce pain (Grade: conditional recommendation; low certainty evidence).[16]

Musculoskeletal pain from ankle sprains

- Evidence-based guidelines from 2018 on ankle sprains treatment recommend:
  - Functional support (4-6 weeks) over immobilization improve self-reported function and prevent recurrence.[18] Ankle braces were reported to have greater efficacy compared to other forms of support (level 2).[18]
    - A few RCTs have shown that a short period (<10 days) of immobilization with a plaster cast or rigid support decreases pain and edema, and improves functional outcome in the treatment of acute lateral ligament injury (level 2). If immobilization is applied to treat pain or edema, it should be for a maximum of 10 days after which functional treatment should be started (level 2).
  - Exercise (± RICE therapy) is also recommended post ankle sprain to aid joint function recovery (level 1).[18]
    - Several trials have found that exercise therapy programs that are initiated early can reduce the prevalence of recurrent injuries and functional ankle instability. They have not been associated with improvement in pain but are associated with a quicker time to recovery and enhanced outcomes (level 1). A few trials contradict these findings, concluding that there is no effect from the addition of supervised exercise therapy to conventional treatment alone which is usually various components of PRICE (level 2).[18]
    - Most evaluations have been in supervised exercise programs. Whether exercise therapy should be supervised or not remains unclear due to contradictory evidence and requires further research.[18]
    - There is no evidence that RICE alone, or cryotherapy, or compression therapy alone has any positive influence on pain, swelling or patient function (level 2).[18]

- CADTH published two Rapid Response Reports in 2020, one evaluating exercise therapy and the other evaluating functional supports in *ankle sprains*.[19,20]

  Exercise Therapy Clinical Questions: What is the clinical effectiveness of exercise for the treatment of individuals with ankle sprain?

  - 1 SR found no significant differences in pain, function, and subjective ankle instability between exercise therapy programs + usual care vs. usual care alone. Usual care = various components of PRICE. There was a significant reduction in favor of exercise-based rehabilitation plus usual care for ankle re-injury compared with usual care alone at 7 to 12 months, but not at 3 to 6 months of follow-up.[19]
  - 1 SR and 2 RCTs, reported no significant differences between exercise programs when compared to each other for outcomes including pain, function, and subjective ankle instability.[19]
  - **Conclusion: Evidence in this review showed that overall there were no significant differences in the effectiveness between exercise interventions compared with usual care (PRICE) and between different programs**. Future well-controlled studies are needed to determine the effectiveness of different types of exercise programs with specific content and volume that is optimally suited for the general population, competitive sport medicine settings, or populations of different grades of ankle injury.[19]

  External Supports Clinical Questions: What is the clinical effectiveness of external supports for the treatment of individuals with ankle sprain?

  - The external supports identified in this review were stockings, elastic bandages, cohesive tape, lace-up ankle supports, semi-rigid ankle supports or posterior rigid supports, and short-leg casts.[20] Most of the comparisons were between different types of external support with very few comparisons with no support/placebo.[20]
  - 1 SR, 1 RCT and 1 cohort study found that for most evaluations there were no significant differences between different external supports. The SR concluded that semi-rigid or posterior rigid ankle supports and stockings were the most effective functional interventions for acute ankle sprain treatment.[20]
    - The SR included 2 very small RCTs investigating compression stockings (Class II/15-20mmHg) to non-compression (placebo stocking or elastic bandage), yielding contradictory results.[20]
  - Treatment with bandages, tape and semi-rigid or posterior rigid supports may be associated with some complications, however the risk of these complications was unclear.[20]
  - **Bottom line: Based on the available evidence there is insufficient information to support use of a particular type of external support in the treatment of ankle sprains**.

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ACUTE LOW BACK PAIN

SUMMARY STATEMENTS

- Acute low back pain (ALBP) is nonspecific pain lasting < 6 weeks.
  - Subacute low back pain lasts 6 weeks to 3 months.
  - Pain lasting > 3 months is considered chronic pain.
- Lifetime prevalence of low back pain in the adult general population is estimated to be as high as 84%. Recurrence is very common. Among those who have an episode of acute or subacute low back pain, 34% to 59% have persistent chronic back pain.[1]
- Goals of pharmacotherapy for *acute* low back pain are to reduce pain intensity, increase activity, and improve function.
  - Based on data from clinical trials studying commonly used back pain outcome measures, a 30% change from baseline may be considered a clinically meaningful improvement when comparing before and after measures for individual patients.
  - Prescribe medications at the lowest effective dose for the shortest period of time.
- Patients should be informed that acute low back pain often improves over time, regardless of treatment.

QUESTION 1: WHAT IS THE EVIDENCE OF EFFICACY AND SAFETY FOR THE PHARMACOLOGICAL OPTIONS IN THE TREATMENT OF ACUTE LOW BACK PAIN (ALBP)?

What to expect from pharmacotherapy

- It should be noted that non-pharmacological options are the preferred initial treatment for acute low back pain and that most patients improve over time regardless of treatment.
- A comprehensive systematic review performed to develop recommendations for the American College of Physicians (ACP) reported no large effects for any pharmacotherapy for acute or subacute low back pain.
- Guidelines have assessed the evidence for benefits and harms of pharmacotherapy differently; therefore, recommendations are also different.

QUESTION 1a. WHAT IS THE ROLE OF ORAL NSAIDs IN THE TREATMENT OF ALBP?

Pain and function: Oral NSAIDs provide a small improvement in pain intensity (moderate quality evidence) and function (low quality evidence) compared to placebo as demonstrated in an AHRQ Systematic Review[6, 8] and a 2020 Cochrane Review.[9]

- Mean differences in *pain intensity scores* on a 0-100 visual analogue scale **vs. placebo**:
  - Weighted mean difference of -8.39 (95% CI -12.68 to -4.10).[6,8]
  - Difference of -7.29 (95% CI -10.98 to -3.61) points on 0-100 VAS; N=815 (4 RCTs).[9]
  - A reduction in score of < 10 points is considered a small effect in the AHRQ report, and the Cochrane Review defined 10 points as the minimally important difference.

- The proportion of patients experiencing global improvement was statistically significantly greater in the NSAID group vs. placebo: Relative risk (RR) 1.40 (95% CI 1.12-1.75); NNT 7 (95% CI 5 – 10).[9]
- Both COX-2 selective and non-selective NSAIDs provide similar improvement in pain.[6-9]

***Adverse effects*:** NSAIDs (non-selective and selective) may increase the risk for adverse effects compared to placebo**,** although serious harms are rare and an increase in risk is not demonstrated in all studies.

- The 2020 Cochrane review found no clear difference in the proportion of participants experiencing adverse events in the comparison of NSAID vs placebo; as well as the comparison of selective COX-2 inhibitors versus non-selective NSAIDs (very low quality evidence).[9]
  - Long-term safety of NSAIDs was unable to be assessed due to short-term treatment and follow-up trials.[9]
    - Consider gastroprotection in patients at high risk for GI adverse effects.
    - Consider NSAID risks for cardiovascular and renal adverse effects when prescribing NSAIDs.
    - See section specifically addressing NSAID risks for additional details on adverse effects.

Clinical Practice Guidelines consider short-term use of NSAIDs as a first line pharmacotherapy in the treatment of acute low back pain.[4, 8, 11, 15-17]

QUESTION 1b. WHAT IS THE ROLE OF TOPICAL NSAIDs IN TREATMENT OF ALBP?

- Evidence for topical NSAIDs for acute musculoskeletal pain is derived from a 2015 Cochrane Review of 61 studies (N= 5311), *including 2 studies in acute low back pain.*[18]
  - *Pain:* Topical NSAIDs result in more patients experiencing at least 50% pain relief than topical placebo (moderate or high quality evidence).
    - A NNT below 4, representing clinical success, was reported for the following: (moderate to high quality evidence) (NNTs rounded up)
      - Diclofenac, (Emulgel formulation®) NNT 2 (95% CI 2 to 3)
      - Ketoprofen gel NNT 3 (95% CI 2 to 4)
  - It is questionable whether this evidence can be applied to treatment of acute low back pain since only two studies for this indication were included in the analyses. Refer to the section on Acute Musculoskeletal Pain for additional information on topical NSAIDs.
  - Although systemic absorption of topical NSAIDS is considered low (6%) this is dependent on the size of the area and amount applied. The area should not be covered with an occlusive dressing, as this will increase absorption (*see Table 2 on page 21 in the Acute Musculoskeletal Pain section*).

Clinical practice guidelines for acute low back pain do not include recommendations for topical NSAIDs; however, expert opinion suggests "Topical therapies such as NSAIDs could represent an option for the relief of low back pain associated with muscle spasm or tightness".

QUESTION 1c. WHAT IS THE ROLE OF SKELETAL MUSCLE RELAXANTS (SMRs) IN THE TREATMENT OF ALBP?

- *Pain relief:* Meta-analyses of the effect of SMRs report a small improvement in pain relief vs. placebo (moderate to high quality evidence).[6,7,20]
    - Mean difference in pain scores reached the predefined clinically meaningful change of at least 20 points: - 21.3, (95% CI -29.0, -13.5). 5 studies (N= 496).[20]

- *Function:* There is no evidence that SMRs improve function[6,7,20]

- *Adverse effects:* SMRs increased the risk of adverse effects vs. placebo in the AHRQ systematic review.[6,7]
    - The AHRQ (8 RCTs, moderate quality) reports an increased risk for:
        - Any adverse event, RR 1.50 (95% CI 1.14–1.98)
        - CNS (primarily sedation) RR 2.04 (95% CI 1.23–3.37)
    - No statistically significant increase was reported in a 2017 MA by Shaheed[20]

- *Cyclobenzaprine*
    - Cyclobenzaprine is commonly prescribed for low back pain. A meta-analysis of 10 RCTs rated as moderate quality, found cyclobenzaprine 10-60 mg daily improved back pain by day 10 *compared with placebo*.[22]
        - OR 4.7 (95% CI 2.7 to 8.1), NNT 3 (95% CI 2-4)
    - *Dose of cyclobenzaprine*
        - A publication in Canadian Family Physician refers to a meta- analysis reporting pain relief using a dose of cyclobenzaprine 5 mg tid, which is lower than the common 10 mg tid dose.[23]
        - Pain relief at 7 days was achieved in 50% of patients taking 5 mg tid vs 38% taking placebo (NNT 9) with no difference between the 5 mg and 10 mg doses. Adverse events, however, were higher with the 10 mg dose.
        - Somnolence rates :
            - 5 mg tid: 29%
            - 10 mg tid: 38% NNH 12 over 7 days of treatment
    - The cyclobenzaprine product monograph suggests a starting dose of 5 mg three times daily.[21,24]
    - Cyclobenzaprine is structurally similar to tricyclic antidepressants and has a similar adverse event profile of CNS and cardiac conduction abnormalities.[21]

- *Clinical practice guidelines*: There are contradictory recommendations for the use of SMRs in the guidelines:
  - The ACP guidelines have a strong recommendation for use of SMRs for acute low back pain for short term treatment (1 week).[8]
  - Kaiser Permanente, Washington recommends AGAINST the use of SMRs to treat acute low back pain due to small benefits and high occurrence of adverse events.[17]
  - NICE does not include a recommendation for or against SMRs.[15]

- Muscle relaxants should be used with caution in the elderly.[25,26]
  - Muscle relaxants increase the risk of hospitalization or an urgent care visit in people ≥ 65 years old; OR 1.32 (95% CI 1.16 to 1.50)[25]
  - Beers criteria: strong recommendation that muscle relaxants be avoided in the elderly due to adverse effects such as sedation, which are additive with other CNS depressants.[26]

- Muscle relaxants to **avoid** due to lack of evidence and adverse effects: [6-8]
  - Baclofen and dantrolene
  - Benzodiazepines

QUESTION 1d. WHAT IS THE ROLE OF ACETAMINOPHEN IN THE TREATMENT OF ALBP?

Acetaminophen vs. placebo

- *Pain:* Systematic reviews report that acetaminophen 4 g per day offers no benefit compared with placebo (low quality evidence). [6-8, 29]
  - Evidence for acetaminophen is primarily derived from the large, well-designed, 4 week PACE randomized controlled trial.[28]
    - Time to recovery was a median of 17 days with regular 4g/day; 17 days with acetaminophen given as required and 16 days with placebo.
      - No significant differences between acetaminophen groups and placebo and no differences between groups in pain, function and time to sustained recovery.
    - The PACE trial, while well designed, has some limitations that should be considered when interpreting results. For example, participants in the acetaminophen regular administration group did not adhere to the trial defined dose of 4 g per day. The authors state the results should be replicated before acetaminophen is completely dismissed in the management of low back pain.

Acetaminophen vs NSAIDs

- Evidence from small head to-head trials showed *no difference* between acetaminophen and NSAIDs. Both treatments demonstrated small benefits.[6-8]
  - Intravenous acetaminophen has similar efficacy as either morphine or an NSAID for treatment of mechanical low back pain in the emergency room.[31]

Clinical practice guidelines: Based primarily on the PACE trial evidence, several guidelines no longer recommend acetaminophen for acute low back pain.[8,15] Other guidelines acknowledge insufficient evidence for the efficacy of oral acetaminophen but include it as an option because of a stronger safety profile compared with other agents (consensus recommendations).[4,17,33]

QUESTION 1e. WHAT IS THE ROLE OF <u>COMBINATION THERAPY</u> IN THE TREATMENT OF ALBP?

- The AHRQ systematic review reports inconsistent evidence of benefit for the addition of SMRs to NSAIDs vs. NSAIDs alone (low level evidence).[6,7]

- Three RCTs, enrolling patients during an emergency room visit for LBP, found that adding cyclobenzaprine, orphenadrine, methocarbamol, baclofen, tizanidine or oxycodone/acetaminophen to NSAIDs (naproxen or ibuprofen studied) did not improve function or pain outcomes compared with NSAIDs alone and had the potential for increased risk.[36-38]

- Similarly, a 2018 MA addressing the effect of combination pharmacotherapy (NSAIDs + SMR or opioids) vs NSAIDs on acute low back pain reports no evidence of benefit for relief of pain or improvement in function compared with monotherapy (6 RCTs). An increased risk for adverse effects was demonstrated with combination therapy.[40]

- A 2020 Cochrane Review included a comparison of NSAIDs vs. acetaminophen + codeine.[9] The review reports no clear statistical or clinical differences between groups for pain intensity or global improvement.

Clinical Practice Guidelines:

- ACP guidelines report the inconsistent benefit for combining NSAIDs + muscle relaxants and have no statement regarding combinations in pharmacotherapeutic options.[8] Other guidelines warn of additive side effects if SMRs are taken with other CNS depressant medications.[4]

QUESTION 1f. WHAT IS THE ROLE OF <u>ORAL OPIOIDs</u> IN THE TREATMENT OF ALBP?

- Evidence for the use of opioids in acute low back pain is lacking.
  - <u>ACP guidelines</u> suggest there was insufficient evidence found in the AHRQ Systematic Review to determine the effectiveness of opioids vs. placebo in the treatment of acute low back pain and provide no recommendation for their use.[6,8]

- Resources providing a recommendation for the use of opioids in acute low back pain include notes of caution.[4,11,15,45]
  - Routine use is **NOT** recommended and only if alternative therapies such as NSAIDs are contraindicated or ineffective.

- **If used,** the lowest effective dose of immediate-release opioids should be prescribed for short durations (e.g., 3 days) and in no greater quantity than needed for the expected duration of pain severe enough to require opioids use.

➢ Choosing Wisely Canada, Opioid Wisely resources note the most common entry point to prescription opioid addiction is through opioids prescribed for back pain. Adequate pain control using opioids is frequently not achieved and patients face the added risks of physical dependence and withdrawal hyperalgesia, which can lead to continued use.[47] *Statement: Don't use an opioid analgesic medication as first-line treatment for acute, uncomplicated, mechanical, back-dominant pain.* https://choosingwiselycanada.org/campaign/opioid-wisely/

QUESTION 1g. WHICH MEDICATIONS OR INTERVENTIONS HAVE INSUFFICIENT EVIDENCE FOR USE IN ALBP?

➢ *Medications*
- Based on the AHRQ 2016 systematic review there is insufficient evidence to determine the effectiveness of *opioids, antidepressants, benzodiazepines, or anti-seizure medications, versus placebo in patients with acute or subacute LBP*. [6-8]
- *Gabapentanoids:* A 2017 RCT in acute and chronic sciatica [48] and a 2018 meta-analysis,[49] which primarily studied chronic LBP and lumbar radicular pain, reported lack of efficacy for gabapentanoids and an increased risk for adverse effects.
- *Systemic Corticosteroids:* Low quality evidence showed no difference in pain or function between a single intramuscular injection of methylprednisolone or a 5-day course of prednisolone compared with placebo in patients with acute LBP.[8]

➢ *Interventions not recommended*
- Imaging tests are not helpful for recovery or management of acute or recurring low back pain unless there are signs of serious pathology.[50]
- ACP guidelines suggest the following are **NOT** recommended [8]
  - Bedrest
  - Shoe Insoles/Orthoses
  - Lumbar supports

QUESTION 2: WHAT ARE THE NON-PHARMACOLOGICAL OPTIONS FOR TREATING ALBP?

➢ *The AHRQ systematic review and ACP guidelines report the following results:*
- *Non-pharmacological therapy* with evidence of benefit include: [6-8]
  - Superficial heat (moderate quality evidence)
  - Massage, acupuncture, or spinal manipulation (low quality evidence)
  - Low level laser therapy + NSAID vs. NSAID**:** (low quality evidence)
- *Evidence is insufficient* to determine the effectiveness of transcutaneous electrical nerve stimulation, electrical muscle stimulation, inferential therapy, short-wave

diathermy, traction, superficial cold, motor control exercise, Pilates, tai chi, yoga, or psychological therapies.[6-8]

- *Physical Activity*: Physical activity is recommended. There is insufficient evidence to recommend for or against any specific kind of exercise, or the frequency/intensity of training.[11,16]

- *Patient Education:* All patients with nonspecific low back pain should be offered information on the nature of low back pain, reassurance about the likely low risk of serious underlying disease and advice on evidence-based self- management.[51] Patients should be made aware that most patients with acute or subacute low back pain improve over time regardless of treatment.[8]

- The North American Pain Society guidelines recommend back schools.[11]

Prescriber Resources and Patient Information

PHYSICIAN On-line Resources for Acute Low Back Pain

- Centre for Effective practice tools (many resources)
  - https://cep.health/tools/
  - Clinically Organized Relevant Exam (CORE) Back Tool 2016 https://cep.health/clinical-products/low-back-pain/
  - Manual Therapy as an Evidence-Based Referral for Musculoskeletal Pain 2020 https://cep.health/clinical-products/manual-therapy/
- 2020 North American Spine Society Evidence based guidelines for multidisciplinary Spine Care
  - https://www.spine.org/Portals/0/assets/downloads/ResearchClinicalCare/Guidelines/LowBackPain.pdf
- Accelerating Change Transformation Team (ACTT) (formerly Toward Optimal Practice-TOP) Evidence informed primary care management of low back pain –
  - https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=acute%20low%20back%20pain
- Evidence-Informed Primary Care Management of Low Back Pain (3rd edition, 2015; minor revision2017). Institute of Health Economics Alberta
  - https://www.ihe.ca/research-programs/hta/aagap/lbp#aagaplbpptres
- Choosing Wisely Canada. Opioid Wisely: Spine Recommendation #6 https://choosingwiselycanada.org/campaign/opioid-wisely/
- Traeger A, et al. Diagnosis and management of low-back pain in primary care. *CMAJ* 2017; 189:E1386-95. https://www.cmaj.ca/content/cmaj/189/45/E1386.full.pdf
- Patient-centred, pragmatic prescribing for acute non-specific low back pain (Australian) 2018
  - https://www.nps.org.au/news/patient-centred-pragmatic-prescribing-for-acute-non-specific-low-back-pain
- Qaseem A et al 2017 Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians
  - https://www.acpjournals.org/doi/10.7326/M16-2367
- Adult acute and subacute low back pain: Institute for Clinical Systems Improvement; 2018
  - https://www.icsi.org/wp-content/uploads/2019/08/March-2018-LBP-Interactive2.pdf
- NICE
  - https://www.nice.org.uk/guidance/NG59/chapter/Recommendations#assessment-of-low-back-pain-and-sciatica
- How to talk to your patient about goals of therapy for low back pain https://prc.coh.org/pdf/Goals-FF%205-10.pdf

PATIENT On-line Resources for Acute Low back Pain

- Evans M. Low back pain [video file]. 2014.
  - https://www.youtube.com/watch?v=BOjTegn9RuY
- So your back hurts information pamphlet
  - https://www.iwh.on.ca/sites/iwh/files/iwh/tools/so_your_back_hurts_2010.pdf
- Saskatchewan Ministry of Health. General recommendations for maintaining a healthy back: Patient information [Internet]. 2010
  - http://www.sasksurgery.ca/pdf/recommendations-for-back-health.pdf
- Toward Optimized Practice, Institute of Health Economics. What you should know about your acute low back pain [Internet]. 2015 [cited 2016 Feb 19].
  - https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-Patient-Handout-Acute.pdf#search=acute%20low%20back%20pain
- Choosing Wisely Canada. Imaging tests for lower back pain: When you need them – and when you don't.
  - http://www.choosingwiselycanada.org/materials/imaging-tests-for-lower-back-pain-when-you-need-them-and-when-you-dont/
- NSHA Managing low back pain 2018
  - https://www.nshealth.ca/sites/nshealth.ca/files/patientinformation/1967.pdf

BACKGROUND

Prevalence

- The lifetime prevalence of low back pain in the adult general population is variable but estimated to be as high as 84%. Among those who have an episode of acute or subacute low back pain, 34% to 59% have persistent chronic back pain.[1]
- A six year study (2009-2015) using administrative data from the emergency department at the Halifax Infirmary found a prevalence of 3.17% for a primary complaint of back pain. The majority of patients (60.8%) had low back pain with no potential nerve root involvement.[2]
- A retrospective study at the QEII using the data from 2009-2015 reported that those presenting with low back pain had pain scores of moderate intensity (57.6%), followed by severe (32.6%) and mild (9.9%). Laboratory investigations were conducted on 22.5% and 30% received an imaging study. 60% of patients received medications during their stay in the ED: Ibuprofen (28.3%), hydromorphone (24.9%), and acetaminophen (21.5%).[3]
- Once a patient experiences back pain it is estimated that the likelihood of recurrence at one year ranges from 24% to 80%.[4]

Factors affecting progression to chronic low back pain

- An acute episode of low back pain can lead to chronicity. Factors that influence chronicity include depression, employment status and chemical dependency. Chronic low back pain (pain lasting greater than 12 weeks) is a leading cause of disability and cost.[4]
- The risk factors for chronicity of pain (yellow flags) described by the Centre for Effective Practice Clinically (CEP) Organized Relevant Exam (CORE) Back Tool include:[5]
    - Belief that back pain is harmful or potentially severely disabling.
    - Fear and avoidance of activity or movement.
    - Tendency to low mood and withdrawal from social interaction.
    - Expectation of passive treatment(s) rather than a belief that active participation will help. https://cep.health/clinical-products/low-back-pain/

Diagnosis of Acute Low Back Pain

- For established approaches for diagnosis of acute low back pain please refer to resources such as the Clinically Organized Relevant Exam (CORE) Back Tool, Centre for Effective Practice available at:[5] https://cep.health/clinical-products/low-back-pain/

Evidence sources

- The evidence for pharmacological therapies is primarily derived from the most recent systematic reviews for treatment of acute low back pain.
    - A systematic review by the Agency for Healthcare Research and Quality (AHRQ) [6,7] was performed to inform the American College of Physicians (ACP) clinical practice guidelines for low back pain.[8] It includes recommendations for pharmacologic and non-pharmacologic therapy for acute, subacute and chronic low back pain.

- A Cochrane Review addressing the use of NSAIDs for acute low back pain was updated in 2020.[9]
- Additional systematic reviews or clinical trials are included to update or compliment the evidence from systematic reviews.

- Evidence for non-pharmacological therapies has been primarily derived from the AHRQ systematic review, the Canadian Agency for Drugs and Technology in Health (CADTH) resources and the North American Spine Society.[6,7, 10,11]
- The quality of the studies of pharmacotherapy for acute low back pain ranges from very low to very high depending on the treatment.
  - The AHRQ systematic review states ***no pharmacotherapy has a "large" effect on pain relief or improvement in function***.[6,7]
- Application to practice is considered in this document by providing recommendations from various clinical practice guidelines for each of the clinical questions.
- Evidence for the treatment of chronic low back pain or radicular pain is not included in this report.

Outcome measures in clinical trials of low back pain

Chiarotto A et al 2018 reported recommendations on core outcome measurement instruments for clinical trials in patients with non-specific low back pain (nsLBP).[12] Using a Delphi process and an international multidisciplinary panel, the core outcome measures include those for physical functioning, pain intensity, health related quality of life and mortality.

Table 1 Core outcome measurement instruments for clinical trials in nonspecific low back pain[12]

Core Outcome Domain	Instrument	Availability (All but SF-12 may have a charge to use)
Physical functioning	Oswestry Disability Index (ODI) version 2.1a 24-item Roland Morris Disability Questionnaire (RMDQ-24)	https://eprovide.mapi-trust.org/instruments/oswestry-disability-index http://www.rmdq.org/download.htm
Pain intensity	Numeric Rating Scale	Various numerical or visual analogue scales used
Health-related quality of life	Short Form Health Survey 12 (SF12) 10-item PROMIS Global Health (PROMIS-GH-10)	https://www.physio-pedia.com/12-Item_Short_Form_Survey_(SF-12) https://www.hss.edu/physician-files/huang/SF12-RCH.pdf https://www.apta.org/patient-care/evidence-based-practice-resources/test-measures/patient-reported-outcomes-measurement-information-system-global-10-promis-global-10
Mortality **Number of deaths**	Number of deaths in clinical trials	

AHRQ SR Definitions for Magnitude of Effects, based on mean between group differences [6,7]

Pain

- Slight/small effect**:** 5–10 points on 0- to 100-point VAS or 0.5–1.0 points on 0- to 10- VAS
- Moderate effect: 10–20 points on 0- to 100-point VAS or > 1–2 points on 0- to 10- VAS
- Large/substantial effect: >20 points on 0- to 100-point or >2 points on 0- to 10- VAS

Function

- Slight or small effect: 5–10 points on the ODI or 1–2 points on the RDQ
- Moderate effect: >10–20 points on the ODI or >2–5 points on the RDQ
- Large/ substantial effect: >20 points on the ODI or >5 points on the RDQ

Pain or function (Standardized Mean Difference - SMD)

- Slight or small effect: 0.2– 0.5 SMD
- Moderate effect: > 0.5– 0.8 SMD
- Large/ substantial effect: >0.8 SMD

ODI = Oswestry Disability Index; RDQ = Roland Morris Disability Questionnaire; SMD = standardized mean difference; VAS = visual analogue scale

North American Spine Society Grades of Evidence [11]

A: Good evidence (Level I studies with consistent findings) for or against recommending intervention.

- It is *recommended* to follow the recommendation

B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.

- It is *suggested* to follow the recommendation

C: Poor quality evidence (Level IV or V studies) for or against recommending intervention.

- *May be considered* as an option

I: There is insufficient or conflicting evidence not allowing a recommendation for or against intervention.

- *Insufficient evidence* to make a recommendation for or against

QUESTION 1: WHAT IS THE EVIDENCE OF EFFICACY AND SAFETY FOR THE PHARMACOLOGICAL OPTIONS IN THE TREATMENT OF ACUTE LOW BACK PAIN (ALBP)?

What to expect from therapy

- A comprehensive systematic review performed to develop recommendations for the American College of Physicians (ACP) reported *no large effects* for any pharmacotherapy for acute or subacute low back pain.[6,7,8]
- Guidelines differ in their interpretation of the evidence and resulting recommendations for treatment of low back pain.
  - Differences relate to consideration of potential harms from adverse effects that may outweigh the modest benefit from pharmacotherapy.
- The ACP guidelines suggest that, " Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select **non-pharmacologic treatment** with superficial heat (moderate quality evidence), massage, acupuncture, or spinal manipulation (low quality evidence). The only two pharmacological treatments recommended are NSAIDs or skeletal muscle relaxants (moderate-quality evidence) (Grade: strong recommendation)."[8]

Goals of therapy for acute low back pain

- **Goals of pharmacotherapy** for *acute LBP* are to **reduce pain intensity, increase activity and improve function.**
- Based on data from clinical trials studying commonly used back pain outcome measures, a 30% change from baseline may be considered a clinically meaningful improvement when comparing before and after measures for individual patients [13, 14]
- See the definitions of magnitude of effect from meta-analyses (page 39-40) and the descriptions of minimally important differences provided in the summary of evidence within the clinical questions.

QUESTION 1a. WHAT IS THE ROLE OF ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) IN THE TREATMENT OF ALBP?

- A 2020 Cochrane Review[9] and a 2016 systematic review by the AHRQ[6,7] report the most recent evidence for the efficacy and safety of NSAIDs for the treatment of ALBP.
  - The Cochrane Review of randomized controlled trials assessed the effects of NSAIDs compared to placebo or alternative treatments in adults ≥ 18 years. Outcomes included pain reduction, disability, global improvement, adverse events, and return to work.[9]
    - The review included 32 trials, N= 5356 with an age range of 16 to 78 years, in primary and secondary care.
    - Follow-up ranged from one day to six months.
    - Diclofenac was the most common NSAID evaluated (5 of the 9 NSAID trials vs placebo; Ibuprofen was studied in 2 of the 9).
    - **Results (see data in table below) NSAIDs vs. placebo**
      - **Pain intensity reduction:** moderate quality evidence showed that NSAIDs are slightly more effective.
      - **Disability improvement**: high quality evidence showed that NSAIDs are slightly more effective.
      - **Global improvement** low quality evidence showed that NSAIDs are slightly more effective
      - **Adverse events or return to work** very low quality evidence of no clear difference after 7 days.

Table 2 Results van der Gaag Cochrane review NSAIDs in acute low back pain[9]

Outcomes	Mean difference in score (95%CI) Placebo	NSAIDS	Relative effect 95%CI	GRADE of Evidence	Comments
Pain Intensity *N=815 (4 RTCS)* *VAS (0 to 100; Follow-up 7 to 15 d*	Change in pain score from baseline Mean 7.9 to 33.9	Change in pain score lowering compared with placebo Mean change -7.29 (-10.98 to -3.61 points lower than placebo) I^2 35%	-	Moderate	Questionable clinical relevance MID is 10 points (0 to 100 scale)
Disability *N= 471 (2 RCTS)* *RMDQ (0 to 24; lower = better) Follow-up: 7 to 14 d*	Mean 6-7.3	2.02 lower (2.89 to 1.15 lower than placebo) I^2 0%	-	High	Questionable clinical relevance MID is 2.4 points on a 0-24 scale
Global Improvement *N=1201 (5 RTCs)* *Various dichotomized Likert scales; lower = better* *Follow-up 1 to 15 days*	**Proportion experiencing improvement**				
	367 per 1000	514 per 1000 (412 to 643) I^2 52%	RR 1.40 (1.12-1.75)	Low	Questionable clinical relevance NNT 7 (95%CI 5 – 10)*
Adverse effects ***N=1394 6 RCTs*** *Follow up 1 day to 12 weeks*	111 per 1000	95 per 1000 (70-130) I^2 0%	RR 0.86 (0.63 to 1.18)	Very low	Not statistically significant
Return to work % *1 RCT follow-up 7 d*	212 per 1000	314 per 1000 (208 to 473)	RR 1.48 (0.98-2.23)	Very low	Not statistically significant

MID = minimally important difference'*NNT calculated with Dal CME Clinical Significance Calculator http://ktcalc.cme.dal.ca/site/login.php; RR = relative risk

- **Additional outcomes**
  - **Differences between NSAIDs**: Two studies provided **long-term follow-up data**; however neither showed significant differences between different NSAIDs for pain or disability at time frames ranging from 2 to 6 months.
    - **COX-2 inhibitor NSAIDs compared to non-selective NSAIDs:** No clear difference in the short-term reduction of pain intensity was demonstrated between the two classes.
      - ❖ Difference in mean change from baseline -2.60, 95% CI -9.23 to 4.03; 2 RCTs, N = 437 (Low quality evidence.)
  - **Adverse events:** No clear difference in the proportion of participants experiencing adverse events in the comparison of NSAIDs versus placebo and the comparison of selective COX-2 inhibitors versus non-selective NSAIDs. (Very low quality evidence.)
    - Long term safety of NSAIDs was unable to be assessed due to short term treatment and follow-up trials.
- The authors conclude that NSAIDs seem slightly more effective than placebo for short-term pain reduction (moderate certainty), disability (high certainty), and global improvement (low certainty), but the magnitude of the effects is small and probably not clinically relevant. Many studies were relatively old and industry-sponsored. The authors suggest that since acute LBP is a frequent condition and morbidity is high, future research is needed to establish strong, and high-quality evidence regarding the use of NSAIDs in acute low back pain.[9]

➢ The AHRQ SR results are similar to the Cochrane Review for the treatment of acute low back pain with NSAIDs.[6,7] Of note, several of the same trials are included in the Cochrane Review[9] and the AHRQ review. Since it supports the latest version of the American College of Physicians Guidelines the results are summarized below.[8]

- **Results: (Pain intensity, function and global improvement, adverse effects)[6,7]**
    - **Pain Intensity:** Oral NSAIDs provide a small improvement in pain intensity (moderate quality evidence) and function (low quality evidence). Data for the number of trials and population size for each outcome were not provided for each analysis, but have been included when available.
        - Both COX-2 selective and non-selective NSAIDs provide similar improvement in pain.
        - Several randomized, controlled trials (RCTs) showed no difference in the likelihood of achieving pain relief with NSAIDs compared with placebo.
        - Patients with **moderate to severe** pain were more likely to benefit from an NSAID vs. placebo than those with mild pain (based on one piroxicam trial).
        - Benefit in moderate to severe pain at baseline (NSAID 82% vs. placebo 53%) vs. mild pain (49% vs. 38% respectively).
    - In studies of patients without sciatica or in mixed populations with or without sciatica:
        - **Pain intensity:** NSAIDs were associated with greater improvements in pain intensity versus placebo (4 studies; N= 745 patients).
        - Weighted Mean Difference (WMD) −8.39 (95% CI −12.68 to −4.10), P = 0.00013.
    - **Function and global improvement:** NSAIDs resulted in a higher proportion of patients taking NSAIDs experiencing global improvements after follow up of 3 weeks or less (7 studies).
        - RR 1.19 (95% CI 1.07 to 1.33), P = 0.001
    - **Adverse effects:** NSAIDs **increased the risk** for adverse effects (10 studies N=1852) RR 1.35 (95% CI 1.09, 1.68); serious harms were rare.
        - In a separate analysis, COX-2 selective NSAIDs resulted in a lower risk for adverse events than traditional NSAIDs: N=4 studies, RR 0.83 (95% CI 0.70 to 0.99).
- Consider gastroprotective treatment when using NSAIDs in high risk patients.
- For information on NSAID adverse effects and prescribing considerations please refer to NSAID risks section (NSAID risk tools) and Appendix 1 (Drug Tables).
- Clinical practice guideline recommendations are summarized in *Table 3*.

Table 3: Oral NSAIDs for Acute Low Back Pain

Clinical Practice Guideline Recommendations for Oral Non-steroidal Anti-inflammatory (NSAIDs) Acute Low Back Pain	
Source	Recommendation
North American Spine Society: Evidence Based Clinical Guidelines for Multidisciplinary Spine Care **Diagnosis and Treatment of Low Back Pain 2020** [11] https://www.asra.com/advisory-guidelines/article/14/evidence-based-clinical-guidelines-for-multidisciplinary-spine-care-diagnosis-an	Non-selective NSAIDs are suggested for the treatment of low back pain. **Grade of Recommendation: B** There is insufficient evidence to make a recommendation for or against the use of selective NSAIDs for the treatment of low back pain. **Grade of Recommendation: I**
Institute for Clinical Systems Improvement (ICSI) 2018 (Minnesota) [4] Low Back Pain, Adult Acute and Subacute https://www.icsi.org/guideline/low-back-pain/ Recommendation is based on the AHRQ comparative Effectiveness review (Chou, 2016). See below for ACP recommendations based on the same resource.	NSAIDS may be used for short-term pain relief in patients with acute and subacute low back pain. Patients should be counseled on potential side effects. **Quality of Evidence**: Moderate **Strength of Recommendation**: Strong **Benefit** NSAIDs have shown to have small beneficial effect on pain and function. **Harm** Harms of NSAIDs include but are not limited to gastritis, gastrointestinal bleeding, and possible cardiovascular complications. **Benefits/Harms Assessment** After discussing possible side effects with patients, it is reasonable to offer NSAIDs for short-term pain relief.
American College of Physicians **Clinical Practice Guidelines 2017**[8] https://www.acpjournals.org/doi/pdf/10.7326/M16-2367	The full statement on treatment is required to provide context: "Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select NSAIDS or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)"
NICE 2017 UK[15] National Institute for Health and care Excellence Low back pain and sciatica in over 16 years old patients 2017 https://www.nice.org.uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637 (Update due in Sept 2020)	Consider oral NSAIDs for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age. When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.
Alberta Toward Optimized Practice 2017 [16] **Part of: Accelerating Change Transformation Team (ACTT)** https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=low%20back	Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice **NSAIDs.** Serious adverse effects of NSAIDs include gastrointestinal complications (e.g., bleeding, perforation, and increased blood pressure).
Kaiser Permanente Washington guidelines 2017[17] https://wa.kaiserpermanente.org/static/pdf/public/guidelines/back-pain.pdf	For medium- or high-complexity patients, a trial of NSAIDs may be considered if acetaminophen has been ineffective. NSAIDs such as ibuprofen or naproxen should be used with caution in patients with cardiovascular morbidities, risk of gastrointestinal bleeding, or hepatic or renal dysfunction.

