

# Choices Before Opioids



## For CNCP

Academic  
Detailing  
Service





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“Seek simplicity, and mistrust it.”



## **Table of Contents**

Tables, figures and appendices.....	4
Abbreviations.....	5
Summary.....	6
Introduction.....	12
Acetaminophen.....	18
Non-Steroidal Anti-inflammatory drugs (NSAIDs).....	21
Tricyclic Antidepressants.....	31
Serotonin Norepinephrine Reuptake Inhibitors.....	36
Gabapentinoids.....	44
Cannabinoids.....	53
Combinations.....	62
Tramadol.....	62
Non-opioids compared to Opioids.....	69
Appendixes.....	72
References.....	76



## **Tables, Figures and Appendices**

Table 1: Measure of treatment effect.....	14
Table 2: Cochrane Review: oral NSAID vs placebo in fibromyalgia .....	22
Table 3: Cochrane Review: topical NSAIDs in osteoarthritis.....	27
Table 4: Cochrane Review: duloxetine in neuropathic pain.....	37
Table 5: Cochrane Review: duloxetine in fibromyalgia.....	38
Table 6: Cochrane Review: duloxetine in low back pain.....	40
Table 7: Meta-analysis: duloxetine in osteoarthritis.....	42
Table 8: Meta-analysis: gabapentinoids in neuropathic pain.....	45
Table 9: Cochrane Review: gabapentin in neuropathic pain.....	46
Figure 1: Increased risk of ulcer complications with several factors.....	29
Appendix 1: Comparison of Canada, US and UK Guidelines for low back pain.....	72
Appendix 2: Six Step Approach to Chronic Pain.....	73
Appendix 3: First line therapy for chronic non-cancer pain: Opioids vs Non-opioids.	74
Appendix 4: Second line therapy for chronic non-cancer pain.....	75



## Abbreviations

ABI	Absolute benefit increase
BPI	Brief pain inventory
CBD	Cannabidiol
CI	Confidence interval
CLBP	Chronic low back pain
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CNCP	Chronic non-cancer pain
CRI	Credible interval
DPN	Diabetic peripheral neuropathy
HCP	Health care professional
LFTs	Liver function tests
MCID	Minimum clinically important difference
ME	Morphine equivalent
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT/H	Number needed to treat/harm
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PGIC	Patient global impression of change
PBO	Placebo
PPI	Proton pump inhibitor
RBI	Relative benefit increase
RCT	Randomized controlled trial
RR	Relative risk or rate ratio
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardized mean difference
SNRI	Serotonin norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant
TOP	Toward Optimized Practice
VAS	Visual analogue scale



## Summary

The purpose of this document is to give an update of the evidence for choices of non-opioid drugs to be considered for chronic non-cancer pain prior to considering opioids.

- Conditions to be reviewed include neuropathic pain, fibromyalgia, chronic low back pain and osteoarthritis.
- The focus for outcomes will be on pain relief and improvement in function.

### **Acetaminophen**

**Page 18**

- Neuropathic pain and fibromyalgia
  - Acetaminophen is generally not recommended.
- Chronic low back pain
  - A Cochrane review concluded that acetaminophen does not produce better outcomes than placebo for people with acute low back pain and it is uncertain if it has any effect on chronic low back pain.
- Osteoarthritis
  - A recently published systematic review and meta-analysis reported that acetaminophen versus placebo resulted in a statistically but not clinically significant reduction in pain and disability.
  - Guidelines conditionally recommend acetaminophen as a first line option based on expert opinion of common usage and potential decreased risks/side effects compared to alternatives.

### **Non-steroidal Anti-inflammatory Drugs**

**Page 21**

- Neuropathic pain and fibromyalgia
  - Evidence suggests no statistically significant pain reduction with oral NSAIDs.
  - No trials were identified using topical NSAIDs.
- Chronic low back pain
  - A Cochrane Review reported
    - A statistically significant improvement in pain reduction with NSAIDs versus placebo which was no longer statistically significant when a sensitivity analysis was performed on trials with a low risk of bias.
    - No difference in benefit between NSAIDs, NSAID vs acetaminophen, NSAID vs pregabalin.
    - For the comparison of NSAID (celecoxib) vs tramadol, in the outcome of patients achieving  $\geq 30\%$  improvement in pain, celecoxib showed benefit over tramadol (NNT 8).
  - No trials were identified using topical NSAIDs for chronic low back pain.



- Osteoarthritis
  - A Network Meta-analysis reported that all NSAIDs improved osteoarthritic pain versus placebo.
    - Some NSAIDs showed statistically significant benefit that reached the minimum clinically important difference; some showed statistically significant benefit, but not all participants reached the minimum clinically important difference.
  - A Cochrane Review reported moderate quality evidence for efficacy for topical diclofenac and ketoprofen in patient reported pain relief of 50% or greater.
- Risks
  - Cardiovascular
    - Based on two meta-analyses and the Precision trial, it is difficult to conclude that one specific NSAID confers lower cardiovascular risk than others.
  - Gastrointestinal
    - NSAIDs increase the risk of ulcer complications.
    - The highest risk for upper gastrointestinal bleed for non-aspirin NSAID users occurs within the first 30 days of use.
    - There are recommendations for gastroprotection depending on patient risk factors.
    - There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding.

**Tricyclic antidepressants**

**Page 31**

- Neuropathic pain
  - TCAs are not officially approved in Canada for the treatment of neuropathic pain.
  - Cochrane Reviews suggest that the evidence for benefit is weak.
  - Another systematic review and meta-analysis reported
    - NNT of 4 (95% CI 3 to 4) for 12 weeks for active pain relief
    - NNH of 13 (95% CI 9 to 24) for adverse events
  - Evidence indicates a trial is warranted; however, a minority will achieve satisfactory pain relief.
  - Recommended as a first line option for neuropathic pain by the Canadian Pain Society.
- Fibromyalgia
  - TCAs are not officially approved in Canada for the treatment of fibromyalgia.
  - A Cochrane Review of amitriptyline reported:
    - NNT of 4 (95% CI 3 to 7) for patients experiencing at least a 50% pain reduction
    - NNH 3 (95% CI 3 to 5) for patients experiencing at least 1 adverse event.
  - Nortriptyline has not been shown to be better than amitriptyline for fibromyalgia.
  - Guidelines list TCAs as a treatment option for fibromyalgia.



- Chronic low back pain
  - Results of 4 RCTs reported no effect of TCAs on either pain relief or improvement in function compared to placebo for low back pain.
- For osteoarthritis
  - There is insufficient evidence to support the use of tricyclic antidepressants in the treatment of osteoarthritis.
- Risks/harms
  - Side effects include: drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmias and QTc interval prolongation.
  - Tertiary amine TCAs (amitriptyline, imipramine and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of **major anticholinergic and sedative side-effects** and potential for falls.
  - An increased risk of sudden cardiac death has been reported with TCAs at doses greater than 100 mg/day.

### Serotonin norepinephrine reuptake inhibitors

Page 36

#### Duloxetine

- Duloxetine has the official indication for the 4 conditions: neuropathic pain (diabetic peripheral neuropathy), fibromyalgia, chronic low back pain and osteoarthritis.
- Neuropathic pain
  - A Cochrane Review of duloxetine in **neuropathic pain** reported
    - Patients experiencing  $\geq 50\%$  improvement in pain at 12 weeks:
      - NNT 5 (95% CI 4 to 7) for duloxetine 60mg and NNT 7 (95% CI 5 to 12) for 120mg
    - Patients with adverse events leading to discontinuation;
      - NNH 18 (95% CI 13 to 30) for duloxetine 60mg and NNH 10 (95% CI 7 to 13) for duloxetine 120 mg
- Fibromyalgia
  - There is evidence rated as low quality leading to NNTs 8 and 7 and NNHs 18 and 10 for duloxetine 60mg and 120 mg respectively.
- Chronic low back pain
  - There is evidence suggesting a consideration of duloxetine for use when there is a neuropathic component.
- Osteoarthritis
  - There is evidence suggesting duloxetine might be a treatment option for patients who have an inadequate response to both non-pharmacologic and other pharmacologic treatment options.
  - The most commonly reported side effects include: nausea, dry mouth, constipation, somnolence, fatigue and dizziness.



- Venlafaxine
  - Venlafaxine does not have the official indication for any of the 4 chronic pain conditions.
  - There is limited evidence rated as low quality evaluating venlafaxine for neuropathic pain, fibromyalgia, chronic low back pain, or osteoarthritis.

### **Gabapentinoids**

Page 44

- Official indication:
  - Gabapentin: As an adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.
  - Pregabalin:
    - The management of neuropathic pain associated with:
      - Diabetic peripheral neuropathy
      - Postherpetic neuralgia.
    - The management of neuropathic pain associated with spinal cord injury.
    - The management of pain associated with fibromyalgia.
- Neuropathic pain
  - Gabapentin: Results of a Cochrane Review
    - Patients experiencing  $\geq 50\%$  improvement in pain: NNT 7 (95% CI 5 to 9)
    - Adverse events leading to discontinuation: NNH 30 (95% CI 20 to 65)
  - Pregabalin: Results of a Cochrane Review
    - Patients experiencing  $\geq 50\%$  improvement in pain: NNT 4 to 6 (95% CI 3 to 14)
    - Adverse events leading to discontinuation: NNH 9 to 17
    - There was a greater response to higher doses with the lowest NNT for postherpetic neuralgia and painful diabetic neuropathy observed at 600 mg/day.
    - Higher doses lead to more patients discontinuing therapy due to adverse events.
- Fibromyalgia
  - Gabapentin: Results of a Cochrane Review
    - Concluded that there was insufficient evidence to support or refute the use of gabapentin in fibromyalgia.
  - Pregabalin: Results of a Cochrane Review
    - Concluded that some patients may achieve good pain relief with lower doses; however, 450 mg/day appeared to provide the best balance between benefit and adverse events.
      - For  $> 50\%$  improvement in pain: NNT 10 (95% CI 7 to 15)
      - Adverse event withdrawal: NNH 11 (95% CI 8 to 17)
- Chronic low back pain
  - Gabapentinoids: One meta-analysis of 8 studies
    - Results showed minimal improvement in pain with an increase in adverse events with gabapentin compared to placebo. Evidence rated as very low quality.



- Osteoarthritis
  - No RCTs evaluating gabapentinoids versus placebo in osteoarthritis were found.
- Risks/harms
  - Gabapentinoids should be used with caution in patients at risk of substance abuse.
  - There is an increased risk of death when moderate to high doses (> 900 mg/day) of gabapentin are co-prescribed with opioids.
  - In chronic low back pain patients, adverse events (dizziness, fatigue, difficulties with mentation, and visual disturbances) were more common with gabapentin compared to placebo with NNH ranging from 6-8.

**Cannabinoids:**

**Page 53**

- May be suggested as a third line option for neuropathic pain after an adequate trial of at least 3 prescribed non-opioid analgesics. Benefits are limited and there is a high risk of harms.
- In general, evidence has a very high risk of bias and the long term consequences are unknown.
- Products available can have far higher concentrations of THC and CBD than those researched.

**Combination therapy:**

**Page 62**

- There are many trials published looking at various combinations and doses of medications for various pain states but the availability of good quality trials for any one specific combination is lacking.

**Tramadol**

**Page 62**

- Tramadol is an **opioid analgesic** officially indicated for the treatment of mild-moderate pain.
- In Canada, it is a prescription medication but NOT regulated as a narcotic or controlled drug.
- Tramadol
  - Has low binding affinity to the  $\mu$  opioid receptor.
  - Inhibits the reuptake of norepinephrine and serotonin.
    - This leads to a potential increased number of drug interactions and an additional risk of adverse events beyond those related to its opioid properties.
- Neuropathic pain
  - Results of a Cochrane Review rated LOW quality evidence **for tramadol versus placebo**
    - $\geq 50\%$  improvement in pain (pooled from 3 of the trials)
      - Event Rate: tramadol 53% versus placebo 30%
      - NNT 4 (95% CI 3 to 9) for 4 to 6 weeks
    - Adverse events leading to discontinuation
      - Event Rate: tramadol 15% versus placebo 3%
      - NNH 8 (95% CI 6 to 14) for 4 to 6 weeks



- **Authors' comments:** The evidence of benefit for tramadol was of low or very low quality (small, largely inadequate studies, with potential risk of bias increasing the apparent benefits). It does not provide a reliable indication of the likely benefit.
- Fibromyalgia
  - There is limited evidence for use in fibromyalgia.
- Chronic low back pain
  - Results of a Cochrane review: Tramadol vs. placebo
    - Standardized mean difference (favouring tramadol)
      - Pain -0.55 (95% CI -0.66 to -0.44) Rated low quality evidence
      - Function -0.18 (95% CI -0.29 to -0.07) Rated moderate quality evidence
    - **Authors' comment:** There is some evidence for short term efficacy of tramadol compared to placebo for chronic low back pain.
- Osteoarthritis
  - Results of a Cochrane Review for tramadol versus placebo
    - ≥ 50% improvement in pain (pooled from 4 trials); duration 8-12weeks
      - Event rates: Tramadol or tramadol/acetaminophen 69% versus placebo 50%
      - NNT 6 (95% CI 4 to 9)
    - Adverse Events leading to discontinuation (pooled from 4 trials)
      - Event rates: Tramadol 20% versus placebo 8%
      - NNH 8 (95% CI 7 to 12)
    - **Authors' conclusions:** Tramadol or tramadol/acetaminophen decreases pain intensity, produces symptom relief and improves function, but the benefits are small. Adverse events often cause participants to stop taking the medication.
- Risks/harms
  - As an opioid tramadol carries a risk of addiction, abuse and misuse.
  - Tramadol's dual mechanism of action is reflected in the listed side effects, warnings and precautions and drug interactions. Please refer to the official product monograph for complete details.