QUESTION 1b. WHAT IS THE ROLE OF TOPICAL NSAIDs IN THE TREATMENT OF ALBP?

- A Cochrane review by Derry et al. (2015) reviewed topical NSAIDs for acute musculoskeletal pain (included two trials assessing the use of topical agents for ALBP).[18]
  - The systematic review included 61 studies.
    - N=5311 participants treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID.
  - **Pain Relief:** Topical NSAIDs result in more patients experiencing at least 50% pain relief than matching topical placebo (moderate or high quality data).
  - Numbers needed to treat (NNT) below 4, which serves as a marker for clinical success, have been demonstrated for three drugs:

Table 4 Results Derry Cochrane Review Topical NSAIDs in Acute Musculoskeletal Pain[18]

	Outcome of at least 50% pain relief		
	Relative Risk (95% CI) vs placebo	NNT (95% CI)	**Quality of evidence**
Diclofenac, (Emulgel formulation®)	3.4 (2.7 to 55) 2 studies N= 314	1.8 (1.5 to 2.1)	High
Ketoprofen gel	2.2 (1.7 to 2.8) 5 studies, N= 348	2.5 (2.0 to 3.4)	Moderate
Ibuprofen gel	2.7 (1.7 to 4.2) 2 studies N=241	3.9 (2.7 to 6.7)	Moderate

  - It is questionable whether this evidence can be applied to treatment of acute low back pain since only two studies for this indication were included in the analyses.
  - Refer to the section on Acute Musculoskeletal Pain for additional additional details on the evidence for topical NSAIDs (pages 19-22).

Clinical Practice Guidelines – Topical NSAIDs

- Clinical practice guidelines for acute low back pain do not include recommendations for topical NSAIDs; however, expert opinion suggests "Topical therapies such as NSAIDs could represent an option for the relief of low back pain associated with muscle spasm or tightness".
- The Alberta, Toward Optimized Practice 2017 guideline states there is inconclusive evidence to recommend for or against the use of topical NSAIDs for acute or subacute low back pain. The guideline does not reference the Derry Cochrane Review.[16]

QUESTION 1c. WHAT IS THE ROLE OF SKELETAL MUSCLE RELAXANTS IN THE TREATMENT OF ALBP?

Skeletal Muscle Relaxants (SMRs) vs. placebo

- The AHRQ SR for acute LBP found SMRs superior to placebo for **short-term pain relief**.[6,7]

- **Results:**
  - Studies included various muscle relaxants including cyclobenzaprine, tizanidine, chlorzoxazone and carisoprodol. The evidence is primarily, but not exclusively, based on the non-benzodiazepine vs. placebo results of a Cochrane Review by van Tulder 2003 (edited 2017).[19]
  - The AHRQ review included a total of 25 trials, enrolling 20-562 patients.[6,7]
    - 22 studies (17 high quality) were included in the Cochrane Review and three additional fair quality trials were assessed.
    - Short-term pain relief was defined as a ≥ two-point or 30% improvement on a 0-10 VAS pain scale. The evidence was rated as being of moderate quality.
- **Pain relief:** SMRs increased the chance for clinically relevant pain relief:
  - After 2 to 4 days (4 trials N=294; RR 1.25, 95% CI 1.12 to 1.41) I^2 =0%
  - After 5 to 7 days (3 trials N=244; RR 1.72, 95% CI 1.32 to 2.22) I^2 =0%
- **Function**: The effects of muscle relaxants on function were unable to be determined due to lack of evidence, as most trials did not report this outcome.
  - There was no clear difference between the different SMRs included in the studies.
  - Evidence from the van Tulder Cochrane review reported that skeletal muscle relaxants **increased the risk** for:[19]
    - Any adverse event; 8 trials RR 1.50 (95% CI 1.14 to 1.98)
    - CNS events; 8 trials RR 2.04 (95% CI 1.23 to 3.37)

➢ A <u>systematic review and meta-analysis published in 2017</u> presented similar results of efficacy. Four muscle relaxants were considered in the analysis for acute low back pain: eperisone, carisoprodol, thiocolchicoside, and tizanidine. Of these, tizanidine is the only SMR available in Canada.[20]

- **Results:**
  - **Pain relief:** Five trials (N=496 participants) provide high quality evidence that muscle relaxants result in clinically significant pain relief in the short term for the treatment of acute LBP.
  - Pain relief was reported as the mean difference in pain scores on a 0-100 scale. A 10 point difference was considered a minimal difference, and a 20 point difference considered clinically significant.
    - MD 21.3, (95%CI -29.0, -13.5)
  - **Adverse Events:** Median adverse event rate for muscle relaxants was similar to placebo 14.1%, interquartile range (IQR 7.0-28.7%) and 16.0% (IQR 4.1-31.2%); p = 0.5, respectively.
    - No eligible trials were found for the use of benzodiazepines in ALBP.
    - There was no information on long-term outcomes and little evidence presented on disability.

- The generalizability of these results to muscle relaxants commonly used in Canada is limited, since they were not studied in the clinical trials included in the analyses.

Cyclobenzaprine

Cyclobenzaprine is commonly prescribed for low back pain. The Health Canada approved indication for cyclobenzaprine is for muscle spasm associated with acute musculoskeletal conditions. The CPhA monograph suggests that acute neck or back pain is not considered a Health Canada approved use.[21]

- Browning et al. (2001) performed a systematic review and meta-analysis of cyclobenzaprine RCTs for the treatment of back pain. Study duration was a median of 14 days.[22]
  - **Results:**
    - **Improvement in back pain:** Of the 14 studies identified for the review, 10 were included in the analysis of global improvement. Cyclobenzaprine (10 to 60 mg per day) was associated with improvement in back pain by day 10 compared to placebo.
      - OR 4.7 (95% CI 2.7-8.1). **NNT 3 (95% CI 2-4)**
      - The effect size was greater in the first 3 days of treatment than after either 1 or 2 weeks.
      - Measures of local pain, muscle spasm, tenderness to palpitation, activities of daily living and range of motion also favored cyclobenzaprine.
  - **Adverse effects:** The benefit of muscles relaxants comes at the price of greater adverse effects.
    - Drowsiness, dry mouth, and dizziness were more common in the cyclobenzaprine group.
    - Any AE rates: 53% for muscle relaxants vs 28% placebo. **(NNH 4)**

- A 2015 publication in *Canadian Family Physician*, Tools for Practice addresses the use of cyclobenzaprine for acute low back pain.[23]
  - **Results:** The evidence referenced in this publication includes 3 SRs, (including 9 to 46 RCTs and 820 to 5401 patients) of *non-benzodiazepine muscle relaxants vs. placebo*.
  - **Pain scores** at 10 days were statistically significantly lower by approximately 12 points on a 100-point visual analogue scale.
    - Numbers needed to treat:
      - Pain reduction at 2 to 7 days; **NNT 4 to 7**
      - Global efficacy at 2 to 4 days; **NNT 4.**
  - Results specifically for cyclobenzaprine versus placebo:
    - **Global improvement** (1 systematic review of 14 RCTs, N= 3023.)
      - **NNT 3 at 10 days.**

- **Pain relief** (pooled results from 4 RCTs)
  - Pain relief (N=1389 patients) was achieved at 7 days in 50% of those taking **5 mg** of cyclobenzaprine 3 times daily versus 38% taking placebo; p <0.001; **NNT 9.**

- No difference in pain relief was shown between cyclobenzaprine 5 mg or 10 mg.
- **Adverse events** include dose-related somnolence and dry mouth.
  - Somnolence
    - Placebo 10%
    - 5 mg three times daily 29%
    - 10 mg three times daily 38%
    - **NNH 12** (meaning for every 12 patients treated with 10 mg vs. 5 mg one person will report somnolence as an adverse effect. Treatment duration was 7 days.)
  - Discontinuation due to somnolence
    - Placebo 0.8%
    - 5 mg three times daily 2.5%
    - 10 mg three times daily 5.2%
    - **NNH 37** (meaning that for every 37 patients treated with 10 mg vs 5 mg, one patient will discontinue due to somnolence. Treatment duration was 7 days)

Cyclobenzaprine dose

- The CPhA cyclobenzaprine monograph references the study referred to in the Tools for Practice, which reported that cyclobenzaprine 5 mg TID is as effective as 10 mg TID, and that the lower dose produces less sedation.[21,24]
  - The monograph states that cyclobenzaprine is available only as a 10 mg tablet, and splitting tablets may result in increased variation in the administered dose. However, the potential lower risk of adverse events may be preferred, especially in elderly patients.
  - The dosing tables in the monograph suggest:
    - A starting dose of 5 mg tid and a maximum of 30 mg per day for 7 days for acute neck or back pain.
    - For the management of acute muscle spasm and associated pain, cyclobenzaprine should not be used for longer than 2–3 weeks, as efficacy is questionable after this time period. The table states not a Health Canada approved indication.

Adverse Effects of Skeletal Muscle Relaxants

- The data presented in the AHRQ systematic review reports sedation, drowsiness and dizziness as adverse events related to skeletal muscle relaxants.[6,7]
  - Increased risk of *any adverse event* vs. placebo
    - RR 1.50 (CI, 1.14–1.98) based on 8 RCTs of moderate quality.
  - Increased risk of central nervous system events vs placebo (primarily sedation)

- RR 2.04 (CI, 1.23–3.37) based on 8 RCTs of moderate quality.

- Cyclobenzaprine is structurally similar to tricyclic antidepressants and has a similar adverse event profile, including CNS effects and cardiac conduction abnormalities.[21]

Skeletal muscle relaxants in the elderly

- Spence et al 2013 reported the effects of skeletal muscle relaxants and subsequent risk of injury in a retrospective case-control study of people aged 65 years or older enrolled in an integrated health care system.[25]
  - Cases were defined as patients with a documented injury resulting in either a hospitalization, or an emergency department or urgent care visit.
  - SMR exposure for cases and controls within 60 days prior to the visit for an injury was evaluated.
  - The base population included 322,806 older adults, from which 27,974 injuries were identified and matched with 104,303 controls.
    - A SMR was used by 365 (1.3%) of the cases compared with 801 (0.77%) used by the control group in the 60 days prior to the injury.
    - The risk of injury was significantly increased for patients using any SMR compared to no use (adjusted OR 1.32, 95% CI 1.16-1.50; $p < 0.001$). Analysis of individual muscle relaxants revealed increased risk as well:
      - Carisoprodol (OR 1.73, 95% CI 1.04-2.88; $p = 0.036$)
      - Methocarbamol (OR 1.42, 95% CI 1.16-1.75; $p = 0.001$)
      - Cyclobenzaprine (OR 1.22, 95% CI 1.02-1.45; $p = 0.029$).

- The 2019 Beer's Criteria states muscle relaxants should be used with caution in the elderly.[26] "Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable." There is a strong recommendation based on moderate quality evidence to avoid.[26]

- **Skeletal muscle relaxants to AVOID** [6,7,8]
  - Based on the AHRQ systematic review, due to lack of evidence and side effects the following are not recommended in the treatment of acute low back pain:
    - Baclofen and dantrolene
    - Benzodiazepines

Clinical Practice Guideline Recommendations for Skeletal Muscle Relaxants

- Skeletal muscle relaxants are not *consistently* considered standard first line therapy due to the risk of central nervous system side effects such as sedation, which are additive with other CNS depressants. Recommendations range from providing strong recommendations for their use, to those recommending AGAINST their use.

- The 2017 Kaiser Permanente Washington guidelines [17] include skeletal muscle relaxants in the list of medications which are NOT recommended to treat acute low back pain due

to small effects and high occurrence of adverse events. The recommendation differs from the ACP recommendation, although both cite the AHRQ systematic review as a source for their evidence update. https://wa.kaiserpermanente.org/static/pdf/public/guidelines/back-pain.pdf

- The North American Spine Society 2020 update[11] and NICE 2017[15] guidelines on acute low back pain do not provide a statement on muscle relaxants.

Table 5 Skeletal Muscle Relaxants for the Treatment of Acute Low Back Pain

Clinical Practice Guideline Recommendations for Skeletal Muscle Relaxants Acute Low Back Pain	
Source	**Recommendation**
Institute for Clinical Systems Improvement (ICSI) 2018 (Minnesota)[4] Low Back Pain, Adult Acute and Subacute **https://www.icsi.org/guideline/low-back-pain/** Recommendation is based on the AHRQ comparative Effectiveness review (Chou, 2016). See below for ACP recommendations based on the same resource.	Muscle relaxants may be used as a short-term option in the treatment of acute low back pain; however, possible side effects should be considered. Quality of Evidence: Moderate; Strength of Recommendation: Weak **Benefit** Skeletal muscle relaxants have been found to help with short-term pain relief in acute low back pain. **Harm** Muscle relaxants are central nervous system (CNS) depressants and cause additive sedation and other adverse effects, especially in combination with opioids. Sedative hypnotics have significant side effects, specifically in the geriatric population. Additive side effects when taken with other CNS depressants are potential for dependence and withdrawal symptoms. **Benefits/Harms Assessment** Muscle relaxants should not be used as the standard first-line treatment but may provide short-term benefit in some patients. Risk of significant side effects, and potential for dependence and withdrawal outweigh the benefit for long-term use.
American College of Physicians Clinical Practice Guidelines 2017[8] **https://www.acpjournals.org/doi/pdf/10.7326/M16-2367**	The full statement on treatment is required to provide context: "Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs **or skeletal muscle relaxants** (moderate-quality evidence). (Grade: strong recommendation)"
Alberta Toward Optimized Practice 2017[16] **Part of: Accelerating Change Transformation Team (ACTT)** https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=low%20back	Muscle relaxants (e.g., cyclobenzaprine) may be appropriate in selected patients for symptomatic relief of pain and muscle spasm. Caution must be exercised with managing side effects, particularly drowsiness, and also with patient selection given the abuse potential for this class of drugs
Kaiser Permanente Washington guidelines 2017[17] **https://wa.kaiserpermanente.org/static/pdf/public/guidelines/back-pain.pdf**	Recommend **AGAINST** the use of SMRs to treat acute low back pain due to small effects and high occurrence of adverse events.
Beers Criteria (2019)[26] **https://onlinelibrary.wiley.com/doi/full/10.1111/jgs.15767**	There is a strong recommendation based on moderate quality evidence to avoid muscle relaxants in the elderly. "Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable."

QUESTION 1d. WHAT IS THE ROLE *OF* ACETAMINOPHEN IN THE TREATMENT OF ALBP?

Acetaminophen vs placebo

- The 2017 AHRQ systematic review, to inform the ACP guidelines identified 10 trials evaluating acetaminophen in low back pain.[6,7,8]

- Previous versions of the ACP guidelines (2007) were based on 9 of these 10 trials. These earlier guidelines recommended either acetaminophen or NSAIDS as first-line medication options.[27]
- The additional trial identified for the update was the PACE study, published in 2014.[28]
- The PACE trial resulted in a change in the recommendation to exclude acetaminophen as a pharmacological option in acute low back pain. The level of evidence to support this was considered low quality.

➢ The PACE trial represents the largest, highest quality RCT of acetaminophen in acute low back pain.[28]

- PACE was a multicenter, double-dummy, randomized, placebo controlled trial. (N=1652). Characteristics of the trial shown in *Table 6*.

Table 6 PACE Trial Characteristics[28]

PICO	
Patients	Patients from primary care with acute low back pain Mean age 45 years Mean time since onset of pain approximately 10 days Mean pain intensity score of 6 on a 0-10 scale.
Intervention/ Comparator	Three arms: Acetaminophen 665 mg tablets three times daily (total of 6 tablets or 3999 mg/d, N=550) As-needed acetaminophen 500 mg tablets (up to 4000 mg/d, N= 549) Placebo (N= 553) 4 weeks of medication and 12 weeks of follow-up Rescue medications for continuing severe pain = 2 days of naproxen 250 mg (two tablets initially, then one tablet every 6–8 h as needed.
Outcomes	**Primary**: Recovery defined as the first day of 0 or 1 pain intensity maintained for 7 consecutive days. Data obtained at 1,2,4 and 12 weeks follow up, as recorded daily in a patient diary **Secondary**: pain intensity, disability, function, global rating of symptom change, sleep quality, and quality of life, adherence to drug (daily and at 4 weeks); concomitant treatment use and work absenteeism (at 4 and 12 weeks); adverse events (at 1, 2, 4, and 12 weeks); treatment satisfaction and patient masking (at 12 weeks).

- **Results[28]**
  Median daily doses
  - Regular administration group: Median dose of 2660 mg/d until recovery.
    - Doses were higher in the first two weeks: 3500mg/d week 1 and 2800mg/d in week 2.
    - Adherence to the 6 tablets per day was not achieved in this group.
  - As needed group median dose: week 1: 1000 mg; week 2: 500 mg.
  - Rescue medication (naproxen) was used in 1% or less of patients although results indicate "use of other drugs" during the trial as 20% in the regular administration group and 23% in as needed and placebo groups.
- **Primary outcome**: **Median time to recovery:** No significant differences between any of the three groups:

  - Regular administration: 17 days (95% CI 14–19);
    - HR 0.99, 95% CI 0.87–1.14 vs placebo;
    - HR 1.05, 0.92–1.20 vs as needed group
  - As needed group: Time to recovery 17 days (15–20);
    - HR 1.05, 0.92–1.19 vs placebo
  - Placebo time to recovery: 16 days (14–20)
- **Sustained recovery** at 12 weeks: (no difference between groups)
  - Regular administration 85%
  - As-needed group 83%
  - Placebo group 84%
- At 4 weeks there were no differences for scheduled or as needed acetaminophen and placebo in:
  - **Pain**: Differences in pain scores on a 0-10 point scale were ≤ 0.20 points.
  - **Function**: ≤ 0.60 points on a 0-14 point RDQ scale.
- **Additional outcomes:**
  - Other health services were used by 30% of patients in all groups.
  - Average of zero days of work missed in all groups.
  - Satisfaction with treatment: Regular administration 76%; as needed 72% and placebo 73%.
  - There was no difference in effect between groups for any of the secondary outcomes (pain intensity, disability, function, global rating of symptom change, sleep quality, and quality of life).
  - Serious adverse events were the same between acetaminophen groups and placebo.
- **Limitations and observations of PACE trial**
  - A potential limitation of the PACE trial is that patients entered the trial after a mean of 10 days since onset of pain. No days of work were missed by any participants and over 70% of patients in all groups were satisfied with the treatment they received. Given the favorable prognosis and natural history of acute low back pain, patients may have been on the way to recovery by this point in time.
  - The outcome of median time to recovery does not provide insight into whether some patients received benefit early in therapy, the time during which the most acute pain may be experienced.
  - The authors state they cannot disregard the possibility of a placebo effect in the PACE trial and suggest the provision of advice and reassurance of the favorable prognosis might be the more important factor in management of acute low back pain than drug therapy and that research should be done on this.
  - The authors state that “although the findings call into question the use of acetaminophen to improve outcomes for acute low back pain, these

results should be replicated before paracetamol is completely dismissed in the management of low-back pain."[28]

- A Cochrane Review published in 2016 which included three trials N=1825 (2 trials high quality) reported no effect of acetaminophen 4g per day vs. placebo for any of the outcomes measured. This result is based primarily on the results of the PACE trial.[28,29]

Acetaminophen vs. NSAID

The literature reviewed above for acetaminophen vs. placebo is quoted frequently to suggest there is no benefit for acetaminophen in the treatment of acute low back pain.[8] However, evidence of the comparison of acetaminophen vs. NSAIDs (a first line drug) suggests no statistically significant difference between these two pharmacological therapies.[6, 7]

- The AHRQ systematic review reports the following results for this comparison.[6, 7]
  - **Results** :
    Pain Intensity:
    - No difference between acetaminophen and NSAIDs in pain intensity
    - Standardized mean difference (SMD) 0.21 (95% CI -0.02 to 0.43) at ≤ 3 weeks based on 3 low-quality trials. The authors state that estimates favored NSAIDs.
  - **Global improvement (function):**
    - No differences in the likelihood of experiencing global improvement
      - RR 0.81; 95% CI 0.58 to 1.14) at ≤3 weeks, 3 trials. The authors state that estimates favored NSAIDs.
  - **Adverse effects:**
    - Acetaminophen was associated with a lower risk for adverse effects vs. NSAIDs
      - RR 0.57 95% CI 0.36-0.89.

- The 2020 Cochrane Review by van der Gaag[9] included a comparison of NSAIDs with acetaminophen. The review includes 3 trials rated as being either low or very low quality.
  - Treatment duration in these studies ranged from two days to four weeks.
  - **Pain Intensity:** Two studies were able to be pooled (N = 289) which showed no clear difference in pain relief: (SMD -0.12, 95% CI -0.35 to 0.12).
  - Outcomes of disability, return to work adverse events showed no clear differences between acetaminophen and NSAIDs.

Intravenous Acetaminophen

- A formulation of intravenous acetaminophen is now available in Canada.[30]
- A randomized, double-blind study with three arms compared the efficacy of intravenous acetaminophen 1 gm, 50 mg of dexketoprofen (not available in Canada, but related to

ketoprofen) and 0.1 mg/kg morphine in patients with acute mechanical LBP, administered in an emergency room.[31]

- The study included adults 18-55 years old with moderate or severe LBP with an onset within the past week. N= 137; mean age 32; 61% male
- Pain outcomes were measured on a 100 mm visual analogue scale (VAS) and a 4 point verbal rating scale (VRS is a 4 point pain scale: No pain, Mild pain, Moderate pain, Severe pain.)
    - 30 minute median reduction in VAS score:
        - Acetaminophen 65 mm (95% CI 58 to 72)
        - Morphine 67 mm (95% CI 60 to 73)
        - Dexketoprofen 58 mm (95% CI 50 to 64)
        - Morphine was not superior to acetaminophen at 30 minutes (difference in VAS: 3.8 ± 4.9 (95% CI −6 to 14).
        - The difference in VAS between morphine and dexketoprofen in reducing pain was 11.2±4.7 (95% CI 2 to 21).
- Similar results were shown for VRS scores. At 30 minutes the median score was reduced from 4 to 1 in all three groups.
- At least one adverse event was experienced by more participants in the morphine group: acetaminophen 8.7%; morphine 15.5% and dexketoprofen 8.7%.
- The authors concluded that intravenous acetaminophen has similar efficacy to either morphine or an NSAID for treatment of mechanical low back pain in the emergency room.[31]

Adverse effects of Acetaminophen

- Adverse reactions are uncommon when acetaminophen is used at regular doses for short-term use, in low-risk populations. However, acetaminophen is the leading cause of serious liver injury in Canada, mostly due to unintentional overdoses and caution is warranted in high-risk populations. [32]
- Please refer to the drug tables in Appendix 1.
- The AHRQ systematic review and clinical practice guidelines report the following results for the adverse effects associated with acetaminophen: [6,7,8]
    - Versus placebo: No difference in risk for serious adverse events (moderate quality; 1 RCT).
    - Versus NSAIDs: A systematic review found that acetaminophen was associated with lower risk for adverse events; RR 0.57 (95% CI, 0.36–0.89) (moderate quality; 3 RCTs).

Guideline Recommendations for Acetaminophen in Acute Low Back Pain

- While acknowledging there is insufficient evidence for efficacy, acetaminophen continues to be recommended in some guidelines as an option for pain management in acute and subacute low back pain due to the low risk of harm compared with other agents. See Table 7 and note the ICSI, Kaiser Permanente and Alberta TOP guidelines.[4,16,17]

- Oliveira et al. 2018 provided an updated overview of the recommendations regarding the diagnosis and treatment contained in current clinical practice guidelines for patients with non-specific low back pain in primary care.[33]
    - 15 clinical practice guidelines published between 2010 and 2017, from 15 different countries, including Canada were compared. The Canadian guideline used was the Toward Optimized Practice (TOP, 2015), evidence-informed primary care management of low back pain.
    - Recommendations in favor of acetaminophen were in 57% of guidelines, and 36% advise against its use.

Table 7 Acetaminophen

Clinical Practice Guideline Recommendations for Acetaminophen Acute Low Back Pain	
Source	**Recommendation**
North American Spine Society: Evidence Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Low Back Pain 2020 [11] https://www.asra.com/advisory-guidelines/article/14/evidence-based-clinical-guidelines-for-multidisciplinary-spine-care-diagnosis-an	**No recommendation made** for acetaminophen.
Institute for Clinical Systems Improvement (ICSI) 2018 (Minnesota) [4] Low Back Pain, Adult Acute and Subacute https://www.icsi.org/guideline/low-back-pain/	**Based on Consensus** Acetaminophen may be used as an option for pain relief in patients with acute and subacute low back pain. Patients should be counseled on potential side effects.
American College of Physicians **Clinical Practice Guidelines 2017** [8] https://www.acpjournals.org/doi/pdf/10.7326/M16-2367	**Do not recommend** Low-quality evidence showed no difference between acetaminophen and placebo for pain intensity or function through 4 weeks or between acetaminophen and NSAIDs for pain intensity or likelihood of experiencing global improvement at 3 weeks or earlier.
NICE 2017 UK (Update due in Sept 2020) [15] National Institute for Health and care Excellence Low back pain and sciatica in over 16 years old patients 2017 https://www.nice.org.uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637	**Do not** offer paracetamol (acetaminophen) alone for managing low back pain. **With weak opioids:** Consider weak opioids (with or without acetaminophen) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
Alberta Toward Optimized Practice 2017 [16] **Part of: Accelerating Change Transformation Team (ACTT)** https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=low%20back	Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. **First choice acetaminophen**; second choice NSAIDs.
Kaiser Permanente Washington guidelines 2017 [17] https://wa.kaiserpermanente.org/static/pdf/public/guidelines/back-pain.pdf	Most pharmacologic options for non-specific back pain have clear risks that outweigh any potential benefit. Monotherapy with acetaminophen or NSAIDs is recommended. The dosages below may be modified based on patient risk factors. **Acetaminophen** Because of its stronger safety profile, acetaminophen is the preferred drug for initial treatment of nonspecific back pain. Recommended initial dose: 500–650 mg t.i.d. Maximum daily dose: 3,000 mg (In Canada max is 4,000 mg/d) Note: In patients with liver disease or alcohol use problems, the daily dose of acetaminophen should not exceed 1,000–1,500 mg

Why try a medicine that has not shown statistically significant benefit in clinical trials?

- Despite evidence to suggest little to no benefit with acetaminophen for low back pain some guidelines continue to include it in recommendations.
- Efficacy statistics are based on population data which include those who respond well and those who don't. If there is an indication that some patients in a clinical trial received benefit, even a small improvement in pain may be appreciated by the patient, especially if potential benefit outweighs harm.[34] https://www.nps.org.au/assets/4c10bf19773943e8-69b68fc2512d-NPS2170_MW_News_LBP_v2.pdf

QUESTION 1e. WHAT IS THE ROLE OF COMBINATION THERAPY IN THE TREATMENT OF ALBP?

Skeletal muscle relaxants or opioids plus NSAID vs. NSAID alone

- The ACP guideline recommendation on the efficacy and safety of combining a muscle relaxant with an NSAID is based on the results of a Cochrane Review [19] and two clinical trials.[35, 36]
    - The guidelines state that low quality evidence showed ***inconsistent findings*** for the effect on pain intensity with a combination of skeletal muscle relaxant plus an NSAID versus the NSAID alone.

- The full-length publication of the AHRQ comparative effectiveness review states:[6]
    - **Pain Intensity:** The systematic review found no difference between a skeletal muscle relaxant plus an NSAID versus the NSAID alone in the likelihood of experiencing a 2-point or greater difference or 30 percent improvement on a 0-10 VAS after 2 to 4 days.
        - 2 trials N=469; RR 1.56, 95% CI 0.92 to 2.70; I^2=84%.
        - The authors suggest the estimate favored the combination but it was not statistically significant and associated with high degree of heterogeneity.
    - **Global improvement**: The combination was associated with greater likelihood for global improvement at 2 to 4 days (4 trials; RR 2.04, 95% CI 1.05 to 4.00; I^2=89%); but not at 5 to 7 days (4 trials; RR 1.47, 95% CI 0.88 to 2.44; I^2=34%).
    - One fair-quality (n=197) trial referenced, but not included in the Cochrane Review, compared tizanidine plus the NSAID, aceclofenac with aceclofenac alone.[35]
        - **Resting Pain**: The combination was associated with greater improvement after 3 days (mean change −3.01 vs. −1.90 on a 0 to 10 VAS, p=0.0001) and 7 days (−5.88 vs.−4.35, p=0.0001). Similar results were reported for pain with movement.
        - The combination was also associated with higher likelihood of experiencing a good or excellent **treatment response** (75% vs. 34%; RR 1.28, 95% CI 1.07 to 1.52.)
        - There were no differences in risk of any **adverse event** between skeletal muscle relaxants plus an NSAID versus the NSAID alone: 2 trials RR 1.30, 95% CI 0.62 to 2.75.
    - The Friedman 2015 trial found no effects on pain or function for the combination of naproxen plus the muscle relaxant cyclobenzaprine compared with the NSAID alone.[36]
        - Friedman and colleagues have conducted several studies of combination therapies for acute low back pain in patients presenting to an emergency room. The studies consistently report that the addition of cyclobenzaprine, orphenadrine, methocarbamol, baclofen, tizanidine,

diazepam, metaxalone, or oxycodone/acetaminophen to NSAIDs (naproxen or ibuprofen were studied) does not improve function or pain outcomes compared with NSAIDs alone and there is potential for increased risk of adverse events.[36 -39] Several methodological limitations to these studies have been noted:

- Patients were enrolled from one or two urban emergency rooms which makes generalizability uncertain.
- Patients took medications prn and follow up assessment was done by telephone interviews.
- Trials combining NSAIDs with opioids did not assess long term harms or risk for abuse, overdose or addiction.

- A 2018 meta- analysis by Song et al. studying the effect of combination pharmacotherapy (NSAIDs + SMR or opioids) vs. NSAIDs alone on acute low back pain, reports no evidence of benefit for relief of pain or improvement in function compared with monotherapy (6 RCTs).[40]
  - Average trial duration: 6.6 days; Average patient age: 44.7
    Pain intensity: (4 trials):
    - Differences between combined and monotherapy negligible and not statistically significant (SMD, −0.08; 95% CI, −0.49 to 0.3; p= 0.68; I^2> 50%)

    Physical function (2 trials):
    - No difference observed between combination or monotherapy after pooling different combination therapy groups (weighted mean difference, 0.70; 95% CI, −0.40 to 1.81; P= 0.851; I^2= 0%)

    Adverse effects were significantly higher for combination therapy
    - Vs. placebo (P<0.05; RR, 1.80; 95% CI, 1.33-2.42; I^2 >50%)
    - Vs. monotherapy (P<0.05; RR, 1.44; 95% CI, 1.01-2.06; I^2> 50%).

- The 2020 Cochrane Review by van der Gaag[9] included a comparison of NSAIDs vs. the combination of acetaminophen plus codeine (2 studies N=162).
  - Both studies used the combination product with codeine 30 mg and the dose was either one tablet every 4 hours or two tablets every 4-6 hours.
  - **Pain Intensity**: Data was inadequately reported so trials could not be combined in a meta-analysis however low quality evidence suggested no clear statistical or clinical differences between the groups.
  - **Global improvement:** No difference between groups (moderate quality evidence)
    - RR 1.01 (95% CI 0.81 -1.25)

- Consider additive CNS effects with skeletal muscle relaxants and other CNS depressant medications.

Clinical Practice Guideline Recommendations for Combination therapy

The North American Spine Society, NICE and Kaiser Permanente guidelines no not provide a recommendation for combination therapy in acute low back pain.

Table 8 Combination therapy

Clinical Practice Guideline Recommendations for combination therapy Acute Low Back Pain	
Source	**Recommendation**
Institute for Clinical Systems Improvement (ICSI) 2018 (Minnesota) [4] Low Back Pain, Adult Acute and Subacute https://www.icsi.org/guideline/low-back-pain/ Recommendation is based on the AHRQ comparative Effectiveness review (Chou, 2016). See below for ACP recommendations based on the same resource.	Guidelines provide a recommendation for SMRs but point out the harms with combination therapy ○ Muscle relaxants are central nervous system (CNS) depressants and cause additive sedation and other adverse effects, especially in combination with opioids. Sedative hypnotics have significant side effects, specifically in the geriatric population. Additive side effects when taken with other CNS depressants are potential for dependence and withdrawal symptoms.
American College of Physicians Clinical Practice Guidelines 2017 [8] (Update due in Sept 2020) https://www.acpjournals.org/doi/pdf/10.7326/M16-2367	Inconsistent benefit for combination of SMR + NSAID vs NSAID alone. A statement on combination therapy is not included in treatment recommendations for acute low back pain.
Alberta Toward Optimized Practice 2017 [16] **Part of: Accelerating Change Transformation Team (ACTT)** https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=low%20back	Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. Only consider adding a short course of muscle relaxant (benzodiazepines, cyclobenzaprine, or antispasticity drugs) on its own, or added to NSAIDs, if acetaminophen or NSAIDs have failed to reduce pain.

QUESTION 1f. WHAT IS THE ROLE OF ORAL OPIOIDs IN THE TREATMENT OF ALBP?

- Evidence for the use of opioids in ***acute*** low back pain is lacking**.**
  - A systematic review and meta- analysis published in 2016 evaluated the efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain and found ***no*** placebo-controlled trials for use of opioids in acute low back pain. All of the studies identified were in chronic LBP (13 studies N= 3419).[41]

- The AHRQ systematic review also reports that the majority of systematic reviews and trials identified for the use of opioids were conducted in patients with chronic low back pain.[6,7]
  - The review reports the results of one of the trials previously mentioned by Friedman et al. This study was in patients aged 21-64, presenting to the emergency room with acute low back pain.[36]
  - The addition of oxycodone 5 mg/acetaminophen 325 mg to naproxen 500 mg bid showed no mean improvement on the Roland-Morris Disability Questionnaire (RMDQ) compared with naproxen alone over a 7 day period. However, both groups achieved a clinically significant reduction in the RMDQ.

- Mean Improvement in RMDQ at 7 days:
  - Naproxen + placebo 9.8 (98.3% CI 7.9-11.7)
  - Naproxen + oxycodone/ acetaminophen 11.1 (98.3% CI 9-13.2)
- Adverse effects were more likely in the oxycodone/acetaminophen + naproxen group compared with naproxen alone:
  - Absolute increase 19% [7% to 31%]; **NNH 5.3 (95% CI, 3 to 14).**
  - The trials did not assess long term harms or risk for abuse, overdose or addiction.

- One RCT referenced in the 2020 North American Spine Society low back pain guidelines studied the use of an extended-release combination formulation of 75mg tramadol and 650 mg acetaminophen (N=141) compared to placebo (N=136) for treatment of acute LBP.[11,42]
  - This was a double-blind, multicenter, randomized controlled trial in patients aged 18-80 years with pain rated as at least 2 out of 4 and intensity as 2 out of 11.
  - Dose of medication or placebo: 1-2 tablets every 10-12 hours for 2.5 days.

  Results:
  - **Pain intensity** (4-point scale) and pain relief (5-point scale):
    - Tramadol/acetaminophen significantly decreased pain intensity (p=0.038) and resulted in greater pain relief (p=0.026) during the 50 hour observation period.
  - **Adverse events**: Placebo (2.2%) and tramadol/acetaminophen (12.1%). Most of the adverse events were mild-to-moderate and considered to be at least possibly related to the treatment.
  - A limitation of this study is that the comparison was placebo rather than a non-opioid alternative.

- A recent systematic review and meta-analysis by researchers at McMaster University reported the results of ***adverse outcomes*** associated with prescription opioids for acute low back pain. Both randomized controlled and observational studies were considered for inclusion in the review.[43]
  - Out of 13,889 studies screened a total of 4 studies were included in the full review, and of these, 2 studies were included in the meta-analysis.
  - Adverse outcomes of interest included *prescription abuse, misuse, continued long-term use, development of opioid use disorder, unemployment, social adversity, marital discord, criminal activity, and mortality*.
  - **Results**: Prescribing opioids for ALBP is:
    - Significantly associated with long term continued opioid use (1.57, 95% CI, 1.06-2.33).
    - Not associated with unemployment duration (3.54, 95% CI, -7.57 to 14.66).
  - Many limitations were reported:

- Statistical and clinical heterogeneity due to differences in methodology, study design, risk of selection or performance bias.
- Studies had an unclear or high risk of bias and poorly defined side effects.

- The authors concluded that due to the lack of literature examining long-term adverse outcomes associated with prescribing opioids for ALBP, no definitive conclusions can be made.
  - *Available literature suggests there seems to be a risk associated with prescribing opioids for ALBP; however, further investigations are needed.*

- A systematic review of harms and benefits of opioids for management of non-surgical acute and chronic low back pain published in 2019 reports similar findings to those reported by Sanger et al. with respect to a lack of evidence for the use of opioids in acute low back pain and increased risk of adverse effects.[44]
  - **Higher harms** and **higher severe harms** were associated with the use of opioids vs. placebo and non-opioid therapies.
  - The authors also report that 70% of the studies favoring the use of opioid for the treatment of LBP demonstrated conflicts of interest that call to question the results of those trials.