**Non-opioids compared to Opioids**

- The focus of this document is on choices before opioids for chronic non-cancer pain. However, prescribers may be interested in comparative efficacy and safety between non-opioids and opioids. For reference, the results of systematic reviews of evidence comparing opioids vs. non-opioids from the latest Canadian Opioid Guidelines have been summarized in Appendices 3 and 4. We have also provided a brief summary of the recently published SPACE trial.
- Please refer to the complete opioid guidelines available at [http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ\\_01may2017.pdf](http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf)



## Introduction

The purpose of this document is to give an update of the evidence for choices of non-opioid drugs to be considered for chronic non-cancer pain prior to considering opioids.

The following medications will be reviewed:

- Acetaminophen
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Antidepressants
  - Tricyclic antidepressants (TCAs)
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Gabapentinoids
- Cannabinoids
- Combination therapy
- Tramadol (opioid)

We will focus on the management of 4 conditions:

- Neuropathic pain
- Fibromyalgia
- Low back pain
- Osteoarthritis

Official indications, guideline recommendations and evidence will be presented as well as number needed to treat (NNT) and number needed to harm (NNH) with 95% confidence intervals and time frames where possible. A cost table will also be provided.

In general, trials are versus placebo and are relatively short ( $\leq 12$  weeks with a few exceptions). Data from head-to-head trials will be presented where available.

According to our local content reviewer, chronic pain not caused by cancer is a complex illness that affects 1 in 5 Canadians.

- It is often related to several different medical conditions including (but not limited to) diabetes, arthritis, fibromyalgia and osteoporosis.
- The “chronicity” of chronic pain is associated with central sensitization or amplification, a process that “winds-up” the pain system keeping it in a persistent state of hyperactivity long after tissue has healed.
- Recurrent and unpredictable flare-ups of chronic pain make pain assessment and function management challenging.
- See Appendix 2 for a “Six Step Approach to Chronic Pain”.



There are 4 P's to pain management:

- Pharmacological,
- Physical,
- Psychological and
- Preventive.<sup>1</sup>

### Goals of therapy

- It is important for patients to have realistic expectations for therapeutic interventions.
- All medications including cannabis are tools used in the treatment of CNCP and should be used concurrently with consideration of the other tools available to the patient.
- Goals for pharmacologic treatment of CNCP
  - Reduction in pain of 30 to 40%
  - Avoidance of sedation
  - Improvement in function (patient specific and easily measurable).
- Emphasize the value of a **long-term, holistic approach**, focusing on **incremental gains in function**, no matter how small.
  - Is progress being achieved?
  - Is life and overall functioning slowly improving?
  - Is the patient able to have a meaningful life beyond their pain experience?<sup>1</sup>
- Pain self-management programs are very important and help patients to:
  - Shift from an acute model of care to a chronic pain model.
  - Develop a “toolbox” or strategies to manage and prevent chronic pain flare-ups. (Activity pacing, breathing techniques, mindfulness, boundary setting, to mention a few).
  - Learn about the role of pharmacology in managing their pain (harms and benefits).
- Potential benefits and harms of each treatment option can vary considerably depending on the patient, the chronic condition and the dose/intensity of the intervention.<sup>1</sup>

### Outcomes

- The focus for outcomes will be on pain relief and improvement in function.
- Throughout the document, we will report dichotomous outcomes when available.
- **NOTE:** When the treatment increases the probability of a good event e.g., % of patients achieving a reduction in pain, the therapy that provides benefit will have a relative benefit increase (RBI) and an absolute benefit increase (ABI).
  - NNT becomes the number of patients who must receive the treatment to create 1 additional improved outcome in comparison with the control treatment. (<https://hiru.mcmaster.ca/hiru/glossary.htm>)



## Measure of Treatment Effect

- In our previous Academic Detailing Document (2010) on Chronic Non-Cancer Pain the standardized mean difference was discussed as a means of describing the difference between two treatment groups where outcomes are measured on a continuous scale (e.g: 0-10 on a Visual Analogue Scale {VAS}).
  - The standardized mean differences from individual studies are then pooled using meta-analysis to arrive at an overall pooled standardized mean difference which is sometimes referred to as the **effect size**.<sup>2</sup>

**Table 1: Measure of treatment effect**

Standardized mean difference	Effect Size	Clinical meaning
< 0.5	Small	Mean difference less than 10% of the scale (e.g. < 10 mm on a 100 mm VAS)
0.5 to < 0.8	Medium	Mean difference 10% to 20% of the scale
≥ 0.8	Large	Mean difference > 20% of the scale

- The standardized mean difference can make it difficult to determine what percentage of patients will experience clinically relevant pain relief.
  - Individual response to pain medication varies greatly. Some will have very good pain relief, while others will have little or no pain relief.
  - Reporting the average pain relief will not indicate what percentage (even if it is very small) of patients that will have very good pain relief.
- Studies that have looked at patient centred outcomes have indicated that patients require a significant degree of pain reduction (typically greater than 50%) to be considered clinically and personally meaningful.<sup>3</sup>
- Groups such as IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) have sought to define outcomes in chronic pain trials to reflect patient centred outcomes.<sup>4</sup>
  - A responder analysis indicates the percentage of the study population who had at least 50% reduction in pain (or its equivalent). The data are able to be presented in a dichotomous fashion. Patients either achieved 50% pain reduction or they didn't.
  - Presenting data in a dichotomous fashion permits calculation of number-needed-to-treat (NNT) and number-needed-to-harm (NNH).
- IMMPACT definitions for moderate and substantial benefit in chronic pain studies are as follows:<sup>4</sup>
  - At least 30% pain relief over baseline (moderate)
  - At least 50% pain relief over baseline (substantial)
  - Much or very much improved on Patient Global Impression of Change (PGIC) (moderate)
  - Very much improved on PGIC (substantial).



- **Local reviewer opinion** suggests there are limitations concerning the tools used to assess and manage chronic pain in the clinical setting which can contribute to stigma, over-medication and missed diagnosis if these shortcomings are not appreciated.
  - Pain scales are often seen as the "gold standard" of pain assessment but fail to help health care providers (HCP) appreciate the multidimensional features of pain and how to best support patients back to a functional quality of life. Pain is a physical, psychosocial and spiritual experience.
  - Pain scales accurately reflect the severity of pain experienced by the patient, but they do not always tell us what is occurring physiologically at the tissue level. This makes pain assessment and pain management challenging.
  - Pain scales should be viewed as "suffering scales" to better reflect this complexity.
  - Listening to the patient's pain story, acknowledging suffering, then carefully examining them for any new pathology or progression of a pre-existing disease can help reduce missed diagnosis. At the same time, we can validate the patient's pain experience regardless of what is found or not found on investigation.

### Therapeutic Implications

- The NNTs presented throughout this document for various drugs underscores what most clinicians know through practice.
  - With NNTs of 6 to 8 for most drug interventions, it is evident that most do not provide adequate pain relief in the majority of patients.
  - One review article<sup>5</sup> captures this observation. The authors argue that "The principles should be to measure pain, expect and recognize analgesic failure, and to react to it, pursuing analgesic success rather than blindly accepting failure."
    - The exposure to potential harm is obviously minimized by closely monitoring who benefits from a medication intervention and discontinuing the medication for those who do not have a clear benefit.
    - There is not always good evidence to define starting, stopping and switching rules.
    - Given the complexity of chronic pain conditions it is not surprising that the minority of patients will benefit from any one intervention.
- The NNTs/NNHs and 95% intervals presented in this document should be interpreted **with caution**. They are mostly based on **low quality evidence**.

### Trial of Therapy

- An adequate trial will generally include a titration period and an evaluation period. It is important to assess both benefits and harms.
- In general, a trial of 2 weeks at a **tolerated/titrated dose** is adequate to assess benefit.



### **Sources of Evidence**

- We have reviewed Cochrane Reviews where available, systematic reviews and meta-analysis and randomized controlled trials.
- We have frequently referenced the Alberta College of Family Physicians Tools for Practice.
- We also want to acknowledge the Saskatoon RxFiles program. The “Pain Mini-Book: Update on Pain Management & Opioids in CNCP” produced in November 2017 has served as an excellent resource during the preparation of this document and is referenced many times. We want to thank the developers of RxFiles for their collaboration.

### **Cochrane Levels of Evidence**

- Cochrane performed their analyses using 3 tiers of evidence:
  - First Tier evidence: derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to a substantial reduction in pain intensity, intention-to-treat analysis without imputation for dropouts; patient population of at least 200, 8 to 12 weeks’ duration and parallel design)
  - Second Tier evidence: derived from data that failed to meet one or more of first tier criteria; were considered at some risk of bias; with adequate numbers in the comparisons
  - Third Tier evidence: data involving small numbers of participants that were considered highly likely to be biased or used outcomes of limited clinical utility, or both.

### **Non-opioids versus opioids**

- The focus of this document is on choices before opioids for chronic non-cancer pain. However, prescribers may be interested in comparative efficacy and safety between non-opioids and opioids. For reference, the results of systematic reviews of evidence comparing opioids vs. non-opioids from the latest Canadian Opioid Guidelines have been summarized in Appendices 3 and 4. We have also provided a brief summary of the recently published SPACE trial.
- Please refer to the complete opioid guidelines available at [http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ\\_01may2017.pdf](http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf)



Choosing Wisely Canada (<https://choosingwiselycanada.org/recommendations/>)

➤ **Family Medicine**

- ***Don't initiate opioids long-term for chronic pain until there has been a trial of available non-pharmacological treatments and adequate trials of non-opioid medications.***

*Depending on the pain mechanism and patient co-morbidities, this can include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclics and gabapentinoids. Other non-medication modalities for managing acute, subacute and chronic pain may include exercise, weight loss, cognitive-behavioural therapy, massage therapy, physical therapy and/or spinal manipulation therapy. An opioid trial should be guided by clear criteria for monitoring the success of an opioid trial and a plan for stopping opioids if criteria are not met. [Family Medicine Recommendation #13](#)*

**Useful Links:**

Nova Scotia Pain Self-Management Programs

- To obtain information on the Pain Self-Management Program (PSMP) in each region, it is best to contact each regional clinic to get details. The Nova Scotia Health Authority (NSHA) public link for the clinics and contact information is

<http://www.nshealth.ca/service-details/Chronic%20Pain%20Services>

- The NSHA public website also has information on a few specific PSMPs (Halifax, Windsor, Berwick and South Shore).

<http://www.nshealth.ca/servicedetails/Chronic%20Pain%20Self%20Management%20Program>

Choosing Wisely Canada

<https://choosingwiselycanada.org/recommendations/>

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

<http://nationalpaincentre.mcmaster.ca/guidelines.html>

Understanding pain in less than 5 minutes

<https://www.youtube.com/watch?v=5KrUL&tOaQs>



## Acetaminophen

- Official indication: treatment of mild-moderate pain and reduction in fever.<sup>6</sup>

### ***Neuropathic pain (acetaminophen)***

- Acetaminophen is generally not recommended in guidelines.
- We were unable to find any RCTs evaluating acetaminophen in neuropathic pain.

### ***Fibromyalgia (acetaminophen)***

- According to the 2012 Canadian Guidelines, acetaminophen, although traditionally recommended as a step one agent in the analgesic ladder by the World Health Organization, has never been formally examined in fibromyalgia.<sup>7</sup>
  - It is generally considered a safe drug but should be used with caution regarding hepatotoxicity when doses above 2 grams a day are used continuously.
- We were unable to find any RCTs of monotherapy in fibromyalgia.

### ***Low back pain (acetaminophen)***

- Analgesics are the most frequently prescribed medications for the treatment of low back pain.<sup>8</sup>
- Most of the evidence is in acute low back pain.
- A recently published systematic review reported no effect of acetaminophen compared to placebo for **acute or chronic** low back pain in the outcomes of pain and function.<sup>9</sup>
- One RCT assessed the efficacy of acetaminophen taken regularly or as-needed to improve time to recovery from pain, compared with placebo, in patients with **acute** low back pain.<sup>10</sup>
  - Double blind RCT, N=1652, duration of 4 weeks
  - Compared acetaminophen 3,990 mg/day versus as needed  $\leq$  4000 mg/day versus placebo
  - Outcomes evaluated: time to recovery, pain intensity, disability, function, global symptom change or quality of life.
  - Results: no effect on any outcome at any time
  - Authors interpretation: Findings suggest that regular or as-needed dosing of acetaminophen does not affect recovery time compared with placebo in low back pain and question the widely held endorsement in this patient group.
- A Cochrane Review<sup>8</sup> by Saragiotto evaluated acetaminophen in low back pain.
  - Trials compared acetaminophen to placebo.
  - Primary outcome: pain and disability
  - Secondary outcomes: quality of life, function, adverse effects, global impression of recovery, sleep quality, patient adherence and use of rescue medication



- Author's conclusion: acetaminophen does not produce better outcomes than placebo for people with acute low back pain, and it is uncertain if it has any effect on chronic low back pain.

➤ Guideline Placement

- Toward Optimized Practice (TOP) Guidelines list acetaminophen as the first line option for acute and **chronic low back pain**. This recommendation is based on expert opinion of common usage and decreased risk of side effects compared to alternative analgesics.<sup>11</sup>
- Guidelines from the American College of Physicians do not recommend acetaminophen for chronic low back pain.<sup>12</sup>
- See Appendix 1 for comparison of Guidelines.

***Osteoarthritis (acetaminophen)***

Acetaminophen is frequently recommended as a starting medication for the management of osteoarthritis.

- A recently published systematic review and meta-analysis of randomized placebo controlled trials evaluated the efficacy and safety of acetaminophen for osteoarthritis of the hip or knee.<sup>13</sup>
  - 7 RCTs N= 3153
  - Acetaminophen ~3-4 g/day versus placebo
  - Duration of follow-up: greater than 2 weeks up to 3 months
  - **Results:** acetaminophen versus placebo resulted in a statistically but not clinically significant reduction in pain and disability.
    - Weighted mean difference for pain relief -3.7 (95% CI -5.5 to -1.9)
    - Weighted mean difference for disability -2.9 (95% CI -4.9 to -0.9)
    - Minimal clinically important difference: 9 mm in a 0-100 VAS
  - The quality of evidence based on GRADE was rated as "high quality".
- The conclusion that acetaminophen provides no **clinically meaningful** impact on osteoarthritis has been reached by other authors.<sup>14</sup>
- Guideline Placement:
  - American College of Rheumatology 2012 Recommendations conditionally recommend acetaminophen for management of knee and hip OA.<sup>15</sup> These recommendations are being updated in 2018.

***Risks/Harms***

- Hepatic risk
  - Elevated liver enzymes (1.5 times the upper limit of the reference range or over)



- Acetaminophen at regular doses of < 4 gm/day increases the risk nearly 4 times versus placebo in patients with osteoarthritis.<sup>13,14</sup>
- NNH = 21 for 3 to 6 months
- According to the official product monograph<sup>6</sup> there is increased hepatic risk in patients with
  - Chronic/extensive alcohol use (≥ 3 drinks/day)
  - Liver disease
  - Malnutrition
  - Other risk factors for hepatic disease.
- In patients at risk, consider monitoring liver function tests (LFTs) every 3 to 6 months.
- Avoid or limit acetaminophen use (≤ 2 g/day) in patients with cirrhosis.<sup>6</sup>
- Overdose risk:
  - Generally considered safe at doses ≤ 4g/day.
    - TOP Guidelines suggest ≤ 3 g/day for long term use.<sup>11</sup>
  - Overdose is possible with
    - Acute ingestion of a high dose (≥ 200mg/kg or 10g)
    - Repeated supratherapeutic ingestion (over a 48 hr period: 150mg/kg or 6 g/day, whichever is less)
    - In patients with risk factors overdose may present with repeated exposure to lower doses (100mg/kg daily or ≤ 4g/day).
    - Patients can **unintentionally overdose** due to **cumulative exposure** from ingestion of multiple and/or combination OTC products containing acetaminophen.<sup>1</sup>

#### SUMMARY for Acetaminophen

- Neuropathic pain and fibromyalgia
  - Acetaminophen is generally not recommended.
- Chronic low back pain
  - A Cochrane review concluded that acetaminophen does not produce better outcomes than placebo for people with acute low back pain and it is uncertain if it has any effect on chronic low back pain.
- Osteoarthritis
  - A recently published systematic review and meta-analysis reported that acetaminophen versus placebo resulted in a statistically but not clinically significant reduction in pain and disability.
  - Guidelines conditionally recommend acetaminophen as a first line option based on expert opinion of common usage and potential decreased risks/side effects compared to alternatives.



## **Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**

- Official indication: anti-inflammatory, analgesic and antipyretic agent
- Below is the statement from Choosing Wisely Canada regarding NSAIDs. Guidelines generally suggest NSAIDs as first or second line therapy for low back pain and osteoarthritis with consideration being given for potential differences in gastrointestinal, liver and cardio-renal toxicity and the person's risk factors including age.

### **Choosing Wisely Canada<sup>16</sup>**

Do not prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) in individuals with hypertension or heart failure or chronic kidney disease of all causes, including diabetes.

*The use of NSAIDs, including cyclo-oxygenase type 2 (COX-2) inhibitors, for the pharmacological treatment of musculoskeletal pain can elevate blood pressure, make antihypertensive drugs less effective, cause fluid retention and worsen kidney function in these individuals. Other medication prescribed by a healthcare professional may be safer than and as effective as NSAIDs.*

### **Neuropathic Pain (NSAIDs)**

- Oral NSAIDs: Cochrane Review 2015<sup>17</sup> by Moore
  - Very low quality evidence
  - Included 2 randomized placebo controlled trials (N=251) in patients with a neuropathic component to chronic low back pain or post herpetic neuralgia
  - One of the studies (209 patients) involved an experimental NSAID (COX-2 inhibitor) in patients with post herpetic neuralgia.
  - Of the remaining 42 patients, 16 had neuropathic pain and were treated with celecoxib (dosed at 3-6mg/kg/day for 4 weeks).
  - **Primary Outcomes:**
    - Patient-reported pain relief of 30% or greater
    - Patient-reported pain relief of 50% or greater
    - Patient Global Impression of Change (PGIC) much or very much improved
    - Patient Global Impression of Change (PGIC) very much improved
  - Neither of the trials showed statistically significant pain reduction for NSAIDs alone for the treatment of neuropathic pain.
  - **Adverse Events:**
    - Event rates were low and insufficient for any analysis.
  - Authors comment: There is no good evidence to support or refute the use of NSAIDs to treat neuropathic pain.

- Topical NSAIDs: Cochrane Review 2017<sup>18</sup> by Derry
  - No trials were identified using topical NSAIDs for the treatment of neuropathic pain.
- Guideline Placement:
  - NSAIDs are not listed as a treatment option for neuropathic pain in the Canadian Pain Society 2014 Guidelines.<sup>19</sup>

### ***Fibromyalgia (NSAIDs)***

- Oral NSAIDs: Cochrane Review 2017<sup>20</sup> by Derry
  - Low quality evidence
  - Inclusion criteria: patients over 18 years diagnosed with fibromyalgia
  - Included 6 randomized placebo controlled trials (N=292)
  - NSAIDs included in trials were: ibuprofen 2400 mg daily, naproxen 1000 mg daily, etoricoxib 90 mg daily and tenoxicam 20 mg daily
  - Treatment duration varied from 3-8 weeks
  - **Primary Outcomes:**
    - Participant-reported pain relief of 50% or greater or PGIC very much improved (substantial improvement)
    - Participant-reported pain relief of 30% or greater or PGIC much or very much improved (moderate improvement)
  - Not all studies reported relevant outcomes
  - **Results:**
    - There was **no statistically significant difference** between NSAIDs and placebo for any of the primary outcomes.

**Table 2: Cochrane Review: Oral NSAID vs placebo in fibromyalgia<sup>20</sup>**

	Event rates from meta-analysis		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 3-8 weeks
	NSAID	PBO		
Patients experiencing ≥ 50% improvement in pain	11%	18%	ABI 7% (with placebo)	NS
Patients experiencing ≥ 30% improvement in pain	22%	26%	ABI 4% (with placebo)	NS
Adverse events	5%	2%	ARI 3%	NS

NSAID – nonsteroidal anti-inflammatory; PBO – placebo; CI – confidence interval; ABI- absolute benefit increase; ARI– absolute risk increase; NS – not significant

- Topical NSAIDs: **Cochrane Review 2017<sup>18</sup>** by Derry
  - No trials identified using topical NSAIDs for the treatment of fibromyalgia.



➤ Guideline Placement:

- Canadian Guidelines suggest there is little rationale for the use of NSAIDs for the treatment of fibromyalgia.<sup>7</sup>
- NSAIDs are not listed as a treatment option in the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the National Health Service (NHS).<sup>21</sup>

**Chronic Low Back Pain (NSAIDs)**

➤ NSAIDs: **Cochrane Review 2016**<sup>22</sup> by Enthoven

- Included 13 randomized control trials (N=4807)
- Low quality evidence
- Inclusion criteria: participants aged 18 years or older who were treated for non-specific chronic low back pain (defined as pain for at least 12 weeks)
- Exclusion criteria: participants with sciatica or with specific low back pain caused by pathological entities, such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis or fractures
- 6 trials studied NSAIDs vs. placebo
- The remainder of the trials compared NSAIDs to an active comparator
  - 3 trials compared 2 types of NSAIDs
  - 1 trial compared NSAID vs. acetaminophen
  - 1 trial compared NSAID vs. tramadol
  - 1 trial compared NSAID vs. pregabalin
  - 1 trial compared NSAID vs. exercise therapy (home based)
- Only the results from the NSAIDs vs. placebo trials could be pooled.
- **Primary Outcomes:**
  - Mean difference from baseline in
    - Pain intensity (e.g. visual analogue scale {VAS} or Numerical Rating Scale {NRS})
    - Global measure (e.g. overall improvement, proportion of participants that recover)
    - Back pain-specific functional status (e.g. Roland Disability Questionnaire [validated], Oswestry Scale [validated])
  - Return to work (e.g. return to work status, number of days off work)
  - Adverse events (proportion of participants experiencing adverse events)
- **Results:**
  - **NSAIDs vs. Placebo**
    - N = 1354
    - Trials were 4-16 weeks in duration (mean follow-up 56 days).
    - Included naproxen as the most common NSAID (the other NSAIDs were piroxicam patch, valdecoxib and etoricoxib which are not available in Canada)



- The pooled mean difference in pain intensity score (0-100mm VAS) from baseline was statistically significant in favour of NSAIDs vs placebo.
  - -6.97 (95% CI -10.74 to -3.19)
  - Effect size = LOW
- Three of the RCTs were considered low risk of bias (the other three were considered high risk).
  - A sensitivity analysis was performed on the low risk trials.
  - The difference between NSAIDs and placebo on pain intensity score (on 0 to 100 mm VAS) became smaller and was no longer statistically significant.
    - -5.03 (95% CI -10.37 to 0.32)
- **Comparison between NSAIDs**
  - No significant difference was found for any comparison.
    - Ibuprofen (1600 mg/day) vs diclofenac (100 mg/day) for 2 weeks (N = 62)
    - Piroxicam (20 mg/day) vs indomethacin (75 mg/day) for 6 weeks (N = 28)
    - Diclofenac 150 mg/day vs etoricoxib 60 mg/day for 4 weeks (N = 440)
- **NSAID vs. acetaminophen**
  - Published in 1982; N = 30; duration 4 weeks
  - Diflunisal 1000mg/day vs. acetaminophen 4000mg/day
    - No significant difference was found.
    - No difference in adverse drug reactions
- **NSAID vs. tramadol**
  - N = 1593; duration 6 weeks
  - Celecoxib 400mg/day and tramadol 200mg/day
    - 63% of patients in the celecoxib group vs 50% of patients in the tramadol group achieved  $\geq 30\%$  improvement in pain from baseline, measured with 11-point numerical rating scale.
      - NNT = 8 (favouring celecoxib) (95% CI 5 to 12)
      - Adverse events were slightly less with celecoxib than tramadol.
- **NSAID vs. pregabalin**
  - N = 42; duration 4 weeks
  - Celecoxib vs pregabalin (dose was based on weight)
    - No significant difference was found in any outcome.
    - No difference in adverse drug reactions.
- **Return to work**
  - None of the included trials provided data on this outcome.
- **Adverse Events**



- Proportion of patients experiencing adverse events was not statistically significantly different between NSAIDs and placebo.
    - 44% of patients in the NSAID group and 41% in the placebo group
  - These results did not change when NSAIDs were broken down to selective and non-selective.
- Topical NSAIDs: **Cochrane Review 2017<sup>18</sup>** by Derry
  - No trials were identified using topical NSAIDs for the treatment of chronic low back pain.
- Guideline Placement:
  - Toward Optimized Practice 2017: Oral NSAIDs are listed as 2<sup>nd</sup> line (after acetaminophen). There is inconclusive evidence to recommend topical NSAIDs for the treatment of chronic low back pain.<sup>11</sup>
  - See Appendix 1 for Guidelines comparison chart.

### ***Osteoarthritis (NSAIDs)***

- Oral NSAIDs: **Network meta-analysis<sup>23</sup>** by da Costa
  - Included 76 randomized control trials (N = 58,451)
  - Trials included were generally high quality but the majority used the last observation carried forward method so they were at risk of incomplete outcome data bias.
  - Patients with knee or hip osteoarthritis were included.
  - Interventions included comparison of any of the following: NSAIDs, acetaminophen or placebo.
  - Trial durations were 12 weeks or less.
  - **Primary Outcomes**
    - Pain Scores
      - Median minimum clinically important difference
        - Effect Size = -0.37
        - 9mm difference on a 100mm VAS
    - NSAID vs. Placebo (only NSAIDs available in Canada are presented)
      - Pooled effect size showed all interventions (irrespective of dose) improved osteoarthritic pain compared to placebo.
      - For six interventions (acetaminophen <2000 mg/day and 3000 mg/day, diclofenac 70 mg/day, celecoxib 100mg/day, naproxen 750 mg/day, and ibuprofen 1200 mg/day), not enough statistical evidence was available to support superiority when compared with placebo.
        - Acetaminophen had a null effect on pain at various doses.
          - Effect Size= -0.18 (favouring treatment)
          - 4.1 mm difference on a 100 mm VAS scale



Diclofenac 150mg/day had a moderate to large effect size and was the only NSAID to demonstrate a statistically significant effect that reached the minimum clinically significant difference.