- The CDC guideline for prescribing opioids for chronic pain evaluated the effect of opioid therapy for acute pain on long-term use and it references studies of patients who underwent low-risk surgery or experienced low back pain from injury. The studies revealed that opioid therapy prescribed for acute pain was associated with greater likelihood of long-term use.[45]

- One of the studies referenced by the CDC, Webster et al. 2007, reported on the relationship between early opioid vs. late prescribing for acute low back pain using data from workers' compensation claims.[46]
  - Patients prescribed opioids within 15 days following the onset of pain had an increased likelihood of receiving five or more opioid prescriptions 30–730 days following onset. The use of opioids increased with higher morphine milligram equivalents (MME) given during early exposure:
    - Early vs. no early opioid use according to dose:
      - 1–140 MME/day adjusted OR 2.08 (95% CI = 1.55–2.78)
      - ≥450 MME/day adjusted OR 6.14 (95% CI = 4.92–7.66)

- *Recommendations for the use of opioids in the treatment of acute low back pain either state there is no evidence to support their use, or they should be used with caution. Cautious use of opioids should be considered only if other effective pharmacologic and nonpharmacologic treatment options fail or are not appropriate and, if used, a short duration (e.g. 3 days) is recommended. Patients should be informed that ALBP often improves over time regardless of treatment. See guideline statements in Table 9.*

Table 9 Opioids for the treatment of acute low back pain

Clinical Practice Guideline Recommendations for Opioids Acute Low Back Pain	
Source	**Recommendation**
North American Spine Society: Evidence Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Low Back Pain 2020 [11] https://www.asra.com/advisory-guidelines/article/14/evidence-based-clinical-guidelines-for-multidisciplinary-spine-care-diagnosis-an	The use of opioid pain medications should be cautiously limited and restricted to short duration for the treatment of low back pain. Grade of Recommendation: B *Work Group Narrative*: There are limited data that support the short-term effectiveness of opioid pain medication for low back pain. There remain concerns in study design including the role of enriched enrollment and high dropout rates in these trials. The trials also report high rates of adverse events, which may factor into the high dropout rates. As there are few studies evaluating the efficacy and safety of opioids for low back pain beyond 12 weeks and given the concerns associated with the use of opioids with the availability of other effective pharmacologic and nonpharmacologic treatment options, we recommend the cautious use of opioid pain medication in those with low back pain and, when utilized, that a short duration is recommended.
Institute for Clinical Systems Improvement (ICSI) 2018 (Minnesota) [4] Low Back Pain, Adult Acute and Subacute https://www.icsi.org/guideline/low-back-pain/ Recommendation is based on the AHRQ comparative Effectiveness review (Chou, 2016). See below for ACP recommendations based on the same resource.	In general, opioids are not recommended for acute and subacute low back pain. (Consensus recommendation) If non-opioid options have been tried and the clinician feels that a trial of opioids are necessary, the first opioid prescription for acute pain should be the lowest possible effective strength of a short-acting opioid, not to exceed 100 MME total. (Note: US guideline differs from Canadian) Patients should be instructed that three days or less will often be sufficient. **Benefit**: Restricting opioid prescriptions will lead to decreased adverse events from opioids, including those as significant as addiction and death. **Harm:** There are some patients who may benefit from opioids for pain relief. **Benefits/Harms Assessment:** In general, the risks of opioids outweigh the pain relief that opioids may provide. Non-pharmacologic and other pharmacologic treatments should be used.
American College of Physicians Clinical Practice Guidelines 2017[8] https://www.acpjournals.org/doi/pdf/10.7326/M16-2367	Evidence was insufficient to determine effectiveness of opioids versus placebo in patients with acute or subacute low back pain.
NICE 2017 UK (Update due in Sept 2020) National Institute for Health and care Excellence Low back pain and sciatica in over 16 years old patients 2017 https://www.nice.org.uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637	Do not routinely offer opioids for managing acute low back pain Consider weak opioids (with or without acetaminophen) for managing acute low back pain, only if an NSAID is contraindicated, not tolerated or has been ineffective.
Alberta Toward Optimized Practice 2017 [16] **Part of: Accelerating Change Transformation Team (ACTT)** https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf#search=low%20back	Cautious and responsible use of opioids should only be considered for carefully selected patients with severe acute pain not controlled with acetaminophen and NSAIDs, at a minimum effective dose only for a limited period of time, usually less than one to two weeks. Ongoing need for opioids is an indication for reassessment. In general, opioids and compound analgesics have a substantially increased risk of side effects and risk of dependence compared with acetaminophen alone. Advise patient to avoid driving until cognitive side effects have been ruled out.
Kaiser Permanente Washington guidelines 2017[17] https://wa.kaiserpermanente.org/static/pdf/public/guidelines/back-pain.pdf	Opioids are rarely indicated for the treatment of back pain. Opioid prescriptions for acute back pain, if made, should be limited to 3 days and followed by a check-back with the patient.
Opioid Wisely Canadian Spine Society Choosing Wisely Canada Statements. [47] https://choosingwiselycanada.org/campaign/opioid-wisely/	**Don't use an opioid analgesic medication as first-line treatment for acute, uncomplicated, mechanical, back-dominant pain.** Over 90% of acute low back pain is a mechanical problem that is often self-limiting and can be controlled with physical treatment and non-narcotic medication. The most common entry point to prescription opioid addiction is through opioids prescribed for back pain. Adequate pain control using opioids is frequently not achieved and patients face the added risks of physical dependence and withdrawal hyperalgesia, which can lead to continued use. Spine Recommendation #6

QUESTION 1g. WHICH MEDICATIONS OR INTERVENTIONS HAVE INSUFFICIENT EVIDENCE FOR USE IN ALBP?

Medications

- **Antidepressants, anti-seizure medications and benzodiazepines**
  - Based on the AHRQ systematic review there is insufficient evidence to determine the effectiveness of the following classes of drugs vs. placebo:[6,7,8]
    - Antidepressants
    - Benzodiazepines
    - anti-seizure medications
  - The North American Spine Society 2020 make the following statements, although all of the studies included in the review address chronic low back pain:[11]

- There is insufficient evidence to make a recommendation for or against the use of anticonvulsants for the treatment of low back pain.
- Antidepressants are not recommended for the treatment of low back pain. **Grade of Recommendation: A**

- **Gabapentanoids:** A 2017 randomized controlled trial in acute and chronic sciatica [48] and a 2018 meta-analysis,[49] which primarily studied chronic low back pain and lumbar radicular pain, reported lack of efficacy for gabapentanoids and an increase in AEs.

- **Systemic Corticosteroids**
  - Low quality evidence showed no difference in pain or function between a single intramuscular injection of methylprednisolone or a 5-day course of prednisolone compared with placebo in patients with acute low back pain.[6,7,8]
  - The North American Spine Society suggests that the use of oral or IV steroids is not effective for the treatment of low back pain. Grade of Recommendation: B[11]

- **Opioids**
  - Some guidelines suggest opioids have insufficient evidence for use in acute low back pain and risk of harms may outweigh any potential benefits.
  - See *Table 9* for guideline recommendations.

Interventions not recommended

- Imaging tests are not helpful for recovery or management of acute or recurring low back pain unless there are signs of serious pathology.
  - **Choosing Wisely Canada:** Don't routinely image patients with low back pain regardless of the duration of symptoms unless: (a) there are clinical reasons to suspect serious underlying pathology (i.e., red flags), or (b) imaging is necessary for the planning and/or execution of a particular evidenced-based therapeutic intervention on a specific spinal condition.[50]
- The American College of Physicians suggest the following are NOT recommended:[8]
  - Bedrest
  - Shoe Insoles/Orthoses
  - Lumbar supports

QUESTION 2: WHAT ARE THE <u>NON-PHARMACOLOGICAL OPTIONS</u> FOR TREATMENT OF ALBP?

- **Non-drug options** are generally preferred for the initial management of acute low back pain over pharmacological treatments.[8, 15, 51]

- American College of Physicians (ACP) Clinical Practice Guidelines:[8]

- **Recommendation:** Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select non-pharmacologic treatment.
- The ACP guidelines included a summary of the evidence for non-pharmacologic interventions. The following were shown to be effective for improving pain and function in patients with acute or subacute low back pain:
    - **Superficial heat** (moderate quality evidence and moderate improvement in pain and function)
    - **Massage** (low quality evidence and small to moderate improvement in pain and function).
    - **Acupuncture** (low quality evidence for a small effect on improving pain but not function)
    - **Spinal manipulation** (low quality evidence for a small effect on improving function compared with sham manipulation but not when compared with inert treatment.)
    - **Low level laser therapy + NSAID vs. NSAID:** (low quality evidence for a large benefit in pain and moderate benefit at 3 weeks with combination).
    - **Evidence was insufficient** to determine the effectiveness of transcutaneous electrical nerve stimulation (TENS), electrical muscle stimulation, inferential therapy, short-wave diathermy, traction, superficial cold, motor control exercise (MCE), Pilates, tai chi, yoga, psychological therapies, multidisciplinary rehabilitation, ultrasound, and taping.

- **Physical activity**: Guidelines frequently suggest staying as active as possible.
    - The AHRQ systematic review did not report an improvement in pain or function with exercise vs. usual care.[6,7,8]
    - UK guidelines endorse exercise as a non-pharmacologic option for acute nonspecific low back pain.[15]

- **Patient education**
    - A 2017 Canadian review article summarizing the latest guidelines from the US and UK on the diagnosis and management of low back pain in primary care reports evidence that, although current major guidelines recommend providing advice and reassurance to patients, only 21% of clinicians do this.[51] This is based on a systematic review of 14 RCTs that found patient education in primary care reduced the psychological distress and use of health care related to low-back pain but education itself did not improve pain or function in patients with acute low back pain.
    - A key point in the article is that all patients with nonspecific low back pain should be offered information on the nature of low back pain, reassurance about the

likely low risk of serious underlying disease and advice on evidence–based self-management.

- The authors provide examples of dialogue with patients with acute non –specific , persistent and radicular low back pain:[51] https://www.cmaj.ca/content/cmaj/suppl/2017/11/08/189.45.E1386.DC1/170527-view-1-at.pdf
- Example dialogue with a patient experiencing non-specific acute low back pain:
    - *"Acute low back pain recovers quickly – most people are substantially better or fully recovered in 2 weeks, although it is common for the pain to recur. Because it recovers so well on its own, a lot of the treatments out there for low back pain – including drugs and non- drug options such as massage, don't add any benefit beyond simply waiting for the pain to go away on its own. I'm not concerned that you have any of the serious causes of low back pain, so there is no need for any X-Rays or scans at this stage. In fact, imaging shows changes that occur with age, even in people without back pain so the findings are not that helpful. For now I'd suggest you stay as active as you can. To help with the pain you could try heat packs or some anti-inflammatory medication (may not be suitable for everyone). We can reassess the need for medication or other therapies at our review within the next week or two (mutually decided with the patient). How do you feel about that approach?"*
- NSH patient education material: Managing low back pain 2018[52] https://www.nshealth.ca/sites/nshealth.ca/files/patientinformation/1967.pdf
- See additional links to patient information following the summary statements above.

➢ *Table 10* highlights some of the non-pharmacological therapies endorsed by major clinical practice guidelines or Health Technology Assessment Agencies (CADTH) based on systematic evidence reviews.[10]

- Of note, much of the evidence for non-pharmacological therapy has been studied in chronic low back pain rather than acute low back pain.

Table 10. Non-pharmacological treatments for Acute Low Back Pain

Intervention	Recommended - Yes, No or No mention Quality of evidence			
	NA Spine Society 2020[11]	**UK NICE 2016[15]**	**US ACP 2017[8]**	**CADTH[10]**
Advice to stay active vs. bed rest	Yes Grade B	Yes	Yes	No mention
Exercise	Yes Grade A	Yes	No mention	No mention
Self-directed McKenzie Exercises vs usual medical care	Insufficient evidence	No mention	No mention	No mention
Massage	No mention for massage No additional benefit if combined with exercise.	Yes (with exercise)	Yes Low Quality	May have positive effects on pain and function
Spinal manipulation	No –Grade A Option – Grade C	No	Yes Low Quality	May have positive effects on pain and function Low-quality
Superficial heat	Yes Grade B	No mention	Yes Moderate	
Physiotherapy	No mention	Yes (Psychologically informed)	No mention	May be effective (low to moderate quality)
Low level laser therapy +NSAID vs NSAID	No mention	No mention	YES Low Quality	No mention
Acupuncture	No Insufficient evidence	No	Yes Low quality	No mention
Education	Yes (Back School) Grade A	No mention	No mention	No mention
Psychological	No mention for acute LBP	No mention	No mention	Some evidence for CBT to reduce disability and improve function, particularly when combined with physiotherapy and personalized.

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ACUTE POST-SURGICAL PAIN

SUMMARY STATEMENTS

- This section of the evidence review focuses on the treatment of postoperative pain with oral medications in adult patients who are opioid naïve prior to surgery. The treatment of postsurgical pain with IV medications and the provision of procedural pre-medications are not included.
- Most of the included systematic reviews (SRs) with meta-analyses (MAs) pool RCTs of different surgical procedures that result in the same expected level of postsurgical pain (moderate to severe pain).
    - No MAs evaluating post-discharge prescribing were found.
- Most MAs report pain outcomes using scales that measure pain intensity, for example the 100 point Visual Analogue Scale (VAS) and the 10 point Numerical Rating Scale (NRS), but do not evaluate function or other pain characteristics.
    - A number of cohort studies have established a pain intensity equivalent to mild pain (< 4 on a 10 point NRS, < 40 on a 100 point VAS) as acceptable after surgery.[1,2]
- RCTs assessing the efficacy of oral medications in post-surgical pain generally utilize 2 different approaches.
    - The first approach evaluates the effect on <u>established pain</u>. Analgesics are compared to placebo as single dose monotherapy administered hours to days after the surgical procedure in patients <u>experiencing moderate to severe pain.</u>
        - Pain is measured immediately before the intervention and then following the intervention (e.g. 6h after).
        - A reduction of 50% on pain scales in patients with moderate to severe post-surgical pain in most cases will reduce pain to a mild intensity and is considered a clinically important outcome.
        - A NNT ≥ 10 for achieving at least a 50% reduction in pain is reported to be unacceptably high in the treatment of postoperative pain according multiple Cochrane reviews.[4]
    - The second approach evaluates an analgesic for <u>preventing pain</u>, where the medication is compared to placebo; both are initiated prior to or during surgery and are most often continued for 24-48 hours postoperatively. Patients in both the comparator and placebo groups also receive opioids as needed (i.e. morphine administered via PCA device).
        - Predominantly these types of studies evaluate the impact on overall opioid consumption and a reduction in opioid related side effects.
        - It has not been determined how much opioid sparing is required to significantly reduce the incidence of opioid related adverse effects. A minimal clinically important difference was defined as a difference in 24 hour morphine consumption of 10 mg in one RCT following total knee arthroplasty.[3]

QUESTION 1: WHAT IS THE EVIDENCE FOR ORAL NON-OPIOID PHARMACOLOGICAL THERAPIES IN THE MANAGEMENT OF POST-SURGICAL PAIN?

QUESTION 1a: WHAT IS THE EVIDENCE FOR <u>ACETAMINOPHEN</u> IN MODERATE TO SEVERE POST-SURGICAL PAIN?

- Established pain in patients:
  - The NNT to achieve at least a 50% reduction on pain scales over 4 – 6 hours with acetaminophen compared to placebo ranges from 3.5 to 4.6, depending on dose.[4]

- Prophylactic effect:
  - When acetaminophen is used to prevent postsurgical pain there is a small opioid sparing effect compared to placebo (MD 6-9 mg morphine equivalents/24 hours); however, the opioid sparing effect is likely not clinically relevant.[6,7,8]
    - Acetaminophen does not improve pain scores significantly compared to placebo.[6,8]

- MAs/SRs report no differences in safety outcomes between acetaminophen and placebo.[4,5,6,7,8]

QUESTION 1b: WHAT IS THE EVIDENCE FOR <u>NSAIDs/COX-2 INHIBITORS</u> IN MODERATE TO SEVERE POST-SURGICAL PAIN?

- Established pain:
  - The NNT to achieve at least a 50% reduction on pain scales over 4-6 hours with NSAIDs compared to placebo ranges from 2 to 9, depending on drug and dose.[4] For example;
    - Ibuprofen 400 mg: NNT 2.5 (95% CI 2.4 to 2.6)[4]
    - Naproxen 500/550 mg: NNT 2.7 (95% CI 2.3 to 3.3)[4]
  - When celecoxib is compared to placebo for at least a 50% reduction on scales over 4-6 hours the NNT is 4.2 (95% CI 3.4 to 5.6) for 200 mg and 2.6 (95% CI 2.3 to 3.0) for 400 mg.[4]
  - MAs report no differences in safety outcomes between NSAIDs/COX-2 inhibitors and placebo.[5]

- Prophylactic effect:
  - An NSAID used to prevent post-surgical pain results in a morphine sparing effect compared to placebo.
    - MD -10.18 mg/24 hours (95% CI -8.72 to -11.65 mg/24 hours) to -12.9 mg/24 hours (95% CI -10.6 mg to -15.1 mg/24 hours). [6,7,8]

- An NSAID in combination with an opioid reduce postoperative nausea and vomiting. [6,7,8]
- A COX-2 inhibitor used to prevent post-surgical pain results in a morphine sparing effect.
    - MD -7.2 mg/24 hours (95% CI -3.8 mg to -10.6 mg/24 hours) with low dose regimens to -13 mg/24 hours (95% CI -10.1 mg to -16.8 mg/24 hours) with high dose regimens. [6,7,8]
    - COX-2 inhibitors do not reduce opioid related AE.[6,7,8]

- MAs reported rates of surgical bleeding.
    - Surgical bleeding occurred at a rate of 0.2% to 0.4% in control groups vs. 1.7% to 2% with NSAIDs (**NNH 65**). This outcome was reported in RCTs which evaluated diclofenac, ketoprofen and ketorolac.[7.8] This outcome has not been reported in RCTs evaluating other NSAIDs.
        - Post-surgical bleeding risk was not evaluated for COX-2 inhibitors. Zero surgical bleeding complications were reported in RCTs.[7.8]

QUESTION 1c: WHAT IS THE EVIDENCE FOR <u>MULTIMODAL ANALGESIA</u> (THE COMBINATION OF ACETAMINOPHEN AND NSAID) IN MODERATE-SEVERE POST-SURGICAL PAIN?

- Multimodal analgesia is based on the premise that the concurrent use of non-opioid analgesics can have additive, if not synergistic, effects that produce superior analgesia than a single analgesic.

- Established pain:
    - To achieve at least a 50% reduction on pain scales over 4-6 hours with an NSAID + acetaminophen combination vs. placebo the NNT 1.5 to 1.6.
    - Fewer AE are reported with ibuprofen + acetaminophen compared to placebo[4]
        - To prevent 1 AE, the NNT 5.4 (95% CI 3.6 to 11) for ibuprofen 200mg + acetaminophen 500mg and the NNT 5.1 (95% CI 3.5 to 9.5) for ibuprofen 400 mg + acetaminophen 1000 mg.[4]

- Prophylactic effect:
    - The combination of an NSAID + acetaminophen reduces morphine consumption significantly compared to placebo.[6,7,8]
        - For example, acetaminophen + ibuprofen is associated with a clinically significant reduction in morphine/24 hours compared to placebo, MD -22.8 mg/24 hours (95% CI – 14 mg to -31.5 mg/24 hours).[6]
    - The combination of an NSAID + acetaminophen is associated with a significantly greater reduction in pain scores (approximately 30%) both during mobilization and at rest compared to either agent alone.[9]

- An NSAID + acetaminophen combination does not result in an increased rate of AE compared to the individual agents. One MA reported that patients experience fewer AE with a combination of ibuprofen + acetaminophen compared to those who receive placebo.[6,9]

QUESTION 1d: WHAT IS THE EVIDENCE FOR <u>GABAPENTIN/PREGABALIN</u> IN MODERATE TO SEVERE POST-SURGICAL PAIN?

- There is insufficient good quality evidence to routinely recommend the use of gabapentin or pregabalin in the management of postoperative pain.

Gabapentin

- Established Pain:
  - When a single dose of gabapentin 250 mg is compared to placebo for reducing pain scores by at least 50% the NNT 11 (95 % CI 6.4 to 35).[4,10] However, an NNT > 10 may be considered unacceptably high in the treatment of postoperative pain.[4,10]

- Prophylactic Effect:
  - Morphine consumption is reduced with gabapentin compared to placebo, with a MD of - 3.1 mg/24 hours (95% CI -0.5 mg to -5.6 mg) in studies with low risk of bias and -7.3 mg/24 hours (95% CI -8.84 to -5.98) in all studies.[11]
  - Gabapentin has little effect on morphine consumption compared to placebo at 24 hours when used in combination with other non-opioid analgesics as part of a multimodal regimen.[11]
  - Gabapentin has no impact on pain compared to placebo as reported on pain scales at 24 hour both at rest and during mobilization.[11]
  - The risk of nausea, vomiting, sedation, dizziness and serious AE were not significantly different between groups.[11]

Pregabalin

- Established pain:
  - There is no evidence for pregabalin in the treatment of established pain.

- Prophylactic effect:
  - Pregabalin reduces opioid requirements at 24 hours compared to placebo, MD 5 to 10 mg. The reduction in morphine consumption is less when added to other non-opioid analgesics (MD < 4mg/24 hours) and likely not clinically relevant.[12,13]
  - Pregabalin produces small improvements in pain scales at 24 hours compared to placebo, for example a reduction of 0.45 on 0 – 10 VAS scale (95% CI 0.25 mm to 0.64 mm), but the improvements are unlikely to be noticeable clinically.[12,13]
  - Pregabalin may decrease the incidence of postoperative nausea and vomiting (NNT 12; 95% CI 6 to 16.2) but produces an increase in sedation at 24 hours

(NNH 6; 95% CI <1 to 13.7).[13] The risk of serious AE may be increased with perioperative pregabalin (RR 2.9; 95% CI 1.2 to 6.8).[12]

In September 2019 Health Canada issued a safety warning advising Canadians to exercise caution when taking gabapentin or pregabalin with opioids. The warning states that gabapentinoids when used with opioids increase the risk of opioid overdose. Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression (slowed breathing), increased sedation (sleepiness), dizziness, fainting, and death. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/71003a-eng.php

QUESTION 1e: WHAT DO CLINICAL PRACTICE GUIDELINES RECOMMEND FOR ORAL NON-OPIOID ANALGESIA IN ADULT PATIENTS AFTER SURGERY?

- The American Pain Society, American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' (APA/ASA) postoperative guidelines recommend:
  - The use of multimodal analgesia for the treatment of postoperative pain (strong recommendation, high-quality evidence).[14]
  - Postsurgical patients be treated with acetaminophen and/or NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence).[14.] Non-opioid analgesics should be administered around the clock.

QUESTION 2: IS THERE EVIDENCE TO GUIDE THE PRESCRIBING OF ORAL OPIOIDS AFTER SURGERY?

- Several observational studies have found that opioid use following surgery increases the chance of chronic opioid use both at >90 days and at 1 year.[15,16]

- The risk of chronic opioid use after surgery is associated with the duration of the initial opioid prescription after surgery.[17]

- Although opioids are often used to manage severe acute postoperative pain, recent observational studies and MA show that patients often receive more opioids for home use than is necessary for pain for many procedures.[18,19]
  - 67% to 92% of patients have unused opioids following surgery and most patients stop or do not use their opioids due to adequate pain control.[18,19]

QUESTION 2a: WHAT DO GUIDELINES RECOMMEND FOR PRESCRIBING ORAL OPIOIDS AFTER SURGERY?

- According to the 2020 Canadian Consensus Statement for the Prescription of Pain Medicine at Discharge after Elective Adult Surgery and the 2015 Washington State Agency Medical Directors' Group (AMDG) Interagency Guideline on Prescribing Opioids for Pain (with a supplemental guidance published in 2018, Bree Collaborative).[21,22,23]
  - The goal of pain management in the postoperative setting is to facilitate recovery and improve function. [21,22,23]

- Focus on postoperative functional goals, the ability to eat, move, breathe deeply and sleep.[21]

➢ The guideline/consensus statements group surgeries by different durations of recovery and recommend the amount of opioid and the duration of therapy based on the expected rate of recovery and level of pain severity.

- Guides for the expected rate of recovery of different surgical procedures are available (see page 90-91).[22,23]
- Not all patients will require opioids after surgery. If opioids are prescribed use the lowest effective dose on an as needed basis.[21,22,23]
- Prescriptions for opioid should be written at discharge, not before. Opioid prescriptions should have a 30 day expiry from date of discharge.[23]
- Patients should be instructed to only fill an opioid prescription if their pain is not well managed with other therapies or if they are having difficulty completing activities of daily living secondary to pain. [21,22,23]
- Opioids should be used for a limited duration of time. It is important to educate patients that pain will improve day by day.[21,22]
- Avoid excess prescription quantities. The dose and duration should be limited to short, renewable courses (e.g. 1 week).[21,22,23]

Table 1 Recommended duration and quantity of opioids after surgery

Washington State AMDG 2018 Supplement[22]	2020 Canadian Consensus Statement[23]
• Only use in severe pain • If the expected rate of recovery is rapid, prescribe ≤ 3 days (e.g. 8-12 pills) • If a medium term recovery is expected, prescribe ≤ 7 days (e.g. up to 42 pills) • If the expected rate of recovery is delayed, prescribe ≤14 days • For exceptional cases that warrant > 14 days of opioid treatment, the surgeon should re-evaluate before refilling opioids and taper off opioids within 6 weeks after surgery. • These numbers are based on data that opioids prescribed as above are adequate to treat postoperative pain in >75% of patients without refills. • Very few patients with an expected medium term recovery require longer than 7 days of therapy. • Use opioids on a PRN basis. • Avoid routine prescribing of the number of pills that equals the total allowable maximum dosing. • Patients are expected to need less frequent dosing as pain resolves and need a lower number of pills (as little as half) for a specified timeline.	• Patients with an expected rapid recovery (resume regular activities within 2 weeks from discharge) should be prescribed enough opioid for 0–3 days following discharge (maximum 12 tablets). • Patients with an expected moderate recovery (resume regular activities within 4 weeks from discharge) should be prescribed opioids for a maximum of 7 days following discharge (maximum 30 tablets). • Patients with an expected long-term recovery (resume regular activities longer than 4 weeks from discharge) should be prescribed opioid for a maximum of 14 days following discharge (maximum 60 tablets). • A part-fill or second prescription should be given to patients with an expected moderate or long term recovery to reduce the number of opioid containing tablets distributed at one time. • Do not prescribe an opioid to patients who have not received any in the last 24 hours of hospital stay. • Day surgery patients should be prescribed medications based on an expected rapid recovery.

➢ There is no optimal number of pills for any given procedure. The recommendations in the AMDG Guidelines and Canadian Consensus Statement are intended to serve as a general framework for managing postoperative pain, while minimizing leftover pills.[21,23]

QUESTION 2b: WHAT OBSERVATIONAL EVIDENCE WAS USED TO INFORM THE DURATION AND QUANTITIES OF ORAL OPIOIDS AFTER SURGERY?

➢ The Washington State AMDG Guidelines and Canadian Consensus Statement utilize evidence predominantly from observational trials to inform their recommendations.

- A large cohort study evaluated opioid use in over 200,000 patients after surgery and estimated an optimal length of opioid prescription.[31]
    - 4 - 9 days for general surgery procedures, 4 -13 days for women's health procedures, 6 - 15 days for musculoskeletal procedures.[31]
- Several cohort studies and one RCT compared the impact of prescribing a smaller number of opioid pills compared to "usual" opioid prescribing after surgery.[18,25,26,27,28,29,30,34] Patients that were prescribed fewer pills,
    - Consumed less opioid medication
    - Had similar improvements on pain and/or satisfaction scores
    - Had no differences in prescription refills
- Researchers from the University of Michigan have evaluated both a large health database and published cohort studies to establish opioid quantities that meet or exceed self-reported use of opioids for 75% of patients.[24]
    - These analysis guidelines/recommendations quantities of oral opioid tablets for specific surgical procedures.
- A number of cohort studies evaluating the impact of guidelines to promote a reduction in the quantity of prescribed opioids found that,
    - Opioid quantities (similar to those established by the University of Michigan researchers) result in a 20% to 50% reduction in the number of pills prescribed with no increase in refills.[25,32,33]

QUESTION 2c: WHAT IS THE EVIDENCE FOR THE EFFICACY OF SINGLE DOSE ORAL OPIOIDS IN THE TREATMENT OF MODERATE TO SEVERE POST-SURGICAL PAIN?

- The Washington State AMDG Guidelines and Canadian Consensus Statement both recommend that short acting opioids at the lowest effective dose be used on a PRN basis to minimize the amount of opioids used after surgery.[21,22,23]

- MAs have evaluated the effect of a single dose of oxycodone, codeine, tramadol, acetaminophen + codeine, tramadol + acetaminophen, ibuprofen + codeine, and ibuprofen + oxycodone, in reducing pain scores by 50% in patients with moderate to severe post-surgical pain. Other oral opioids have not been evaluated due to a lack of RCTs.

- Opioids have variable efficacy compared to placebo.
    - Oxycodone 5 mg vs placebo: no difference.[4]
    - Oxycodone 15 mg vs. placebo NNT = 5 (95% CI 3-11).[4]
    - Codeine 60 mg vs. placebo NNT 12 (95% CI 9-18), considered of limited clinical value since an NNT ≥ 10.[4]
    - Tramadol 50 mg and 75 mg vs. placebo NNT 10 which, considered of limited clinical value, unpublished studies.[39]
    - Tramadol 100 mg and 150 mg vs. placebo NNT 5, unpublished studies.[39]

- Adding a non-opioid analgesic to the opioid improves outcome results.
  - Acetaminophen + codeine compared to placebo
    - NNT 7 (95% CI 5-12) with low doses of acetaminophen.[4]
    - NNT 3 (95% CI 2-3) with high doses of acetaminophen.[4]
  - Tramadol 75 mg + acetaminophen 650 mg vs. placebo: NNT 3.[38]
  - Note: MAs have found a NNT 1.5 to 1.6 for a single dose of acetaminophen + ibuprofen compared to placebo in reducing pain scores by at least 50% in adults experiencing moderate to severe post-surgical pain, which is lower than the NNTs for opioid + non-opioid combinations.[4]

- When an opioid is added to a non-opioid analgesic the increase in efficacy is variable.
  - Oxycodone 5 mg + ibuprofen 400 mg vs. ibuprofen 400 mg: no difference.[40]
  - Ibuprofen (200 mg – 400 mg) + codeine (20 mg – 60 mg) vs. ibuprofen (200 mg – 400 mg): NNT 8 (95% CI not reported).[41]
  - Acetaminophen 1000 mg + codeine 60 mg vs. acetaminophen 1000 mg alone; NNT 6 (95% CI 3 to 15).[42]

Prescriber Resources and Patient Information

TOOLS FOR PRESCRIBERS	TOOLS FOR PATIENTS/ PATIENT INFORMATION
• Institute for Safe Medication Practices. Opioid stewardship; 2019: https://www.ismp-canada.org/opioid_stewardship/ • Choosing Wisely Canada: Opioid Wisely: https://choosingwiselycanada.org/campaign/opioid-wisely/ • Acute Care Opioid Treatment and Prescribing Recommendations: https://www.michigan.gov/documents/lara/Acute_Care_Opioid_Treatment_and_Prescibing_Recommendations_Surgical_-_FINAL_620739_7.PDF • Opioid Prescribing Engagement Network (OPEN) Prescribing Recommendations: https://opioidprescribing.info/ • PROSPECT Procedure Specific Postoperative Pain Management: https://esraeurope.org/prospect/ • American Academy of Orthopedic (AAOS) Pain Alleviation Toolkit: https://www.aaos.org/quality/patient-safety/pain-alleviation-toolkit/ • Supplemental Guidance on Prescribing Opioids for Postoperative Pain developed by the Dr. Robert Bree Collaborative and the Washington Agency Medical Directors' Group in collaboration with an advisory group of the state's academic leaders, pain experts and surgeons in general care and specialty areas in response to the growing opioid crisis: http://www.breecollaborative.org/wp-content/uploads/Final-Supplemental-Bree-AMDG-Postop-pain-091318-wcover.pdf	• Michigan OPEN Opioid Fact Sheet: https://michigan-open.org/wp-content/uploads/2020/05/Surgical-READY-TO-PRINT-non-prof-print.pdf • Health Canada Opioids Medicines Information for Patients and Families https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/policies/warning-sticker-opioid-patient-information-handout/information-handout.pdf • Health Quality Ontario Patient Reference Guide Opioid Prescribing for Acute Pain Care for People 15 Years of Age and Older: https://www.hqontario.ca/portals/0/documents/evidence/quality-standards/qs-opioid-acute-pain-patient-guide-en.pdf • Choosing Wisely Canada Opioids: When you need them - and when you don't: https://choosingwiselycanada.org/wp-content/uploads/2018/02/Opioids-When-you-need-them-and-when-you-dont.pdf • American Academy of Orthopedic Surgeons (AAOS) Patient Safety Information: https://www.aaos.org/PainReliefToolkit/?ssopc=1 • Washington State Department of Health Prescription Opioids for Surgical Pain: https://www.doh.wa.gov/Portals/1/Documents/Pubs/631079-SurgicalPain.pdf • Institute for Safe Medication Practices. Opioid stewardship; 2019. https://www.ismp-canada.org/opioid_stewardship/

Links to Guidelines:

- The Enhanced Recovery After Surgery (ERAS) Society, Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines. http://dx.doi.org/10.1016/j.anclin.2017.01.018
- Guidelines on the Management of Postoperative Pain Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council https://www.jpain.org/article/S1526-5900(15)00995-5/pdf
- Interagency Guideline on Prescribing Opioids for Pain developed by the Washington State Agency Medical Directors' Group (AMDG) in collaboration with an Expert Advisory Panel, Actively Practicing Providers, Public Stakeholders, and Senior State Officials. http://www.agencymeddirectors.wa.gov/files/2015amdgopioidguideline.pdf
- Consensus Statement for the Prescription of Pain Medication at Discharge after Elective Adult Surgery. https://www.tandfonline.com/doi/citedby/10.1080/24740527.2020.1724775?scroll=top&needAccess=true

BACKGROUND

- This review focuses on SRs and MAs of RCTs evaluating the efficacy and safety of **oral** medications for the treatment of postoperative pain in adult patients who are opioid naïve prior to surgery.
- Literature searches were conducted up to June 2020. MAs have concentrated on immediate postoperative pain rather than longer-term outcomes. No MAs focusing on post-discharge prescribing were found.
- Most MAs report pain outcomes using scales that measure pain intensity, for example the 100 point Visual Analogue Scale (VAS) and the 10 point Numerical Rating Scale (NRS), but do not evaluate function or other pain characteristics. Several cohort studies have established a pain intensity equivalent to mild pain (< 4 on a 10 point NRS or < 40 on a 100 point VAS) as acceptable pain control after surgery.[1,2]
- RCTs assessing the efficacy of oral medications in post-surgical pain generally utilize two different approaches.
    - The first approach evaluates the effect on **established pain**. Analgesics are compared to placebo as single dose monotherapy administered hours to days after the surgical procedure in patients experiencing moderate to severe pain. Pain is measured using standard pain scales immediately before the intervention and then using pain intensity and pain relief scales following the intervention.
        - Half the maximum possible pain relief or better (at least 50% pain relief) is generally considered a clinically important outcome across different pain conditions. [1,2] A reduction of 50% in pain scales in patients with moderate to severe pain in most cases should reduce pain to a mild intensity on pain scales.
        - An NNT ≥ 10 for achieving at least a 50% reduction in pain is reported to be unacceptably high in the treatment of postoperative pain according to multiple Cochrane reviews.[4]
    - The second approach evaluates an analgesic for **preventing pain**, where the medication is compared to placebo; both are initiated prior to or during surgery and most often continued for 24-48 hours postoperatively. Patients in both the comparator and placebo groups also receive opioids as needed (i.e. via PCA).
        - Predominantly these types of studies evaluate the impact on overall opioid consumption and a reduction in opioid related side effects.
        - It has not been determined how much opioid sparing is required to significantly reduce the incidence of opioid related adverse effects. An MID was defined as a difference in 24 hour morphine consumption of 10 mg in one RCT following total knee arthroplasty.[3]
- Most of the included evaluations pool trials of different surgical procedures that result in the same expected level of postsurgical pain (moderate to severe pain). Several reviews also considered outcomes for specific types of surgical procedures within the review.

QUESTION 1: WHAT IS THE EVIDENCE FOR ORAL NON-OPIOID PHARMACOLOGICAL THERAPIES IN THE MANAGEMENT OF MODERATE TO SEVERE POST-SURGICAL PAIN?

QUESTION 1a: WHAT IS THE EVIDENCE FOR ACETAMINOPHEN FOR POST-SURGICAL PAIN?

- **Established Pain:**
  - A Cochrane review of MAs evaluated the effect of a single dose of acetaminophen to relieve moderate to severe acute postoperative pain. The MAs that were included in the review were previous Cochrane Reviews that included DB RCTs and evaluated established postsurgical pain in adults. Pain was assessed by participants using standard pain intensity and pain relief scales.[4]
  - The primary outcome reported in the review was the number of participants with at least 50% improvement in pain over 4-6 hours compared with placebo.[4]
  - Pooled analyses found that the NNT to achieve at least a 50% maximum pain relief over 4 to 6 hours for acetaminophen is as follows: [4]
    - **Acetaminophen 500 mg**: NNT 3.5 (95% CI 2.7 to 4.8; 6 studies, N=561)
    - **Acetaminophen 600/650 mg:** NNT 4.6 (95% CI 3.9 to 5.5; 19 studies, N=1,886)
    - **Acetaminophen 975/1000 mg:** NNT 3.6 (95% 3.2 to 4.1 ; 28 studies, N=3,232)
      The mean or median time to re-medication ranged from 3-4 hours
  - Another Cochrane Review of MAs evaluated the adverse events associated with a single dose of oral analgesic for acute postoperative pain in adults. For acetaminophen, the proportion of participants reporting an adverse event ranged from 7% and 18% and the proportion of participants with an adverse event with placebo ranged from 6% and 16%. There were no statistically significant differences between acetaminophen and placebo for any adverse event comparison (35 trials, N=4,183).[5]

- **Prophylactic Effect:**
  - Two network MAs[6, 7] and a MA [8] have evaluated the efficacy of adding a non-opioid analgesic to morphine (administered via a PCA device) and compared this regimen to morphine alone in adult patients who have undergone major surgery. These MAs pooled RCTs where morphine plus either acetaminophen, an NSAID, or a COX-2 inhibitor were compared to placebo over 24 hours.
  - 24 hour morphine consumption was significantly decreased with acetaminophen compared to placebo (WMD -8.31 mg (95% CI -5.72 mg to -10.9 mg) 10 trials, N=713 with multiple doses[8], MD -6.34 mg (95% CI -3.65 mg to -9.02 mg) 10 comparisons[7], MD -10.5 mg (95% CI -6.9 mg to -14.1 mg). [6]
  - However, the addition of oral acetaminophen did not reduce the occurrence of morphine related adverse effects [6,7,8] and did not significantly improve pain intensity as reported on pain scales. [6,8]

- There were no differences between oral acetaminophen and placebo for safety outcomes.[6,7,8]

QUESTION 1b: WHAT IS THE EVIDENCE FOR NSAIDs/COX-2 INHIBITORS FOR POST-SURGICAL PAIN?