- Effect Size = -0.57 (favouring treatment)
  - 14mm difference on a 100mm VAS scale
  - The following NSAIDs and doses were **statistically significant** and their point estimate of benefit reached **the minimum clinically important difference**. However, their confidence interval extended above the minimum clinically important difference.
    - Ibuprofen 2400mg/day: Effect Size = -0.42
    - Naproxen 1000mg/day: Effect Size = -0.40
    - Diclofenac 100mg/day: Effect Size = -0.41.
  - **Adverse events:** No analysis was done on adverse events in this meta-analysis.
  - **Authors conclusion:** On the basis of the evidence to date, diclofenac 150 mg/day is the most effective NSAID available at present in terms of improving both pain and function. **Nevertheless, in view of the safety profile of these drugs, both efficacy and safety have to be considered in selecting the preparation and dose for individual patients.**
  - **NOTE:** According to the **official product monograph**, the maximum recommended daily dose of diclofenac is 100mg/day.<sup>6</sup>
- Topical NSAIDs: **Cochrane Review 2016**<sup>24</sup> by Derry
- Included 39 randomized control trials; N = 10, 631; duration 6 to 12 weeks
  - Inclusion criteria: adult participants (16 years or older) with chronic musculoskeletal pain of at least three months' duration and at least moderate intensity
  - Exclusion criteria: participants with neuropathic pain or fibromyalgia
  - Majority of trials were for osteoarthritis of the knee.
  - 33 trials compared topical NSAID vs. carrier alone.
    - 5 of these included a treatment arm with an oral NSAID
      - Ketoprofen gel vs. oral celecoxib vs. placebo
      - Ketoprofen gel vs. oral celecoxib vs. placebo
      - Elternac gel vs. oral diclofenac vs. placebo
      - Diclofenac topical vs. oral diclofenac vs. placebo
      - Diclofenac solution (Pennsaid®) vs. oral diclofenac vs. placebo
    - 1 trial included a treatment arm with a topical non-NSAID
      - Addition of piroxicam to topical glyceryl
    - 2 trials compared a topical NSAID to a different oral NSAID
      - Topical piroxicam gel vs. oral ibuprofen
      - Topical diclofenac gel vs. oral ibuprofen

- 4 trials compared a topical NSAID to another topical treatment
  - Indomethacin gel vs diclofenac gel
  - Flurbiprofen topical vs. piroxicam cream
  - Piroxicam gel vs. a homeopathic gel
  - Ibuprofen gel vs. arnica gel
- **Results:**
  - Moderate quality evidence for efficacy for **diclofenac** and **ketoprofen**
  - Very low quality evidence for harmful effects
  - **Primary Outcome:** Patient-reported pain relief of 50% or greater at 6-12 weeks

**Table 3: Cochrane Review: Topical NSAID in osteoarthritis<sup>24</sup>**

	Event rates		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 6-12 weeks
	Topical NSAID	Carrier		
Patients experiencing ≥ 50% improvement in pain	Diclofenac 60%	50%	ABI 10%	NNT 10 (95% CI 7 to 16)
Local adverse events	Diclofenac 12%	7%	ARI 5%	NNH 16 (95% CI 12 to 23)
Patients experiencing ≥ 50% improvement in pain	Ketoprofen 63%	48%	ABI 15%	NNT 7 (95% CI 5 to 9)
Local adverse events	15%	13%	ARI 2%	NS
	Topical NSAID	Oral NSAID		
Patients experiencing ≥ 50% improvement in pain	55%	54%	ABI 1% (favoring topical)	NS Low quality evidence
Gastrointestinal adverse events	16%	26%	ARI 10% (with oral)	NNH 11 with oral (95% CI 8 to 17) Low quality evidence

NSAID – nonsteroidal anti-inflammatory; CI – confidence interval; ABI – absolute benefit increase; ARI – absolute risk increase; NNT/H number needed to treat/harm; NS – not significant

Guideline Placement: American College of Rheumatology 2012<sup>15</sup>

- There was no strong recommendation made for which therapy should be initial therapy.
  - Hand OA:
    - Conditionally recommend that health professionals should use one or more of the following:
      - Topical NSAIDs, including trolamine salicylate
      - Oral NSAIDs, including COX-2 selective inhibitors
      - **NOTE: According to official product monographs in Canada, the concomitant use of oral and topical NSAIDs is contraindicated.**
    - Conditionally recommend that persons ≥ age 75 years should use topical rather than oral NSAIDs. In persons < age 75 years, the technical expert panel expressed no preference for using topical rather than oral NSAIDs.
  - Knee OA:



- Conditionally recommend that patients should use **one** of the following:
  - Oral NSAIDs
  - Topical NSAIDs
- Hip OA:
  - Conditionally recommend that patients should use oral NSAIDs
  - Topical NSAIDs are not recommended.

### **Risks/Harms**

#### **Cardiovascular Risk (NSAIDs)**

- Do different NSAIDs have different cardiovascular risk?
  - A review<sup>25</sup> of two large meta-analyses looking at the cardiovascular safety and effects of NSAIDs concluded that COX-2 inhibitors and most traditional NSAIDs increase risk of serious CV events and death.
  - PRECISION trial 2016<sup>26</sup>
    - A non-inferiority trial conducted by industry.
    - N = 24,081; mean age 63 years; duration of treatment 20 to 34 months
    - Randomized double blind three arm trial in arthritis patients with increased cardiovascular risk
      - Increased CV risk was defined as presence of, or high risk for, CVD.
      - Diabetes mellitus was considered a CV disease risk equivalent.
    - Treatment groups (dose titration upwards was permitted):
      - celecoxib 100mg bid (up to 200 mg bid) or
      - ibuprofen 600mg tid (up to 800 mg tid) or
      - naproxen 375mg bid (up to 500 mg bid)
    - Mean ( $\pm$ SD) daily dose
      - Celecoxib 209  $\pm$  37 mg
      - Naproxen 852  $\pm$  103 mg
      - Ibuprofen 2045  $\pm$  246 mg
    - The primary outcome was the first occurrence of CV death, nonfatal MI or nonfatal stroke.
      - The overall event rate was 2.3 % for celecoxib, 2.5% for naproxen and 2.7 % for ibuprofen.
      - Celecoxib was non-inferior for the primary CV outcome to prescription-level dosing of both naproxen and ibuprofen.
    - **Limitations:**
      - More than 25% of patients were lost to follow up.
      - 7 out of 10 patients discontinued assigned treatment

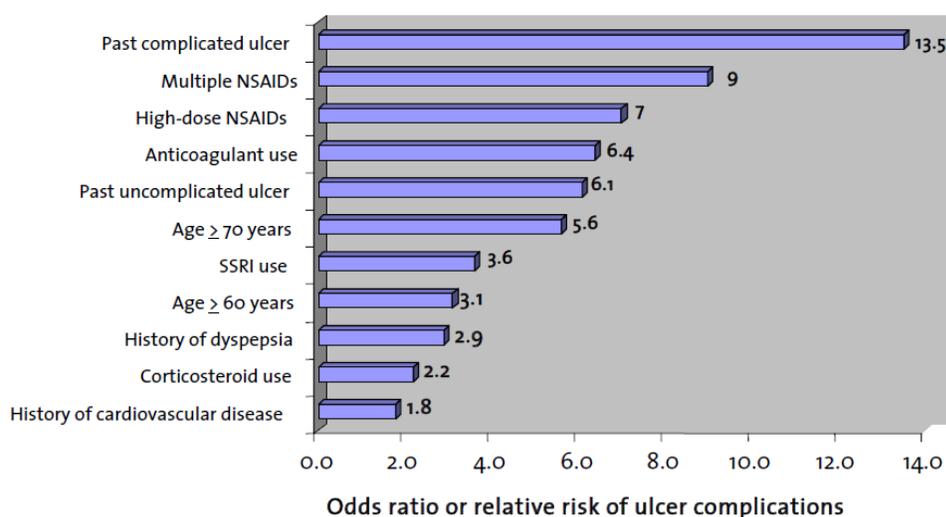


- **CONCLUSION:** In the doses used in the Precision trial, there was no difference in the primary outcome of first occurrence of CV death, nonfatal MI or nonfatal stroke between, celecoxib, ibuprofen or naproxen. Based on the meta-analyses and the Precision trial, it is difficult to conclude that one specific NSAID confers lower cardiovascular risk.

### Gastrointestinal Risk (NSAIDs)

- The following figure gives the increased risk of ulcer complications with several factors as documented by COMPUS in 2007.<sup>27</sup>

**Figure 1: Increased Risk of ulcer complications with several factors<sup>27</sup>**



- The highest risk for upper GI bleed (UGIB) for non-aspirin NSAID users (compared to non-users) occurs **within the first 30 days of use**.<sup>27</sup>
- Recommendations for gastroprotection are suggested for patients requiring anti-inflammatory therapy.<sup>28</sup>
  - High risk patients (previous UGIB; age 75 years or older; concomitant treatment with steroids or anticoagulants; or 2 or more other risk factors)
  - Patients previously treated for a complicated ulcer or dyspepsia.
- **Gastroprotective agents:**
  - Proton Pump Inhibitor (PPI): Predictable and prolonged acid suppression with effective ulcer healing and prevention
    - There is no difference between single dose and double dose therapy for the treatment of NSAID induced ulcers.<sup>27</sup>
  - Misoprostol: Effective for the prevention of gastric ulcer but has higher incidence of side effects.<sup>29</sup>



- There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding.<sup>30, 31</sup>

#### SUMMARY for Non-steroidal Anti-inflammatory Drugs

- Neuropathic pain and fibromyalgia
  - Evidence suggests no statistically significant pain reduction with oral NSAIDs.
  - No trials were identified using topical NSAIDs.
- Chronic low back pain
  - A Cochrane Review reported
    - A statistically significant improvement in pain reduction with NSAIDs versus placebo which was no longer statistically significant when a sensitivity analysis was performed on trials with a low risk of bias.
    - No difference in benefit between NSAIDs, NSAID vs acetaminophen, NSAID vs pregabalin.
    - For the comparison of NSAID (celecoxib) vs tramadol, in the outcome of patients achieving  $\geq 30\%$  improvement in pain, celecoxib showed benefit over tramadol (NNT 8).
  - No trials were identified using topical NSAIDs for chronic low back pain.
- Osteoarthritis
  - A Network Meta-analysis reported that all NSAIDs improved osteoarthritic pain versus placebo.
    - Some NSAIDs showed statistically significant benefit that reached the minimum clinically important difference; some showed statistically significant benefit, but not all participants reached the minimum clinically important difference.
  - A Cochrane Review reported moderate quality evidence for efficacy for topical diclofenac and ketoprofen in patient reported pain relief of 50% or greater.
- Risks
  - Cardiovascular
    - Based on two meta-analyses and the Precision trial, it is difficult to conclude that one specific NSAID confers lower cardiovascular risk than others.
  - Gastrointestinal
    - NSAIDs increase the risk of ulcer complications.
    - The highest risk for upper gastrointestinal bleed for non-aspirin NSAID users occurs within the first 30 days of use.
    - There are recommendations for gastroprotection depending on patient risk factors.
    - There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding.



## Tricyclic Antidepressants (TCAs)

- Official indication:
  - Health Canada-approved Indications
    - TCAs are approved for the management of major depressive disorder.
  - Uses without Health Canada Approval
    - Included in the list of unapproved uses is the treatment of chronic conditions associated with pain such as fibromyalgia, irritable bowel syndrome and neuropathic pain.<sup>6</sup>

### ***Neuropathic pain (TCAs)***

- Tricyclic antidepressants (TCAs) are recommended as first line agents by the Canadian Pain Society.<sup>19</sup> They are widely used to treat chronic neuropathic pain, usually at doses lower than those at which they exert an antidepressant effect.<sup>32</sup>
- The following includes a summary of the evidence for TCAs in the treatment of neuropathic pain as reported in Cochrane Reviews.
  - A 50% reduction from a baseline pain score has been promoted as a more clinically relevant outcome for neuropathic pain because it correlates with improvement in function, quality of life and comorbidity.<sup>33</sup>
  - None of the 4 Cochrane Reviews found studies that provided either first or second tier evidence. (See page 16 for Cochrane Levels of Evidence)
  - Amitriptyline<sup>34</sup> Cochrane Review by Moore
    - The objective of the systematic review was to assess the analgesic efficacy for relief of chronic neuropathic pain and the adverse events associated with its use in clinical trials.
    - Review included randomized, double-blind studies of at least 4 weeks duration comparing amitriptyline to placebo or another active comparator.
    - Included 17 studies; N=1342; study quality was modest and most were at high risk of bias due to small size.
    - Amitriptyline was significantly better than placebo in 2 of 7 studies **reporting useful efficacy data** (very low quality evidence).
    - Combining results from 4 studies (N=382 participants), a statistically significant benefit for amitriptyline compared to placebo was reported.
      - Risk ratio (RR) 2 (95% CI 1.5 to 2.8)
      - NNT 5 (95% CI 4 to 9) for 4 to 8 weeks
      - Due to the low quality of the evidence, the authors comment that this is probably an overestimate of the treatment effect.



- More participants experienced at least one adverse event:
  - Amitriptyline 55% vs placebo 36%
  - Risk Ratio 1.5 (95% CI 1.3 to 1.8)
  - NNH 5 (95% CI 4 to 9)
- Serious adverse events were rare: adverse event and all-cause withdrawal rates were not different but were rarely reported.
- Conclusions:
  - Most studies were small, relatively old and used methods or reported outcomes that are now recognized as overestimating benefits.
  - Compared to placebo, it is estimated that amitriptyline provides
    - NNT 5 for pain relief
    - NNH 5 for patients experiencing at least one adverse event.
  - The lack of supportive unbiased evidence for a beneficial effect should be balanced against decades of successful treatment of neuropathic pain.
  - Evidence suggests a trial is warranted; however, a minority will achieve satisfactory pain relief.
- Nortriptyline<sup>32</sup>, desipramine<sup>35</sup> and imipramine<sup>36</sup> have all been assessed as therapies for chronic neuropathic pain in adults by the Cochrane Collaboration.
  - There were few studies in each Review: all studies had one or more sources of potential bias.
  - No study provided first or second tier evidence for any outcome.
  - The authors report that data from individual studies could not be combined, but individually studies indicate some benefit versus placebo at the expense of increased adverse events.
  - Conclusion:
    - There was insufficient data of adequate quality, to conclude that these drugs work or do not work for chronic neuropathic pain conditions assessed in the studies.
- Another report<sup>37</sup> summarizing the information from these Cochrane Reviews suggests that the benefit from tricyclic antidepressants for neuropathic pain is weak and it is not possible to estimate a NNT.
- Figures for NNT and NNH have been published in a systematic review and meta-analysis funded by the International Association for the Study of Pain.<sup>38</sup>
  - They included RCTs of placebo-controlled and active comparator trials of 3 weeks or more duration. Few studies lasted longer than 12 weeks with the longest lasting 24 weeks.
  - Unpublished trials with available results were included and publication bias was assessed.