NSAIDs

➢ Established Pain:

- In the Cochrane Review of MA when NSAIDs were compared to placebo for at least a 50% improvement in pain scales over 4 to 6 hours, NNTs ranged from 1.9 to 8.3, depending on drug and dose: [4]

Table 2 Results for NSAIDs/doses for which Cochrane reviews found reliable results not subject to potential publication bias:[4]

*NSAID**	Strength	NNT (95% CI)	# Studies	# Participants
Diclofenac	25 mg	2.4 (2.0 to 2.9)	4	502
	50 mg	2.1 (1.9 to 2.5)	7	757
	100 mg	1.9 (1.7 to 2.3)	6	589
Ibuprofen	100 mg	4.3 (3.2 to 6.4)	4	396
	200 mg	2.9 (2.7 to 3.2)	18	2,103
	400 mg	2.5 (2.4 to 2.6)	51	5,604
	600 mg	2.7 (2.0 to 4.2)	3	203
Naproxen	400/440 mg	2.7 (2.2 to 3.5)	3	334
	500/550 mg	2.7 (2.3 to 3.3)	9	784
Ketoprofen‡	12.5 mg	2.4 (1.9 to 3.1)	3	274
	100 mg	2.1 (1.7 to 2.6)	5	321
Flurbiprofen‡	25 mg	3.3 (2.5 to 4.9)	3	208
	100 mg	2.5 (2.0 to 3.1)	7	416
Diflunisal	500 mg	2.6 (2.1 to 3.3)	6	391
	100 mg	2.1 (1.8 to 2.6)	5	357
Etodolac‡	100 mg	4.8 (3.5 to 7.8)	5	498
	400 mg	3.3 (2.7 to 4.2)	3	222

*NSAIDs currently available in Canada are included in the table. Diflunisal and etodolac listed as dormant by Health Canada without any sales in previous 12 months (January 19, 2021)
‡ Not all strengths are included in table. Highest and lowest strength presented.
The mean/median time to re-medication for NSAIDs ranged from 4-10 h.

- The Cochrane Review that evaluated the adverse events associated with single dose analgesia for acute postoperative pain in adults reported that for most comparisons NSAIDs were not significantly different compared to placebo.[5] Aspirin 1000 mg and diflunisal 1000 mg had an adverse event rate significantly higher than placebo resulting in an NNH of 7.5 (95% CI 4.8 to 17) for aspirin 1000 mg and 7.7 (95% CI 4.8 to 20) for diflunisal 1000 mg.[5]

➢ Prophylactic Effect:

- The two network MAs [6,7] and MA [8] that evaluated the efficacy of adding a non-opioid analgesic to morphine versus morphine alone found that 24 hour morphine consumption was significantly decreased with NSAIDs vs. placebo.

- WMD -10.3 mg (95% CI -2.34 mg to -18.3 mg, N=1,029) with single doses and WMD -19.7 mg (95% CI -13 mg to -26.3 mg, N=528) with multiple dose regimens[8]
- MD -10.18 mg (95% CI -8.72 mg to - 11.65 mg; 33 comparisons) [7]
- MD –12.9 mg (95% CI –10.6 mg to -15.1 mg)[6]

- NSAIDs had a statistically significant benefit in reducing nausea or postoperative nausea and vomiting (PONV) at 24 hours compared with placebo.
  - ARR 6.8%; NNT 15 (95% CI 9 to 47)[8]
  - OR 0.70 (95% CI 0.53 to 0.88) nausea and PONV[7]
  - OR 0.70 (95% CI 0.58 to 0.83) nausea; OR 0.73 (95% CI 0.57 to 0.92) vomiting[6]
- The most commonly reported adverse effects related to NSAIDs were surgical bleeding, GI bleeding and renal impairment[7,8]
  - Surgical bleeding occurred at a rate of 0.2% to 0.4% in control groups vs. 1.7% to 2% with NSAIDs (NNH 65). This outcome was reported using RCTs which evaluated diclofenac, ketoprofen and ketorolac. This outcome has not been reported in RCTs evaluating other NSAIDs.[7,8]
- Refer to the NSAID section for risk factor assessment tools and information regarding gastrointestinal, cardiovascular and/or renal toxicity.

COX-2 inhibitors

- Established Pain:
  - The Cochrane Review of MAs evaluated the efficacy or COX-2 inhibitors compared to placebo for reducing moderate to severe pain by 50%. When celecoxib was compared to placebo for at least a 50% maximum pain relief over 4-6 hours the NNTs were 4.2 (95% CI 3.4 to 5.6; 4 studies. N=705) for 200 mg and 2.6 (95% CI 2.3 to 3.0; 5 trials, N=722) for 400 mg.[4]
  - The Cochrane Review of MAs evaluating AEs associated with COX-2 inhibitors for acute postoperative pain in adults reported that for most comparisons there were no statistically significant differences between celecoxib vs. placebo.[5]

- Prophylactic Effect:
  - The two network MAs [6,7] and MA [8] that evaluated the efficacy of adding a non-opioid analgesic to morphine vs. morphine alone found that 24 hour morphine consumption was significantly decreased with COX-2 inhibitors vs. placebo.
  - The mean difference in morphine consumption with COX-2 inhibitors vs. placebo over 24 hours was:
    - WMD -7.2 mg (95% CI -3.8 mg to - 10.6 mg) with 200 mg celecoxib, -10 mg (95 % CI -6.58 mg to - 13.4 mg) with multiple low dose regimens, and -13.3 mg (95% CI -8.81 mg to - 17.8 mg) with multiple high dose regimens; 13 trials (N=1,812)[8]
    - MD -10.92 mg (95% CI -12.77 to - 29.08)[7]
    - MD –13.5 mg (95% CI –16.8 mg to –10.1 mg)[6]

- COX-2 inhibitors did not reduce the incidence of morphine related AEs.[6,7,8]
- The adverse effect profiles for COX-2 inhibitors were similar to NSAIDs.[8]
- An increased risk of post-surgical bleeding was not evaluated because zero surgical bleeding complications were reported in the COX-2 inhibitor RCTs.[7,8]
- Refer to NSAID pharmacotherapy tables and risk factor tables for considerations such as differences between NSAIDs for gastrointestinal, cardiovascular or renal toxicity.

QUESTION 1c: WHAT IS THE EVIDENCE FOR MULTIMODAL ANALGESIA (THE COMBINATION OF ACETAMINOPHEN AND NSAIDs) FOR POST-SURGICAL PAIN?

- Established pain:
  - The Cochrane Review of MAs which evaluated single dose analgesia included an evaluation of the combination of NSAIDs plus acetaminophen. All of the included RCTs evaluated the combination of ibuprofen + acetaminophen.
  - The Cochrane Review found that ibuprofen + acetaminophen combination was significantly more effective than placebo for at least 50% maximum pain relief over 4-6 hours, with the following NNT: [4]
    - **Ibuprofen 200 mg + acetaminophen 500 mg:** NNT of 1.6 (95% CI 1.5 to 1.8; 3 studies, N=508)
    - **Ibuprofen 400 mg + acetaminophen 1000 mg**: NNT of 1.5 (95% CI 1.4 to 1.7; 3 studies, N=543)

      The combination of acetaminophen + ibuprofen resulted in lower NNTs vs. either medication alone.
  - The Cochrane Review of MAs which evaluated the AEs associated with single dose analgesia compared ibuprofen + acetaminophen to placebo. The review reported fewer AEs with the combination vs. placebo.[5] NNT to prevent one AE:
    - **Ibuprofen 200 mg + acetaminophen 500 mg:** 5.4 (95% CI 3.6 to 11; 3 studies, N=508)
    - **Ibuprofen 400 mg + acetaminophen 1000 mg**: 5.1 (95% CI 3.5 to 9.5; 3 studies, N=543)

- Prophylactic effect:
  - A NMA evaluating RCTs in adults after major surgery evaluated the combination of an NSAID + acetaminophen vs. placebo when added to morphine. Morphine consumption was significantly reduced with a mean difference of –22.8 mg (95% CI -31.5 mg to –14 mg) with the NSAID + acetaminophen vs. placebo.[6] Mean 24 hour morphine consumption:
    - **Ibuprofen 400 mg + acetaminophen 1000 mg:** 20 mg
    - **Ibuprofen 200 mg + acetaminophen 500 mg**: 28 mg
    - **Ibuprofen 400 mg**: 26 mg
    - **Acetaminophen 1000 mg**: 36 mg

- One SR of 21 DB RCTs (N=1,909) compared an NSAID + acetaminophen combination to the individual drugs for pain relief in acute post-operative pain. The review found that the combination is associated with a significantly greater reduction in morphine consumption and pain scores vs. either agent alone.[9]
    - Over 24 hours, pain intensity was on average 35.0% ± 10.9% lower (as reported on pain scales) and morphine supplementation was on average 38.8% ± 13.1% lower, with the combination vs. acetaminophen alone.[9]
    - Over 24 hours, pain intensity was on average 37.7% ± 26.6% lower (as reported on pain scales) and morphine supplementation was on average 31.3% ± 13.4% lower with the combination vs. an NSAID alone.[9]
- Both the NMA and SR found that an NSAID + acetaminophen combination does not result in an increased rate of AEs vs. individual agents or vs. placebo.[6,9]

QUESTION 1d: WHAT IS THE EVIDENCE FOR GABAPENTIN AND PREGABALIN FOR POST-SURGICAL PAIN?

Gabapentin

- Established Pain:
    - A Cochrane Review evaluated the effect of gabapentin for the relief of established moderate to severe postoperative pain in adults. Four unpublished studies were included; participants were treated with a single dose of gabapentin 250 mg (N=177), 21 with gabapentin 500 mg (N=21), or with placebo (N=172). At least 50% pain relief over 6 hours was achieved by 15% with gabapentin 250 mg and 5% with placebo; giving a risk benefit = 2.5 (95% CI 1.2 to 5.0) and an NNT = 11 (95 % CI 6.4 to 35).[10] There were too few patients treated with gabapentin 500 mg to undertake an evaluation of efficacy for this strength.[10]
    - The Cochrane Review of MAs review also reported that the NNT for at least a 50% maximum pain relief over 4-6 hours with gabapentin 250 mg compared with placebo is 11 (95 % CI 6.4 to 35) when 3 unpublished studies with 327 participants were pooled.[4] This review reported that there is no evidence of efficacy with gabapentin 500 mg compared to placebo for this analysis.
    - ***Note*:** An NNT ≥ 10 to achieve a 50% reduction in pain scores was considered unacceptably high for the treatment of acute postoperative pain in 2 of the reviews.[4, 10] While gabapentin 250 mg was statistically superior to placebo in the treatment of established postoperative pain, the NNT of 11 was considered of limited clinical value and inferior to commonly used analgesics.[4,10]
    - The Cochrane Reviews evaluating the adverse events associated with gabapentin in acute postoperative pain in adults reported that for most comparisons there was no statistically significant difference compared to placebo.[4,10]

- Prophylactic Effect:
  - One MA evaluated the effects of perioperative gabapentin on postoperative opioid consumption, pain intensity and adverse effects in surgical patients receiving gabapentin for postoperative pain management.[11]
  - In a variety of surgical indications, gabapentin was minimally opioid sparing.
    - When trials with a low risk of bias were pooled the mean morphine consumption was reduced by MD -3.1 mg/24 hours (95% CI -0.5 mg to -5.6 mg; 13 trials, N=1,362) compared to placebo.[11]
    - When all trials were pooled the mean morphine consumption was reduced by MD -7.3 mg/24 hours (95% CI -8.84 to -5.98; 73 RCTS, N=5,630) compared to placebo.[11]
    - Gabapentin had little benefit on morphine consumption when added to other non-opioid agents (MD -1.2 mg/24 hours in trials with low risk of bias, MD -4.4 mg/24 hours in all trials) compared to placebo.[11]
  - The MA reported that pain at rest was not significantly reduced at 6 hours postoperatively. Pain during mobilization was reduced at 6 hours postoperatively by a mean of -9 mm on 100 VAS scale; 95% CI – 4 mm to -13 mm (7 trials, N=572) which was unlikely to be noticeable clinically. At 24 hours the effect of gabapentin on pain scales produced no improvements at rest nor during mobilization.[11]
  - The risk of nausea, vomiting, sedation, dizziness and serious adverse effects were not significantly different between groups.[11]

Pregabalin

- Established Pain:
  - There is no evidence for pregabalin for this comparison.[4]

- Prophylactic Effect:
  - Two MAs have evaluated the efficacy of pregabalin in treating post-surgical pain in a variety of surgical indications. [12,13]
  - Pregabalin reduced opioid requirements compared to placebo.
    - In one MA when trials with a low risk of bias were pooled the mean morphine consumption was - 5.8 mg/24 hours (95% CI -3.2 mg to – 8.5 mg; 11 trials, N=705) compared to placebo. When all trials were pooled the mean morphine consumption was reduced by a mean of - 10.8 mg/24 hours (95% CI – 8.46 mg to -13.9 mg; 37 trials, N=2,423) compared to placebo. The reduction in morphine consumption is less when pregabalin is added to other non-opioid agents-MD, 3.7 mg/24 hours (95% CI -1.5 mg to -6.0 mg; 9 RCTS, N=585).[12]
    - In the other MA the mean difference in morphine consumption compared to placebo at 24 hours was -9.15 mg (95% CI -7.09 mg to -11.22 mg; 54 RCTS, N=3,543).[13]
  - The effect of pregabalin on pain scales at 24 hours was:

- MD, -0.45 mm VAS 0-10 (95% CI 0.25 mm to 0.64 mm) in one MA (54 RCTS, N=3,543).[13]
- In the other MA there was no significant improvement on pain scales (100 mm VAS) both during rest and mobilization when trials with low risk of bias were pooled. When all trails were pooled there was a small improvement on pain scales at 24 hours during rest MD, -5.3 mm; 95% CI -1.6 mm to -9.1 mm (59 RCTs, N=4,105) and during mobilization MD, -4.2 mm; 95% CI -1.3 mm to -7.0 mm (23 RCTs, N=1,629).[12,13]
- The improvements are unlikely to be noticeable clinically.[12,13]

- Pregabalin may decrease the incidence of postoperative nausea and vomiting (NNT = 12; 95% CI 6 to 16.2) but produces an increase in sedation at 24 hours (NNH = 6; 95% CI <1 to 13.7).[13] The risk of serious adverse events was significantly increased with the perioperative use of pregabalin (RR 2.9; 95% CI 1.2 to 6.8 (10 RCTs, N=730).[12]

In September 2019 Health Canada issued a safety warning advising Canadians to exercise caution when taking gabapentin or pregabalin with opioids. The warning stated that gabapentinoids when used with opioids increase the risk of opioid overdose. Serious side effects of using gabapentinoids and opioids at the same time include respiratory depression (slowed breathing), increased sedation (sleepiness), dizziness, fainting, and death. Available at: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/71003a-eng.php

QUESTION 1e: WHAT DO CLINICAL PRACTICE GUIDELINES RECOMMEND FOR ORAL NON-OPIOID ANALGESIA IN ADULT PATIENTS AFTER SURGERY?

- The American Pain Society, American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' (APA/ASA) Guidelines provided 32 recommendations; 4 of the 32 are based on high-quality evidence, 2 of which pertain to the use of oral non-opioid analgesics.[14]
  - The guidelines recommend that clinicians offer multimodal analgesia for the treatment of postoperative pain (strong recommendation, high quality evidence).[14]
  - The guidelines recommend that postsurgical patients be treated with acetaminophen and/or NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high quality evidence).[14]
    - Acetaminophen and NSAIDs have been evaluated as part of multimodal analgesia in patients also receiving opioids for postoperative pain. Most studies show use of acetaminophen and/or NSAIDs in conjunction with opioids is associated with less postoperative pain or opioid consumption than opioids alone.[14]
    - Non-opioid analgesics should be administered around the clock.[14]

QUESTION 2: IS THERE EVIDENCE TO GUIDE THE PRESCRIBING OF OPIOIDS AFTER SURGERY?

- The perioperative period may be an important time for the development of long term and persistent opioid use, particularly with opioid naïve individuals.

- Several observational studies have found that opioid use following surgery increases the chance of chronic opioid use both at >90 days and at 1 year.
    - A retrospective cohort study evaluated the incidence of persistent opioid use >90 days among opioid naïve individuals after both minor and major surgery. A total of 36,177 patients were included, 29,068 with minor surgery and 7,109 with major surgery.[15]
        - Among patients who were opioid-free in the year leading up to surgery, opioid use beyond 90 days postoperatively occurred in approximately 6.0% of adults following a variety of surgeries.[15]
        - The rates of new persistent opioid use were similar between the two groups of minor and major surgery, ranging from 5.9% – 6.5%. By comparison, the incidence in the non-operative control cohort was only 0.4%.[15]

- Another retrospective cohort study evaluated chronic opioid use at 1 year post discharge in 6,689 opioid naïve patients.[16]
    - Chronic opioid use was more common among patients who received opioids compared to patients who did not receive opioids at 1 year post discharge (4.1 % versus 1.3 %, $p<0.0001$). Receiving an opioid was associated with increased odds of chronic opioid use (OR=4.90, 95 % CI 3.22-7.45) and greater subsequent opioid refills (OR=2.67, 95 % CI 2.29-3.13) 1 year post discharge compared to not receiving an opioid.[16]

- The risk of chronic opioid use after surgery is associated with the duration of the initial opioid prescription after surgery.
    - A retrospective cohort study of more than a million opioid-naïve surgical patients, identified the duration of initial prescription after surgery as a risk factor for later opioid misuse (dependence, abuse, or overdose) diagnoses.[17]
        - The overall rate of postoperative patients subsequently having such a diagnoses was low (0.6%); however, each additional week of opioid therapy prescribed was associated with an adjusted 20% increase in hazard for opioid misuse, with a total 44% increase in hazard if a refill was also needed.[17]

- Although opioids are often used to manage severe acute postoperative pain, recent observational studies show that patients often receive more opioids for home use than is necessary for pain for many procedures.

- One MA of retrospective cohort studies (7 studies, N=810, 7 different procedures) found that 67% to 92% of patients have unused opioids following surgery.[18]
    - Of all the opioid tablets obtained by surgical patients, 42% to 71% went unused.[18]
    - Most patients either stopped or did not use opioids due to adequate pain control. Opioids were also stopped due to adverse events in 16% to 29% of patients.[18]
    - Five studies reported some patients did not use any opioids. Patients either did not fill their prescription (0% to 21%) or filled the prescription but did not take any opioids (7% to 14%).[18]
- Another large cohort study (N= 10,651) published after the MA evaluated the quantity of opioids prescribed and used following surgery (19 different procedures). Opioids were administered to 76% of patients after and the median opioid use was 27% of the total prescribed after surgery.[19]

QUESTION 2a: WHAT DO GUIDELINES RECOMMEND FOR PRESCRIBING ORAL OPIOIDS AFTER SURGERY?

- One of the main principles of post-surgical acute pain management in clinical practice guidelines is the utilization of a multimodal approach in order to reduce the reliance on opioids.
    - The multimodal approach assumes the use of opioids for many postsurgical patients. Although the APA/ASA guidelines note that systemic opioids might not be required in all patients.[14]
    - The APA/ASA guidelines also suggest that opioids be avoided if they are not needed. [14]
        - This suggestion is based on evidence from a retrospective cohort study that evaluated the risk of long term opioid use after low risk surgery in older adults. [14]
        - Among 391,139 opioid-naive patients who underwent short-stay surgery, opioids were newly prescribed to 27,636 patients (7.1%) within 7 days of being discharged from the hospital, and at 1 year after surgery opioids were prescribed to 30,145 patients (7.7%).[20]

- The 2020 Canadian Consensus Statement for the Prescription of Pain Medicine at Discharge after Elective Adult Surgery and the 2015 Washington State Agency Medical Directors' Group (AMDG) Interagency Guideline on Prescribing Opioids for Pain (with a supplemental guidance published in 2018) focus on appropriate prescribing of opioids for postoperative pain, including prescribing opioids at discharge.[21,22]
    - These guidelines/consensus statements are largely based on observational data and expert opinion. For this reason they are not graded.

- **The goal of pain management in the postoperative setting is to facilitate recovery and improve function.** [21,22,23]
- **Focus on postoperative functional goals, the ability to eat, move, breathe deeply and sleep.**[21]

- Recommendations are summarized in *Table 3 and Table 4.*

Table 3

2015 Washington State Agency Medical Directors' Group (AMDG) Interagency Guideline on Prescribing Opioids for Pain (with supplemental guidance published in 2018)[21,22]
• Avoid continuing or adding prescriptions of benzodiazepines, sedative hypnotics, anxioltics or CNS depressants. Counsel about risks of using alcohol and other CNS depressants with opioids. • Inform patient and family which provider will be managing postoperative pain including the prescribing of opioids. Inform them of the planned taper of postoperative opioids. • Inform patients of the dangers of opioid diversion, the importance of secure storage and prompt disposal. Sharing medications is never appropriate. • Reserve opioids for moderate to severe acute pain. Use the lowest possible dose within a multimodal regimen, including NSAIDs and/or acetaminophen, unless contraindicated. o Use short-acting PRN opioids for acute severe pain in the opioid naïve patient. o The prescription may be written for dosing intervals (i.e. prn every four to six hours). Avoid routine prescribing of the number of pills that equals the total allowable maximum dosing. o A patient is expected to need less frequent dosing as pain resolves will likely need a lower number of pills (as little as half) for a specified timeline. o Consider discussing partial refills. • Follow through with the agreed upon preopertive plan to taper off opioids as surgical healing takes place. The goal is always the shortest duration and the lowest effective dose. o Most patients with major surgeries should be able to be tapered within 6 weeks of surgery. (Approximately 20% of dose/week. Tapering may be slower in the 1st week - 10 days and then becomemore rapid with healing). o It may be appropriate to discharge patients on acetaminophen or NSAIDs only, or with a very limited supply of short acting opioids (e.g. 2-3 days) for some minor surgeries • Patients who are unable to taper opioid use to coincide with expected healing or who report pain severe enough to warrant ongoing opioid use after the procedure-specific usual number of days require re-evaluation in an effort to understand the factors delaying a normal course of recovery.

Table 4

Summary of the 2020 Canadian Consensus Statement for the Prescription of Pain Medicine at Discharge after Elective Adult Surgery[23]
• Provide preoperative written and verbal information on pain management options to patients and families/caregivers. • Provide written and verbal information before discharge on the safe storage and disposal of unused opioids. • Before surgery, patients should be assessed for risk factors for increased risk for persistent postoperative opioid use. See the Opioid Acute Pain Prescribing Section for details on risk factors • Non-opioid therapy should be first-line e.g., NSAIDS, acetaminophen, or regional anesthetic techniques. Patients should be discharged with a prescription for the following medications unless contraindicated: o Acetaminophen 1 g PO TID - QID for 7 days then PRN. o NSAIDs PO for 3 days then PRN. o Counsel on how to take scheduled medications and when to stop based on the expected rate of recovery. • Patients should receive a prescription for opioid containing tablets based on in hospital consumption during the previous 24 h and expected functional recovery. o Prescribe the same opioid used in hospital to ensure tolerability. o Do not prescribe an opioid to patients who have not received any in the last 24 hours of hospital stay. o Day surgery patients should be prescribed medications based on an expected rapid recovery. • Prescriptions for opioid should be written at discharge, not before. Opioid prescriptions should have a 30 day expiry from date of discharge. • If opioid are prescribed, they should be short-acting at the lowest effective dose, with the lowest potency, for the shortest duration. o Direct patients to fill opioid prescriptions only if pain is not well managed or if they are having difficulty completing ADL due to pain. • At follow-up ask about postoperative pain and opioid use. Instruct patients to return opioids to local pharmacy if not being used. • If patients require a refill of an opioid before follow-up visit, a maximum of 14 days (and 60 tablets) should be prescribed as part fills at 7-day intervals. • If pain persists >3 months, refer to a transitional/chronic pain clinic. If there is a suspicion that a patient is misusing opioids, the patient should be referred to a transitional/chronic pain clinic

- The goal of pain management in the postoperative setting is to facilitate recovery and improve function.
  - The guidelines and consensus statements have both grouped surgeries by different durations of recovery and recommend the amount of opioid and the duration of therapy based on the expected rate of recovery and level of pain severity. These are summarized in *Table 5 and Table 6* below.

Table 5 – Examples of surgical procedures, expected recovery times, and prescribing recommendations AMDG Supplement 2018[22]

	Rapid recovery	Medium-term recovery	Longer-term recovery
Procedure	• Laparoscopic appendectomy • Inguinal hernia repair • Carpal tunnel release • Thyroidectomy • Laparoscopic cholecystectomy • Breast biopsy/lumpectomy • Meniscectomy • Lymph node biopsy • Vaginal hysterectomy	• Anterior cruciate ligament (ACL) repair • Rotator cuff repair • Discectomy • Laminectomy • Open or laparoscopic colectomy • Open incisional hernia repair • Open small-bowel resection or enterolysis • Wide local excision • Laparoscopic hysterectomy • Simple mastectomy • Cesarean section	• Lumbar infusion • Knee replacement • Hip replacement • Abdominal hysterectomy • Axillary lymph node resection • Modified radical mastectomy • Ileostomy/colostomy creation or closure • Thoracotomy
Prescribe	• Non-opioid analgesics (e.g., NSAIDs and/or acetaminophen) and non-pharmacologic therapies as first-line therapy. • If opioids are necessary, prescribe ≤3 days (e.g., 8 to 12 pills) of short-acting opioids in combination with an NSAID or acetaminophen for severe pain. Prescribe the lowest effective dose strength	• Non-opioid analgesics (e.g., NSAIDs and/or acetaminophen) and non-pharmacologic therapies as first-line therapy. • ≤7 days (e.g., up to 42 pills) of short-acting opioids for severe pain. Prescribe the lowest effective dose strength. • For those exceptional cases that warrant > 7 days of opioid treatment, the surgeon should re-evaluate the patient before a third prescription and taper off opioids within 6 weeks after surgery.	• Non-opioid analgesics (e.g., NSAIDs and/or acetaminophen) and non-pharmacologic therapies as first-line therapy. • ≤14 days of short-acting opioids for severe pain. Prescribe the lowest effective dose strength. • For those exceptional cases that warrant more than 14 days of opioid treatment, the surgeon should re-evaluate the patient before refilling opioids and taper off opioids within 6 weeks after surgery.

Adapted from http://www.breecollaborative.org/wp-content/uploads/Supplemental-Bree-AMDG-Postop-pain-18-0718.pdf

- *These numbers are based on data showing that opioids prescribed as above are adequate to treat postoperative pain in >75% of patients without refills.*[24]
- *Very few patients with an expected medium term recovery require longer than 7 days of therapy.*[21,22,23]

Table 6 - Examples of surgical procedures, expected recovery times, and prescribing recommendations for opioids in the Canadian Consensus Statement for the Prescription of Pain Medicine at Discharge after Elective Adult Surgery 2020[23]

	Rapid recovery Patient resumes most normal activities within 2 weeks	Medium-term recovery Patient resumes most normal activities within 4 weeks	Longer-term recovery Patient resumes most normal activities after 4+ weeks from surgery
Procedure *Breast*	• Breast biopsy • Lumpectomy • Sentinel lymph node biopsy • Simple mastectomy	• Mastectomy with reconstruction • Modified radical mastectomy • Axillary lymph node dissection • Axillary lymph node dissection	
Cardiac	• Cardiac catheterization	• CABG	
General surgery	• Cholecystectomy • Appendectomy • Inguinal/femoral hernia repair • Umbilical hernia repair • Ileostomy/colostomy creation • Colon or rectal resection	• Ileostomy/colostomy creation • Incisional hernia repair • small bowel resection or enterolysis • Low anterior resection • Colon or rectal resection • APR	• Component separation and incisional hernia repair
Gynecologic	• Uncomplicated cesarean section • Uncomplicated labor and delivery	• Vaginal hysterectomy • Abdominal/open hysterectomy • Laparoscopic and robotic hysterectomy	
Neurosurgery and spine	• Microdiscectomy	• Discectomy (open/multilevel) • Laminectomy • Craniotomy	• Lumbar fusion, major spine procedure
Orthopedic	• Arthroscopic partial meniscectomy • Carpal tunnel release • Acute fracture • Minor fracture ORIF • Arthroscopic shoulder decompression	• Arthroscopic ACL/PCL reconstruction • Arthroscopic or mini open rotator cuff repair • Thumb reconstruction • MTP fusion • Major fracture ORIF • Hip fracture (ORIF or arthroplasty) • Total hip arthroplasty • Total shoulder or elbow arthroplasty • Total ankle arthroplasty • Amputation	• Total knee arthroplasty • Osteotomies • Revision surgeries for fracture nonunion • Repair/reconstruction of • Multi-ligament knee injuries
Otolaryngeal	• Thyroidectomy, tonsillectomy • Cochlear Implant		• Partial or complete neck dissection
Thoracic	• VATS	• Thoracotomy	• Esophagostomy
Urological	• Robotic retro pubic prostatectomy • Vasectomy • Transurethral resection of bladder tumor • Ureteral stent placement • Ureteroscopic stone extraction	• Robotic-assisted laparoscopic radical prostatectomy • Robotic assisted laparoscopic partial nephrectomy • Percutaneous nephrectomy	• Open partial nephrectomy • Open cyst prostatectomy with ileal Conduit
Vascular	• Endovascular thoracic/aortic aneurysm repair • Upper extremity dialysis access creation • Carotid endarterectomy	• Inflatable penile prothesis/malleable • penile prothesis placement • Infrainguinal bypass • Hybrid infrainguinal revascularization • Thoracic outlet decompression • Advanced endovascular aortic aneurysm repair	• Open aortic aneurysm repair • Open thoraco-abdominal aneurysm repair • Aorto/thoraco–femoral bypass
Prescribe	0–3 days; maximum 12 tablets	7 days; maximum 30 tablets	14 days; maximum 60 tablets; split

ORIF = open reduction and internal fixation; ACL = anterior cruciate ligament; PCL = posterior cruciate ligament; MTP = First metatarsal-phalangeal; APR = abdominal perineal resection; VATS = video-assisted thorascopic surgery; CABG = coronary artery bypass graft; EVAR =endovascular aortic repair; TEVAR = thoracic endovascular aortic repair; fEVAR = femoral endovascular aortic repair.

Adapted from: Hance A. Clarke, Varuna Manoo, Emily A. Pearsall, Akash Goel, Adina Feinberg, Aliza Weinrib, Jenny C. Chiu, Bansi Shah, Salima S. J. Ladak, Sarah Ward, Sanjho Srikandarajah, Savtaj S. Brar & Robin S. McLeod (2020) Consensus Statement for the Prescription of Pain Medication at Discharge after Elective Adult Surgery, Canadian Journal of Pain, 4:1, 67-85, DOI: 10.1080/24740527.2020.1724775

- A part-fill or second prescription should be given to patients with an expected moderate or long-term recovery to reduce the number of opioid containing tablets distributed at one time.[23]
    - Examples of postoperative pain medications at discharge from elective surgery[23] Rapid recovery example:
        - Acetaminophen 1 g PO TID x 7 days then PRN
        - Ibuprofen 400 mg PO QID x 3 days then PRN
        - Morphine 5 mg tablets take 1-2 tabs q 4 h PRN x maximum of 3 days for severe pain. Maximum 4 tablets/day, dispense quantity 12 tablets.
    - Moderate recovery example:
        - Acetaminophen 1 g PO TID x 14 days then PRN
        - Ibuprofen 400 mg PO QID x 6 days then PRN
        - Hydromorphone 1 mg tablets take 1-2 tabs q 4 h PRN x maximum of 14 days for severe pain. Maximum 4 tablets/day, dispense quantity 15 tablets and 15 in 3 days
    - Long term recovery part fill example:
        - Acetaminophen 1 g PO TID x 14 days then PRN
        - Ibuprofen 400 mg PO QID x 6 days then PRN
        - Hydromorphone 1 mg tablets take 1-2 tabs q 4 h PRN x maximum of 30 days for severe pain. Maximum 4 tablets/day, dispense quantity 30 tablets and 30 in 7 days
    - Prescriptions expire 30 days after date of issue.

QUESTION 2b: WHAT IS THE OBSERVATIONAL EVIDENCE USED TO INFORM THE DURATION AND QUANTITIES OF ORAL OPIOIDS AFTER SURGERY?

- There is no optimal number of pills for any given procedure, so the recommendations in the Washington State AMDG Guidelines and Canadian Consensus Statement are intended to serve as a general framework for managing postoperative pain, while minimizing leftover pills.[22,23]

- The AMDG Guidelines and Canadian Consensus Statement utilize evidence predominantly from observational trials to inform these recommendations.
    - Several cohort studies have compared the impact of prescribing a smaller number of opioid pills postoperatively compared to “usual” opioid prescribing. Patients that were prescribed fewer pills consumed less opioid medication, experienced similar improvements on pain and/or satisfaction scores, with no differences in prescription refills compared to the “usual” groups.[18,25,26,27,28,29,30]
    - A large cohort study tracked general trends in opioid needs following several operation types in 215,140 opioid naïve patients. The goal was to determine optimal ranges of initial durations of opioid prescriptions assuming that the

optimum duration was between the observed median prescription length and the earliest discontinuation of use of refill prescriptions.[31]

- The median observed prescription lengths were 4 days for general surgery procedures, 4 days for women's health procedures, and 6 days for musculoskeletal procedures. The prescription lengths associated with the lowest requirement for refill were 9 days for general surgery, 13 days for women's health, and 15 days for musculoskeletal procedures.[31]
- Using this model, 4 to 9 days for general surgery procedures, 4 to 13 days for women's health procedures, and 6 to 15 days for musculoskeletal procedures were suggested as the average initial lengths of opioid prescription of these types of surgeries.[31]
- Researchers from the University of Michigan have evaluated data from a large health database in addition to published cohort studies to establish opioid quantities that meet or exceed self-reported use of opioids for 75% of patients in specific surgical procedures. From this analysis guidelines/recommendations on suggested quantities have been determined and can be found at the following link[24] (last updated February 2020): https://michigan-open.org/prescribing-recommendations/
    - Note: The number of opioid analgesics and the duration of therapy is intended to serve as a framework for managing pain, while minimizing leftover pills.[24]
    - The quantities are based on different types of surgeries and not all surgeries have been examined yet.[24]
- A number of cohort studies have evaluated the impact of implementing guidelines to promote a reduction in the quantity of prescribed opioids for a variety of surgical procedures (hand surgery, partial mastectomy ± sentinel lymph node biopsy, laparoscopic cholecystectomy, laparoscopic and open inguinal hernia repair).[25,32,33]
    - These studies utilized quantities similar to the quantities established by the University of Michigan researchers.[25,32,33]
      The guidelines resulted in a 20% to 50% reduction in the quantity of pills prescribed without an increase in refills.[25,32,33]
- One open label RCT evaluated whether individualized post discharge oxycodone prescribing guided by inpatient opioid use reduces the number of unused opioid tablets after cesarean birth (N=172).[34]
    - Patients were randomized to a standardized prescription of 30 oxycodone 5 mg or an individualized prescription (calculated based on inpatient opioid use) in addition to routine ibuprofen 600 mg q 6 h and acetaminophen q 6 h PRN. On average the individualized group were prescribed 14 tablets (12 tablets – 16 tablets).[34]
    - Baseline characteristics and inpatient opioid use were similar between groups.[34]

- The individualized group used only half the number of prescribed opioids vs. the standard group, 8 (4–14) vs. 15 96–30), p=0.001. Patient-reported pain outcomes did not differ by group. There were no differences between the standard and individualized groups in the proportion who used no opioids or all opioids dispensed. It was reported that in both groups almost 1/3 of patients who took all of the medication did so because they incorrectly thought that they were following directions to take until finished.[34]

QUESTION 2c: WHAT IS THE EVIDENCE FOR THE EFFICACY OF SINGLE DOSE ORAL OPIOIDS IN THE TREATMENT OF MODERATE TO SEVERE POST-SURGICAL PAIN?

- The AMDG Guidelines and Canadian Consensus Statement both recommend that short acting opioids at the lowest effective dose be used on a PRN basis to minimize the amount of opioids used after surgery.[21,22,23]

- A number of MAs have evaluated the effect of a single dose of opioid in reducing pain scores by 50% in patients with moderate to severe post-surgical pain.
  - Overall, when administered as single doses to reduce moderate to severe postsurgical pain by at least 50%;
    - Opioids have variable efficacy compared to placebo. Oxycodone 5 mg was found to have similar efficacy to placebo, Codeine 60 mg was found to have an NNT 12 which is considered of limited clinical value, and oxycodone 15 mg was found to have an NNT 5.
    - Indirect comparisons suggest that an NSAID + acetaminophen may be more effective (with lower NNTs) than an opioid + NSAID or an opioid + acetaminophen combination.
  - When an opioid is added to a non-opioid analgesic the increase in efficacy ranges from no added benefit as seen with oxycodone 5 mg + ibuprofen 400 mg vs. ibuprofen 400 mg alone, to a modest increase in benefit as seen with an acetaminophen 1000 mg + codeine 60 mg vs. acetaminophen 1000 mg alone (NNT 6).