- The NNT for 50% pain intensity reduction (or 30% reduction or at least moderate pain relief) was the primary effect measure; NNH was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects.
- For TCAs based on 15 studies (N = 948)
  - Event rates for pain relief: TCA 46% vs Placebo 18% (ABI 28%)
    - NNT 4 (95% CI 3 to 4) for 12 weeks
  - Event rates for adverse events were not published.
    - NNH 13 (95% CI 9 to 24) for 12 weeks
- The quality of the evidence was assessed as moderate.
- TCAs generally have similar efficacy.
  - Start low, go slow and adjust for patient factors.
  - Effective dose in trials was 25 to 100 mg/day.
  - Tertiary amine TCAs (amitriptyline, imipramine and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential for falls.<sup>39</sup>
  - An increased risk of sudden cardiac death has been reported with TCAs at doses greater than 100 mg/day.<sup>40</sup>
- Guideline Placement
  - In the 2014 revised consensus statement from the Canadian Pain Society on pharmacological management of chronic neuropathic pain, tricyclic antidepressants are listed as a first line option along with gabapentinoids and serotonin noradrenaline reuptake inhibitors (SNRIs).<sup>19</sup>

### ***Fibromyalgia (TCAs)***

#### Amitriptyline

- Amitriptyline is widely used to treat fibromyalgia and is recommended in many guidelines.
- A recent Cochrane Review<sup>41</sup> by Moore summarized the evidence.
  - Included 9 studies lasting from 6 to 24 weeks; N = 649
  - Most studies were old, small and used methods or reported results that are now recognized as overestimating results.
  - Daily dose 25 mg to 50 mg
  - Only third tier evidence is available. Results are based on **very low quality evidence**.
  - **Results:** based on 4 trials (N=275)
    - Patients experiencing at least 50% pain reduction or equivalent:
      - Event rates: Amitriptyline 36% vs placebo 11%
      - Risk ratio (RR): 3.0 (95% CI 1.7 to 4.9)
      - NNT 4 (95% CI 3 to 7)



- Patients experiencing at least one adverse event:
  - Event rates: amitriptyline 78% placebo 47%
  - RR 1.5 (95% CI 1.3 to 1.8)
  - NNH 3 (95% CI 3 to 5)
- Adverse event and all-cause withdrawal rates were not different.
- Lack of efficacy withdrawals were more common in the placebo group (12% vs 5%).
- There were no consistent differences between amitriptyline and placebo or other active comparators for relief of symptoms such as quality of life, fatigue, poor sleep or tender points.
- Amitriptyline is one treatment option for fibromyalgia; a minority of patients will achieve satisfactory pain relief. Adverse events were high; however, they did not result in increased rates of withdrawal.

#### Nortriptyline

- One 8 week RCT (N=188 Brazilian patients) evaluated amitriptyline, nortriptyline and placebo in patients with fibromyalgia.<sup>42</sup>
  - Outcomes included the number of tender points, the Fibromyalgia Impact Questionnaire and the verbal scale of global evaluation.
  - Results: the 3 groups improved in all parameters (% improved)
    - Fibromyalgia Impact Questionnaire: amitriptyline 36.5%; nortriptyline 26.7%; placebo 24%
    - Number of tender points: amitriptyline 13.9%; nortriptyline 19.5%; placebo 8.57%
    - Verbal scale of global evaluation: amitriptyline 86.5%; nortriptyline 72.2%; placebo 57.6%
  - Patient's subjective global assessment of improvement of amitriptyline versus placebo was the only outcome demonstrating a statistically significant improvement.
  - BOTTOM LINE: Limited data suggest nortriptyline results in improvement of function and global evaluation compared to baseline; similar to amitriptyline.
- Guideline Placement:
  - Canadian Guidelines<sup>7</sup> suggest antidepressants with pain modulating effects (e.g. TCAs) as an option for the management of fibromyalgia.

#### **Chronic Low Back Pain (TCAs)**

- A recently published systematic review of pharmacologic therapies for low back pain<sup>9</sup> referred back to a 2008 Cochrane Review as no new RCTs for TCAs in chronic low back pain were identified.
  - Results from 4 RCTs reported no effect of TCAs on either pain relief or improvement in function compared to placebo.



- Strength of evidence was rated as moderate for pain relief and low for improvement in function.
- **Guideline placement:**
  - Toward Optimized Practice Guidelines suggest there is insufficient evidence to recommend for or against TCAs for acute low back pain with or without leg dominant pain.<sup>11</sup>
  - Guidelines from the American College of Physicians (2017) do not recommend TCAs as an option for chronic low back pain.<sup>12</sup>

### ***Osteoarthritis (TCAs)***

- We were unable to find any published RCTs for tricyclic antidepressants in the treatment of osteoarthritis.
- The NortIKA study with nortriptyline is ongoing.<sup>1</sup>

### ***Risks/Harms***

- TCAs cause numerous side effects including: drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain and arrhythmia.<sup>19</sup>
- Tertiary amine TCAs (amitriptyline, imipramine and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of **major anticholinergic and sedative side-effects** and potential for falls.<sup>39</sup>
- An increased risk of sudden cardiac death has been reported with TCAs at doses greater than 100 mg/day.<sup>40</sup>
- QTc Interval prolongation:
  - TCAs should not be used in patients with congenital long QTc interval.
  - TCAs are associated with torsades de pointes (TdP) in certain circumstances: excessive dose, patients with hypokalemia, when taken with interacting drugs OR by creating conditions that facilitate or induce TdP e.g. inhibiting metabolism of a QTc prolonging medication or by causing an electrolyte disturbance that induces TdP. (Credible meds website <https://www.crediblemeds.org/> )

### **SUMMARY Tricyclic antidepressants**

- Neuropathic pain
  - TCAs are not officially approved in Canada for the treatment of neuropathic pain.
  - Cochrane Reviews suggest that the evidence for benefit is weak.
  - Another systematic review and meta-analysis reported
    - NNT of 4 (95% CI 3 to 4) for 12 weeks for active pain relief
    - NNH of 13 (95% CI 9 to 24) for adverse events



- Evidence indicates a trial is warranted; however, a minority will achieve satisfactory pain relief.
- Recommended as a first line option for neuropathic pain by the Canadian Pain Society.
- Fibromyalgia
  - TCAs are not officially approved in Canada for the treatment of fibromyalgia.
  - A Cochrane Review of amitriptyline reported:
    - NNT of 4 (95% CI 3 to 7) for patients experiencing at least a 50% pain reduction
    - NNH 3 (95% CI 3 to 5) for patients experiencing at least 1 adverse event.
  - Nortriptyline has not been shown to be better than amitriptyline for fibromyalgia.
  - Guidelines list TCAs as a treatment option for fibromyalgia.
- Chronic low back pain
  - Results of 4 RCTs reported no effect of TCAs on either pain relief or improvement in function compared to placebo for low back pain.
- For osteoarthritis
  - There is insufficient evidence to support the use of tricyclic antidepressants in the treatment of osteoarthritis.
- Risks/harms
  - Side effects include: drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmias and QTc interval prolongation.
  - Tertiary amine TCAs (amitriptyline, imipramine and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of **major anticholinergic and sedative side-effects** and potential for falls.
  - An increased risk of sudden cardiac death has been reported with TCAs at doses greater than 100 mg/day.

## **Serotonin Norepinephrine Reuptake Inhibitors**

### **Duloxetine**

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) and weakly inhibits dopamine uptake with central nervous system activity. Its analgesic efficacy in central pain is related to its influence on descending inhibitory pain pathways but the exact mechanism is not known.

- Official indications:
  - Duloxetine has the official indication for the 4 conditions discussed in this document: neuropathic pain (diabetic peripheral neuropathy), fibromyalgia, chronic low back pain, and osteoarthritis.

- Duloxetine trials have a moderate to high risk of bias:
  - Most trials are industry funded.
  - Short duration
    - Primary endpoints were measured at 8-15 weeks.
  - Risk of selective outcome reporting
    - Most trials used the last observation carried forward method which can over estimate treatment efficacy when adverse event rate withdrawals are high.<sup>5</sup>
  - High drop-out rates
  - Possible selective publication due to incomplete reporting of all trials.

**Neuropathic Pain (Duloxetine)**

- Cochrane Review 2014<sup>33</sup> by Lunn
  - Included 9 trials; N = 2776
  - Authors report an adequate amount of MODERATE quality evidence to support use.
  - Included patients with any form of diabetic peripheral neuropathy (DPN) or chronic neuropathic pain (8 trials for DPN; N= 2728 and 1 trial for central neuropathic pain; N= 48).
  - Primary Outcomes:
    - Short-term (up to and including 12 weeks) improvement of pain compared with baseline using validated scales of pain intensity or pain relief (both visual analogue and categorical scales)
    - Where reports expressed pain relief as none, minor, moderate, major or complete, only moderate, major or complete were seen as improvement.
    - Where studies measured pain with a continuous scale, improvement was defined as a reduction of 50% or more from baseline on that scale.

**Table 4: Cochrane Review: Duloxetine vs Placebo in neuropathic pain<sup>33</sup>**

	Event rates from meta-analysis		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 12 weeks
	Duloxetine 60 mg	PBO		
Patients experiencing ≥ 50% improvement in pain	46%	26%	ABI 20%	NNT 5 (95% CI 4 to 7)
Adverse events leading to discontinuation	11%	6%	ARI 5%	NNH 18 (95% CI 13 to 30)
	Duloxetine 120 mg	PBO		
Patients experiencing ≥ 50% improvement in pain	49%	34%	ABI 15%	NNT 7 (95% CI 5 to 12)
Adverse events leading to discontinuation	20%	8%	ARI 12%	NNH 10 (95% CI 7 to 13)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; ARI – absolute risk increase; NNT/H number needed to treat/harm;



- There was similar benefit with 60 mg and 120 mg per day but more patients withdrew due to adverse events with the higher dose.
- **Guideline Placement:**
  - Duloxetine is a 1st line option. TCAs OR gabapentin OR pregabalin are also considered first line options for **neuropathic pain** by the Canadian Pain Society.<sup>19</sup>

**Fibromyalgia (Duloxetine)**

- **Cochrane Review 2014<sup>33</sup> by Lunn**
  - Included patients (N= 2249) with fibromyalgia (6 trials for fibromyalgia and 3 trials for depression with physical symptoms).
  - Authors comment there is low quality evidence for use; more evidence is required to make definitive recommendations.
  - **Primary Outcomes:**
    - Short-term (up to and including 12 weeks) improvement of pain compared with baseline using validated scales of pain intensity or pain relief (both visual analogue and categorical scales)
      - Reports expressing pain relief as none, minor, moderate, major or complete, only moderate, major or complete were seen as improvement.
      - Studies measuring pain with a continuous scale, defined improvement as a reduction of 50% or more from baseline on that scale.

**Table 5: Cochrane Review: Duloxetine vs Placebo in fibromyalgia<sup>33</sup>**

	Event rates from meta-analysis		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 12 weeks
	Duloxetine 60 mg	PBO		
Patients experiencing ≥ 50% improvement in pain	36%	23%	ABI 13%	NNT 8 (95% CI 4 to 21)
Adverse events leading to discontinuation (pooled from all trials)	11%	6%	ARI 5%	NNH 18 (95% CI 13 to 30)
	Duloxetine 120 mg	PBO		
Patients experiencing ≥ 50% improvement in pain	35%	21%	ABI 14%	NNT 7 (95% CI 5 to 11)
Adverse events leading to discontinuation (pooled from all trials)	20%	8%	ARI 12%	NNH 10 (95% CI 7 to 13)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; ARI – absolute risk increase; NNT/H number needed to treat/harm;

- **Guideline Placement:**
  - Duloxetine is recommended in the Canadian Guidelines as a treatment option for **fibromyalgia**.<sup>7</sup>
  - NHS Guidelines (SIGN) suggest duloxetine may be considered as a treatment option.<sup>21</sup>



### ***Chronic Low Back Pain (Duloxetine)***

- There are 3 randomized controlled trials (N=1041 in total) comparing duloxetine to placebo.<sup>43,44,45</sup>
- Patient population in trials (N= 1041)
  - Inclusion:
    - Male and female outpatients ≥ 18 years of age with CLBP as the primary painful condition
    - Pain must have been present in lower back (T-6 or below) for most days for the past 6 months or longer.
    - A weekly mean of 24-hour average pain score ≥ 4 at baseline
    - Patients were to have pain either restricted to low back or associated with radiation to thigh proximally (class 1 and 2 per the Quebec Task Force on Spinal Disorders), with no radicular symptoms or signs.
  - Exclusion:
    - Patients with clinical signs and/or radiographic evidence of spinal stenosis, high-grade spondylolisthesis (grade 3 and 4), and spinal fracture
    - Patients with clinical signs and/or radiographic or electrophysiology evidence of radicular compression
    - A history of more than 1 low back surgery and had a low back surgery within 12 months before study entry
    - Had invasive procedures aimed to reduce low back pain within the past month before study entry
    - Participated in previous studies investigating duloxetine hydrochloride
    - Treated with monoamine oxidase inhibitor within 14 days of randomization
    - Had any previous diagnosis of psychosis, bipolar disorder, or schizoaffective disorder
    - Had current major depressive disorder
    - Had disability compensation or litigation
    - Were female participants who were pregnant or breast-feeding
    - Had body mass index ≥ 40 kg/m<sup>2</sup>
  - The selection of study candidates was not based on either previous or current use of any particular analgesic.
    - Patients regularly using (for ≥ 14 days per month for 3 months before study entry) therapeutic doses of NSAIDs or acetaminophen at the time of the study entry were permitted to continue these therapies as long as the doses or frequency were not changed during the study.
  - Continuation of long-term, regular, nonpharmacological treatments such as physical therapy or relaxation therapy was permitted.



- Use of antidepressants, anticonvulsants, muscle relaxants, or analgesics (other than NSAIDs), and procedures aimed to relieve pain (including acupuncture, chiropractic treatment, and transcutaneous electrical nerve stimulation) **were not allowed during the study.**
- Episodic use of short-acting analgesics (defined as no more than 3 consecutive days or no more than 20 total days) was allowed for the management of breakthrough CLBP (rescue therapy) or acute conditions unrelated to lower back pain.
- **Primary Outcomes:**
  - Changes in Brief Pain Inventory (BPI) 24-hour average pain score during the 12 and 13 week trial for 2 of the trials
  - Reduction in pain severity measured by the weekly mean of the 24-hour average pain ratings (on a scale of 0-10) after 13 weeks of treatment
  - **Duloxetine vs Placebo<sup>43</sup>**
    - The primary outcome, changes in Brief Pain Inventory (BPI) 24-hour average pain score was statistically significant ( $p \leq 0.001$ ). The actual numbers were not documented in the paper; however, baseline numbers were provided and the results presented in a graph.
    - The number of patients receiving duloxetine achieving 50% improvement in pain at 12 weeks was **statistically significant** in one of the three trials.
      - This was a secondary efficacy measure.

**Table 6: Duloxetine vs Placebo in low back pain<sup>43</sup>**

	Event rates		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 12 weeks
	Duloxetine 60 mg	PBO		
Patients experiencing $\geq 50\%$ improvement in pain	49%	35%	ABI 14%	NNT 8 (95% CI 4 to 23)
Adverse events leading to discontinuation	15.2%	5.4%	ARI 9.8%	NNH 11 (95% CI 6 to 26)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; ARI – absolute risk increase; NNT/H number needed to treat/harm;

- Guideline Placement:
  - Towards Optimized Practice: There is inconclusive evidence for use of duloxetine for **chronic low back pain** unless there is a neuropathic component.<sup>11</sup>
  - See Appendix 1 for a comparison chart of guidelines.

### ***Osteoarthritis (OA) of the Knee (Duloxetine)***

Sensitization of the central nociceptive processing has been increasingly recognized as a potential contributor to pain in knee OA patients.

- There are 2 RCTs providing evidence suggesting that duloxetine may be effective.<sup>46,47</sup> Results have been pooled in a meta-analysis.<sup>48</sup>



- Duration 13 weeks; N = 487
- Inclusion criteria
  - Male and female outpatients of  $\geq 40$  years of age, who met the American College of Rheumatology clinical and radiographic criteria for the diagnosis of osteoarthritis of the knee with pain for  $\geq 14$  days of each month for 3 months before study entry
  - A mean score  $\geq 4$  on the 24-hour average pain score (0–10)
  - Patients with bilateral osteoarthritis were required to identify an index knee on which to base ratings throughout the study.
  - Patients had to agree to maintain their usual activity level throughout the course of the study.
- Exclusion criteria
  - Patients were excluded if they had a body mass index  $> 40 \text{ kg/m}^2$  (one study used  $> 30 \text{ kg/m}^2$ )
  - A confounding painful condition that would interfere with assessment of the index joint
  - A diagnosis of inflammatory arthritis or an autoimmune disorder
  - They had received invasive therapies to the knee in the past 3 months, knee arthroscopy of the index knee within the past year, or joint replacement of the index knee at any time.
  - Those who had a prior synovial fluid analysis indicative of a diagnosis other than osteoarthritis.
  - Non-ambulatory, or required the use of crutches or a walker
  - Patients who had psychiatric disorders, including major depressive disorder
  - Previous exposure to duloxetine
  - Women who were pregnant or breastfeeding
  - A history of substance abuse or dependence, positive urine drug screen for any substance of abuse, existence of any serious medical or psychiatric condition that could compromise participation in the study, a history of recurrent seizures, uncontrolled narrow angle glaucoma, acute liver injury or severe cirrhosis, known hypersensitivity to duloxetine or any of the inactive ingredients, or frequent or severe allergic reactions to multiple medications.
- Patients who entered the trial taking an NSAID or acetaminophen were permitted to continue taking the drug(s) during the study.
- Patients were stratified according to whether they were NSAID/acetaminophen users.
  - An NSAID/acetaminophen user was defined as a patient who took an NSAID or acetaminophen at a therapeutic dose for  $> 14$  days per month for 3 months before study entry.



- Patients were not permitted to have their dose of NSAIDs or acetaminophen increased over doses at Visit 1 but were permitted to have their dose decreased or discontinued. Any change in or initiation of medications during the study required consultation with the investigator.
- Episodic use of short-acting analgesics was permitted for acute injury or surgery or for rescue from an osteoarthritis knee pain flare. “Episodic use” was defined as no more than three consecutive days and was not to exceed 20 total days during the study.
- Primary outcome was based on pooled data from 2 trials (Chappell 2009 & 2011): weekly mean 24-hour average pain scores
- Patients achieving 50% improvement in pain at 13 weeks was **statistically significant**.<sup>48</sup>
  - This was a secondary efficacy measure.

**Table 7: Meta-analysis: duloxetine in osteoarthritis<sup>48</sup>**

	Event rates (pooled data)		Absolute benefit/risk increase (95% Confidence Interval)	NNT/NNH (95% CI) for 13 weeks
	Duloxetine 60 and 120 mg	PBO		
Patients experiencing ≥ 50% improvement in pain	42%	26%	ABI 16%	NNT 7 (95% CI 4 to 13)
Adverse events leading to discontinuation	16%	6%	ARI 9.8%	NNH 10 (95% CI 7 to 20)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; ARI – absolute risk increase; NNT/H number needed to treat/harm

➤ Guideline Placement:

- American College of Rheumatology: Duloxetine is a possible treatment option for patients with **symptomatic OA of the knee** who have not had adequate response to both non pharmacologic and pharmacologic modalities and are either unwilling or not a candidate for total joint arthroplasty.<sup>15</sup>

**Risks/Harms**

- In the evidence reviewed, the NNHs for adverse events leading to discontinuation with duloxetine versus placebo were 9 to 18 for 12 weeks.
- The most commonly reported side effects include nausea, dry mouth, constipation, somnolence, fatigue and dizziness.<sup>33,43,44,45,48,6</sup>

**Venlafaxine**

- Venlafaxine is a serotonin norepinephrine reuptake inhibitor (SNRI).
  - This is the same class of antidepressants as duloxetine.
- It is currently officially indicated for:
  - Depression
  - Generalized Anxiety Disorder



- Social Anxiety Disorder (Social Phobia)
- Panic Disorder<sup>6</sup>
- There is limited low quality evidence evaluating venlafaxine for neuropathic, chronic low back pain, fibromyalgia or osteoarthritis.
- Available evidence is of **low quality** which makes it difficult to make a recommendation for the use of venlafaxine for the treatment of chronic pain.

SUMMARY of serotonin norepinephrine reuptake inhibitors

Duloxetine

- Duloxetine has the official indication for the 4 conditions: neuropathic pain (diabetic peripheral neuropathy), fibromyalgia, chronic low back pain and osteoarthritis.
- Neuropathic pain
  - A Cochrane Review of duloxetine in **neuropathic pain** reported
    - Patients experiencing  $\geq 50\%$  improvement in pain at 12 weeks:
      - NNT 5 (95% CI 4 to 7) for duloxetine 60mg and NNT 7 (95% CI 5 to 12) for 120mg
      - Patients with adverse events leading to discontinuation;
        - NNH 18 (95% CI 13 to 30) for duloxetine 60mg and NNH 10 (95% CI 7 to 13) for duloxetine 120 mg
- Fibromyalgia
  - There is evidence rated as low quality leading to NNTs 8 and 7 and NNHs 18 and 10 for duloxetine 60mg and 120 mg respectively.
- Chronic low back pain
  - There is evidence suggesting a consideration of duloxetine for use when there is a neuropathic component.
- Osteoarthritis
  - There is evidence suggesting duloxetine might be a treatment option for patients who have an inadequate response to both non-pharmacologic and other pharmacologic treatment options.
  - The most commonly reported side effects include: nausea, dry mouth, constipation, somnolence, fatigue and dizziness.
- Venlafaxine
  - Venlafaxine does not have the official indication for any of the 4 chronic pain conditions.
  - There is limited evidence rated as low quality evaluating venlafaxine for neuropathic pain, fibromyalgia, chronic low back pain, or osteoarthritis.



## **Gabapentinoids**

- Official indications<sup>6</sup>
  - Gabapentin: As an adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.
  - Pregabalin:
    - The management of neuropathic pain associated with:
      - Diabetic peripheral neuropathy
      - Postherpetic neuralgia.
    - The management of neuropathic pain associated with spinal cord injury.
    - The management of pain associated with fibromyalgia.
- Gabapentinoids are increasingly used for off-label indications.
- One recent Canadian study has shown that one of the most frequent off label indication is chronic low back pain, and in this study population (taken from a sample of chronic non-cancer pain patients in the Quebec Pain Registry and the Fibromyalgia Patients Registry) 75% of patients had taken pregabalin for off-label conditions.<sup>49</sup>

### **Gabapentin**

- Gabapentin is structurally related to the neurotransmitter GABA; however, gabapentin and its metabolites do not bind to GABA(A) or GABA(B) receptors or influence the degradation or uptake of GABA. The mechanism by which gabapentin exerts its analgesic and anticonvulsant effects is unknown.
- Since the late 1990's gabapentin has been increasingly used for many off-label indications including various types of chronic pain.

### **Pregabalin**

- Pregabalin is a GABA analog that strongly binds to the alpha(2)-delta site in CNS tissues. The exact mechanism of action is not fully understood.
  - Binding to the alpha(2)-delta subunit may be involved in pregabalin's effects on neuropathic pain and seizure control.
  - Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem that modulate pain transmission in the spinal cord.
  - The mechanism of action confers analgesic, antiseizure and anxiolytic effects.<sup>50</sup>

### ***Neuropathic Pain (Gabapentinoids)***

A recently published systematic review and meta-analysis<sup>38</sup> has led to a revision of the recommendations for the pharmacotherapy of neuropathic pain.



- Primary outcome was patients with 30% OR 50% pain reduction OR at least moderate pain relief. Duration: at least 3 weeks.

**Gabapentin (N = 3503)**

- Nine of 14 RCTs with gabapentin (dose range 900-3600 mg/day) showed a positive effect.
  - NNT 6 (95% CI 5 to 8)
  - NNH for one patient to drop out due to adverse events
    - NNH 26 (95% CI 15 to 79)
- Four of 6 RCTs looking at gabapentin extended release (dose range 1200-3600mg/day) showed a positive effect.
  - NNT 8 (95% CI 6 to 13)
  - NNH for one patient to drop out due to adverse events
    - NNH 32 (95% CI 17 to 230)
- There was no evidence of a dose response effect for gabapentin or gabapentin extended release<sup>38</sup>

**Pregabalin (N = 5940)**

- Meta-analysis of 25 placebo controlled trials with pregabalin showed a positive outcome in 18 studies.
  - NNT 8 (95% CI 7 to 9)
  - NNH for one patient to drop out due to adverse events:
    - NNH 14 (95% CI 12 to 17)
- There was a dose response effect with higher response seen at 600 mg compared with 300 mg for pregabalin.

**Table 8: Meta-analysis: gabapentinoids in neuropathic pain<sup>38</sup>**

	Event rates (pooled data) for primary outcome (pain relief)		Absolute benefit increase (95% Confidence Interval)	NNT/NNH (95% CI) for ≥ 3 weeks
	Drug	PBO		
<b>Gabapentin (overall) (N=3503)</b>	35%	20%	ABI 15%	NNT 7 (95% CI 6 to 9)
<b>Pregabalin (N= 5940)</b>	39%	24%	ABI 15%	NNT 8 (95% CI 7 to 9)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; NNT- number needed to treat

Cochrane Review 2017<sup>51</sup> by Wiffen Gabapentin for chronic neuropathic pain in adults

- Included 37 studies, N = 5914 patients with neuropathic pain syndromes, predominantly **post herpetic neuralgia** or **painful diabetic neuropathy** with duration of 2 weeks or longer.
  - Most studies used gabapentin or gabapentin extended release 1200 mg/day or more.
- There was a high risk of bias due to small size of studies and handling of data.

➤ **Results:**

- Post herpetic neuralgia: 8 studies, N = 2260 patients, moderate quality evidence
- Painful diabetic neuropathy: 7 studies, N = 1439 patients, moderate quality evidence

**Table 9: Cochrane Review: Gabapentin in neuropathic pain<sup>51</sup>**

	Event rates In post herpetic neuralgia		Risk Ratio	Absolute benefit increase (95% Confidence Interval)	NNT/NNH (95% CI) for 4 to 12 weeks
	Gabapentin	PBO			
Patients experiencing ≥ 50% improvement in pain	32%	17%	1.8 (95% CI 1.5 to 2.1)	ABI 15%	NNT 7 (95% CI 5 to 9)
Patients experiencing ≥ 30% improvement in pain	46%	25%	1.8 (95% CI 1.6 to 2.0)	ABI 21%	NNT 5 (95% CI 4 to 6)
	Event rates In painful diabetic neuropathy				
	Gabapentin	PBO			
Patients experiencing ≥ 50% improvement in pain	38%	21%	1.9 (95% CI 1.5 to 2.3)	ABI 17%	NNT 6 (95% CI 5 to 8)
Patients experiencing ≥ 30% improvement in pain	52%	37%	1.4 (95% CI 1.3 to 1.6)	ABI 15%	NNT 7 (95% CI 5 to 10)
Overall adverse events leading to discontinuation	NA	NA			NNH 30 (95% CI 20 to 65)

PBO - placebo; CI – confidence interval; ABI – absolute benefit increase; NNT/H number needed to treat/harm; NA – not available

- Evidence for other types of neuropathic pain is limited.
- For all conditions, combined adverse events (dizziness, somnolence, peripheral edema, gait disturbance) were more common with gabapentin vs placebo.
- **Bottom Line:** Moderate quality evidence that gabapentin at doses 1200 mg/day or greater will improve pain in some people with moderate to severe post herpetic neuralgia or painful diabetic neuropathy.