Opioid vs. Placebo

- The Cochrane Review of MAs evaluated the effect of single dose oral analgesics compared to placebo for acute postoperative pain in adults experiencing moderate to severe postsurgical pain.
  - ***Note***: In the Cochrane Review, an NNT ≥ 10 to achieve a 50% reduction in pain scores was considered unacceptably high for acute postoperative pain.[4]
  - The review compared single dose opioids to placebo for the outcome of at least 50% reduction in pain scores over 4 to 6 hours and found the following NNTs: [4]
    - **Codeine 60 mg:** NNT 12 (95% CI 8.4-18) (33 studies, N=2,411)
    - **Oxycodone 15 mg**: NNT 4.5 (95% CI 2.9-11) (3 studies, N=228)

- **Oxycodone 10 mg**: No evidence
- **Oxycodone 5 mg**: No significant advantage over placebo (3 studies, N=317) (evidence for oxycodone was deemed low quality evidence) The mean or median time to re-medication for codeine was 2 hours (similar to placebo) and was not reported for oxycodone.[4]

- While codeine 60 mg was statistically superior to placebo in the treatment of established postoperative pain, the NNT of 12 was considered of limited clinical value and inferior to commonly used analgesics.[4]
- The review also compared combination opioid + non-opioid to placebo for the outcome of at least 50% reduction in pain scores over 4 to 6 hours and found the following NNTs. Tramadol could not be assessed in the Cochrane Review due to few available studies.[4]
  - Acetaminophen + codeine:
    - **300 mg + 30 mg**: NNT 6.9 (95% CI 4.8 – 12) (6 studies, N=690)
    - **600/650 mg + 60 mg:** NNT 3.9 (95% CI 3.3 – 4.7) (17 studies, N=1,413)
    - **800/1000 mg + 60 mg**: NNT 2.2 (95% CI 1.8 - 2.9) (3 studies, N=192)
      Mean or median time to re-medication was 4 hours
  - Acetaminophen + oxycodone:
    - **325 mg + 5 mg:** NNT 3.6 (95% CI 2.1 - 6.3) (3 studies, N=388)
    - **600/650 mg + 10 mg:** NNT 2.7 (95% CI 2.4 – 3.1) (10 studies, N=1,043)
    - **800/1000 mg + 10 mg**: NNT 1.8 (95% CI 1.6 - 2.2) (2 studies, N=289)
      Mean or median time to re-medication was > 9 hours
  - Ibuprofen + codeine:
    - **400 mg + 60 mg**: NNT 2.2 (95% CI 1.9-2.6) (4 studies, N=443)
      Mean or median time to re-medication was not reported
  - Ibuprofen + codeine:
    - **400 mg + 60 mg**: NNT 2.2 (95% CI 1.9-2.6) (4 studies, N=443)
      Mean or median time to re-medication was not reported
  - Ibuprofen + oxycodone:
    - **400 mg + 5 mg**: NNT 2.3 (95% CI 2.0-2.8) (3 studies, N=603)
      Mean or median time to re-medication was not reported

- Very few studies evaluating the efficacy of tramadol for post-surgical pain have been published and results have been mixed with most showing no benefit over placebo.[35,36,37]
  - Two MAs have evaluated the analgesic effect of tramadol compared to placebo in acute moderate to severe pain following surgery or dental extraction using unpublished studies provided by the manufacturer; one evaluated single dose tramadol (18 studies, 17 unpublished, N=3,453) and one evaluated tramadol in

combination with acetaminophen (7 unpublished studies, N=2,094). [38,39] ***Note*: results may not be reliable due to the fact that the included studies were unpublished.**

- For the outcome of at least a 50% reduction in pain scores over 6 hours, one review found for tramadol 75 mg + acetaminophen 650 mg an NNT 2.6, for ibuprofen 400 mg an NNT 2.3, and for acetaminophen 650 mg an NNT 3.6.[38] All were more effective than tramadol 75 mg which had an NNT of 9.9 for the same outcome.[38]

- The other review found a dose response with tramadol for the outcome of at least a 50% reduction in pain scores over 8 hours.[39]
  - Tramadol 50 mg; NNT 9.1
  - Tramadol 75 mg; NNT 9.1
  - Tramadol 100; NNT 4.6
  - Tramadol 150 mg; NNT 4.2
- Results were similar in patients with moderate to severe postsurgical pain (the types of surgeries were not reported).[39]

➢ It is interesting to note that the Cochrane review of MAs found an NNT 1.5 to 1.6 for a single dose of acetaminophen + ibuprofen compared to placebo in reducing pain scores by at least 50% in patients experiencing moderate to severe post-surgical pain.

Opioid vs. NSAID

Ibuprofen vs. oxycodone:

➢ A Cochrane Review compared a single dose oral ibuprofen plus oxycodone to placebo or the same dose of ibuprofen alone or oxycodone alone in patients with moderate to severe pain following dental or abdominal/pelvic surgeries (3 studies, N= 1,202)[40]

- 58% (95% CI 53% - 62%) of patients receiving ibuprofen 400 mg + oxycodone 5 mg, 50% (95% CI 44% - 56%) of patients receiving ibuprofen 400 mg alone, 23% (95% CI 13% - 37%) of patients receiving oxycodone 5 mg alone, and 17% (95% CI 11% - 23%) of patients treated with placebo achieved at least a 50% reduction in pain scores over 6 hours.[40]
  - **Ibuprofen 400 mg + oxycodone 5 mg vs. ibuprofen 400 mg**: no significant difference (2 studies, N=717)
  - **Ibuprofen 400 mg + oxycodone 5 mg vs. oxycodone 5 mg**: NNT 2.9 (95 % CI 2.3-4.0) (2 studies, N= 471)

➢ No studies reported time to medication for the combination of ibuprofen + oxycodone compared to ibuprofen alone.

Ibuprofen vs. codeine:

➢ Another Cochrane Review evaluated a single dose ibuprofen + codeine to placebo or the same dose of ibuprofen alone or codeine alone in patients with moderate to severe pain following dental or gynecological surgeries (6 studies, N=1,342).[41]

- 64% (95% CI 62% - 78%) of patients receiving ibuprofen 400 mg + codeine (20 mg to 60 mg), 55% (95% CI 48% - 58%) of patients receiving ibuprofen 400 mg alone, 33% of patients receiving codeine (20 mg to 60 mg) alone, and 18% (95% CI 4%-38%) of patients treated with placebo achieved at least a 50% reduction in pain scores over 6 hours.[41]
    - **Ibuprofen 400 mg + codeine 20 mg – 60 mg vs. ibuprofen 400 mg:** NNT 7.7 (95% CI 3.7 - 126) (2 studies, N=159)
    - **Ibuprofen 400 mg + codeine 60 mg vs. codeine 60 mg:** too few data for analysis
      One study reported the mean time to re-medication was 3.7 hours for ibuprofen 400 mg + codeine 60 mg and 3.8 hours for ibuprofen 400 mg alone.

Opioid vs. Acetaminophen

- A Cochrane Review compared a single dose oral acetaminophen plus codeine to placebo or the same dose of acetaminophen alone in patients with moderate severe pain following various elective surgeries (i.e. dental, orthopedic, gynecological and general) (26 studies, N= 2,295)[42]

- Participants achieving at least 50% pain relief over 4 to 6 hours: acetaminophen + codeine vs. same dose of acetaminophen.[42]

Dose (mg)	Studies	N=	Acetaminophen + codeine (%)	Acetaminophen (%)	NNT (95% CI)
800-1000/60	4	304	59	42	6.1 (3.6-19)
1000/60	3	217	68	48	5.1 (3.1-15)
600-650/60	10	622	53	41	8.2 (5.0 – 23)

- The weighted mean time for remediation was 3.5 hours for acetaminophen + codeine vs. 3.5 hours for acetaminophen alone.[42]

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Risks Associated with Oral Nonsteroidal Anti-Inflammatory Drugs

SUMMARY STATEMENTS

- NSAIDs are commonly used pain-relieving medications for various pain conditions. Their risks, however, require consideration.[1]
- NSAIDs inhibit prostaglandin and thromboxane-A2 synthesis, by blocking the cyclo-oxygenase (COX) enzymes.[1]
- Based on their mechanism of action, NSAIDs can affect the gastrointestinal (GI), renal and cardiovascular (CV) systems.[1]
- This section aims to review the evidence for the CV, GI and renal risks with NSAID use. It will also review the evidence on NSAIDs and fracture healing impairment.[1]
    - Evidence is primarily based on systematic review (SR) and meta-analysis (MA) of randomized controlled trials (RCTs) and/or observational studies.
    - Due to limitations in study design, evidence from observational data should be interpreted with caution.
- Risk assessment focuses on systemic adverse effects of oral NSAIDs. Topical NSAIDs are addressed in the musculoskeletal section.
- Note: The abbreviation RR is used to present outcomes of both relative risk and rate ratio. Unless otherwise noted RR refers to relative risk. Rate Ratio is used to present results of two of the primary references in this section, the Trelle and CNT meta-analyses.[3,4]

QUESTION 1: WHAT ARE THE MAJOR RISKS WITH NSAID USE?

QUESTION 1a: WHAT ARE THE CARDIOVASCULAR RISKS WITH NSAID USE?

- Outcomes reported in clinical trials include:
    - Major vascular events (MVE) is a composite of non-fatal MI, non-fatal stroke, or vascular death. Vascular death includes coronary, MI, CHD death and fatal stroke.
    - Major coronary events (MCE) is a composite of non-fatal MI or coronary death.

- Both non-selective NSAIDs and COX-2 inhibitors can increase the risk of cardiovascular events. Evidence reveals that different NSAIDs and COX-2 inhibitors have different cardiovascular risk profiles, although the absolute differences may be small and dependent on a patient's baseline risk.[2-4]

- Any benefit shown for a reduction in cardiovascular events must be weighed against other adverse events, such as renal or gastrointestinal toxicity.

- There are conflicting results from studies; however, three meta-analysis concluded that naproxen *may* have the lowest risk for cardiovascular adverse events.[3-6]

- A large 2013 meta-analysis by the COXIB and traditional NSAID Trialists (CNT) of primarily individual participant data from RCTs (280 NSAID vs. placebo trials and 474 NSAID vs. NSAID trials) showed that:[4]
    - *Compared to placebo*, the risk for major MVE was statistically significantly increased with COX-2 inhibitors and diclofenac, whereas the risk was not statistically significantly increased with naproxen and ibuprofen.
    - *COX-2 inhibitors versus high dose naproxen*, COX-2 inhibitors statistically significantly increased risk for both MVE and MCE, whereas the risk was similar for *COX-2 inhibitors versus diclofenac and ibuprofen.*
    - CNT researchers present hypothetical calculations for excess MVE in high risk (2% per year) and low risk (0.5% per year) populations:
        - In a low risk population the absolute risk of major vascular events is small irrespective of the NSAID chosen.
        - In a high risk population an increase of 7-8 more major vascular events per 1000 patients could occur if treated with high dose diclofenac or a COX-2 inhibitor compared with placebo.
- A 2011 network meta-analysis by Trelle et al. of 31 RCTs (NSAID vs NSAID, acetaminophen or placebo) showed no statistically significant difference between celecoxib and either ibuprofen, naproxen or diclofenac in total cardiovascular adverse events based on rate ratio estimates and CrIs presented in Forest plots in the publication. (*no numerical data presented in publication*).[3]
- In a 2011 systematic review of observational studies by McGettigan et al (31 case-control studies, 21 cohort studies) on NSAID use and CV events, including acute MI (the outcome most frequently reported), coronary heart disease (CHD)-related death, and a composite of MI and CHD death or stroke, showed that diclofenac and rofecoxib had the highest cardiovascular risks while naproxen (risk neutral at all doses) and low-dose ibuprofen had the lowest.[5,7]
- In general, clinical trials used doses of COX-2 inhibitors and non-selective NSAIDs higher than what are traditionally used in clinical practice, making generalizability of results to the short term use of lower doses for acute pain difficult.

➢ A 2016 non-inferiority RCT (n=24,081) assessed cardiovascular disease in those with rheumatoid arthritis or osteoarthritis using NSAIDs (PRECISION trial).[6]
- Differences in the first occurrence of an adverse event (death from cardiovascular causes, hemorrhagic death, non-fatal MI, or non-fatal stroke) over approximately 20 months of treatment found that celecoxib was non-inferior to naproxen and ibuprofen with respect to CV risk.

HEART FAILURE (HF)

➢ The large CNT meta-analysis of RCTs found that NSAIDs increase the risk of HF.[4]
- Trials included in the meta-analysis were of at least 4 weeks duration so extrapolation to shorter time frames should be done with caution.

- Both non-selective NSAIDs and COX-2 inhibitors increase the risk for heart failure compared to placebo.
- There was no statistically significant difference in HF risk with COX-2 inhibitors compared to diclofenac, ibuprofen or naproxen.

- In another meta-analysis of RCTs (n=14,111), COX-2 inhibitors were also shown to have an increased risk of overall HF and edema with a relative risk (RR) 1.68, 95% CI 1.22-2.31, compared to placebo in individuals with osteoarthritis.[8]

- Individuals with pre-existing HF are recommended to use alternative analgesics to NSAIDs.[9,10]

MYOCARDIAL INFARCTION (MI)

- The 2013 CNT meta-analysis reported the outcomes of non-fatal MI and the composite outcome of MI or CHD death.[4]
  - Coxibs statistically significantly increased the rate of non-fatal MI vs. placebo.
  - Coxibs, diclofenac and ibuprofen increased the rate of the composite of MI/CHD death vs. placebo.
  - Comparisons between Coxibs and either ibuprofen or diclofenac found no statistically significant differences in non-fatal MI or MI/CHD death.
  - *Coxibs statistically significantly increased the risk of both of these outcomes vs. naproxen* [Presented as Rate Ratio (RR) and either 99% or 95% confidence interval (CI)].
    - Non-fatal MI RR 2.02 ((99% CI 1.35-3.02)
    - MI/CHD death RR 2.11 (95% CI 1.44 -3.09)

- The 2011 network meta-analysis of RCTs by Trelle et al., found no statistically significant increase in the risk of MI for ibuprofen, celecoxib, naproxen or diclofenac compared to placebo.[3]

- Bally et al. report (2017) the results of a meta-analysis of individual patient data (n=446,763) from observational studies which showed an increase in MI risk with NSAID use (including COX-2 inhibitors).[11]
  - Authors state that taking any dose of NSAIDs *for as short as one-week duration* can increase MI risk. The risk of prolonged use (>30 days) is not necessarily greater than shorter duration.

STROKE:

- The network meta-analysis by Trelle et.al did not show a statistically significant difference in stroke risk with naproxen, ibuprofen, and celecoxib. However, **diclofenac**

was associated with a statistically significant increase in stroke risk: Rate ratio (RR) 2.86 (95% CI 1.09-8.36).[3]

- The Coxib and Traditional NSAID Trialists' (CNT) Collaboration meta-analysis of RCTs did not show a statistically significant increase in the risk of the outcome "*any stroke"* with ibuprofen, diclofenac, and naproxen or Coxibs vs. placebo, and no statistically significant differences between Coxibs and any of the non-selective NSAIDs.[4]

- Both the FDA and Health Canada have strengthened their warnings around NSAIDs and heart attack and stroke risks.[12,13] Health Canada has published safety reviews on heart attack and stroke risk with diclofenac and high dose ibuprofen (>2400 mg/day).[13] The CPhA Product Monograph for NSAIDs reference the 2011 network meta-analysis by Trelle et al. to warn on the increased risk of potentially fatal events such as MI and stroke with NSAIDs.[1]

ATRIAL FIBRILLATION (AFib)

- Two large meta-analyses of observational studies found a statistically significant increase in the incidence of atrial fibrillation with NSAID use.[14,15] These results are limited by the observational study design and heterogeneity of pooled results.

NSAID Cardiovascular Warnings and Precautions

- The CPhA NSAID product monograph states:[1]
  - "NSAID use has been associated with an increase in the risk of cardiovascular mortality, myocardial infarction and stroke. Risk increases with dose and duration of use; risk does not decrease with time elapsed since myocardial infarction.
  - Evidence suggests that compared to other NSAIDs, celecoxib, diclofenac and high-dose ibuprofen (>2400 mg/day) are associated with more vascular risk and naproxen is associated with the least risk. Use caution when prescribing ***any NSAID*** in patients with cardiovascular disease, risk factors for cardiovascular disease, cerebrovascular disease or heart failure (NYHA II-IV). The exception is low-dose ASA when used to prevent thrombotic events."
  - NSAIDs are contraindicated in the "perioperative setting of coronary artery bypass graft surgery (CABG) because of the risk of thrombotic events. The exception is low-dose ASA, which is recommended to reduce thrombotic events in the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery Circulation 2011;124(23):2610-42.

WHAT IS THE IMPACT OF NSAID USE WITH HYPERTENSION (HTN)?

- No relevant literature describing the effects of short-term NSAID use on hypertension were found in a CADTH Rapid Response.[16]

- In the treatment of osteoarthritis (OA), a meta-analysis of RCTs assessing 6-week use of COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib, valdecoxib) found an increase in HTN risk, relative risk (RR) 1.45, 95% CI 1.01-2.10) compared to placebo. [8]
    - HTN risk increase was not statistically significant when rofecoxib was removed from the analysis (RR 1.21, 95% CI 0.80-1.83).

- In a non-inferiority RCT of patients with OA (primarily) or rheumatoid arthritis (RA), with increased risk for cardiovascular disease (CVD) (a sub-study of the PRECISION trial), there was a statistically significant increase in ambulatory systolic blood pressure (SBP) with ibuprofen versus celecoxib [difference of 3.9 mmHg (p=0.0009)] after 4 months of use. [17]
    - The percentage of normotensive patients at the start of the study who developed HTN defined by BP ≥ 130/80 was highest with ibuprofen (23.2%), followed by naproxen (19.0%) and celecoxib (10.3%).[17] However, this was based on a post-hoc analysis.

- A RCT of naproxen and acetaminophen for OA treatment assessed their effects on antihypertensive therapy (ramipril, valsartan, and aliskiren). Results showed that with *2 week use of naproxen*, there was a statistically significant increase in both clinic and ambulatory blood pressure in the *ramipril and valsartan* groups but results were not statistically significant in the aliskiren group.[18]
    - Increases in BP with concomitant use of naproxen were: ramipril: 6.8/4.6mmHg (p<0.001); valsartan: 4.1/1.9 mmHg (p<0.05); aliskerin: 2.6/1.2mmHg (not statistically significant).
    - Acetaminophen use for two weeks also resulted in a statistically significant increase in both clinic and ambulatory blood pressure in all three groups although to a lesser extent than naproxen.

Canadian Pharmacists' Association (CPhA) NSAIDs Product Monograph

All NSAIDs can worsen hypertension by increasing blood pressure (BP). Monitoring of BP is recommended when taking NSAIDs while on antihypertensive drugs.[1]

- The CPhA NSAID monograph does not list a drug interaction between calcium channel blockers and NSAIDs; whereas, NSAIDs are suggested to decrease the antihypertensive effects of ACE inhibitors, angiotensin II receptor blockers and beta blockers.

Acetylsalicylic Acid (ASA) and Non-ASA NSAID Combinations

- Concomitant use of ASA and ibuprofen 400 mg may result in a reduced cardioprotective effect of ASA, due to a pharmacodynamic interaction.[19,20]
    - Ibuprofen is recommended to be taken 30 minutes after or 8 hours before immediate-release ASA (81 mg; not enteric-coated).
    - Naproxen may have similar effects and is recommended to be taken 2 hours post ASA.[21]

QUESTION 1b: WHAT ARE THE <u>GASTROINTESTINAL (GI) RISKS</u> WITH NSAID USE?

- The CNT meta-analysis using primarily individual participant data (low risk population) from 754 RCTs showed that **all NSAID regimens**, including COX- 2 inhibitors, statistically significantly increased the risk for any upper gastrointestinal (GI) complication *vs. placebo*.[4]
    - Absolute event rates per annum were presented for the Coxib vs. placebo groups only:
        - **C**oxib group (0·38%) vs. placebo (0·19%) **NNH 527**
    - **Naproxen and ibuprofen were associated with the highest risk**.
    - Comparison of Coxib vs. ibuprofen or naproxen showed that Coxibs were associated with a lower risk of any upper GI complication. Data are presented as rate ratios (95%CI):
        - Coxib vs. Ibuprofen RR 0.40 (95% CI 0.25-0.64)
        - Coxib vs. naproxen RR 0.37 (95% CI 0.28-0.49)
    - There was no statistically significant difference between Coxibs and diclofenac.
    - Any benefit for a reduction in gastrointestinal events must be weighed against other adverse events, such as cardiovascular or renal toxicity.

- A Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response reported that celecoxib might have a lower risk of GI adverse events (GI bleeding or ulcers) compared to other non-selective NSAIDs (as a class); however, only in studies of less than six months duration.[22]

- Nabumetone and meloxicam may also have a lower risk of GI adverse events (such as ulcer complications or symptomatic ulcers) compared to other non-selective NSAIDs (as a class) based on the Drug Effectiveness Review Project (DERP) [23] and Agency for Healthcare Research and Quality (AHRQ) reviews. [24]

USE OF GASTROPROTECTION

- A secondary outcome of the PRECISION trial (2017) reports GI outcomes for celecoxib 100 mg twice daily, ibuprofen 600 mg three times daily or naproxen 375 mg twice daily in patients receiving gastroprotection with esomeprazole 20-40 mg daily. Mean treatment and follow-up durations were 20.3 and 34.1 months.[25]
    - There was a low incidence of clinically significant GI injury (CSGI) in all three treatment arms, with no statistically significantly differences between any of the groups in the intention to treat analysis. The modified intention to treat identified a lower risk of CSGI in the celecoxib group.

- A Cochrane Review by Rostom et al. (2002), found that misoprostol, proton-pump inhibitors (PPIs) and double dose histamine-2-receptor antagonists (H2RAs; e.g., ranitidine 300 mg twice daily) are all effective for long-term prevention (trials included

in meta-analysis were ≥4 weeks duration) of NSAID related endoscopic gastric and duodenal ulcers in patients with arthritis.[26]

- COX-2 inhibitors alone or non-selective NSAIDs with a PPI are equally effective in preventing gastroduodenal ulcers. A limitation to this result is the small trial on which it is based, i.e., 1 RCT in 130 patients and a total of 9 events.

- A network meta-analysis by Yuan et al. concluded that based on low to very low quality evidence, there is no significant difference between PPIs in reducing the risk of ulcer complications with either esomeprazole, omeprazole, lansoprazole or rabeprazole.[27]

- Gastrointestinal and cardiovascular risk stratification should be undertaken to choose the lowest risk option of NSAID and whether gastroprotection is required.[26]
  - As many AEs are related to dose and duration of NSAID therapy, a general rule to decrease risk is to use the lowest effective dose for the shortest period of time.
  - *See the gastrointestinal and cardiovascular risk assessment tools following the GI risk section in main document.*

QUESTION 1c: WHAT ARE THE <u>RENAL RISKS</u> WITH NSAID USE?

NSAIDs and Acute Kidney Injury (AKI):

- Five systematic reviews (one with meta-analysis) [28-32], one RCT [33] and five non-randomized studies were identified as the best available evidence for NSAID use and AKI development.[34]

- Meta-analyses have shown slightly increased serum creatinine levels with NSAID use, however no evidence for AKI.[34]

- Non-randomized trials, however, have shown an increased risk of AKI with NSAIDs, particularly ketorolac.[34]

- There is uncertainty in the risk of AKI in individuals with normal kidney function[28] More evidence is required to determine the absolute risks of AKI with NSAID use.

- Despite the lack of concrete evidence, there are several risk factors that can increase the likelihood of AKI with NSAID use, such as:
  - Chronic kidney disease(CKD),
  - Severe hypercalcemia,
  - Nephrotic syndrome, cirrhosis,
  - Heart failure or volume depletion (diuretic associated or from vomiting and diarrhea) [35]

- In those with CKD, a systematic review of observational studies by Zhang et al. showed a potential association of AKI and NSAID use. [31]

- Subgroup analyses showed that individuals >50 years of age had higher odds of AKI with NSAID use versus the general population (Odds ratio [OR] 2.01, 95% CI 1.52-2.68).

- The concomitant use of an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) with a diuretic and an NSAID ("triple whammy") increased the relative risk of AKI by approximately 30% in a large retrospective nested case-control cohort.[36]
    - Dual therapy with an NSAID and any one of the three above mentioned anti-hypertensives did not increase the risk of AKI.

- There is no evidence to suggest COX-2 inhibitors are safer than non-selective NSAIDs in AKI risk.

NSAIDs and CHRONIC KIDNEY DISEASE (CKD):

- In a systematic review of nine observational studies (primarily low quality) by Yaxley et al., eight trials did not find a statistically significant association between chronic NSAID use and development of analgesic nephropathy, a type of CKD. [37]

- CKD progression was assessed in a meta-analysis of population-based epidemiological studies, (Nderitu et al.) assessing chronic NSAID use (duration of ≥6 months) in ages 45 years and older.
    - NSAIDs were ***not*** associated with accelerated CKD progression, defined as eGFR decline ≥15mL/min/1.73m^2 over 2 years (N= 54,663. Pooled OR 1.04, 95% CI 0.90-1.20).

- Monitoring of renal function is recommended in individuals with CKD and NSAID use, especially in those with risk factors for disease progression.[1]

- NSAIDs require dosage adjustments for those with renal impairment (see Appendix 1 Drug Tables). NSAIDs are contraindicated in those with severe renal impairment (Creatinine clearance [CrCl] <30 mL/min).[1,39]

QUESTION 1d: WHAT IS THE EVIDENCE FOR NSAIDs AND FRACTURE HEALING IMPAIRMENT?

- A 2019 meta-analysis of 16 studies (2 RCTs, cohort and case-control studies) showed an increase in the odds of delayed union or non-union (OR 2.07, 95% CI 1.19 to 3.61) in orthopedic patients.[40,41]
    - Subgroup analysis did not find an increased risk with low-dose, short duration (<2 weeks) NSAID use.

- A 2018 systematic review assessed risk of non-union (via radiographic techniques) with any perioperative NSAID exposure post-fracture osteosynthesis/spinal fusion.[42]
    - Results were inconsistent. Two of the RCTs and eight of the retrospective studies showed no increased risk of non-union with NSAID use post-operatively. However, an increased risk was shown with one of the RCTs and 6 of the retrospective studies.

- Although animal studies have demonstrated that above normal doses of NSAIDs impair bone healing, RCT data in humans, although limited, do not suggest impairment of fracture healing with NSAID use, according to the Tools for Practice article in the journal *Canadian Family Physician*.[43]

- Overall, the evidence surrounding NSAIDs and fracture healing impairment is not clear. There is no high quality robust evidence from large randomized controlled trials on this topic.

- The Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury (2019) state that there is a lack of good quality evidence to suggest fracture healing impairment with NSAID use and recommend the use of NSAIDs for operative and non-operative fracture care.[44]

- Based on the current available evidence from human clinical trials, short term, low dose NSAID use may be safe for pain relief in fracture care.

BACKGROUND

- NSAIDs are commonly used pain-relieving medications for various pain conditions. Their risks, however, require consideration.[1]
- NSAIDs inhibit prostaglandin and thromboxane-A2 synthesis, by blocking the cyclo-oxygenase (COX) enzymes.[1]
    - Non-selective NSAIDs inhibit both forms of COX-1 and COX-2 enzymes. ASA is the only irreversible inhibitor of COX enzymes. Other NSAIDs (e.g., celecoxib) prevent COX-2 selectively, and are thus termed COX-2 inhibitors.
- Diclofenac, etodolac, mefenamic acid, meloxicam and nabumetone may have preference for COX-2 inhibition but are not totally COX-2 selective.[1]
- Prostaglandins synthesized through the COX-1 enzyme are involved in gastric protection, vascular hemostasis and platelet aggregation, immune responses, renal perfusion, and the female reproductive system.
- The COX-2 enzyme is primarily involved in inflammatory responses. Based on their mechanism of action, NSAIDs can affect the gastrointestinal (GI), renal and cardiovascular (CV) systems.[1]
- This section, therefore, aims to review the evidence for the CV, GI and renal risks with oral NSAID use. It will also review the evidence on NSAIDs and fracture healing impairment.
    - Evidence is primarily based on systematic review and meta-analysis of RCTs and/or observational studies.
    - Risk assessment focuses on systemic adverse effects of oral NSAIDs.
    - Topical NSAIDs are addressed in the musculoskeletal section.
- Note: The abbreviation RR is used to present outcomes of both relative risk and rate ratio. Unless otherwise noted RR refers to relative risk. Rate Ratio is used to present results of two of the primary references in this section, the Trelle and CNT meta-analyses.[3,4]

QUESTION 1: WHAT ARE THE MAJOR RISKS WITH NSAID USE?

QUESTION 1a: WHAT ARE THE <u>CARDIOVASCULAR RISKS</u> WITH NSAID USE?

- Cardiovascular outcomes reported in clinical trials include:
    - Major vascular events (MVE) - composite of non-fatal MI, non-fatal stroke, or vascular death. Vascular death includes coronary, MI or CHD death and fatal stroke.
    - Major coronary events (MCE) - composite of non-fatal MI or coronary death.
    - Results also include individual components of the composite outcome; as well as, heart failure, and all-cause mortality.

- Both non-selective NSAIDs and COX-2 inhibitors can increase the risk of cardiovascular events. *Evidence reveals that different NSAIDs and COX-2 inhibitors have different cardiovascular risk profiles, although the absolute differences may be small and dependent on a patient's baseline risk*.[2,3,4]

- A large meta-analysis by the Coxib and Traditional NSAID Trialists (CNT 2013) of primarily individual participant data from RCTs assessed the cardiovascular and gastrointestinal risks of NSAIDs, including COX-2 inhibitors (Coxibs).[4]
    - The patient population in the trials is described as being *low risk* due to few patients having a history of atherosclerosis (9%), of diabetes (9%), or of upper gastrointestinal peptic ulcer disease (7%).
    - Comparisons included traditional NSAID or Coxib vs placebo (or open control) or other NSAIDs. (754 trials of *at least 4 weeks duration*; N=353,809 patients; 297,638 person years).
    - Outcomes assessed included major vascular events, major coronary events, stroke, mortality, heart failure and upper GI complications (composite of: perforation, obstruction or bleed).
        - Stroke, heart failure and upper GI complications are reported separately in this document.
    - The Coxibs (typical daily doses) which provided most of the data were: celecoxib (400 mg), rofecoxib (25mg), etoricoxib (60-90 mg) and lumiracoxib (200 mg). Doses varied for each of the Coxibs.
    - The traditional NSAIDs included and daily doses were: diclofenac 150mg, ibuprofen 2400mg, and naproxen 1000mg.
    - Results for MVE **compared to placebo**: rate ratio (95% Confidence Interval):
        - **Coxibs: 1.37 (1.14-1.66)**
        - **Dicofenac: 1.41 (1.12-1.78)**
        - Naproxen: 0.93 (0.69-1.27)
        - Ibuprofen: 1.44 (0.89-2.33)
    - Absolute event rates for MVE provided for coxibs (1.15%) and placebo (0.82%).
    - COX-2 inhibitors and diclofenac statistically significantly increased the risk of MVE vs. *placebo*, whereas the risk was not statistically significantly increased for naproxen or ibuprofen *vs. placebo*.
    - Mortality from any cause was statistically significantly increased in the Coxib group vs. *placebo* (1.66% vs 1.42%), but was not significantly increased in the naproxen, diclofenac or ibuprofen groups.
    - COX-2 inhibitors, increased both MCE and MVE significantly vs. *naproxen* [rate ratio (RR) 2.11 (95% confidence interval [CI] 1.44-3.09)]. *See Table 1*
    - The researchers conclude that ***"the vascular risks of high-dose diclofenac and possibly ibuprofen are comparable to Coxibs; whereas high-dose naproxen is associated with less vascular risk than other NSAIDs."***
        - *Caution is suggested in the interpretation that naproxen is associated with less risk than other NSAIDs since it is not known if this holds true in*

patients using aspirin, in those using lower doses of naproxen which may not mimic an aspirin-like effect, or with long term use. In addition, naproxen is associated with excess upper GI complications that must be taken into consideration.

- No conclusions can be made from the CNT meta-analysis on whether NSAIDs increase vascular risk immediately after starting treatment.

- The magnitude of excess risk can be predicted based on a patients' baseline risks for the known hazards of NSAIDs.
  - The CNT meta-analysis presented hypothetical calculations of excess risks in patients at high (2% per annum) and low (0.5% per annum) risk for a vascular event predicted the following:
    - In a low risk population the absolute risk of major vascular events is small irrespective of the NSAID chosen.
    - In a high risk population an increase of 7-8 more major vascular events per 1000 patients could occur if treated with high dose diclofenac or a COX-2 inhibitor compared with placebo.
- Comparisons of COX-2 inhibitors vs. placebo, diclofenac, ibuprofen or naproxen are presented in *Table 1*.

Table 1. Primary cardiovascular risks presented as rate ratio (RR) with 95% confidence intervals for COXIB vs comparators [4]

Coxib vs.	Placebo	Diclofenac	Ibuprofen	Naproxen
Major Coronary Events	**RR 1.76 (1.31-2.37)**	RR 1.04 (0.84-1.28)	RR 0.81 (0.41-1.61)	**RR 2.11 (1.44-3.09)**
Major Vascular Events	**RR 1.37 (1.14-1.66)**	RR 0.97 (0.84-1.12)	RR 0.92 (0.58-1.46)	**RR 1.49 (1.16-1.92)**
Mortality from Any-cause	**RR 1.22 (1.04-1.44)**	RR 1.02 (0.84-1.24)	RR 0.78 (0.43-1.42)	RR 1.23 (0.86-1.75)
Heart Failure hospitalization	**RR 2.28 (1.63-3.20)**	RR 1.23 (0.86-1.75)	RR 0.83 (0.42-1.64)	RR 1.17 (0.76-1.79)

RR= rate ratio; CI= confidence interval (note: all CI are 95%)

- The absolute event rates were only provided for Coxibs and placebo. The rate ratios from *Table 1* can be used to estimate the relative increase or decrease in absolute event rates for the other NSAIDs. **Absolute event rates are low.**[4]

Estimated Absolute Event Rates per Annum

	Placebo	Coxib
Major vascular events	0.82	1.15
Major coronary events	0.33	0.63
Heart failure	0.26	0.66
All-Cause mortality	1.42	1.66

- A 2011 network meta-analysis by Trelle et al. assessed NSAID cardiovascular safety.[3]
  - 31 RCTs of any NSAID versus other NSAIDs, acetaminophen, or placebo were included in the analyses.
    - N= 116,249 patients and 115,000 patient years of follow-up
    - NSAIDs: lumiracoxib, rofecoxib, etoricoxib, celecoxib (200-400 mg/day), ibuprofen (2400 mg/day), diclofenac (100-150 mg/day), naproxen (440-1000 mg/day)
  - Population included those with osteoarthritis, rheumatoid arthritis, adenomatous polyps (colon), adjuvant (colon cancer), at risk for prostate cancer, and at risk for Alzheimer's disease.
  - Trials had at least 2 arms and at least 100 patient years of follow-up.
  - Limitations to the applicability of the outcomes to acute pain include that NSAIDs were used for *at least one year* in most of the included trials, no trial used intermittent NSAID dosing and a low number of patients used low dosages of NSAIDs.
  - Outcomes:
    - Primary outcome: fatal or non-fatal MI
    - Secondary outcomes: hemorrhagic/ischemic fatal/non-fatal stroke; cardiovascular (CV) death; death from unknown cause, death from any cause, and Antiplatelet Trialists' Collaboration (APTC) composite outcome (non-fatal MI, non-fatal stroke, or CV death)
  - Results:
    - The network meta-analysis showed no statistically significant difference between celecoxib and either ibuprofen, naproxen or diclofenac in total cardiovascular adverse events (MI, stroke, CV death, death, or the APTC outcome) based on rate ratio estimates and CrIs presented in Forest plots in the publication. (*no numerical data presented in publication*)
  - Limitations (not all inclusive):
    - Due to *low event rates* in the clinical trials the *credibility intervals (CrIs)* for results compared to *placebo* were *wide indicating lack of precision*.
  - Authors' conclusions: "Although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. Naproxen seemed least harmful. Cardiovascular risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug."

- The McGettigan systematic review of *observational s*tudies assessing NSAID use and CV events (31 case-control studies, 184,946 CV events; 21 cohort studies, 2.7 million exposed individuals), found that diclofenac and rofecoxib had the highest CV risks while naproxen and low-dose ibuprofen had the lowest. Data are presented as relative risk (95% CI).[5]
  - **Cardiovascular events** were defined as: Acute MI (most frequently reported outcome), coronary heart disease (CHD)-related death, stroke, or composite of

MI and CHD death. Comparison was between current use vs. non-use or remote use.