Cochrane Review 2009<sup>52</sup> by Moore Pregabalin for **acute and chronic pain** in adults

- Included 19 studies, N = 7003 patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia
  - Doses ranged from 150 mg to 600 mg daily.
  - Study duration was 4-14 weeks, most were longer than 6 weeks.
  - Studies were large with reasonable group sizes.
  - Studies were rated to have a low risk of bias.
  - Almost all studies were drug company funded.
  - Most studies used a short titration period of one week to establish a fixed daily dose.
  - Pregabalin 150 mg was generally ineffective, except in post herpetic neuralgia.



- There was no evidence to support use of pregabalin in acute pain syndromes.
- There was a greater response to higher doses across all conditions with the lowest NNT for postherpetic neuralgia and painful diabetic neuropathy being observed at 600mg/day.
- For fibromyalgia, the lowest NNT was observed at 450 mg/day.
- NNT for 50% pain relief for pregabalin 600mg vs placebo were:
  - Postherpetic neuralgia NNT 4 (95% CI 3 to 5)
  - Painful diabetic neuropathy NNT 5 (95% CI 4 to 7)
  - Central neuropathic pain NNT 6 (95% CI 4 to 14)
  - Fibromyalgia NNT 11 (95% CI 7 to 21)
- Higher doses of pregabalin produced higher adverse event discontinuation rates.
  - NNH at 300 mg across all conditions: 9 to 17
  - NNH at 600 mg across all conditions: 5 to 9

#### 2017 Tools for Practice- Gabapentin and Chronic Pain: Missing Evidence and Real Effect?<sup>53</sup>

- "In carefully selected patients with peripheral neuropathic pain, gabapentin may offer moderate or more pain relief for 1 in every 6-8 patients, but causes adverse events in a similar number. There is no trial evidence pregabalin is superior to gabapentin."
- Guideline Placement:
  - Canadian Pain Society Guidelines: Gabapentinoids are a 1st line option for neuropathic pain. TCAs OR duloxetine are also considered first line options.<sup>19</sup>

#### ***Fibromyalgia (Gabapentinoids)***

- Cochrane Review 2017<sup>54</sup> by Cooper Gabapentin for fibromyalgia pain in adults
  - One study, N = 150 (from 2007)
    - Majority of patients were women (90%) and white (97%).
  - 12 week multicentre, randomized, double-blind, placebo controlled, used doses between 1200-2400 mg/day, titrated over a 6-week period.
  - Diagnosis of fibromyalgia according to American College of Rheumatology 1990 criteria
  - Used last observation carried forward imputation method for drop outs.
  - Outcomes:
    - 30% reduction in pain
      - Event rates: Gabapentin 51% vs Placebo 31% (p=0.014)  
Absolute benefit increase (ABI) 20% NNT 5 for 12 weeks (95% CI not available)  
Very low quality evidence.
    - Adverse events leading to discontinuation:
      - Event rates: Gabapentin 16% vs Placebo 9% (p=0.34)



- 50% reduction in pain was not reported.
- Authors conclusion: Insufficient evidence to support or refute the use of gabapentin in fibromyalgia.
- Cochrane Review 2016<sup>50</sup> by Derry Pregabalin for pain in fibromyalgia in adults
  - Eight trials included in this review, five studies (N = 3283) were classical clinical trial design with randomized placebo control using fixed dose titration strategy.
  - Includes report on 2 studies (N = 1492 patients initial titration, 687 randomized) using enriched enrolment randomized withdrawal (EERW) design, although these did not contribute to the analyses.
  - The authors rate this as high quality evidence as studies were randomized, double blind, and had relatively large numbers of participants (no trial had fewer than 50 participants per arm).
  - **However:** studies lasted 8-13 weeks for the 5 classical trials, and all used last observation carried forward as an imputation method which can overestimate treatment effect.<sup>5</sup> The authors still rate the evidence as high quality as the NNT estimations are similar between last observation carried forward imputed analyses and non-imputed analyses from individual patient data analyses from the same studies.
  - Inclusion criteria:
    - Majority were women (89-95%) and white (76-96%)
    - Mean age 47-50 years
    - Duration of fibromyalgia symptoms averaged 4 years
    - Baseline pain intensity 6.5-7.8/10
    - Diagnosis of fibromyalgia according to American College of Rheumatology 1990 criteria
  - Exclusion criteria:
    - Patients with depression
    - Concomitant medical or rheumatic conditions
    - "Clinically significant or unstable medical or psychological conditions"
    - Trials were with pregabalin monotherapy. Any preexisting therapy was discontinued prior to trial entry.
  - Primary Outcome: Pregabalin vs placebo (8 to 13 weeks)
    - >50% improvement in pain
      - 150 mg NNT = not calculated by authors
      - 300 mg NNT = 14 (95% CI 9 to 32)
      - 450 mg NNT = 10 (95% CI 7 to 15)
      - 600 mg NNT = 11 (95% CI 7 to 21)



- Patient Global Impression of Change: very much improved (substantial benefit)
  - 300 mg NNT = 16 (95% CI 10 to 37)
  - 450 mg NNT = 12 (95% CI 9 to 20)
  - 600 mg NNT = 22 (95% CI 13 to 89)
- A similar magnitude of effect was observed when other outcome measures were examined, such as >30% improvement in pain, or a moderate benefit on the patient global impression of change. NNTs for these outcomes ranged between 7-11.
- Adverse event withdrawals:
  - NNH at 300 mg: 17 (95% CI 10 to 41)
  - NNH at 450 mg: 11 (95% CI 8 to 17)
  - NNH at 600 mg: 6 (95% CI 5 to 8)
- Author's conclusion: Some patients may achieve good relief with lower doses of pregabalin, however 450 mg/day appeared to provide the best balance between benefit and adverse event.
- Guideline Placement:
  - Canadian guidelines for fibromyalgia suggest anticonvulsants as a treatment option.<sup>7</sup>

### ***Chronic Low Back Pain (Gabapentinoids)***

- One meta-analysis<sup>55</sup> of 8 studies examined gabapentinoids in chronic low back pain.
  - Excluded studies in patients of predominant leg pain or spinal stenosis.
  - Studies were 4-14 weeks duration.
  - Doses ranged from 300-3600 mg/day for gabapentin and 100-600 mg/day for pregabalin.
  - Risk of bias in studies due to outcome threshold, assessment time point and low sample size.
  - Pooling of data was performed using pain scores at the end of the studies.
  - Three studies compared gabapentin (N=94) with placebo (N=91) and showed minimal improvement of pain.
    - Mean difference - 0.22, 95% CI - 0.5 to 0.07)
    - GRADE: Very low quality of evidence.
  - There were no studies comparing pregabalin with placebo.
  - Three studies compared pregabalin (N=163) with other medications: tramadol/acetaminophen, amitriptyline, and celecoxib (N=169). The results favoured the other medications group but the clinical relevance of this benefit is questionable.
    - Mean difference 0.42, 95% CI 0.2 to 0.64)
    - GRADE: Very low quality of evidence



- The heterogeneity of studies looking at pregabalin as an adjunct to other agents (buprenorphine, tapentadol, and celecoxib) was too great to allow for pooling of data.
- Adverse event withdrawal rates were not calculated as the reasons for withdrawal were not provided in all studies.
- Dizziness was more common with pregabalin compared to active control with NNH 11 (95% CI 6 to 30).
- **Guideline Placement:**
  - Toward Optimized Practice: There is insufficient evidence to recommend for or against anticonvulsants for acute low back pain with or without leg dominant pain unless there is a neuropathic component to the chronic low back pain.<sup>11</sup>

### ***Sciatica***

- One large, well designed RCT (N = 209) examined pregabalin versus placebo for acute and chronic sciatica and found no significant difference at either 8 or 52 weeks for either leg pain intensity, degree of disability, back pain intensity or other quality of life measures.<sup>56</sup>
  - Inclusion criteria:
    - Sciatica for 1 week to 1 year
    - Median duration of pain was 2 months.
    - Sciatica was defined as pain radiating into one leg below the knee accompanied by at least one of the following: dermatomal leg pain, myotomal weakness, sensory deficits or diminished reflexes.
  - Exclusion criteria
    - Known or suspected serious pathologic condition of the spine
    - Considering or planning to undergo interventional procedures
    - Severe depression or suicidal thoughts
    - Any antidepressant, anticonvulsant or other medication considered for neuropathic pain, and the patient was unable to cease taking such medication.
  - Once in the trial, patients could receive additional analgesic medications if it was considered suitable by the trial clinician.
    - Percentage of patients using other medications: pregabalin 72% vs placebo 16%
    - Other medications used:
      - NSAIDs: pregabalin 35% vs placebo 33%
      - Combination opioid analgesics: pregabalin 25% vs placebo 16%
      - Strong opioid analgesics: pregabalin 16% vs placebo 17%
  - A total of 209 patients were randomized to placebo or pregabalin: 207 patients were included in intent to treat analysis.
    - Mean difference in leg pain intensity score for pregabalin vs placebo at 8 weeks was: 0.5 (95% CI -0.2 to 1.2, p=0.19)



- This outcome was also not significant at week 52, mean difference between treatment groups: 0.3 (95% CI -0.5 to 1.0, p=0.46).
- No effect of pregabalin vs placebo at either week 8 or 52 for extent of disability, back pain intensity, or global perceived effect.
- Strengths of this study:
  - Not industry funded
  - Sample size was statistically powered (with 90% power) to detect clinically important differences of 1.5 points in the leg pain intensity score.
  - 94% of patients in the pregabalin group and 92% of patients in the placebo group completed 8 weeks of trial. 86% in each group completed 52 weeks.
  - Multiple imputation methods were not required as less than 10% of primary outcome data was missing.
- Potential weakness:
  - Data for pain reduction scores are not presented as responder analysis and thus NNTs could not be calculated.

### ***Osteoarthritis (Gabapentinoids)***

- We did not find any RCTs evaluating gabapentinoids versus placebo in osteoarthritis.

### ***Risks/Harms***

#### **Abuse potential:**

- Gabapentin and pregabalin diversion, misuse and abuse are on the rise.
- There is a growing illicit market for pregabalin and gabapentin which are also being bought online from unregulated websites. They are increasingly misused by individuals seeking to mitigate opioid withdrawal or potentiate other substances including opioids and benzodiazepines.<sup>71</sup>
- Euphoria, enhanced sociability, MDMA-like effects and enhanced relaxation have all been cited as potential rewards with use.
- There is an increased risk of harm, including death, when they are used in combination with opioids.<sup>72</sup>
  - There is higher bioavailability of gabapentin when co-prescribed with opioids. This is most likely due to greater absorption as a result of an opioid-induced decrease in intestinal motility.
- A recent case controlled study has shown an increased risk of death when gabapentin is co-prescribed with opioids compared to opioids alone.



- Adjusted OR 1.56 (95% CI 1.06 to 2.28) with moderate dose gabapentin (900 mg to 1800mg)
- Adjusted OR 1.58 (95% CI 1.09 to 2.27) with high dose gabapentin (> 1800 mg/day)<sup>72</sup>
- According to the product monograph, physicians should exercise caution in patients with a history of substance abuse and the patient should be monitored for symptoms of misuse, abuse or dependence.<sup>6</sup>

### SUMMARY for gabapentinoids

- Official indication:
  - Gabapentin: As an adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.
  - Pregabalin:
    - The management of neuropathic pain associated with:
      - Diabetic peripheral neuropathy
      - Postherpetic neuralgia.
    - The management of neuropathic pain associated with spinal cord injury.
    - The management of pain associated with fibromyalgia.
- Neuropathic pain
  - Gabapentin: Results of a Cochrane Review
    - Patients experiencing  $\geq 50\%$  improvement in pain: NNT 7 (95% CI 5 to 9)
    - Adverse events leading to discontinuation: NNH 30 (95% CI 20 to 65)
  - Pregabalin: Results of a Cochrane Review
    - Patients experiencing  $\geq 50\%$  improvement in pain: NNT 4 to 6 (95% CI 3 to 14)
    - Adverse events leading to discontinuation: NNH 9 to 17
    - There was a greater response to higher doses with the lowest NNT for postherpetic neuralgia and painful diabetic neuropathy observed at 600 mg/day.
    - Higher doses also lead to more patients discontinuing therapy due to adverse events.
- Fibromyalgia
  - Gabapentin: Results of a Cochrane Review
    - Concluded that there was insufficient evidence to support or refute the use of gabapentin in fibromyalgia.
  - Pregabalin: Results of a Cochrane Review
    - Concluded that some patients may achieve good pain relief with lower doses; however, 450 mg/day appeared to provide the best balance between benefit and adverse events.
      - For  $> 50\%$  improvement in pain: NNT 10 (95% CI 7 to 15)
      - Adverse event withdrawal: NNH 11 (95% CI 8 to 17)



- Chronic low back pain
  - Gabapentinoids: One meta-analysis of 8 studies
    - Results showed minimal improvement in pain with an increase in adverse events with gabapentin compared to placebo. Evidence rated as very low quality.
- Osteoarthritis
  - No RCTs evaluating gabapentinoids versus placebo in osteoarthritis were found.
- Risks/harms
  - Gabapentinoids should be used with caution in patients at risk of substance abuse.
  - There is an increased risk of death when moderate to high doses (> 900 mg/day) of gabapentin are co-prescribed with opioids.
  - In chronic low back pain patients, adverse events (dizziness, fatigue, difficulties with mentation, and visual disturbances) were more common with gabapentin compared to placebo with NNH ranging from 6-8.

## **Cannabinoids**

The *cannabis* plant has three species:

- *C. sativa* and *C. indica* contain significant amounts of psychoactive cannabinoids and are cultivated for recreational and medicinal use.
  - Cannabis sativa contains greater than 100 phytocannabinoids.
- *C. ruderalis* contains negligible amounts of psychoactive compounds and is cultivated for seeds and fiber (hemp).

Endocannabinoid System:

- CB1 receptors (predominantly at nerve terminals where they mediate inhibition of neurotransmitter release)
- CB2 receptors (mainly expressed by immune cells)
- CB1 and CB2 are targeted by endogenous agonists (such as anandamide or 2-arachidonoyl glycerol)

**Delta-9-tetrahydrocannabinol (THC)** and **Cannabidiol (CBD)** are the cannabinoids that have been investigated for medicinal purposes.