- Moderate to high heterogeneity was found for all of the following analyses (reported I^2 of 70-87%). The risk of bias of individual studies was assessed using the Newcastle–Ottawa Scale. Fully reported case-control studies scored 7–8 points out of 9, and cohort studies scored 7–8 points out of 10 points.
    - Diclofenac: RR 1.40 (95% CI 1.27-1.55)
    - Naproxen: RR 1.09 (95% CI 1.02-1.16)
    - The CV risks for celecoxib (RR 1.17, 95% CI 1.08-1.27) and ibuprofen (RR 1.18, 95% CI 1.11-1.25) were similar.
- Selected pair-wise comparisons indicate increased risk of CV events with diclofenac for several comparisons:
    - Diclofenac vs. celecoxib: RR 1.15 (99% CI 1.02-1.30), n=19 studies
    - Diclofenac vs. ibuprofen: RR 1.13 (99% CI 1.03-1.24), n=27 studies
    - Diclofenac vs. naproxen: RR 1.22 (99% CI 1.11-1.35), n=25 studies
    - Naproxen vs. celecoxib: RR 0.96 (99% CI 0.81-1.13), n=23 studies
    - Naproxen vs. ibuprofen: RR 0.92 (99% CI 0.87-0.99), n=32 studies
- Doses used in studies varied and a **dose-response relationship was noted for ibuprofen with an increased risk only with higher doses** (defined variably as daily doses *>1200mg to ≥1800mg*); whereas naproxen was **risk-neutral at all doses.**
- Although celecoxib was not significantly different from naproxen based on pair-wise comparisons, the authors are hesitant to recommend celecoxib in patients with cardiovascular risks due to evidence from RCT data and the COX-2 selectivity of celecoxib. The authors question the continued clinical use of indomethacin due to its cardiovascular risks and the known gastrointestinal and central nervous system effects.
    - Cardiovascular relative risk:
        - Indomethacin use vs non-use RR 1.30 (95% CI 1.19-1.41)
        - Indomethacin use vs. naproxen RR 1.23, (99% CI 1.10-1.39)

- A 2016 non-inferiority RCT (n=24,081) assessed cardiovascular disease in those with rheumatoid arthritis or osteoarthritis using NSAIDs (PRECISION trial).[6]
    - The primary outcome was a composite of death from cardiovascular causes, including hemorrhagic death; non-fatal MI; or non-fatal stroke and met the Antiplatelet Trialists' Collaboration (APTC) criteria for this composite endpoint
    - Mean doses and ± standard deviation presented below:
        - Celecoxib: 209 ± 37 mg/day
        - Naproxen: 852 ± 103 mg/day
        - Ibuprofen: 2045 ± 246 mg/day
    - Treatment duration: 20.3 ± 16.0 months
    - Mean follow-up period: 34.1 ± 13.4 months

- **Result:** Celecoxib was non-inferior to naproxen and ibuprofen with respect to CV risk.
    - Hazard Ratios for the primary outcome are shown in *Table 2.*
        - ***Absolute event rates in the intention-to-treat analyses: celecoxib 2.3%, naproxen 2.5%, ibuprofen 2.7%.***
- It is important to note that concerns have been raised since this study's publication.
    - Low levels of adherence and retention were reported (68.8% stopped the study drug).
    - Doses of celecoxib were restricted based on legislated maximum doses whereas naproxen and ibuprofen could be titrated to effect. This may have resulted in different levels of drug exposure.[45]

Table 2. Primary outcome of APTC end point.[6]

Celecoxib vs.	Naproxen	Ibuprofen
Primary APTC endpoint	Adjusted HR 0.93 (95% CI 0.76-1.13)	Adjusted HR 0.85 (95% CI 0.70-1.04)

APTC = Antiplatelet Trialists' Collaboration; CI= confidence interval; HR= hazard ratio

Summary: There are conflicting results from studies; however, the CNT, Trelle et al. and McGettigan et al. meta-analyses' have concluded that of all studied NSAIDs, naproxen *may* have the lowest risk for cardiovascular adverse events.[3-5] On the other hand, the PRECISION trial reports no significant differences between celecoxib, naproxen, or ibuprofen.[6] Any benefit must be weighed against other adverse events, such as renal or gastrointestinal toxicity.

NSAID Cardiovascular Warnings and Precautions

- The CPhA NSAID product monograph states:[1]
    - "NSAID use has been associated with an increase in the risk of cardiovascular mortality, myocardial infarction and stroke. Risk increases with dose and duration of use; risk does not decrease with time elapsed since myocardial infarction.
    - Evidence suggests that compared to other NSAIDs, celecoxib, diclofenac and high-dose ibuprofen (2400 mg/day) are associated with more vascular risk and naproxen is associated with the least risk. Use caution when prescribing *any NSAID* in patients with cardiovascular disease, risk factors for cardiovascular disease, cerebrovascular disease or heart failure (NYHA II-IV). The exception is low-dose ASA when used to prevent thrombotic events."

HEART FAILURE

- NSAID use is hypothesized to exacerbate heart failure (HF) by inhibiting renal COX-2 enzymes, thus decreasing salt and water excretion and increasing total body volume.[46]
    - Additionally, NSAIDs cause vasoconstriction by inhibiting prostaglandin synthesis, thus further exacerbating HF.[47]

- The increased HF risk with NSAID use is evident from the large meta-analysis of RCTs by the Coxib and traditional NSAIDS Trialists' (CNT) Collaboration, previously described.[4]
    - Trials included in the meta-analysis were of at least 4 weeks duration so extrapolation to shorter time frames should be done with caution.
    - All NSAIDs show a statistically significant increase in rates of heart failure hospitalization compared to placebo presented as rate ratio (95% confidence interval)
        - **Diclofenac: 1.85 (1.17-2.94)**
        - **Naproxen: 1.87 (1.10-3.16)**
        - **COX-2 inhibitor: 2.28 (1.62-3.20)**
        - **Ibuprofen: 2.49 (1.19-5.20)**
    - Summary of results: All of the traditional NSAIDs and COX-2 inhibitors included in this meta-analysis were associated with a statistically significant increase in risk of hospitalization for heart failure compared to placebo.

- A meta-analysis of COX-2 inhibitor RCTs (N=14,111; celecoxib, rofecoxib, etoricoxib and valdecoxib) reported an increased relative risk of overall HF and edema (RR 1.68, 95% CI 1.22-2.31, I^2=0%) in individuals with osteoarthritis, compared to placebo.[8]
    - Studies were published from 1999 to 2017, and ranged from 6 weeks to 24 months of follow-up.
    - Twenty of the forty RCTs included celecoxib. Thirty-one of the forty RCTs were included in the HF and edema analysis.
    - The evidence was rated as having a high level of certainty using GRADE (Grading of Recommendations, Assessment, Development and Evaluations).
    - The increase in HF/edema risk was evident with removal of rofecoxib from the analysis (RR 1.67, 95% CI 1.21-2.29, I^2 0% for celecoxib and etoricoxib only).
    - The risk of congestive HF was not statistically significant (RR 1.18, 95% CI 0.24-5.71, I^2=0%).

- A meta-analysis of 6 observational studies (3 case-control and 3 cohort, n=161,472) also showed increased risk of HF exacerbation with conventional NSAID use [pooled relative risk (RR) 1.39 (95% CI 1.20-1.62, I^2=15%)] versus non-use.[46]
    - Four of the six studies reported on the relative risk of HF exacerbations with celecoxib and rofecoxib:

- RR 1.34 (95% CI 0.98-1.85), which is not statistically significantly different from the pooled RR of conventional NSAIDs (p=0.87).
- The pooled RR of rofecoxib (2.04, 95% CI 1.68-2.48) was significantly higher than conventional NSAIDs (p=0.02).

- A meta-analysis of seven epidemiological studies showed a higher risk of HF incidents with NSAID use [relative risk (RR) 1.17 (95% CI 1.01-1.36, I^2=53%)] in individuals taking NSAIDs versus those not taking NSAIDs.[47]
  - Compared to non-users, pooled analyses from five studies showed an increased incidence of HF in NSAID users (RR 1.35, 95% CI 1.15-1.57, I^2=0%).
  - For COX-2 inhibitor users, pooled RR of two studies showed a higher risk (RR 1.03, 95% CI 0.92-1.16) though this difference was not statistically significant.

- In 2016, a nested case-control study also showed an increased risk of HF with both COX-2 inhibitors and traditional NSAIDs.[48]
  - Mean age (±SD) was 77 (±11) for cases and 76(±10) for controls.
  - This study found that hospital admissions for HF were increased in those exposed to NSAIDs/COX-2 inhibitors.
  - Any NSAID use in the preceding 14 days increased HF hospital admission risk compared to past use (>183 days) (adjusted OR 1.19, 95% CI 1.17-1.22).

Choosing Wisely and Product Monograph Statements

- **Choosing Wisely**: NSAIDs can cause fluid retention and are to be avoided in those with heart failure.[9,10]
- **CPhA NSAIDs Monograph**: NSAIDs are contraindicated in those with severe uncontrolled heart failure. The monograph states that all NSAIDs can increase fluid retention and thus worsen heart failure.[1]

MYOCARDIAL INFARCTION (MI)

- The Coxib and Traditional NSAID Trialists' Collaboration (CNT) MA included assessments of risk of non-fatal myocardial infarction (MI); as well as, the MCE composite of death by MI or coronary heart disease (MI/CHD death). Results in *Table 3* are NSAID **compared to placebo** and presented as rate ratio RR; (99% or 95% confidence interval):[4]

Table 3

	Non-Fatal MI:	MI/CHD Death (MCE):
Coxib	**1.71 (1.23-2.37)**	**1.76 (1.31-2.37)**
Diclofenac	NSS[a]/NR[b]	**1.70 (1.19-2.41)**
Ibuprofen	NSS/NR	**2.22 (1.10-4.48)**
Naproxen	NSS/NR	0.84 (0.52-1.60) (p=0.90 = NSS)

[a]Not Statistically significant; [b]Not reported: point estimate and confidence interval not reported, only shown in forest plot. MCE= Major Coronary Events. Bolded results above are statistically significant.

- Coxibs statistically significantly increased the rate of non-fatal MI compared with placebo (*Table 3*).
- Coxibs, diclofenac and ibuprofen increased the rate of the composite of MI/CHD death compared to placebo (*Table 3*).
- Comparisons between Coxibs and either ibuprofen or diclofenac found no statistically significant differences in non-fatal MI or MI/CHD death.
- Coxibs statistically significantly increased the risk of both outcomes vs. naproxen. Presented as rate ratio (RR) and either 99% or 95% CI.
    - Non-fatal MI RR 2.02 ((99% CI 1.35-3.02)
    - MI/CHD death RR 2.11 (95% CI 1.44 -3.09)

- The network meta-analysis of 29 RCTs (554 accumulated events) by Trelle et al., **found no statistically significant increase in the risk of MI compared to placebo** for the following comparisons. The point estimates for diclofenac and naproxen are below 1 which the authors interpret as no evidence of increased risk; however, the wide confidence intervals demonstrate imprecision in the result and do not exclude the possibility of harm. Data are presented as rate ratio (RR) and 95% Credibility Interval.[3]
    - Diclofenac: RR 0.82, 95% CrI 0.29-2.20
    - Naproxen: RR 0.82, 95% CrI 0.37-1.67
    - Celecoxib: RR 1.35, 95% CrI 0.71-2.72
    - Ibuprofen: RR 1.61, 95% CrI 0.50-5.77

- Bally et al. reports a meta-analysis (2017) of individual patient data (n=446,763) from observational studies which also showed an increase in acute MI risk with NSAID use (including COX-2 inhibitors). [11]
    - Mean age of participants in studies ranged from 58 to 78 years old.
    - The adjusted odds ratio (OR) for NSAID use of *any dose* for 1-7 days is presented in *Table 4.*
    - The meta-analysis found a relation between increasing NSAID dose and risk of acute MI, ***although taking any dose of an NSAID for as short as one-week duration can increase acute MI risk.***
    - The authors state: "Short term use for 8-30 days at a high daily dose (celecoxib >200 mg, diclofenac >100 mg, ibuprofen >1200 mg, and naproxen >750 mg) is associated with the greatest harms, without obvious further increases in risk beyond the first 30 days"

Table 4 Risk of MI with NSAID use of any dose vs. non-use for 1-7 days. [11]

	Celecoxib	Ibuprofen	Diclofenac	Naproxen	Rofecoxib
OR (95% CI)	1.24 (0.91-1.82)	1.48 (1.00-2.26)	1.50 (1.06-2.04)	1.53 (1.07-2.33)	1.58 (1.07-2.17)

CI = credible intervals; MI = myocardial infarction; OR = odds ratio

STROKE

- The CNT Collaboration meta-analysis assessed stroke risk of various traditional NSAIDs and COX-2 inhibitors.[4]
    - Risk of any stroke **compared to placebo:** Rate ratio (95% confidence interval):
        - Coxib: RR 1.09 (0.78-1.52)
        - Naproxen: RR 0.97 (0.59-1.60)
        - Diclofenac: RR 1.18 (0.79-1.78)
        - Ibuprofen: RR 0.97 (0.42-2.24)
    - No significant differences were shown in comparisons between Coxibs and diclofenac, ibuprofen and naproxen in the risk of any stroke.
    - The author's state there was no evidence that any NSAID statistically significantly increased the risk for stroke.

- The network meta-analysis of RCTs by Trelle et al. found **diclofenac** to be associated with a statistically significant increase in stroke risk (hemorrhagic or ischemic fatal or non-fatal) with ibuprofen on the border of statistically significant increased harm; whereas, naproxen, and celecoxib did not show a significant increase in risk **vs placebo**. All of the point estimates for the rate ratios are above 1, which does not rule out a potential increase in risk with any of the NSAIDS, and the wide 95% credibility intervals indicate imprecision in the results.[3]
    - Naproxen: RR 1.76 (95% CrI 0.91-3.33)
    - Ibuprofen: RR 3.36 (95% CrI 1.00-11.60)
    - **Diclofenac: RR 2.86 (95% CrI 1.09-8.36)**
    - Celecoxib: RR 1.12 (95% CrI 0.60-2.06)
    - The network meta-analysis of *between* drug comparisons showed that diclofenac also increased the risk of stroke vs. celecoxib; whereas comparisons between other NSAIDs did not show a statistically significant difference.[3]

- A systematic review and meta-analysis of 10 observational studies (n=1,489,120) showed a small (though not statistically significant increase in hemorrhagic stroke risk in those taking NSAIDs (as a class), RR 1.09 (95% CI 0.98-1.22, I^2=28%). [49]
    - Similar results were achieved with subgroup analyses.
    - For individual NSAIDs, a statistically significant increase in hemorrhagic stroke was observed with diclofenac (RR 1.27, 95% CI 1.02-1.59) and meloxicam (RR 1.27, 95% CI 1.08-1.50).
    - No statistically significant increases in risk were observed with ibuprofen, indomethacin, or naproxen.

***Health Canada, FDA and Monograph Warnings (MI or Stroke)*:**

- In 2015, the U.S. Food & Drug Administration (FDA) strengthened its warnings on the use of NSAIDs, stating that within the first weeks of use, there is a possibility of a heart attack or stroke.[12]

- Health Canada issued a safety warning in 2015 regarding the risk of CV mortality, MI, and stroke with high doses of ibuprofen (2400 mg/day). They advised that the risk of MI and stroke increases with dose and duration of ibuprofen use and is similar to the risk of other NSAIDs, including celecoxib and diclofenac.[13]

- Health Canada published a safety review in 2014 of MI and stroke risk with the use of diclofenac. They stated that diclofenac is associated with an increased risk of serious cardiovascular and stroke adverse events, particularly at higher doses (≥ 150 mg/day). This risk may be comparable to COX-2 inhibitors.[50]

- The product monograph for NSAIDs cites the network meta-analysis by Trelle et al.[3] under the "Serious Warnings and Precautions" section and warns of the increased risk of potentially fatal events such as MI and stroke with NSAIDs.[1]
    - The monograph also states NSAIDs are contraindicated in the "perioperative setting of coronary artery bypass graft surgery (CABG) because of the risk of thrombotic events. The exception is low-dose ASA, which is recommended to reduce thrombotic events in the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery Circulation 2011;124(23):2610-42]."

ATRIAL FIBRILLATION (AFib)

- A 2017 meta-analysis by Liu et al of 5 observational studies (n=7,250,695) found the risk of AFib to be increased with non-aspirin NSAID current use [relative risk (RR) 1.12, 95% CI 1.06 to 1.18, I^2=65%].[14]
    - New users were found to be at higher risk (RR 1.53, 95% CI 1.37 to 1.70).
    - Both selective and non-selective NSAIDs increased risk.

- Similarly, a 2020 meta-analysis of 8 observational studies, N= 14,806,420 (including the 5 in the Liu meta- analysis) showed an elevated increased AFib risk with NSAID use [relative risk (RR) 1.29, 95% CI 1.19-1.39, I^2=68%].[15]

- Although the two MA of observational studies suggest a potential association of AFib incidence with NSAID use, they are limited by the observational study design and heterogeneity of pooled results. There was limited information on individual NSAIDs or doses.

WHAT IS THE IMPACT OF NSAIDS ON HYPERTENSION (HTN)?

- NSAID-related increases in blood pressure (BP) levels are due to inhibition of prostaglandin synthesis and resulting vasoconstriction.[46]
- No relevant literature describing the effects of short-term NSAID use on hypertension were found in a CADTH Rapid Response.[16]

- Curtis et al. report a meta-analysis of 15 RCTs, COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib, valdecoxib) were shown to increase the relative risk (RR 1.45, 95% CI 1.01-2.10, I2=25%) compared to placebo, for OA treatment over 6 weeks.[8]
    - HTN risk difference was not statistically significant with rofecoxib removal from the analysis: RR 1.21, 95% CI 0.80-1.83, I2=20%.

- In a non-inferiority RCT with patients with OA (primarily) or RA, with increased relative risk for CVD (a sub-study of the PRECISION trial), there was a significant increase in ambulatory SBP with ibuprofen versus celecoxib [difference of -3.9 mmHg (p=0.0009)] after 4 months of use.[17]
    - Doses: celecoxib 100–200 mg BID, ibuprofen 600–800 mg TID, naproxen 375–500 mg BID
    - The change in mean 24-h SBP from baseline at 4 months is shown in *Table 5*.
    - The percentage of normotensive patients at the start of the study who developed HTN defined by BP ≥ 130/80 was highest with ibuprofen (23.2%), followed by naproxen (19.0%) and celecoxib (10.3%).[17] However, this was based on a post-hoc analysis.

Table 5. Change in mean 24-h SBP from baseline at 4 months with celecoxib, ibuprofen, and naproxen.[17]

	Celecoxib	**Ibuprofen**	**Naproxen**
Change in mean 24-h systolic blood pressure (SBP)	-0.3 mmHg (95% CI -2.25-1.74)	**3.7 mmHg (95% CI 1.72-5.58)**	1.6 mmHg (95% CI -0.40-3.57)

- A RCT studied the effects of naproxen and acetaminophen for OA treatment on antihypertensive therapy (ramipril, valsartan, and aliskiren). Results showed that with 2-week use of naproxen, there was a statistically significant increase in both clinic and ambulatory blood pressure in the ramipril and valsartan groups but results were not statistically significant in the aliskiren group.[18]
    - Dosing: Naproxen 500 mg/day, acetaminophen 2 g/day
    - N=174 (58/group) with essential HTN (38% had untreated HTN, and most patients had HTN history for <10 years), between 40-65 years of age (mean 57.4 years) randomized to ramipril, valsartan, aliskiren for 8 weeks.
    - N=135 with normalized blood pressure while on antihypertensive therapy randomized to naproxen or acetaminophen for 2 weeks.
    - Increases in BP with naproxen:
        - Ramipril 5 mg/day:
            - mean increase of clinic SBP/DBP: 6.8/4.6 mmHg, p<0.001
            - 24-h ambulatory SBP/DBP: 6.6/4.5 mmHg, p<0.01
        - Valsartan 160 mg/day:

        - mean increase of clinic SBP/DBP: 4.5/1.9 mmHg, p<0.05
        - 24-h ambulatory SBP/DBP: 4.1/2.3 mmHg, p<0.05
    - Aliskiren 150 mg/day:
        - mean increase of clinic SBP/DBP: 2.6/1.2 mmHg, not statistically significant
        - 24-h ambulatory SBP/DBP: 2.3/1.2 mmHg, not statistically significant
- Additionally, though less than naproxen, acetaminophen use for two weeks resulted in a statistically significant increase in both clinical and ambulatory blood pressure in all groups.
    - Ramipril 5 mg/day:
        - mean increase of clinic SBP/DBP: 4.4/2.9 mmHg, p<0.05
    - Valsartan 160 mg/day:
        - mean increase of clinic SBP/DBP: 3.8/2.3 mmHg, p<0.05
    - Aliskiren 150 mg/day:
        - mean increase of clinic SBP/DBP: 4.1/2.4 mmHg, p<0.05
- Therefore, both acetaminophen and naproxen have the potential to impact the treatment of hypertension. Monitoring of BP while on antihypertensive medications and acetaminophen or naproxen use is recommended.

Choosing Wisely and Product Monograph Statements

- **Choosing Wisely**: NSAIDs are not advised for use in those with HTN. NSAIDs can increase BP and decrease antihypertensive medication effectiveness when used for musculoskeletal pain treatment.[9,10]
- **CPhA NSAIDs Monograph:** All NSAIDs can worsen hypertension by increasing BP. Monitoring BP is recommended when taking NSAIDs while on antihypertensive drugs.[1]

Note: *The CPhA NSAID product monograph does not list a drug interaction between calcium channel blockers and NSAIDs; whereas, NSAIDs are suggested to decrease the antihypertensive effects of ACE inhibitors, angiotensin II receptor blockers, beta blockers and diuretics.*

ASA and Non-ASA NSAID Combinations or Concurrent use of ASA and Non-ASA NSAID

- The FDA states that concomitant use of ASA and ibuprofen 400 mg may result in reduced cardioprotective effects of ASA due to a pharmacodynamic interaction.[51,52]
    - Ibuprofen is therefore recommended to be taken 30 minutes after or 8 hours before immediate-release ASA (81 mg; not enteric-coated)**.** [52]

- The pharmacodynamic interaction of ASA and non-ASA NSAIDs results from competitive COX-1 inhibition.[52]

    - The COX-1 enzyme inhibits thromboxane's formation from arachidonic acid, thus inhibiting thromboxane-induced platelet aggregation.
    - ASA irreversibly inhibits the COX-1 enzyme, thereby leading to inhibition of platelet aggregation.

- Non-ASA NSAIDs (e.g., ibuprofen), reversibly inhibit the COX-1 enzyme and therefore have a reversible effect on platelet inhibition.
- ASA and ibuprofen bind to nearby sites on the COX-1 enzyme.
- Therefore, when the two medications are taken concomitantly, ibuprofen will prevent ASA binding to the COX-1 enzyme, thereby reducing overall COX-1 inhibition and reducing ASA's irreversible antiplatelet effects.

- In molecular interaction studies, ASA's antiplatelet effects were reduced with concomitant ibuprofen, naproxen or celecoxib but not with meloxicam, rofecoxib or diclofenac use. [52]

- In a systematic review of the clinical cardiovascular outcomes of ASA and NSAID interactions, 12 studies (cohorts and case-controls) were reviewed.[53]
  - For naproxen and ibuprofen, 6 and 8 studies respectively showed that there was no decrease in the cardio-protective effects of ASA with concomitant use.
  - For ibuprofen, however, two other studies showed a reduction in ASA's cardioprotective effects.
  - Although evidence is limited, the systematic review concluded that meloxicam and rofecoxib do not result in decreased clinical ASA effects, which is consistent with the molecular interaction studies. For diclofenac and celecoxib, the clinical data were not conclusive as some studies suggested reduced benefit from ASA while others did not.

- Drug interaction databases and the NSAID product monograph also identifies the ASA and non-ASA NSAID interaction concerning decreased antiplatelet effects of ASA, increased risk of GI bleeds, and increased risk of CV events.[1,21,54]
  - Ibuprofen is suggested to be taken at least 2 hours after or 8 hours before *immediate-release* ASA.[21,54]
  - Naproxen is recommended to be taken 2 hours after ASA.[21]
  - The peak interference with ASA function may be later with enteric-coated ASA compared to what has been observed in studies with immediate-release ASA.[21] Consider spacing the NSAID greater than 2 hours after enteric-coated ASA (delayed-release) administration, due to a longer time to peak platelet inhibition.
  - The CPhA product monograph drug interaction tables suggest to "avoid combining 2 NSAIDs. Risk of gastrointestinal bleeding increases, even when low doses of ASA are combined with other NSAIDs. Ibuprofen, naproxen and mefenamic acid may decrease the cardioprotective effect of ASA by binding to the active site on COX; *give ASA 2 h before NSAIDs*."[1]

QUESTION 1b: WHAT ARE THE GI RISKS WITH NSAID USE?

- NSAIDs cause symptomatic peptic ulcer disease primarily due to post absorptive inhibition of gastrointestinal mucosal cyclooxygenase (COX) activity rather than only by topical injury to the epithelium.[55]

- The Coxib and Traditional NSAID Trialists' (CNT) Collaboration Meta-Analysis of primarily individual participant data from 754 RCTs (280 trials NSAID vs. placebo, n=124,513 and 474 trials NSAID vs. NSAID, n=229,296), quantified the CV and GI risks of different NSAIDs (including COX-2 inhibitors), in those with *low CV or GI risk*. RCTs were *at least 4 weeks duration*.[4]
  - Major CV outcomes have been discussed previously.
  - Upper GI complications included outcomes of perforation, obstruction or bleed.
  - The *typical daily doses* of the Coxibs and NSAIDs included in the analyses were:
    - Celecoxib 400 mg, rofecoxib 25mg, etoricoxib 60-90 mg, lumiracoxib 200 mg, diclofenac 150 mg/day, ibuprofen 2400 mg/day and naproxen 1000 mg/day.
    - The doses for the NSAIDs were *higher* than commonly used in clinical practice.
  - **All NSAID** regimens, including Coxibs, statistically significantly increased upper gastrointestinal complications vs. **placebo**. (Data are presented as rate ratio with 95% confidence interval). Naproxen and ibuprofen were associated with the highest risk.
    - **Diclofenac: 1.89 (95% CI 1.16-3.09(p=0.0106**
    - **Naproxen: 4.22 (95% CI 2.71-6.56) p<0.0001**
    - **Coxib: 1.81 (95% CI 1.17-2.81) p=0.0070**
    - **Ibuprofen: 3.97 (95% CI 2.22-7.10) p<0.0001**
  - **The absolute event rates** of upper GI events per annum are provided only for the COX-2 inhibitor group (0·38%) vs. placebo (0·19%). **NNH 527**
    - *Absolute risks for the other NSAIDs* can be roughly estimated using the rate ratios vs. placebo. For example; if the risk of GI complications in the placebo group is 0.19% and naproxen or Ibuprofen increase this by approximately 4 times (rate ratios are close to 4 for both); then the absolute event rates would be approximately 0.76%. The confidence interval indicates an increase in rate of events of up to 7 times that of placebo which corresponds to an absolute event rate of approximately 1.33%.
  - Two percent of the upper GI complications were reported as being fatal.
  - Comparisons of upper GI complications for Coxib vs. traditional NSAIDS are presented in *Table 6.*

Table 6. Upper GI complication risks with COX-2 inhibitors versus placebo, diclofenac, ibuprofen, and naproxen. Data presented as rate ratio (RR) with 95% confidence intervals.[4]

Coxib vs.	Placebo	Diclofenac	Ibuprofen	Naproxen
Bleed	RR 2.22 (1.35-3.65)	RR 1.01 (0.75-1.36)	RR 0.55 (0.24-1.30)	RR 0.34 (0.23-0.49)
Perforation	RR 0.51 (0.06-4.68)	RR 0.49 (0.13-1.37)	-	RR 0.78 (0.17-3.61)
Obstruction	RR 0.49 (0.05-4.78)	RR 1.18 (0.20-7.00)	-	-
Unknown	RR 1.50 (0.35-6.35)	RR 0.76 (0.22-2.68)	RR 0.32 (0.18-0.58)	RR 0.39 (0.25-0.60)
Subtotal: any complication	**RR 1.81 (1.17-2.81)**	RR 0.94 (0.72-1.24)	**RR 0.40 (0.25-0.64)**	**RR 0.37 (0.28-0.49)**

- **The statistically significant and substantial *relative reduction* in rate of GI complications between COX-2 inhibitors and ibuprofen or naproxen should be considered within the context of the absolute event rates: i.e., Coxib group (0·38%) vs. placebo (0·19%) per annum.**
- There was no statistically significant difference in GI complications between COX-2 inhibitors and diclofenac.
- These results cannot necessarily be extrapolated to *lower doses* of NSAIDs typically used for *short-term* treatment of *acute pain*.

- A 2013 CADTH Rapid Response report[7] cited the CNT meta-analysis[4] and two other systematic reviews, by the Agency for Healthcare Research and Quality (AHRQ)[24] and the Drug Effectiveness Review Project (DERP),[23] in the evidence review of GI adverse events with NSAID use.
  - The report concluded that celecoxib might have a lower risk of GI adverse events (GI bleeding or ulcers) compared to other non-selective NSAIDs (as a class); however, only in studies of less than six months duration.[7]

- The 2011 AHRQ review reported that meloxicam (7.5 mg/day) and etodolac (600 mg/day) resulted in a lower relative risk of ulcer complications or symptomatic ulcers compared to non-selective NSAIDs (as a class). Differences in the outcome of ulcer complications alone did not reach statistical significance [7,24]
  - Meloxicam vs. non-selective NSAIDs: RR 0.53 (95% CI 0.29-0.97)
  - Etodolac vs. non-selective NSAIDs: RR 0.32 (95% CI 0.15-0.71)

- The DERP review also showed that nabumetone might reduce the relative risk of GI AEs versus non-selective NSAIDs in the short term (<6 months). However, meloxicam did not have an advantage over non-selective NSAIDs for GI AEs over the long-term (≥6 months).[23]

- In the Curtis et al meta-analysis of RCTs, COX-2 inhibitors (**celecoxib**, rofecoxib, etoricoxib, valdecoxib) were shown to have an increased risk of overall upper GI complications (n=23,974; RR 1.19 (95% CI 1.03-1.38, I^2=0%) and abdominal pain

(n=9,907; RR 1.40 (95% CI 1.08-1.80, I^2=0%) **compared to placebo**, in individuals with OA. Assessment of evidence was considered high based on GRADE.[8]

- Henry et al report the relative risks with **low vs high doses of NSAIDS.** The publication reports there was an arbitrary cut-off for dose, however the difference in relative risks demonstrate the dose response effect for GI adverse events.[56]

Low dose ibuprofen	RR 1.6, 95% CI 0.8-3.2
High dose ibuprofen	RR 4.2, 95% CI 1.8-9.8
Low dose naproxen	RR 3.7, 95% CI 1.7-7.7
High dose naproxen	RR 6.0, 95% CI 3.0-12.2
Low dose indomethacin	RR 3.0, 95% CI 2.2-4.2
High dose indomethacin	RR 7.0, 95% CI 4.4-11.2

- **Ketorolac** is associated with a high risk of GI toxicity (up to 5.5 times greater than other NSAIDs) especially in higher doses, older patients, and for use > 5 days.[57]
  - Product monograph states ketorolac should only be given for a maximum of 5 days post-surgical or 7 days for musculoskeletal pain.[1]

- Risk for GI complications may occur early and an increased risk persists over time. Consider gastroprotection in at-risk patients when starting regularly scheduled NSAID therapy.[62]

USE OF GASTROPROTECTION

- For prevention of NSAID related endoscopic gastric and duodenal ulcers in patients with arthritis, misoprostol, proton-pump inhibitors (PPIs) and double dose histamine-2-receptor antagonists (H_2RAs; e.g., ranitidine 300 mg twice daily) are effective, based on a 2002 Cochrane review by Rostrom et al.[26]
  - 41 RCTs of ≥4 week duration were included in the meta-analyses.
  - *COX-2 inhibitors alone or NSAIDs with a PPI are equally effective in preventing gastroduodenal ulcers*. This result is based on 1 RCT in 130 patients who experienced 9 events.
  - Clinical ulcer (perforation, ulcer or bleed: NSAID + PPI vs COX-2 inhibitor OR 2.03 95% CI 0.49, 8.51)

- A network meta-analysis(2016) by Yuan et al.[27] provided similar final recommendations to the Cochrane Review[26]
  - The NMA included 82 trials enrolling 125, 053 participants.
  - The event rate probabilities for ulcer complications were less than 1% in all groups studied.

- No statistically significant difference was observed in the relative risk of having the primary outcome of ulcer complications (bleeding, perforation and obstruction), with non-selective NSAID plus PPI or COX-2 inhibitor use:
    - RR 1.45 (95% CI 0.75-2.82), moderate quality evidence (GRADE).
        - This outcome is based on 4 RCTs with 20 events in the NSAID + PPI group and 14 events in the COX-2 inhibitor group.
- **Selective COX-2 inhibitors plus PPIs reduce the relative risk of ulcer complications compared to COX-2 inhibitors alone:**
    - RR 0.06 (95% CI 0.01-0.48), moderate-quality evidence (GRADE).
    - A limitation to this evidence is that the outcome is based on 2 RCTs with 0 events in the COX-2 + PPI group and 14 in the COX-2 group.

- A 2007 CADTH project (COMPUS) summarized evidence on the use of PPIs to prevent NSAID –induced ulcers. They note that evidence suggests that, "*patients taking concomitant low-dose ASA for cardiovascular protection did not have any significant reduction in GI toxicity with celecoxib over the other NSAIDs. Of further note, the patient populations in the six-month CLASS trial actually continued on therapy for between 12 and 15 months. Subsequent publications on* ***data from the longer studies showed much of the benefit of celecoxib was lost****, with no significant risk reduction in serious GI complications and symptomatic ulcers compared to both traditional NSAIDs."* [58]

- **PPIs** significantly *reduced the risk* of ulcer complication (primary outcome) **compared to placebo** (RR 0.19, 95% CI 0.20-0.42, pairwise meta-analysis) **and histamine receptor antagonists (H_2RAs**; RR 0.26, 95% CI 0.09-0.81, pairwise meta-analysis), in a network meta-analysis by Yang et al. (2017).[59]
    - No significant difference was found in the risk of ulcer complication with PPIs and misoprostol 200 mcg four times daily:
        - There was *no significant difference between PPIs in the risk of ulcer complications with either esomeprazole, omeprazole, lansoprazole or rabeprazole* pairwise meta-analysis based on low to very low-quality evidence RR 1.50 (95% CI 0.06 to 36.58). However, esomeprazole had a greater risk reduction in endoscopic peptic ulcers compared to pantoprazole:
            - RR 3.06 (95% CrI 1.07-6.84), very low GRADE evidence
        - For safety, a lower risk of GI AEs (RR 0.86, 95% CI 0.79-0.94, pairwise meta-analysis) and withdrawals due to GI AEs (RR 0.66, 95% CI 0.50 to 0.88, pairwise meta-analysis) was observed with PPIs than with placebo.

- A secondary outcome of the PRECISION trial analyzed the risk for clinically significant GI injury (CSGI) for celecoxib 100-200 mg twice daily, ibuprofen 600-800 mg three times daily or naproxen 375-500 mg twice daily plus all patients received esomeprazole 20-40 mg daily N= 24,081 patients. The mean treatment and follow-up durations were 20.3 and 34.1 months.[25]

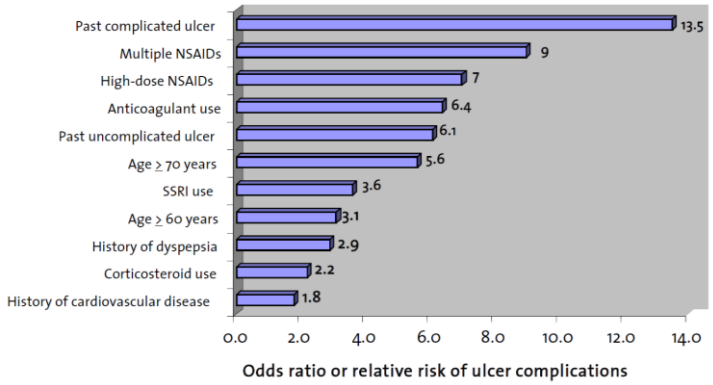
- There was a low incidence of CSGI in all three treatment arms and there was **no statistically significant differences between any of the groups** in the intention to treat (ITT) analysis.
- ITT population rates per 100 patient years for CSGI were: 0.32 celecoxib, 0.43 ibuprofen, 0.33 naproxen and concomitant PPI.
    - Numbers needed to harm (NNH) for a CSGIE event were never less than 200 per annum. (A higher NNH indicates greater safety.)
- Modified intention to treat analysis (MITT) reported events which occurred while actively taking the treatments or within 30 days. CSGI rates were similarly low however, celecoxib was statistically lower than ibuprofen or naproxen.

- A 2017 RCT reported the difference between celecoxib/esomeprazole and naproxen/esomeprazole, in preventing GI bleeds in a high risk population in patients who were on long-term low-dose ASA for cardiovascular disease and had a history of upper GI bleed while taking an NSAID.[60]
    - Doses included were celecoxib 100 mg twice/day plus esomeprazole 20 mg once/day or naproxen 500 mg twice/day plus esomeprazole 20 mg once/day for 18 months. N=514
    - The cumulative incidence of recurrent upper GI bleed was 5.6% (95% CI 3.3-9.2) in the celecoxib group and 12.3% (8.8-17.1) in the naproxen group (log-rank test p=0.008, crude HR 0.44, 95% CI 0.23-0.82, p=0.010).
    - There was no statistically significant difference in cardiovascular outcomes between groups and no GI bleeding related deaths were reported.
    - This indicates a lower rate of GI bleeds with celecoxib/esomeprazole versus naproxen/esomeprazole.
    - *Celecoxib with gastroprotection may, therefore, be an option for individuals with high-risk of GI bleeds.*

Risk factors associated with NSAID- related GI adverse events and risk reduction strategies

- The 2007 CADTH project on PPIs (COMPUS) developed a reference document for Academic Detailing and provide the following graphic for risk factors associated with GI complications and NSAID –associated GI complications:[61]

Figure 1. Risk factors for NSAID-associated GI complications



https://www.cadth.ca/sites/default/files/compus/reports/compus_PPI_Upskilling-document.pdf

- Risk for GI complications may occur early and an increased risk persists over time. Consider gastroprotection (concomitant PPI) in at-risk patients when starting regularly scheduled NSAID therapy.[62]
- Risk reduction considerations include identification of high-risk patients and selection of strategies to manage complications.
    - **Baseline risk assessment**: what is the individual's baseline risk for GI, CV or renal complications?
        - Consideration of the patient's **baseline risk** and the magnitude of risk increase is required to weigh the benefits to risk when prescribing an NSAID.[63,64]
        - Assess risks for all potential complications
            - For example, if both GI and CV risk factors exist, then the risk may be unacceptable and alternative therapy should be chosen or multiple risk reduction strategies required.
- Meta-analyses and RCTs have limitations which make choosing one NSAID over another difficult, especially for short-term use for acute pain. For example;
    - Doses of NSAIDs, particularly non-selective NSAIDs, used in clinical trials have often been higher than typical doses in clinical practice. Higher risks are generally associated with higher doses[1,5]
    - There is very little evidence on the risks associated with short-term or intermittent use however, as mentioned above some CV and GI adverse events can occur early in therapy.
    - As a general rule, NSAIDs that have a lower risk for GI complications (COX-2 selective inhibitors) are those that have a higher CV risk and vice versa.

Table 7: Considerations for GI, CV and Renal Adverse Events associated with NSAID Therapy

Gastrointestinal Considerations	*CV and Renal Considerations*
➢ Increased risk for GI adverse events from NSAIDs[63] • Age > 65 years • High dose NSAID • History of peptic ulcer disease (PUD) • Concomitant ASA (including low dose) corticosteroid or anticoagulant use • *H pylori* status is a consideration if initiating long term NSAID therapy ➢ 1-2% of NSAID users will develop serious GI complications yearly, a rate that is 3-5 times higher than non-users but not every user is at equal risk of developing the complications.[63] • For example, in low risk patients the absolute risk increase is small, irrespective of NSAID regimen chosen.[4] (See risk stratification tool) ➢ The following strategies reduce the risk of NSAID related endoscopic gastric and duodenal ulcers: misoprostol 200 mcg qid, single dose proton-pump inhibitors (PPIs) and double dose histamine-2-receptor antagonists (H2Ras; e.g., ranitidine 300 mg twice daily).[26] ➢ COX-2 inhibitors with or without a PPI have a modestly lower relative risk for GI events compared with traditional NSAIDs.[26] ➢ An NSAID plus PPI is considered to have a similar rate of GI complication as a COX-2 inhibitor alone.[26] ➢ Concomitant use of low-dose ASA and a COX-2 inhibitor may negate the GI protective benefit of the COX-2 inhibitor.[51,52] ➢ Some non-selective NSAIDs have higher rates of GI adverse events than others. • For example indomethacin, piroxicam and ketorolac demonstrate increased GI adverse effects within the first week.[65] ➢ Risk for GI adverse events increases with higher doses and longer duration of therapy. GI complications may occur early and an increased risk persists over time.[62] • Consider adding a PPI when starting a regularly scheduled NSAID in at-risk patients. (see risk stratification tool on page 128)	There is increased risk of adverse events in patients with a **history of a CV event (existing CV disease)** or factors which increase risk: (See risk stratification tool page 127) https://ccs.ca/images/Guidelines/Tools_and_Calculators_En/FRS_eng_2017_fnl1.pdf ➢ Diabetes Mellitus ➢ Hypertension ➢ Hyperlipidemia (total cholesterol, HDL-C) ➢ Obesity ➢ Smoking ➢ Age (especially ≥ 70 years) All NSAIDs, including COX-2 inhibitors and non-selective NSAIDs are: ➢ Contraindicated in those with severe uncontrolled heart failure.[1] ➢ Associated with an increased risk of myocardial infarction and stroke.[1,13] ➢ Increased risk of MI can occur in the first week of therapy. [11] ➢ Associated with increased blood pressure and may decrease the effectiveness of medications used to control hypertension.[1,10] ➢ Contraindicated in patients with reduced kidney function, CrCL < 30 ml/min.[1] ➢ NSAIDs may reduce the effectiveness of low-dose ASA.[1,21,54]

General Prescribing Principles

- No NSAID is without risk
- The lowest effective dose of any NSAID, for the shortest period of time will impact the risk for serious adverse events.[64]
- Administration of NSAIDs for a short period of time (less than one week) in healthy people is unlikely to result in any clinically significant gastroduodenal toxicity.[65]

Cardiovascular Risk Factor Assessment for NSAID Use[1-7]

Step 1 Assess CV risk factors [1]

- History of CV event (Established CV disease)
- Diabetes Mellitus
- Hypertension
- Hyperlipidemia (total cholesterol, HDL-C)
- Obesity
- Smoking
- Age (especially ≥ 70 years)

Canadian Cardiovascular Society Framingham Risk calculator (copy and paste in internet browser)**:**
https://ccs.ca/images/Guidelines/Tools_and_Calculators_En/FRS_eng_2017_fnl1.pdf
https://ccs.ca/calculators-and-forms/

Step 2 Determine if NSAID therapy is appropriate.[2,3]

If CV risk is high, the risk of taking any NSAID may outweigh the benefit.
Consider the contraindications and precautions to prescribing any NSAID:

All NSAIDs including COX-2 inhibitors and non-selective NSAIDs are:

- Contraindicated in those with severe uncontrolled heart failure.
- Associated with an increased risk of myocardial infarction and stroke.
  - Increased risk of MI can occur in the first week of therapy
- Associated with increased blood pressure and may decrease the effectiveness of medications used to control hypertension.
- Contraindicated in patients with reduced kidney function CrCL < 30 ml/min
- NSAIDS may reduce the effectiveness of low-dose ASA

Step 3 Choose NSAID with Lowest Cardiovascular Risk [4-7]

NSAIDs with Lower CV risk

- Naproxen 500 mg twice daily; low-dose ibuprofen (< 2400 mg/day)

NSAIDs with Higher CV risk

- NSAIDs with higher COX-2 selectivity may be associated with higher CV risk (e.g., celecoxib, meloxicam) and are generally avoided in patients who have, or are at high risk of CV disease.
- Diclofenac has been shown to increase the risk of stroke.

Note: Consider gastroprotection in patients with elevated GI risk, especially if taking concomitant ASA (see GI risk factor tool); risk for GI complications occur within the first 30 days of NSAID therapy and persist over time.

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Gastrointestinal (GI) Risk Factor Assessment for NSAID Use[1-7]

Step 1. Assess GI risk factors to determine risk level (high , medium, low)

Risk Factors[1]

- Age > 65 years
- High dose NSAID
- History of peptic ulcer disease
- Concomitant ASA (including low dose), corticosteroid or anticoagulant use

H pylori infection is an independent and additive risk factor if considering long term NSAID therapy

High GI Risk	Medium GI Risk	Low GI Risk
➢ Previous history of peptic ulcer disease (especially if recent, or complicated ulcer) ➢ >2 risk factors	➢ 1-2 risk factors	➢ No risk factors

Step 2 Determine if NSAID therapy is appropriate:

If the GI risk is high, the risk of taking any NSAID may outweigh the benefit.

Step 3 Choose NSAID with lower risk or appropriate gastroprotective strategy. Consider dose and duration. [a]

➢ Avoid NSAIDs if possible ➢ COX-2 inhibitor + PPI unless also at high cardiovascular risk [7]	➢ COX-2 inhibitor [b] ± PPI Or ➢ Low dose NSAID + PPI **Note**: NSAID + PPI considered similar risk as COX-2 Inhibitor[7]	➢ Low dose NSAID and shortest duration possible [c] ➢ Gastroprotection is not required. **Note:** Some non-selective agents have higher risk than others [e]

[a] Risk increases with higher doses and longer duration of therapy; GI complications may occur early and an increased risk persists over time.
[b.] COX-2 inhibitors such as celecoxib modestly reduce GI complications compared with traditional NSAIDs
[c.] The lowest effective dose and shortest duration of any NSAID is a general rule
[d] Standard one daily dose of PPI for gastroprotection; alternative agents include misoprostol 200mcg qid or double dose H2RA;
[e] Indomethacin, piroxicam and ketorolac are considered higher risk for GI events

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Options for lowering NSAID GI and CV Risks			
Cardiovascular Risk [a]	**Gastrointestinal Risk [b]**		
	Low	**Medium**	**High**
Low CV risk	Any NSAID alone (Lowest dose/shortest duration)	COX-2 inhibitor [b] ± PPI *or* Low-dose NSAID + PPI [c]	**Avoid all NSAIDs** **Use alternative therapy** *or* COX-2 inhibitor + PPI
High CV risk	Naproxen 500 mg bid *OR* Low-dose ibuprofen (< 2400 mg/day) + PPI if taking ASA[d]	Naproxen 500 mg bid *OR* Low-dose ibuprofen (< 2400 mg/day) + PPI	**Avoid all NSAIDs** **Use alternative therapy**

a, b See GI and CV risk assessment tools;
c. Use single daily dose PPI for gastroprotection. Alternative agents include misoprostol 200mcg qid or double dose H2RA (e.g., ranitidine 300 mg bid;
d. Ibuprofen is suggested to be taken at least 30 minutes post or 8 hours before immediate release ASA, Naproxen is recommended to be taken 2 hours post ASA

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QUESTION 1c: WHAT ARE THE RENAL RISKS WITH NSAID USE?

NSAIDS AND ACUTE KIDNEY INJURY (AKI)

- Five systematic reviews [28-32] (one with meta-analysis), one randomized controlled trial [33] and five non-randomized studies were identified as the best available evidence for NSAID use and AKI development [34]

- A systematic review (Bell, 2018) of 26 trials (RCTs or quasi-RCTs, n=8943) assessed post-operative renal function with peri-operative use of NSAIDs in patients with normal kidney function.[28]
    - NSAIDs used:
        - ketorolac, indomethacin, diclofenac, ASA, ibuprofen, naproxen, tenoxicam, etodolac, ketoprofen and COX-2 inhibitors
        - various administration routes (intravenous, intramuscular, oral, etc.)
    - The evidence for post-operative relative risk of each outcome compared to placebo were rated as low certainty due to study designs:
        - AKI (n=7066, RR 1.79, 95% CI 0.50-7.96, I^2=59%)
        - Serum creatinine (SCr) (n=794, MD 3.23 µmol/L, 95% CI -0.80 to 7.26, I^2=63%)
    - Authors conclude a lack safety evidence for peri-operative NSAID use and uncertainty of their renal effects in patients with normal kidney function.

- AKI risk with NSAID use in those with chronic kidney disease (CKD) was assessed in a sub-analysis of a systematic review by Zhang et al., of 10 observational studies (n=1,609,163) of medium to high-quality.[31]
    - All of the included 10 trials assess risk of acute kidney injury with NSAID use. Five of those studies included people with pre-existing chronic kidney disease.
    - Eight of the trials revealed a statistically significant association with NSAID use and AKI (OR 1.73, 95% CI 1.44-2.07, I^2=89%).
    - Of the five studies that included data on individuals with CKD, four revealed a statistically significant association between NSAID use and AKI when compared to patients who did not use NSAIDs. [Crude OR 1.63 (95% CI 1.22-2.19, I^2=71%)].
    - Heterogeneity was high for pooled results.
    - Subgroup analyses showed that individuals >50 years of age had higher odds of AKI with NSAID use versus the general population (OR 2.01, 95% CI 1.52-2.68, I^2=62%).
    - Additionally, the use of a COX-2 selective NSAID was not associated with lower odds of AKI.

- Overall, evidence of AKI with NSAID use is inconclusive.
    - Systematic reviews and meta-analyses show slightly increased SCr levels with NSAID use, however no evidence for AKI.[34]

- Non-randomized trials have shown an increased risk of AKI with NSAIDs, particularly ketorolac.[34]
- More evidence is required to determine the absolute risks of AKI with NSAID use.

➢ Despite the lack of concrete evidence, there are several risk factors that can increase the likelihood of AKI with NSAID use:[35]
- CKD
- severe hypercalcemia
- nephrotic syndrome
- cirrhosis
- heart failure or volume depletion (diuretic associated or from vomiting and diarrhea).

➢ Concomitant use of other medications [i.e., diuretics, ACE-Is, or ARBs] can increase the likelihood of developing AKI.[35,36]
- In a large retrospective nested case-control cohort of triple therapy of a diuretic with an ACE-I or ARB and NSAID resulted in an increased risk of AKI [Rate ratio (RR) 1.31 (95% CI 1.12-1.53)].[36]
  - Additionally, the risk was highest in the first month of triple therapy.
  - However, the concomitant use of any of the three antihypertensive medications with an NSAID (dual therapy) did not increase the risk of AKI.
- There is no evidence to suggest COX-2 inhibitors are safer than non-selective NSAIDs in terms of AKI risk.

➢ **Canadian Pharmacists' Association(CPhA) NSAIDs Monograph:[1]**
- Patients at risk of acute renal failure are those with hypovolemia, shock, cirrhosis, sodium depletion, dehydration, hemorrhage, heart failure, pre-existing renal impairment (GFR <60 mL/minute) and those taking certain drugs (e.g., ACE-I, ARBs, beta blockers, cholestyramine, corticosteroids, etc., see product monograph for full list).
- NSAID dose and duration may affect renal impairment risk.

➢ NSAIDs are considered one of the risk factors for contrast induced AKI, as they are considered nephrotoxic drugs by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on acute kidney injury.[39]

NSAIDS AND CHRONIC KIDNEY DISEASE (CKD)

➢ In a systematic review of nine observational studies (Yaxley, et al) of primarily low-quality, eight trials did not find a statistically significant association between chronic NSAID use and development of analgesic nephropathy, a type of CKD.[37]

- CKD progression was assessed in a systematic review of population-based epidemiological studies assessing chronic NSAID use (duration of ≥6 months) in ages 45 years and older.[38]
    - NSAIDs were not statistically significantly associated with accelerated CKD progression, defined as eGFR decline ≥15mL/min/1.73m^2 over 2 years (pooled OR 1.04, 95% CI 0.90-1.20, I^2=52%)
    - In subgroup analyses, however, high-dose NSAID use increased the risk of accelerated CKD progression (OR 1.26, 95% CI 1.06-1.50, I^2=0%), while regular-dose NSAID use did not (OR 0.96, 95% CI 0.86-1.07, I^2=0%).
    - Results are limited by the lack of a clear definition of 'high-dose' and 'regular-dose' NSAID.
    - There was no clear evidence of the development of moderate to severe CKD with chronic NSAID use.

- Overall, there is a paucity of high-quality evidence suggesting the risk of CKD development with NSAID use.
    - Lower doses of NSAIDs may be safer than higher doses.

Guideline statements and monograph warnings

- The National Institute for Health and Care Excellence (NICE) Guidelines on CKD management suggest an association with CKD progression and chronic NSAID use in those with existing CKD.[67]
    - Additionally, the guidelines state that a reversible decrease in glomerular filtration rate (GFR) may occur as a result of acute NSAID use.
    - Monitoring of renal function is indicated in individuals with CKD and NSAID use, especially in those with risk factors for disease progression.
- **Choosing Wisely**: NSAIDs can worsen kidney function in those with CKD of any cause, including diabetes and should, therefore, be avoided.
- NSAIDs require dosage adjustments for those with renal impairment (see Appendix 1 Drug Tables).
- **CPhA NSAIDs Monograph**: NSAIDs are contraindicated in those with severe renal impairment (CrCL <30 mL/min).[1]
- The 2012 KDIGO guidelines recommend avoiding NSAID use in those with GFR <30 mL/min/1.73m^2 and in those taking renin-angiotensin-aldosterone system blockers. The guidelines also recommend against prolonged NSAID use in those with GFR <60 mL/min/1.73m^2.[68]

QUESTION 1d: WHAT IS THE EVIDENCE FOR NSAIDS AND <u>FRACTURE HEALING IMPAIRMENT</u>?

- The proposed mechanism by which NSAIDs may impact bone healing is by decreasing the inflammatory response mediators(prostaglandins) through COX enzyme inhibition [69]

- The Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury (2019) outline four commonly cited clinical studies and two meta- analyses assessing NSAID use and fracture healing. [44]
    - The meta-analyses state that there is no high quality evidence to suggest impairment of fracture healing with NSAID use.
    - The four clinical studies often cited are limited by study design (three are observational studies) and sample size (one is anRCT[2]).
    - The guidelines conclude that there is a lack of good quality evidence to suggest fracture healing impairment with NSAID use and recommend the use of NSAIDs for operative and non-operative fracture care.

- A 2019 meta-analysis of 16 studies (RCTs, cohort and case-control studies) showed an increase in the odds of delayed union or non-union (OR 2.07, 95% CI 1.19 to 3.61) in orthopedic patients.[40,41]
    - Only two of the included studies were RCTs, [70,71] while majority of studies were retrospective cohorts.
    - Most studies included ketorolac with varying doses and duration. Other NSAIDs included were ibuprofen, indomethacin, and diclofenac. Some studies did not specify NSAID, dose or duration studied.
    - Authors state there was significant heterogeneity amongst the included studies (I^2=77.25%).
    - Subgroup analysis of long bones showed an increased risk of delayed union or non-union (89 cases exposed to NSAIDs, 239 not exposed to NSAIDs; 6 studies, OR 2.34, 95% CI 1.12 to 4.90).
    - Subgroup analysis of low NSAID dose (<125 mg/day of diclofenac, 150 mg/day of indomethacin, or 120 mg/day of ketorolac) and short duration, (<2 weeks duration) in adult patients did not show a statistically significant increase in risk of delayed union or non-union (, OR 1.68, 95% CI 0.63-4.46).
    - A subgroup analysis of NSAID use in pediatric patients showed no statistically significant increase in the risk of delayed union or non-union (4 studies, OR 0.58, 95% CI 1.12-4.90).
    - Author's conclusions: "Based on the available literature, NSAID exposure seems to increase the risk of a delayed union or non-union in a healing bone. No significant effect exists in the pediatric population. In contrary to previous reports, we did not find a differential effect based on the type of bone. In our analysis, a low dose or short duration of NSAID treatment did not show an increased risk of bone healing complication, but this analysis was limited by a low number of included studies."[40]
        - Authors state that high quality studies are still required but that NSAIDs should not be used in those at increased risk of non-union or delayed union based on their findings.

- A 2018 systematic review assessed the risk of non-union (via radiographic techniques) with any perioperative NSAID exposer post fracture osteosynthesis/spinal fusion.[42]
    - 19 studies were included: 4 RCTs[70,72-74] (total n= 350) and 15 retrospective studies.
    - 8 different NSAIDs were included in the studies, the most common being ketorolac (9 studies).
    - Sample sizes ranged from 42-9995. RCTs included small number of participants (range from 42-112). The study with 9995 patients did not state the type of NSAID used or duration of therapy.
    - Surgery types varied but primarily involved long bones or spine.
    - NSAID use duration varied from 48 hours to >3 months.
    - There were many sources of heterogeneity amongst the included studies.
    - Results:
        - Based on two RCTs and eight retrospective studies, there was no increased risk of non-union with NSAID use post-operatively.
        - However, an increased risk was shown with one RCT and six retrospective studies. Thus, results were inconsistent.
        - Incidence of non-union with one week perioperative indomethacin exposure was not increased in one RCT, although 6 weeks exposure increased non-union for acetabular fracture risk.
        - Peri- operative celecoxib, rofexocib or low dose ketorolac (<110 mg/day) with short-term use were not associated with statistically significantly increased risk of non-union.
        - However, non-union in spine surgery incidence increased with higher doses of ketorolac in one retrospective cohort.
    - Author's conclusions: "Overall, the evidence in clinic human studies was not sufficiently robust to show a clear association between the use of NSAIDs and an increased risk of non-union in the bone healing process." [42]
        - "Considering the negative results found in animal and laboratory data and according to expert opinions the following measures could be considered: Restrict standard use of NSAIDs to no >14 days and evaluation of risk/benefit ratio in patients at high risk for delayed fracture healing."

- Although animal studies have demonstrated that higher than normal doses of NSAIDs impair bone healing, RCT data, though limited, do not suggest impairment of fracture healing with NSAID use, according to the Tools for Practice article in the journal *Canadian Family Physician*.[43]
    - The document outlines two older RCTs (n=140) that indicate no difference with malunion, non-union, or healing of Colles fractures with the use of 14 days of flurbiprofen [72] or 8 weeks of piroxicam [73] respectively, compared to placebo.

These RCTs were also included in a 2018 systematic review.[42] The document also outlines the study by Burd et al. [74] as misleading and outlines its limitations.
- They also outline a RCT of children with arm fractures (n=336) [75] that also showed no difference in fracture non-union after 12 months with ibuprofen or acetaminophen and codeine use.
- The document suggests that "patients should not be denied NSAIDs for short-term pain relief".

- A 2019 RCT aimed to assess the efficacy of ibuprofen for Colles' fracture pain relief without bone healing impairment.[76]
  - Patients included were aged 40-85 years with acute, unstable, older type III-IV Colles' fractures who needed surgical treatment (n=95).
  - The study was a randomized, 1:1:1 controlled, triple-blind, clinical trial with three treatment groups.
    - Group one received ibuprofen 600 mg three times daily for seven days.
    - Group two received 600 mg ibuprofen three times daily for three days, then placebo three times daily for 4 days.
    - Group three received placebo three times daily for 7 days.
  - All patients received 1 g of acetaminophen four times daily for seven days and six 50 mg tramadol tablets as needed.
  - Patients received surgery 1-3 days post injury and surgeries were all done by the same surgeon.
  - Patients were assessed at one week (radiological assessment), two weeks (radiological assessment, pain diary), six weeks (radiological assessment, external fixation removal, wrists range of motion measurement), three months [range of motion, DASH score (30 question survey)], and one year (range of motion, DASH score).
  - The primary outcome was radiological migration of bone fragments (changes in radius tilt, length and inclination) during and 6 weeks post-surgery.
  - Results:
    - Radiological migration did not statistically or clinically significantly differ amongst the groups ($0.064 \leq P \leq 0.81$).
    - Mean pain score did not statistically significantly differ between group at any time of follow-up ($p=0.13$).
    - In the ibuprofen groups, tramadol use [median 1 (0-9) tablets], was less compared to the placebo group [median 2 (0-7) tramadol tablets] in the first three days ($p=0.035$).
    - GI disorder was the most common complication in the ibuprofen groups. There was a significant difference between ibuprofen (7-days) and placebo in number of AEs ($p=0.043$).

- Limitations:
    - The baseline characteristics table does not provide sufficient information to determine whether patients were similar at baseline and whether randomization was adequate.
    - Authors state the radiological and functional outcomes were non-inferiority design. They suggest that their sample size was still appropriate for a non-inferiority trial.
    - There was no standardization with X-ray picture use, according to the authors.
    - Due to various reasons, ibuprofen was not necessarily started at the same time point of the fracture inflammation phase.
    - Overall, the study is limited in its analysis of outcomes.
- Authors Conclusions:
    - "The treatment with ibuprofen had an opioid-sparing effect and did not demonstrate any harmful influence on a patient's radiological and functional outcomes. These findings may offer support as an indication for ibuprofen treatment in the acute facture phase; however, the risks of ibuprofen's side effects need to be considered."

- In summary overall, the evidence surrounding NSAIDs and fracture healing impairment is not clear. There is no high quality robust evidence on this topic.
    - RCTs conducted on this topic are small in size and considered low quality (with risks of bias).[40,42,44] The majority of other clinical studies on this topic are retrospective studies with lots of potential biases.
    - Systematic reviews and meta-analyses include both RCTs and retrospective studies, with different NSAIDs used and with some studies not outlining NSAID dose or duration used.
    - Based on the current available evidence from human clinical trials, short-term, low dose NSAID use may be safe for pain relief in fracture care.[40,42-44]

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CANNABINOIDS

BACKGROUND

- Cannabis refers to the plant *Cannabis sativa.*[1] Cannabis can contains over 100 active compounds known as cannabinoids, which can have different effects on the body.[1]
- Cannabinoids are similar to certain naturally occurring compounds in the body known as endocannabinoids.[1,2] Both endocannabinoids and cannabinoids activate certain cannabinoid receptors in the body. Currently, the two most well-known cannabinoid receptors are CB1 and CB2.[1,2]
    - CB1 receptors are found in the central and peripheral nervous systems. These receptors may play a role in memory, mood, sleep, appetite and pain.[1,2]
    - CB2 receptors are found predominantly in the cells of the immune system. These receptors may play a role in reducing inflammation.[1,2]
- Two of the main active components of cannabis are delta-9-tetraydrocannabinol (THC) and cannabidiol (CBD) which are the cannabinoids that have been investigated for medicinal purposes.[1,2] These compounds work on the cannabinoid receptors CB1 and CB2.[1,2]
    - TCH is the primary psychoactive constituent. It is highly lipophilic and is stored in fatty tissue, it is metabolized by hepatic CYP450 3A4 and 2C9, and is excreted in feces and urine. THC is partial agonist at both CB1 and CB2 receptors.[1,2]
    - CBD is non-psychotropic and may modulate some of the undesirable effects of TCH when administered together. CBD may have anxiolytic and anti-inflammatory properties.[1,2]
    - Each strain of cannabis has a specific THC-to-CBD ratio; this leads to different physiologic effects based on the concentration of THC and CBD.[1,2]
- Cannabis products come in a variety of forms including tablets/capsules, edibles, oils, topicals, inhalants, etc.[1]
- Patients authorized by their health care provider are able to access cannabis for medical purposes (medicinal cannabis).[1,3] Note: Cannabis has not been approved for use as a medicine for any indication by Health Canada.[1,3]
- There are two Health Canada approved pharmaceutical cannabinoid products:
    - Nabiximols (Sativex®) is an oromucosally delivered spray prepared from extracts of *Cannabis sativa* (standardized 27 mg/ml delta-9-THC and 25 mg/ml cannabidiol). It is approved in Canada for advanced cancer pain and Multiple Sclerosis (MS) associated pain and spasticity.[1,2]
    - Nabilone (Cesamet® and generics) is a synthetic analogue of THC which is approved in Canada for the treatment of chemotherapy induced nausea and vomiting.[1,2]

QUESTION 1: IS THERE EVIDENCE OF EFFICACY FOR CANNABINOIDS OR CANNABIS IN THE MANAGEMENT OF ACUTE PAIN?

- A 2017 SR evaluated the analgesic efficacy of cannabinoid medication in the management of acute pain (7 RCTs, N=611). The SR concluded that there is no benefit of cannabinoid use compared to placebo or other active comparators in acute pain management (post-surgical pain) (moderate quality evidence).[4]
    - Nabilone was evaluated in 1 trial, all other comparisons were with products that are not available on the Canadian market.[4]
        - The nabilone trial demonstrated analgesia that was inferior to placebo. The remaining 4 RCTs that evaluated oral cannabinoids reported similar analgesic effects between cannabinoids and placebo.[4]
        - 2 RCTs evaluated IM levonantradol; 1 found no difference between levonantradol and placebo and 1 found that analgesia was with an IM levonantradol was superior to placebo.[4]
    - The dosing administration times varied amongst studies, with some products were administered within hours to days post-surgery while others were administered preoperatively and postoperatively.[1] T he longest duration trial was over 24 hours postoperatively.[4]
    - Two studies evaluated third molar tooth extraction while the other studies included different surgery types (e.g., gynecology, plastic, renal surgery, etc.).[4]
    - There was substantial heterogeneity among the included studies (due to varying cannabinoid products, dosing, dosing administration, pain assessments, populations, surgery types, etc.).[4]
- There are no clinical trials evaluating the efficacy of cannabis in patients experiencing acute pain.

QUESTION 2: WHAT IS THE EVIDENCE OF SAFETY FOR CANNABINOIDS IN ACUTE PAIN?

- The SR found that 5 of 7 RCTs reported more AE with cannabinoid medications compared to placebo when administered for a short duration of time for acute pain. Most AE were reported as mild to moderate in severity.[4]
    - The results varied amongst the included studies. Evaluating AE were difficult due to differences between studies in reporting and defining AE.[4]

Guideline statement:

- The College of Family Physicians published a guideline for prescribing medical cannabinoids in primary care in 2018. The guidelines strongly recommend against use of medical cannabinoids for acute pain management owing to evidence of no benefit and known harms (strong recommendation).[5]
    - In these guidelines, medical cannabinoids included pharmaceutically derived cannabinoids (e.g. nabilone and nabiximols) and medical cannabis.[5]

Additional points to consider with the use of cannabis and cannabinoids:

- There are a known contraindications, side effects and drug interactions both with pharmaceutical cannabinoids and cannabis. Contraindications that apply to the use of prescription cannabinoid-based therapies also apply to the use of cannabis, especially THC-predominant cannabis.[1]
- Cannabis can affect the cardiovascular, gastrointestinal, ophthalmologic, psychiatric, respiratory, and the central nervous system.[1,2] The psychiatric effects of cannabis use include anxiety, fear, distrust, paranoia, and panic.[1,2]
- AE are common. A 2018 SR of MAs assessed the AE of medical cannabinoids when used in the treatment of chronic pain, spasticity, or nausea and vomiting.[6]
    - 5 MAs evaluated overall AE and all 5 reported SS results (NNH = 5 to 8).[6]
    - 5 of 8 MAs showed SS increased withdrawal due to AEs (NNH = 8 to 22).[6]
    - There were also specific AEs in MAs with SS results such as "feeling high" (NNH 2 to 4), sedation (NNH 5), and disorientation and confusion (NNH 15), among others.[6]
    - RCTs enrolling cannabinoid-naïve patients had more frequent reports of psychosis compared to RCTs enrolling patients with past cannabinoid use.[6]
- According to Health Canada Guidelines cannabis should not be used in patients:[1]
    - Under the age of 25. [1]
    - With a history of hypersensitivity to any cannabinoid or to smoke.[1]
    - With severe cardiovascular or cerebrovascular disease, respiratory disease, severe liver disease, or severe renal disease.[1]
    - With a history of psychiatric disorders or a familial history of schizophrenia.[1]
    - With a history of substance abuse including alcohol abuse.[1]
    - Women not on a reliable contraceptive, those planning to become pregnant, are pregnant, or are breastfeeding[1]
- Heavy machinery use and driving are prohibited under cannabis influence as cannabis use can result in somnolence (7%), dizziness (3–10%), confusion, "high" state (euphoria, relaxation, distorted perception), decreased reactivity, and psychomotor impairment.[2]
- Cannabis use can lead to tolerance, dependence, and withdrawal.[1,2]
- Cannabis may also be involved in pharmacokinetic and pharmacodynamic interactions with other medications and substances.[1] These interactions likely vary in their clinical significance given the wide variability in products, potencies, ratios of THC and CBD, doses, routes of administration, populations using cannabinoids and other factors.[1] Some of the more clinically significant interactions may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol.[1]
    - Drug interaction databases such as Lexicomp and Micromedex include pharmaceutical cannabinoids, cannabidiol and cannabis.[7,8] Health care professionals with access to these databases should check for drug interactions for patients taking these products.

- More information on the health effects, harms, contraindication and drug interactions of cannabis and cannabinoids, along with appropriate monitoring of patients using cannabis can be found in the following resources:
  - RxFiles Cannabinoids Overview: CANNABINOIDS-Newsletter-CHT-QandA-RxFiles.pdf
  - CADTH Evidence Tool for Clinicians: https://cadth.ca/sites/default/files/pdf/htis/2020/Cannabis%20evidence%20tool%20for%20clinicians.pdf
- Communication with patients who are interested in starting cannabis, or are using cannabis recreationally for the treatment of pain is important. The following link provides a resource for patient information to assist patients in making informed decisions:
  - The RxFiles: Cannabis, questions about cannabis and the answers that may surprise you: Cannabis-Medical-Patient-Booklet.pdf (rxfiles.ca)

Bottom line:

- Cannabinoids have a lack of efficacy in the treatment of acute pain. Clinical trials have not evaluated cannabis in patients experiencing acute pain.
- The 2018 College of Family Physicians guideline for prescribing medical cannabinoids in primary care strongly recommend against the use of medical cannabinoids for acute pain management owing to evidence of no benefit and known harms (strong recommendation).
- AE with cannabinoids and cannabis are common. Patients should be informed of the potential risks associated with cannabis use.

Prescriber Resources and Patient Information

Practitioner Resources:	Patient Resources:
CADTH Cannabis Evidence Bundle: https://www.cadth.ca/evidence-bundles/medical-cannabis-evidence-bundle **Health Impacts of Cannabis (Canadian Centre on Substance Use and Addiction):** https://www.ccsa.ca/research-cannabis **Canada's Lower-Risk Cannabis Use Guidelines:** Evidence Brief_ENG_APR-29-19.indd (canada.ca) **Government of Canada: Cannabis Education Resources:** https://www.canada.ca/en/services/health/campaigns/cannabis/education-resources.html **Canadian Medical Association - Cannabis:** https://www.cma.ca/cannabis **Canadian Public Health Association – Resources:** https://www.cpha.ca/resources **Information for Health Care Professionals: Cannabis and the Cannabinoids:** For health care professionals: Cannabis and cannabinoids - Canada.ca **Canadian Family Physicians: Simplified guideline for prescribing medical cannabinoids in primary care**. Simplified guideline for prescribing medical cannabinoids in primary care | The College of Family Physicians of Canada (cfp.ca)	**Government of Canada: Cannabis Education Resources:** https://www.canada.ca/en/services/health/campaigns/cannabis/education-resources.html **Canadian Medical Association- Lower risk cannabis use postcard:** Cannabis & Your Health/Le cannabis et votre santé (cma.ca) **Canadian Medical Association- Lower risk cannabis use borhure:** 10 WAYS to Reduce Risks to Your Health When Using Cannabis (cma.ca) **Canadian Medical Association – Lower risk cannabis use youth brochure:** the Blunt Truth Useful tips about safer ways to use cannabis (cma.ca)

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OPIOID PRESCRIBING PRINCIPLES

BACKGROUND

- The Government of Canada considers the opioid crisis a "complex public health issue".[1]
  - Opioid overdoses have increased in Canada due to high opioid prescribing rates and the illegal use of potent synthetic opioids (e.g., fentanyl and carfentanil).
  - There were greater than 14,700 opioid overdose-related deaths in Canada between January 2016 and September 2019.

- Opioid use and overdose deaths have also been an ongoing concern in Nova Scotia, with 59 reported opioid-related deaths in 2019.[3] This is an increase from 54 deaths in 2018, but a decrease from 63 in 2017.[3]
  - As of November 2020, there have been 20 confirmed opioid-related deaths in Nova Scotia in 2020.
  - In response to the opioid crisis, the Nova Scotia government developed the Nova Scotia Opioid Use and Overdose Framework in 2017.[4]This framework outlines key focus areas for effectively responding to the opioid crisis including understanding the issue, prevention, harm reduction, treatment and prescribing practices, and criminal justice and law enforcement.
  - As part of the harm reduction strategy, access to free naloxone kits is provided in Nova Scotia through the Nova Scotia Take Home Naloxone Program.[3] Over 15,400 naloxone kits have been dispensed since January 2016, with 149 reported opioid overdose reversals.
  - Educational resources for practice change in opioid prescribing are a key component of Nova Scotia's multi-phase Opioid Use and Overdose Framework.

ACUTE PAIN MANAGEMENT AND OPIOID PRESCRIPTIONS

- Many individuals receive their first opioid prescription for acute pain.[5] There is concern for these patients because of the risk of acute use turning into chronic use of opioids.[6]

- Acute pain typically presents for less than three months and is caused by trauma, surgery, or damage to tissues.[7,8]

- Acute pain conditions include acute flares of osteoarthritis, acute migraine headaches, post-surgical, dental, acute musculoskeletal, and low back pain.

- The characteristics of initial opioid prescriptions and the likelihood that they would lead to long-term opioid use was described in a CDC Morbidity and Mortality Weekly Report.[5]

- The CDC report included a sample of opioid naïve, cancer-free adults who were followed from the date of their first prescription until loss of enrollment, study end date, or discontinuation of opioids (≥ 180 days opioid free).
- Within the first few days of opioid use, particularly with > 3-5 days of use, the risk for chronic opioid use was increased.
    - The likelihood of chronic opioid use increased with each additional day of medication supplied, starting with the third day. The sharpest increases in chronic opioid use were observed after the fifth and thirty-first day on therapy, following a second prescription or refill, with cumulative dose ≥700 morphine milligram equivalents, and an initial 10- or 30-day supply.

➢ A 2020 systematic review of observational studies found that in high risk patients (defined as patients receiving wage replacement or workers' compensation benefits, Veterans Affairs claimants, and those with comorbid substance use disorder) prolonged opioid use following an initial prescription for acute musculoskeletal injury was 27% compared to 6% in the general population.[9]

- Past or present substance use disorder was associated with prolonged opioid use (low certainty evidence grading), as were older age and greater physical comorbidity (moderate certainty evidence)
- Additionally, four prescribing factors identified by several studies were associated with increased risk of prolonged opioid use:
    - Prescribing opioids > 7 days
    - Higher morphine milligram equivalent dose
    - Long-acting versus short-acting opioids
    - > 1 refill in the first month
- The authors of the systematic review recommend restricting opioid prescriptions for acute musculoskeletal injuries to < 7 days, using lower doses, and not prescribing opioids in those with past or current substance use disorder potentially help to reduce prolonged opioid use.

➢ A prospective analysis of high school students showed a 33% increase in the risk of opioid use after high school in students who had been prescribed an opioid prior to the 12th grade.[10]

➢ *CDC Guidelines:*

- The CDC guidelines for opioid prescribing in chronic pain suggest high risk practices, such as long-acting opioid prescriptions for acute pain, concomitant opioid and benzodiazepine prescribing, and prescribing high opioid doses have led to increasing numbers of opioid overdoses.[6]
- The CDC Guidelines state that "**fewer days"** supply will minimize the number of pills available for **unintentional or intentional diversion**."

- *Clinician Confidence:*
  - Clinicians have admitted to lacking confidence in prescribing opioids safely and in detecting aberrant use.[6]
  - Resources addressing opioid prescribing practice can foster practice change and improve patient care and safety.[6]

ROLE OF OPIOIDS IN SPECIFIC ACUTE PAIN CONDITIONS

The evidence-based role of opioids in the acute pain conditions included in this Academic Detailing document are presented in this section. For details of the included evidence please see the individual sections for each of these conditions.

ACUTE MUSCULOSKELETAL PAIN

- Based on limited low-quality evidence from systematic reviews of randomized controlled trials, there is no difference between oral nonsteroidal anti-inflammatory drugs (NSAIDs) and other oral analgesics (acetaminophen or opioids) in pain reduction for individuals with acute musculoskeletal pain (strains, sprains, contusions and soft-tissue injuries).[6,11]

- The evidence-based guidelines published in the British Medical Journal on the diagnosis, treatment, and prevention of ankle sprains (2018) only include NSAIDs as pharmacological therapy for reducing pain and swelling.[12]

- The 2020 Nonpharmacologic and Pharmacologic Management of Acute Pain from Non-Low Back, Musculoskeletal Injuries in Adults: A Clinical Guideline From the American College of Physicians and American Academy of Family Physicians recommends NSAIDs for pain reduction and function improvement and acetaminophen for pain reduction, based primarily on a 2020 network meta-analysis by Busse and colleagues .[13,14] The guidelines recommend against opioids for acute musculoskeletal injury pain treatment due to lack of a benefit compared to NSAIDs and acetaminophen and increased harms (GI and neurological).[13]

POST-SURGICAL PAIN

- There is evidence from meta-analyses that the use of NSAIDs or NSAIDs plus acetaminophen in postoperative pain reduce opioid consumption and improve outcomes on pain scores.

- One of the main principles for post-surgical acute pain management is the utilization of a multimodal approach to reduce the reliance on opioids. Clinical practice guidelines recommend patients be treated with acetaminophen and an NSAID (unless contraindicated).[15-18]

- The multimodal approach assumes the use of opioids for many postsurgical patients in addition to non-opioid analgesics. However, guidelines note that systemic **opioids may not be required in all patients**.
- For patients with mild to moderate pain after surgery, it may be appropriate to discharge patients on acetaminophen and/or NSAIDs only**.**
- If opioids are prescribed after surgery, patients should be instructed to fill the prescription only if their pain is not well managed with other therapies or they are having difficulty completing activities of daily living secondary to pain.

ACUTE LOW BACK PAIN

- Evidence for the use of opioids in acute low back pain is lacking. The 2017 American College of Physicians (ACP) evidence based guidelines suggest there is insufficient evidence to determine the effectiveness of opioids vs. placebo in the treatment of acute low back pain. Therefore, ACP guidelines provide no recommendation for the use of opioids.[19]

- Resources that do provide a recommendation for the use of opioids in acute low back pain include notes of caution stating that routine use is not recommended, use should be of short duration and only used if alternative therapies such as NSAIDs are contraindicated or ineffective.[20-22]

- Choosing Wisely Canada, Opioid Wisely resources note the most common entry point to prescription opioid addiction is through opioids prescribed for back pain.[23] Adequate pain control using opioids is frequently not achieved and patients face the added risks of physical dependence, withdrawal, and opioid-induced hyperalgesia, which can lead to continued use of the opioid.
    - **Statement:** Don't use an opioid analgesic medication as first-line treatment for acute, uncomplicated, mechanical, back-dominant pain.

- Opioids should not routinely be offered for treatment of acute low back pain. Opioids should only be considered if other effective pharmacologic and non-pharmacologic treatment options fail or are not appropriate.[19-21,23]
    - Patients should be informed that acute low back pain often improves over time regardless of treatment.

Bottom line: For treatment of acute low back pain, cautious use of opioids should be considered only if other effective pharmacologic and non-pharmacologic treatment options fail or are not appropriate. If opioids are used, a short duration (e.g., 3 days) is recommended. Patients should be informed that acute low back pain often improves over time regardless of treatment.

KEY OPIOID PRESCRIBING PRINCIPLES IN ACUTE PAIN

GOALS OF THERAPY:

- A pain-free outcome may not be possible for all acute pain conditions.
- Clinically meaningful reductions in acute musculoskeletal pain vary in clinical trials and are based on the pain assessment method used.
- A decrease in pain intensity in the absence of improved function is not considered meaningful improvement except in very limited circumstances such as catastrophic injuries (e.g. multiple trauma, spinal cord injury, etc.).[18]
- The goal of post-surgical pain management is not to be pain free, but to reach a mild level of pain such that daily activities are manageable while recovering. [15,17,18]
- Goals of pharmacotherapy for acute low back pain are to reduce pain intensity, increase activity, and improve function. Based on data from clinical trials studying commonly used back pain outcome measures, a 30% change from baseline may be considered a clinically meaningful improvement when comparing individual patients.[24]

RISK ASSESSMENT:

- To reduce chronic opioid use and/or opioid use disorder, risk mitigation strategies should be in place.
- As recommended by the CDC guidelines and the Institute for Safe Medication Practices Canada, whenever possible benzodiazepines and opioids should not be concomitantly prescribed due to the increased risk of fatal overdose.[6,25]
- Other substances that may affect the central nervous system (CNS) should be taken in account when considering opioid prescribing (e.g., alcohol, cannabis, cocaine, anticholinergics, etc.).[26]
- The use of gabapentin or pregabalin with opioids may also lead to increase adverse effects (e.g. respiratory depression) and opioid overdose, based on a Health Canada advisory statement.[27]
- It is recommended that prescribers check eAccess on the Nova Scotia Prescription Monitoring Program website (http://www.nspmp.ca) for recent or current use of opioids and all monitored drugs prior to writing an opioid prescription.
- It is also recommended to check the Nova Scotia Drug Information System (DIS) (https://novascotia.ca/dhw/ehealth/dis/) for other medications that the patient may be taking.

The College of Physicians and Surgeons of Nova Scotia (CPSNS) have established professional standards regarding the initiation of opioid therapy in acute pain.[28]

CPSNS Professional Standards

When opioids are considered for acute pain management, they must be prescribed only when necessary, in the lowest effective dose, and for the shortest duration required. Three days will often be sufficient; more than seven days will rarely be needed. (*CDC Guidelines for Prescribing Opioids for Chronic Pain).*

Physicians must:

1. perform and document a relevant and appropriate clinical assessment;
2. assess the patient's level of pain and consider multimodal treatment measures for pain control including non-narcotic analgesics, adjunctive medications, and non-pharmacology therapies;
3. screen for risk factors for opioid misuse and use caution when prescribing opioids for these patients;
4. check the Nova Scotia Prescription Monitoring Program (NSPMP) for the medication profile of patients before prescribing opioids;
5. explain treatment goals, duration of therapy, side effects, risks, benefits, and harms of opioids and document informed consent;
6. initiate opioid treatment for acute pain with immediate release opioids and avoid use of long acting or extended release formulations;
7. not exceed a seven-day supply of opioid medications unless extenuating circumstances are clearly documented in the medical record or the patient has been reassessed;
8. collaborate and communicate with the patient's health care team;
9. avoid prescribing opioids and benzodiazepines concurrently whenever possible – document your reasons for concurrent prescribing of these medications as concurrent prescribing is generally contraindicated;
10. use caution in prescribing sedative hypnotics, carisoprodol, and tramadol concurrently with opioids; and
11. inform patients how to safely and securely store opioids and dispose of any unused supply.

- The CSPNS professional standards note that the risk of inappropriate opioid use may be greater in patients with:
  - Personal history of substance use disorder involving any substance, including alcohol;
  - Family history of substance use problem or addiction;
  - Concomitant psychiatric problems or diagnosis;
  - Concomitant use of other psychiatric medications, benzodiazepines, other prescription opioids;
  - Exposure to physical, sexual, or emotional abuse or trauma especially at young age;

- Duration of days of the initial opioid prescription (greater number of days associated with continuation of opioid therapy); and
- Higher morphing milligram equivalents per day (use lower doses if prescribed.

- A 2019 systematic review evaluated factors associated with opioid addiction as well as screening tools for identifying adult patients with either high or low risk of developing symptoms of prescription opioid addiction. The review found few quality studies are available and concluded no specific symptoms, signs, or screening tools were particularly useful for identifying those at lower risk.[29]

OPIOID PRESCRIBING THRESHOLDS

- In most circumstances, opioids are not recommended for general acute pain treatment.

- If opioids are prescribed for the treatment of acute pain, the **lowest effective dose** of an **immediate release** opioid for the **shortest duration** is suggested by several guidelines including the CDC Guideline for prescribing opioids for chronic pain and the AMDG Interagency Guideline on Prescribing Opioids for Pain.[18]
    - *"Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids."*

- Controlled release formulations are not recommended.
    - Long-acting opioids have been shown to significantly increase the risk of both overdose and long-term opioid use.[5,30,31]

Dosage:

- The CDC chronic pain guidelines state that "clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day." [5]
    - "When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should start opioids at the lowest possible effective dosage (utilizing the lowest starting dosage on product labeling for patients not already taking opioids)." "Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels."

- The CDC guidelines also state that "long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids".[5]

- The Canadian chronic pain guidelines also recommend the same thresholds when starting long term opioid therapy.[32]

    - Recommendation 6: "for patients with chronic non-cancer pain who are beginning long-term opioid therapy we recommend restricting the prescribed dose to **less than 90mg morphine equivalents daily** rather than no upper limit or a higher limit on dosing." (strong recommendation)
    - Recommendation 7: "for patients with chronic non-cancer pain who are beginning opioid therapy, we suggest restricting the dose to **less than 50mg morphine equivalents daily**." (weak recommendation)
        - The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.
    - Observational studies in patients taking chronic opioid therapy have found a progressive increase in the risk of unintentional non-fatal and fatal overdose with increasing doses. These serious outcomes are rare in those prescribed < 50 MED, but increase in those prescribed doses of 50 – 90 MED, and though still rare, are increased in those prescribed doses > 90 MED. [32]
    - Note: Common opioid prescriptions may exceed these thresholds. See *Table 1*

Table 1: Examples of prescriptions seen in community pharmacies for acute/post-surgical pain

Drug and Strength:	Common Instructions:	Morphine Equivalents/24 hours at maximum dose based on SIG
Hydromorphone 2mg	Take 1-2 tablets PO q4-6 hours PRN	120mg
Tylenol #3 (Acetaminophen 300mg,codeine 30mg, caffeine 15mg)	Take 1-2 tablets PO q 4-6 hours PRN	54mg
Percocet (acetaminophen 325mg and oxycodone 5mg)	Take 1-2 tabs PO q4-6 hours PRN	90mg

See Acute Pain Drug Tables in Appendix 1 for morphine equivalent dose conversions for select opioids and for information on starting doses in opioid naïve patients.

Duration:

- ≤ 3 days opioid quantity is appropriate for most acute pain based on the CDC guidelines and general consensus and > 7 days opioid quantity is rarely required for non-traumatic, non-surgical acute pain.[5] **Do not** prescribe more than the required quantity of opioid

for acute pain management. Do not prescribe additional quantities to have "on-hand" in case pain does not improve beyond the expected time-frame. The College of Physicians and Surgeons of NS' *Professional Standards Regarding Initiation of Opioid Therapy for Acute Pain* (see figure above) states that "three days will often be sufficient; more than 7 days will rarely be needed." Professional standard #7 within this document states that physicians must "not exceed a seven-day supply of opioid medications unless extenuating circumstances are clearly documented in the medical record or the patient has been reassessed."[28]

Bottom line: Most acute pain conditions will not require treatment with an opioid. If an opioid is deemed necessary, three days or less is sufficient. Prescriptions greater than 7 days will require a thorough patient assessment, documentation, and should be given as part fills to limit supply on hand and allow for regular reassessment of opioid need.

** Doses ≤50 mg morphine equivalents per day have been studied in chronic pain and shown to be associated with **lower risk of overdose.**[32] Most acute pain conditions can be managed with doses significantly lower than 50 mg morphine equivalents per day morphine equivalents.

- The duration of opioid therapy after surgery should be based on the expected rate of recovery and level of pain severity in patients already receiving multimodal therapy with acetaminophen and an NSAID (unless contraindicated).[15,17,18]

- Post-surgical guidelines and consensus statements have grouped surgeries by different durations of recovery. Examples of recovery time are provided in *Table 2*.

Table 2. Example of Post-surgery expected rate of recovery

	Rapid recovery	Medium-term recovery	Longer-term recovery
Procedure	• Dental procedures (extractions or simple oral surgery) • Laparoscopic appendectomy • Inguinal hernia repair • Carpal tunnel release • Thyroidectomy • Laparoscopic cholecystectomy • Breast biopsy/lumpectomy • Meniscectomy • Lymph node biopsy • Vaginal hysterectomy	• Anterior cruciate ligament (ACL) repair • Rotator cuff repair • Discectomy • Laminectomy • Open or laparoscopic colectomy • Open incisional hernia repair • Open small-bowel resection or enterolysis • Wide local excision • Laparoscopic hysterectomy • Simple mastectomy • Cesarean section	• Lumbar infusion • Knee replacement • Hip replacement • Abdominal hysterectomy • Axillary lymph node resection • Modified radical mastectomy • Ileostomy/colostomy creation or closure • Thoracotomy

Reference: *Agency Medical Directors' Group (AMDG). Summary of Opioid Prescribing Practices for Perioperative Pain. FY19-217 (11-2018). Available from http://www.agencymeddirectors.wa.gov/Files/FY19217SummaryOpioidPrescPerioperativePain.pdf.*

- Post-surgical guidelines and consensus statements have used the expected rate of recovery as a guide to provide a framework for the duration of opioid therapy, along with number of pills (see *Table 3*)

Table 3: Recommended duration and quantity of opioid pills after surgery based on the expected rate of recovery

Washington State AMDG 2018 Supplement	2020 Canadian Consensus Statement
• Only use in severe pain. • If the expected rate of recovery is rapid, prescribe ≤ 3 days (e.g. 8-12 pills). • If a medium term recovery is expected, prescribe ≤ 7 days (e.g. up to 42 pills). • If the expected rate of recovery is delayed, prescribe ≤14 days. • For those exceptional cases that warrant more than 14 days of opioid treatment, the surgeon should re-evaluate the patient before refilling opioids and taper off opioids within 6 weeks after surgery. • These numbers are based on data showing that opioids prescribed as above are adequate to treat postoperative pain in >75% of patients without refills. • Very few patients with an expected medium term recovery require longer than 7 days of therapy. • Use opioids on a PRN basis. • Avoid routine prescribing of the number of pills that equals the total allowable maximum dosing. • Patients are expected to need less frequent dosing as pain resolves and need a lower number of pills (as little as half) for a specified timeline.	• Patients with an expected rapid recovery (resume regular activities within 2 weeks from discharge) should be prescribed enough opioid for 0–3 days following discharge (maximum 12 tablets). • Patients with an expected moderate recovery (resume regular activities within 4 weeks from discharge) should be prescribed opioids for a maximum of 7 days following discharge (maximum 30 tablets). • Patients with an expected long-term recovery (resume regular activities longer than 4 weeks from discharge) should be prescribed opioid for a maximum of 14 days following discharge (maximum 60 tablets). • A part-fill or second prescription should be given to patients with an expected moderate or long term recovery to reduce the number of opioid containing tablets distributed at one time. • Do not prescribe an opioid to patients who have not received any in the last 24 hours of hospital stay. • Day surgery patients should be prescribed medications based on an expected rapid recovery.

PROVIDING INFORMATION/PATIENT COUNSELLING:

- Communicate realistic goals of therapy (as outlined above) with patient.
- If you do not feel that opioids are the best analgesic option for your patients' pain, please refer to *Table 4* for some key communication points.
- If opioids are considered, provide patients and families with adequate information about the benefits and the risks of opioid use, to ensure that patients can make informed decisions about their care.[33]
  Examples of *patient information sheets* are provided below:
  - https://www.ismp-canada.org/download/OpioidStewardship/Opioids-ShortTermPain-EN.pdf [34]
  - https://www.ismp-canada.org/download/OpioidStewardship/opioid-handout-bw.pdf
  - https://choosingwiselycanada.org/wp-content/uploads/2018/02/Opioids-When-you-need-them-and-when-you-dont.pdf [23]
  - https://medlineplus.gov/safeopioiduse.html [35]
  - https://www.hqontario.ca/portals/0/documents/evidence/quality-standards/qs-opioid-acute-pain-patient-guide-en.pdf [33]
  - https://www.cdc.gov/drugoverdose/pdf/AHA-Patient-Opioid-Factsheet-a.pdf [5]

- Counsel patients on non-pharmacological pain management in addition to pharmacological pain management, whenever appropriate (see specific condition sections within this document for evidence on non-pharmacological therapy).

- Patients should be counselled on potential adverse effects to any opioids.
    - *Clinical Expert Opinion: Adverse effects like euphoria and increased energy may indicate a higher risk for OUD. Encourage patients to report these adverse effects to their health care provider.*

- Counsel patients on safe storage and disposal of narcotic medications. Opioid medications should be stored in a location that is secure and outside of reach of children and/or pets. Excess unused opioid medications should be returned to a pharmacy for safe disposal.

- Counsel patient on dangers of prescription opioid diversion. Sharing is never appropriate and is illegal.[18]

- For surgical patients inform the patient and family which provider will be responsible for managing postoperative pain, including who will be prescribing any opioids. Instruct the patient and family on the planned taper of postoperative opioids.
    - Inform patients that opioids should only be used for a limited duration of time. With improved healing expected each day the requirements for opioids are expected to be reduced with time.

- All patients with non-specific low back pain should be offered information on the nature of low back pain, reassurance about the likely low risk of serious underlying disease and advice on evidence based self-management.[36]

- Leverage the clinical expertise of the patient's community pharmacist.
    - A narrative review of programs that used community pharmacists to prevent, identify, and treat opioid use disorder showed benefit in identifying issues around appropriate prescribing, aberrant use, and development of OUD. The review showed that when prescribers work with pharmacists, opioid stewardship was more successful.[37]

NALOXONE KITS:

Respiratory and central nervous system depression are known adverse effects of all opioids. Therefore, all patients taking opioids are at risk of overdose.[32] Even offering the kit can lead to increased vigilance on the part of the patient and their family. As such, all patients can be offered a naloxone kit, especially those at higher risk of overdose (e.g. taking other CNS depressants, history of opioid overdose, etc). Naloxone kits are available at all community pharmacies in NS and through the Take Home Naloxone Program http://www.nsnaloxone.com/

FOLLOW-UP:

- Re-evaluate patients whose acute pain condition does not improve or worsens beyond the expected time frame of improvement.[5]

- Always evaluate for reversible causes of pain.

- Have a plan for how and when to discontinue opioids if treatment has not resulted in clinically meaningfully improvement in function and pain or the patient has had a severe adverse outcome.[18]

- Strongly consider tapering the patient off opioids as the acute pain episode resolves. Taper opioids by 6 weeks if clinically meaningful improvement in function and pain has not occurred.

- After surgery, use an agreed upon preoperative plan to taper off opioids as healing takes place. The goal is always the shortest duration and lowest effective dose:
    - Patients who are unable to taper opioids to coincide with expected healing or who report pain severe enough to warrant ongoing opioid use after the procedure-specific usual number of days require re-evaluation.
    - If more than 7 days of opioid treatment after surgeries with an expected medium term recovery or 14 days of opioid treatment after surgeries with an expected longer term recovery are required, the surgeon should re-evaluate the patient before refilling opioids and taper off opioids within 6 weeks after surgery.[17]

Table 4: How to talk to your patients about opioid prescriptions

This table was adapted with permission from A Crawley BSP, L Regier BSP. PRESICRBING OPIOIDS SAFELY: An Approach. RxFiles. February 2020

"*if you feel starting a prescription for an opioid might not be a good idea for your patient at any point in a condition, you have an opportunity to stop and communicate to the patient your concern and reasons around not initiating opioids. Although it may be uncomfortable at first to say no, in the long run you are doing your patient a great service and practicing compassionate, evidence-based medicine*." – Sarah Liskowich, MD, CCFP	
Use active listening skills. Sit with the patient to bring you to the same level. Listen to the patient's story, and reflect his/her words back to show that you're listening. Ask questions with a neutral tone. Does he or she perceive a large benefit with opioids? Are his or her expectations unrealistic (e.g. goal of "zero pain"?) Do opioids provide an "escape" from difficult life circumstances? Is there fear of withdrawal, or fear of unmanageable pain? Ensure your patient knows that you care about him/her, and want him/her to do well.	- *It sounds like there's a lot of stress in your life right now.* - *You're saying the pain is making you feel desperate and edgy.* - *I know you're going through a tough time right now, and I'm really sorry about that.*
Where possible, gather objective facts. These may include: pain scores over time, assessment of changes in function, adverse effects, previous history, risk of overdose or addiction (e.g. calculation of ORT scores), presence of pain catastrophizing (e.g. https://www.painbc.ca/sites/default/files/events/materials/Pain_Catastrophizing_Scale.pdf.) This is also where documentation of warning signs (e.g. requests for early refills, see Table 4) is important. Involving a colleague for a second opinion can also bring in valuable information. In the absence of objective facts, consider no therapy changes for a short period (e.g. 3 months) with clear criteria for how a decision will be made after that time.	- *It is my professional responsibility, in providing the best possible patient care, to only prescribe medications when it can be done safely.* - *I cannot in good conscience prescribe a medication that could harm or kill you.* - *You've told me Dilaudid works, but what else have you tried?* - *Before moving ahead, I will need to obtain and consider the initial assessment report regarding your accident and resulting injuries.* - *I haven't met you before, and can't prescribe these types of drugs on the first visit before I have a full history.*
Use the patient's history +/- objective facts to explain your decision. Sometimes focusing on the safety issues of opioids can be valuable (e.g. risk of overdose, presence of adverse effects). It is also helpful to reframe the goal from "pain relief" to "function restoration". It's OK to be honest and straightforward about your reasons for wanting to stop or avoid opioids; in fact, the situation can be viewed as an opportunity to educate patients.	- *It looks like opioids just won't work well for you. I have noticed that…* - *This opioid seems to be doing more to you, than for you.* - *When we first started opioids, your pain was not controlled. Now you are on a high dose of opioids and having side effects…but your pain is still not controlled. It might seem hard to believe, but if we pull back on the opioids you may actually feel better than you do now.* - *When I look at your medical history and other medical conditions, I worry that your risk of overdose with this medicine is just too high.* - *If we combine an opioid with your sleep apnea, it could slow your breathing too much, even to the point of stopping.* - *From what you've told me, I think stress is adding to your pain, and an opioid is not the best way to treat that problem.* -*In the long run, opioids will actually change the way your brain perceives pain. Numbing the pain for a while will make it worse when you finally feel it.*
If you are feeling emotionally pressured, or threatened, it's OK to excuse yourself from the room and/or confer with a colleague. Avoid responding to emotion with emotion, and avoid prescribing emotionally. Try to keep your feelings and the medical facts separated.	
Provide an alternate plan to show that you still support your patient. Encourage non-pharmacological therapies; offer non-opioid medications. Potentially, advise the patient that the pain may resolve on its own without opioids. Referring to a colleague for a second opinion may be helpful. Refer to an addictions medicine specialist if necessary. If discontinuing an opioid, provide reassurance that the opioid will be tapered slowly to prevent withdrawal symptoms and adjuvants prescribed as needed. Aim to be polite but firm!	- *We've talked about some options that may help you control your pain. Out of all those, what would you like to try?* - *There is a strong connection between feeling down and pain, so would you be willing to meet with our mental health specialist?* - *In the meantime, let's work together with your pharmacist on a gradual tapering plan.* - *I know you can do this, and I'll stick with you through it.*

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APPENDIX 1: Acute Pain Drug Tables and Prescribing Considerations

Table 1a. Select Non-Opioid Analgesics for Acute Pain (Oral & Topical)

Name *Trade,* generic	Strength	Adult Dose (Product & CPhA Monographs)	Dose Adjustments (Lexi-Drugs)	Adverse Events	Nova Scotia Pharmacare Status	Cost (McKesson or NS Pharmacare)
ACETAMINOPHEN						
Acetaminophen *Tylenol*, generics	325 mg 500 mg 650 mg (ER)	325-650 mg q4–6h prn 1 g q6h (Extra Strength) 1.3 g q8h prn (ER) **MAX**: 4 g/day	Hepatic: Use with caution (Limited data) Hepatic disease/cirrhosis: ≤2–3 g/ day Hepatic disease/cirrhosis ***and*** active alcohol use: AVOID if possible. Limit to short courses of ≤ 2 g/day Renal: GFR 10–50 mL/min: q6h, GFR <10 mL/ min: q8h	Well tolerated Liver toxicity in higher doses	Not a benefit	$0.03/caplet (325 mg and 500 mg)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ORAL						
Celecoxib *Celebrex*, generics	100 mg 200 mg	400 mg single dose on the first day, then 100–200 mg daily prn **MAX**: 200 mg/day (CV disease, risk factors for CV disease); 400 mg/day	Hepatic: Moderate impairment: ↓ dose by 50% Severe impairment: AVOID Abnormal LFTs (persist/worsen): discontinue Renal: Not recommended in severe impairment and advanced disease	CV: elevated blood pressure, edema CNS: dizziness, hallucinations GI: dyspepsia, ulcer Liver: elevated liver function tests (LFTs) Renal: fluid retention, renal toxicity, increased risk of acute kidney injury in combination with a diuretic and ACEi or ARB	Full Benefit	$0.13-0.25/cap
Diclofenac Potassium *Voltaren Rapide,* generics	50 mg	50 mg q6-8h prn **MAX:** 100 mg/day	Hepatic: No specific dose recommendations. AVOID in patients with severe liver impairment or active liver disease Renal: GFR 30–60 mL/min: reduce the dose GFR <30 mL/min: AVOID		Not a Benefit	$0.39/tab
Diclofenac Sodium *Voltaren,* generics	25 mg, 50 mg 75 mg 100 mg	25 mg TID prn **MAX:** 100 mg/day			Full Benefit	$0.08-0.41/tab
Ibuprofen *Advil, Motrin*, generics	200 mg, 300 mg 400 mg 600 mg	200–400 mg TID–QID prn **MAX:** 1200-2400 mg/day			Full Benefit 300–600 mg tablets	$0.04-0.13/tab
Naproxen *Naprosyn,* generics	250 mg 375 mg 500 mg	250-500 mg BID-TID prn **MAX:** 1500 mg (for limited periods)			Full Benefit	$0.11-0.14/tab
Naproxen Sodium *Aleve*, *Anaprox,* generics	220 mg 275 mg 550 mg	220 mg q8-12h prn **MAX:** 440 mg/day (OTC) 550 mg loading dose, then 275 mg q6-8h prn **MAX:** 1375 mg/day (by prescription)			Full Benefit	$0.05-0.35/tab
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) TOPICAL						
Diclofenac sodium solution 1.5% *Pennsaid*, generics		40 drops topically QID	Hepatic: No specific dosage adjustment. Use with caution Renal: AVOID in advanced renal disease NOTE: Use of topical diclofenac with oral NSAIDs is contraindicated in Canada	Local skin reactions; monitor for NSAID related adverse drug reactions	Not a Benefit	$37.36 (60 mL)
Diclofenac diethylamine gel 1.16%, 2.32% *Voltaren Emugel*		1.16%: 2–4 g TID-QID. 2.32%: 2 g BID **MAX:** 4 g/24 h (2.32%) NOTE: 2–4 g= 4–8 cm			Not a Benefit	$6.34 (30 g 2.32%)

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, BID: twice per day, CPhA: Canadian Pharmacists Association, CNS: central nervous system, CV: cardiovascular, ER: extended release GFR: glomerular filtration rate, LFT: liver function test, q: every, OTC: over the counter, prn: as needed, QID: four times per day, TID: three times per day

- See 'Prescribing Considerations' at the end of tables
- For additional prescribing information, see product monographs. For information on other NSAIDs, see product monographs.

Last updated: January 2021

Table 1b. Select Skeletal Muscle Relaxants for Acute Low Back Pain						
Name *Trade,* generic	**Strength**	**Adult Dose** (Product Monographs)	**Dose Adjustments** (Lexi-Drugs)	**Adverse Events**	**Nova Scotia Pharmacare Status**	**Cost (McKesson or NS Pharmacare)**
Cyclobenzaprine generics	10 mg	5-10 mg TID prn **MAX:** 30 mg/24 h	Hepatic: Caution in mild impairment, start lower initial dose. Avoid in moderate to severe cases	Drowsiness, fatigue, dizziness, anticholinergic effects	Full benefit	$0.11/tab
Methocarbamol/ ASA *Robaxisal Extra-Strength,* generics	400/500 mg	2 caplets q6h prn **MAX:** 8 caplets/24 h	Renal: (ASA) Do not use in CrCl <30 mL/min	Lightheadedness, dizziness, drowsiness, mild nausea, constipation (codeine) **NOTE:** high ASA content (>3.6 g/day) more likely to cause GI AE (Ulcer, dyspepsia, heartburn, epigastric distress)	Not a benefit	$0.50/tab
Methocarbamol/ ASA/Codeine *Robaxisal C ½* *Robaxisal C ¼*	400/325/16.2 mg	1 caplet q6-8h prn **MAX:** 8 caplets/24 h				$1.07/tab
	400/325/32.4 mg	1 caplet q6-8h prn **MAX:** 8 caplets/24 h				$1.21/tab
Methocarbamol/ Acetaminophen *Robaxacet* *Tylenol Back Pain* generics	400/500 mg	2 caplets q6h prn **MAX:** 8 caplets/24 h	Hepatic: (Acetaminophen) Use with caution (Limited data) Hepatic disease/cirrhosis: ≤2–3 g/day Hepatic disease/cirrhosis ***and*** active alcohol use: AVOID if possible. Limit to short courses of ≤ 2 g/day Renal: (Acetaminophen) GFR 10–50 mL/min: q6h GFR <10 mL/min: q8h	Lightheadedness, dizziness, drowsiness, mild nausea, liver toxicity, constipation (codeine)	Not a benefit	$0.35-0.39/tab
Methocarbamol/ Ibuprofen *Robax Platinum* *Motrin Platinum* generics	500/200 mg	1-2 caplets q4-6h prn **MAX:** 6 caplets/24 h	Hepatic: (Ibuprofen) No specific dose recommendations. AVOID in patients with severe liver impairment or active liver disease Renal: (Ibuprofen) GFR 30–60 mL/min: reduce dose GFR <30 mL/min: AVOID	Dyspepsia, ulcer, elevated blood pressure, edema, fluid retention, renal toxicity, elevated liver function tests, dizziness, hallucinations	Not a benefit	$0.36/tab

Abbreviations: AE: adverse events, ASA: acetylsalicylic acid, CrCl: creatinine clearance, GFR: glomerular filtration rate, GI: gastrointestinal, MAX: maximum dose, q: every, QID: four times per day, TID: three times per day

- See 'Prescribing Considerations' at the end of tables
- For additional prescribing information, see product monographs.

Last updated: January 2021

Table 1c. Select Oral Opioids for Acute Pain								
Name *Trade,* generic	**Dosage Form/Strength**	**Starting Dose for Opioid-Naïve Adults**	**Dose Titration/Taper**	**Dose Adjustments** (Lexi-Drugs)	**Adverse Events**	**Nova Scotia Pharmacare Status**	**Morphine Equivalents** (50 mg/day)	**Cost (McKesson or NS Pharmacare)**
Codeine +/- **Acetaminophen** +/- **Caffeine** *Tylenol # 1, 2, 3, 4,* generics	• IR tab: 15 mg, 30 mg • Syrup: 5 mg/mL • Tab with 300 mg or 325 mg acetaminophen: 8, 15, 30, 60 mg	15-30 mg q4h prn* (codeine) T1, T2, T3 do not exceed 12 tabs/24 hours T4 do not exceed 6 tabs/24 hours	Adjust according to clinical response to lowest effective dose. Taper to avoid withdrawal symptoms if prolonged use required. Links: https://cep.health/media/uploaded/20180305-Opioid-Tapering-Tool-Fillable.pdf https://www.deprescribingnetwork.ca/tapering	Hepatic: use lowest possible dose Renal: use lowest possible dose Combination products with acetaminophen are contraindicated in severe hepatic and renal impairment. *Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history. Formulations with acetaminophen: **MAX:** 4 g/day	Constipation Nausea Opioid-use disorder Respiratory depression Sedation	Full benefit (T1 not a benefit)	334 mg/day	$0.02-0.37/tab
Morphine *Doloral, MS-IR, Statex,* generics	• IR tab: 5, 10, 20, 25, 30, 50 mg • IR cap: 5, 10, 20, 30 mg • Syrup: 1 mg/mL, 5 mg/mL	5-10 mg q4h prn *				Full benefit	50 mg/day	*Tablets:* $0.16-0.52/tab *Liquid:* $0.05/ml
Oxycodone +/- **Acetaminophen** *Oxy-IR, Percocet, Supeudol,* generics	• IR tab: 5, 10, 20 mg • Tab: 5 mg with 325 mg acetaminophen	5-10 mg q6h* (oxycodone)				Full benefit	33 mg/day	$0.12-0.79/tab
Hydromorphone *Dilaudid*, generics	• IR tab: 1, 2, 4, 8 mg • Syrup: 1 mg/mL	2-4 mg q4-6h prn*				Full benefit	10 mg/day	*Tablets:* $0.10-0.35/tab *Liquid:* $0.09/ml
Tramadol +/- **Acetaminophen** *Ultram, Tramacet*	• IR tab: 50 mg • Tab: 37.5 mg with 325 mg acetaminophen	25 mg once daily* (tramadol) **MAX:** 400 mg/day		Do not use in severe hepatic or renal impairment Formulations with acetaminophen: **MAX:** 4 g/day	As above + increased seizure risk when used with SSRIs, SNRIs, TCAs, or other tricyclic compounds	Not a benefit	300 mg/day	$0.63-0.64/tab

Abbreviations: IR: immediate release, MAX: maximum dose, prn: as needed, q: every, SNRI: serotonin-norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake-inhibitor, tab: tablet, TCA: tricyclic antidepressant

*Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

- Dosing obtained from product monographs
- See 'Prescribing Considerations' at the end of tables
- For additional prescribing information, see product monographs.

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PRESCRIBING CONSIDERATIONS: *NOTE: not all-inclusive, see product monographs for more information

Many combination products exist over-the-counter that could contain the same ingredient (or class of ingredients) as prescribed medications (e.g. acetaminophen). Additive adverse effects can occur as a result of combining these.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) [1]

- *Diclofenac* most commonly associated with hepatic adverse drug reactions.
- *Celecoxib* may cause an allergic reaction in patients with hypersensitivity to sulfonamides.
- NSAIDs inhibit platelet aggregation and can increase bleeding risk. Use them with caution in patients with platelet disorders or hemophilia or who take anticoagulant drugs.
- Consider lower doses in the elderly due to an increased potential for toxicity.
- Both COX-2 inhibitors and non-selective NSAIDs have the potential for adverse gastrointestinal and cardiovascular events; however not all people are at equal risk and there are differences between agents. Please refer to the NSAID risk section and risk assessment tools.
    - As an example, ketorolac is associated with a high risk of GI toxicity (up to 5.5 times greater than other NSAIDs) especially in higher doses, older patients, and for use > 5 days.
- Contraindications:
    - History of asthma or allergic-type reactions after taking NSAIDs or ASA including ASA intolerance and the Aspirin Triad (asthma, nasal polyps, and ASA intolerance), since fatal anaphylactoid reactions are possible. Cross-reactivity among structurally different nonselective NSAIDs occurs.
    - Perioperative setting of coronary artery bypass graft surgery (CABG) because of the risk of thrombotic events.
    - Severe uncontrolled heart failure since exacerbations can occur

Skeletal Muscle Relaxants[2]

- *Cyclobenzaprine*: Use of monoamine oxidase inhibitors is contraindicated with skeletal muscle relaxants as well as within the preceding 14 days. A starting dose of 5 mg tid prn reduces adverse effects and provides similar pain relief as higher doses.
- Methocarbamol and cyclobenzaprine may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should, therefore, be cautioned accordingly.
- Patients should be cautioned about combined effects of methocarbamol and cyclobenzaprine with alcohol and with other CNS depressants.

Opioids[3]

- *Codeine* is a prodrug that needs to be converted by CYP2D6 to an active metabolite. Genetically determined variations in metabolism mean codeine has an unpredictable effect. In patients who are CYP2D6 ultra-rapid metabolizers, toxicity from codeine can occur even at therapeutic doses. Poor metabolizers of CYP2D6, or patients taking drugs that inhibit CYP2D6, will experience less analgesic effect.
- *Tramadol* in its unconverted state binds weakly to opioid receptors but inhibits the reuptake of norepinephrine and serotonin. Tramadol is converted by CYP2D6 and its' main active metabolite is an opioid. Tramadol metabolism can be highly variable. In patients who are CYP2D6 ultra-rapid metabolizers, opioid associated toxicity with tramadol is more likely to occur even at therapeutic doses. Alternatively, poor CYP2D6 metabolizers are at increased risk of serotonin syndrome due to enhanced inhibition of serotonin reuptake by tramadol. Variable pharmacokinetics along with drug interactions mean tramadol can have unpredictable therapeutic and safety effects.
- Use of monoamine oxidase inhibitors should be avoided while using opioids and within 14 days of use.
- Serotonin syndrome is possible if any opioid is combined with serotonergic drugs.
- Avoid concomitant use of benzodiazepines, alcohol, and other CNS depressants (e.g. gabapentinoids) while using opioids due to additive sedative properties.
- There is no safe dose of opioids. Harms and complications can happen at any dose, but are less likely at lower morphine mg equivalents/day (< 50 morphine equivalents).
- Patients should be educated on overdose risk and use of Naloxone kits.
    - Naloxone only partially reverses the symptoms of tramadol overdose and can increase the risk of tramadol associated seizures.
- Combination products that contain both an opioid and non-opioid analgesic (e.g. acetaminophen, NSAID, or ASA) may result in serious adverse effects. Effects of high doses may include liver toxicity, gastric perforation, hemorrhage and peptic ulcer, renal failure, chronic blood loss anemia and low blood potassium (with potential fatal heart and neurological complications). Unintentional overdose can occur due to cumulative exposures from ingestion of multiple and/or combination OTC products containing the non-opioid analgesics. ***Note:** the use of combination opioid/non-opioid products does not allow routine dosing of non-opioid analgesics and PRN dosing of opioids as recommended after surgery.

ASA: acetylsalicylic acid, CNS: central nervous system, NSAID: non-steroidal anti-inflammatory drug, SNRI: serotonin norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, [1]NSAIDS Canadian Pharmacists Association (CPhA) monograph, [2]Cyclobenzaprine (CphA) and Robaxin monographs, [3]Opioids CPhA monograph, Ultram monograph.
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