- THC:
  - Primary psychoactive constituent
  - Highly lipophilic, stored in fatty tissue
  - Metabolized by hepatic CYP450 3A4 and 2C9, and excreted in feces and urine
  - Partial agonist at both CB1 and CB2 receptors



- CBD:
  - Non-psychoactive
  - May modulate some of the undesirable effects of THC when administered together
  - May have anxiolytic and anti-inflammatory properties<sup>57,58</sup>

#### Nabiximols (Sativex®)

- Oromucosally delivered spray prepared from extracts of *Cannabis sativa* (standardized 27 mg/ml delta-9-THC and 25 mg/ml cannabidiol).
- Approved in Canada for advanced cancer pain and Multiple Sclerosis (MS) associated pain and spasticity.<sup>6</sup>

#### Nabilone (Cesamet® and generics)

- Synthetic analogue of THC.
- Has approval in Canada for the treatment of chemotherapy induced nausea and vomiting.<sup>6</sup>

Dried cannabis is neither FDA or Health Canada approved.

#### ***Fibromyalgia (Cannabinoids)***

- Cochrane Review by Walitt: Cannabinoids for fibromyalgia<sup>59</sup>
  - 2 studies; N = 72
  - One study examined nabilone vs placebo, the other was nabilone vs. amitriptyline.
  - Both were at moderate risk of bias due to potential selective outcome reporting and incomplete outcome data.
  - Study duration was 4-6 weeks.
  - Both studies were conducted in Canada and were partially sponsored by industry.
  - Inclusion criteria was:
    - Continued pain despite the use of other oral medications
    - Diagnosis of fibromyalgia by 1990 American College of Rheumatology Criteria
  - Exclusion criteria:
    - History of substance abuse
    - Current psychotic disorders
    - Unstable cardiac disease
  - Both studies titrated nabilone to a dose of 1mg/day.
  - Outcomes:
    - Studies did not report outcomes for proportion of participants experiencing either 30% or 50% pain relief or who were very much improved.



- One study reported a statistically significant improvement in pain, anxiety and health related quality of life. However, the authors of the Cochrane Review extracted the means and SDs from the figures provided and could not find a significant difference between the SMD for nabilone vs placebo.
- No significant differences between nabilone and placebo were noted for fatigue and depression.
- Nabilone had better effects on sleep than amitriptyline (adjusted difference -3.25, 95% CI -5.26 to -1.24, p<0.05) on a 28-point insomnia scale index.
- Harms:
  - The quality of the evidence for all outcomes of tolerability was very low.
  - One study reported that 3/20 participants in nabilone group dropped out due to adverse events. The other reported 1/32 in nabilone group withdrawing due to adverse events.
  - The most common adverse events were dizziness, dry mouth, drowsiness and vertigo.
- **Author's conclusion:** No convincing, unbiased evidence to suggest that nabilone is of value in treating people with fibromyalgia.

### Systematic review of systematic reviews for medical cannabinoids<sup>60</sup>

- This summary of the existing evidence for medical cannabinoids was recently published in the Canadian Family Physician Journal. The authors are Canadian, led by Dr. G. Michael Allan, Department of Family Medicine, University of Alberta.
- The stated objective was to "determine the effects of medical cannabinoids on **pain, spasticity, and nausea and vomiting**, and to identify **adverse events**."
  - We have focused on the evidence for use in the CNCP conditions included in this document.
- Thirty-one relevant systematic reviews identified: 23 for pain, 5 for spasticity, 6 for nausea and vomiting and 12 for adverse events.
- Seven of 23 pain systematic reviews provided meta-analysis.
- Five of 7 systematic reviews reported the outcome of a 30% or more pain reduction.
  - Two of the 5 meta-analyses reached statistical significance: NNTs were 6 and 14.
- Allan et al <sup>60</sup> conducted a **new meta-analysis** for 15 RCTs examining medical cannabinoids for **pain** with the primary outcome of  $\geq 30\%$  pain reduction. Of these 15 RCTs:
  - 5 RCTs examined inhaled cannabis for neuropathic pain vs placebo
  - 10 RCTs examined buccal spray cannabinoid (nabiximol) vs placebo
  - Most examined neuropathic pain (13/15), the remainder cancer pain (2/15).



- Outcome: 30% or better pain reduction
  - Event Rates: 39% medical cannabis vs. 30% placebo
  - RR: 1.37 (95% CI 1.14 to 1.64)
  - NNT: 11 (95% CI 7 to 19) for up to 15 weeks
- The authors rate the overall quality of evidence for reduction in pain as VERY LOW, due to small RCT size, short duration, quality of included RCTs, potential for unblinding even in studies that were blinded and inconsistent outcome reporting.
- Highest risk of bias was in RCTs of inhaled cannabinoids.
- Sensitivity analyses for 30% pain reduction, based on **cannabinoid type**:
  - Inhaled cannabinoids:
    - Event rates: Inhaled 47% vs placebo 29%
    - RR 1.52 (95% CI 1.17-1.99)
    - NNT 6 (95% CI 4 to 12)
  - Buccal spray cannabinoids:
    - Spray 36% vs placebo 30%
    - RR 1.28 (95% CI 1.02-1.61)
    - NNT 16 (95% CI 9 to 52)
  - No significant difference between these subgroups (p=0.34).
  - No RCTs of oral medications report the outcome of 30% response in pain reduction.
- Sensitivity analyses for the outcome of 30% pain reduction, based on **study size**:
  - Small studies (<150 people):
    - Cannabinoids 42% vs placebo 25%
    - RR 1.56 (95% CI 1.26-1.92)
    - NNT 6 (95% CI 4 to 9)
  - Large studies (>150 people)
    - Cannabinoids 36% vs placebo 33%
    - Non-significant RR: 1.09 (95% CI 0.86-1.39)
  - The difference between large and small studies was **statistically significant** (p=0.03).
- Sensitivity analyses for the outcome of 30% pain reduction, based on **duration of study**:
  - < 1 week:
    - Cannabinoids 55% vs placebo 32%
    - RR 1.58 (95% CI 1.13-2.20)
    - NNT 5 (95% CI 3 to 9)
  - 2- 5 weeks:
    - Cannabinoids 33% vs placebo 18%
    - RR 1.79 (95%CI 1.31-2.43)
    - NNT 7 (95% CI 4 to 13)



- 9-15 weeks:
  - Cannabinoids 37% vs placebo 34%
  - Non-significant RR: 1.07 (95% CI 0.87-1.32)
- The difference between these subgroups was **statistically significant** (p=0.01).
- Conclusion from sensitivity analysis: longer or larger trials found no statistically significant effect for cannabinoids versus placebo for the outcome of 30% pain reduction.
- **Adverse Events:**
  - For findings of harm, this systematic review used systematic reviews of RCTs with meta-analysis focused on the harms of medical cannabinoids OR systematic reviews of RCTs with meta-analysis of adverse events identified in the pain, spasticity, or nausea and vomiting systematic reviews.
  - This will therefore not capture all adverse events which have been reported in case reports, observational or epidemiological studies on the harms of recreational use of cannabis.
  - Adverse events may be underreported as many trials enrolled experienced cannabis users who may have already established efficacy and tolerability.
  - The authors rate the quality of evidence as HIGH: GRADE started high due to meta-analyses of RCTs, but decreased due to imprecision and risk of bias. GRADE was also increased for large magnitudes of effect and confounders that would decrease adverse events (such as selective inclusion of past cannabinoid users).
  - Adverse events: NNH 5-8
  - 5/8 meta-analyses: statistically significant adverse event withdrawal, NNH 8-22
  - Adverse events and estimated event rates for medical cannabinoids vs placebo, as detailed in the Simplified guideline for prescribing medical cannabinoids in primary care.<sup>61</sup> This is the companion document to the Systematic review of systematic reviews.
    - Feeling high: NNH 2-4 (Event rates: 35% vs 3%)
    - Dizziness: NNH 5 (Event rates: 32% vs 11%)
    - Sedation: NNH 5 (Event rates: 50% vs 30%)
    - Speech disorders: NNH 5 (Event rates: 32% vs 7%)
    - Ataxia or muscle twitching: NNH 6 (Event rates: 30% vs 11%)
    - Numbness: NNH 6 (Event rates: 21% vs 4%)
    - Disturbance in attention or disconnected thoughts NNH: 7 (Event rates: 17% vs 2%)
    - Hypotension: NNH 8 (Event rates: 25% vs 11%)
    - Dysphoria: NNH 8 (Event rates: 13% vs 0.3 %)



- Psychiatric: NNH 9 (Event rates: 17% vs 5%)
- Euphoria: NNH 9 (Event rates: 15% vs 2%)
- Impaired memory: NNH 12 (Event rates: 11% vs 2%)
- Disorientation or confusion: NNH 15 (Event rates: 9% vs 2%)
- Blurred vision or visual hallucination: NNH 17 (Event rates: 6% vs 0%)
- Dissociation or acute psychosis: NNH 20 (Event rates: 5% vs 0%)
- Other adverse events such as cannabinoid hyperemesis syndrome or amotivational syndrome may be less likely to be captured given the dose and duration of trials during an RCT.

### ***Neuropathic Pain***

#### **Inhaled Cannabis:**

- **Inhaled cannabis for chronic neuropathic pain: an individual patient data meta-analysis by Andreae<sup>62</sup>**
  - 5 trials, 178 patients, synthesis of original patient data obtained from primary study authors as a Bayesian meta-analysis of RCTs.
  - Characteristics of studies:
    - 3 studies used cannabis as pre-rolled cigarettes, one through a Volcano vaporizer, and one as gelatin capsules smoked through a pipe at home.
    - All 5 studies used identical looking placebo as comparator.
    - All 5 studies used whole cannabis plant provided by the US National Institute of Drug Abuse.
    - 2 studies followed patients for 5-6 hours, 2 studies followed patients for 5 days.
    - The longest study was for 8 weeks, although this was a cross-over trial where the same 23 patients were randomly assigned to receive one of four different potencies of THC for 5 days, followed by a 9 day wash out period between cycles.
    - 2 trials included only patients with HIV related chronic painful neuropathy, 3 trials included patients with neuropathy secondary to trauma, spinal cord injury, diabetes and complex regional pain syndrome.
    - Four trials had prior cannabis experience as a prerequisite for study inclusion.
    - Current cannabis use was an exclusion criterion.
    - Prescribed opiate use not specified as inclusion or exclusion criterion.
    - THC concentration varied from 0 to 9.4%.
    - **THC total daily dose estimates ranged from 0 to 96 mg/day.**
  - Primary outcome was percentage of patients experiencing a 30% pain reduction
    - Based on data from 178 patients with 405 total observed responses
      - Event rates: Cannabis 47% vs placebo 29%



- Odds ratio for >30% pain reduction with cannabis vs. placebo: 3.2 (Credible interval [CRI] 95% 1.59 to 7.24)
  - **NNT 6** (CRI 95% 3 to 14) for 5 days
- Adverse event data were too sparse to be pooled.
- The authors report adverse event withdrawals were rare, however, as the included studies followed patients for 6 hours to 2 weeks, no long term effects could be reported.
- Subjective side effects included anxiety, disorientation, poor concentration, headache, dry eyes, dizziness and numbness.
- **Efficacy and adverse effects of medical cannabis in chronic non-cancer pain. Systematic review of randomized controlled trials by Deshpande.<sup>63</sup>**
  - Examined the same 5 trials as in the meta-analysis by Andreae<sup>62</sup> (detailed above), but stated that the interventions and outcome variable were too heterogeneous to allow for pooling of data.
  - Some points from this review that were not captured in the review by Andreae<sup>62</sup>:
    - Other concomitant analgesic medications were allowed (opiates, anticonvulsants, antidepressants) although the doses were not reported.
    - More than 50% of participants were prescribed concomitant opiates.
  - **Total daily THC consumed during the trials ranged from 1.875 mg to 34 mg/day.**
  - All studies reported a statistically significant benefit in terms of pain relief
    - Clinically meaningful pain reduction was reported in 3 studies with 46%, 52% and 61% of cannabis users reporting benefit versus 18%, 24% and 26% in the placebo group.
    - One study noted that opiate dose did not differ significantly from baseline, following medical cannabis inhalation.
  - Adverse events: smoking cannabis was associated with increased incidence of adverse events in all trials, although serious side effects were rare.
  - One study noted increased adverse events with increased dose of THC: headaches, sedation, dysphoria and poor concentration.
  - Unmasking of placebo occurred in many of the trials, and inappropriate blinding may have caused larger treatment effects.
  - The authors note that the exposure to THC in these studies was extremely low compared to that available in the current marketplace.
    - As an example: 2 g of 12.5% THC would give 250 mg of THC, which is 8 times higher than the maximum dose used in these trials.



➤ Guideline Placement:

- Simplified guideline for prescribing medical cannabinoids in primary care in Canada<sup>61</sup>
  - These Canadian guidelines were developed to assist in decision making with patients and are endorsed by the College of Family Physicians of Canada (CFPC).
  - **Recommend against** medical cannabinoids as 1<sup>st</sup> or 2<sup>nd</sup> line therapy in neuropathic pain owing to limited benefits and high risk of harms (strong recommendation).
  - **Could consider** medical cannabinoids for refractory neuropathic pain, with the following considerations (weak recommendation):
    - A discussion has taken place with patients regarding the benefits and risks of medical cannabinoids for pain.
    - Patients have had a reasonable therapeutic trial of at least 3 prescribed analgesics and have persistent problematic pain despite optimized therapy.
    - Medical cannabinoids are adjuncts to other prescribed analgesics.
  - If considering medical cannabinoids, recommend either nabilone or nabiximols (strong recommendation).
    - Nabilone is off-label for pain, limited evidence of benefit.
    - Nabilone is less expensive than nabiximols, however nabiximols has better evidence.
    - Dosing is more consistent than for smoked cannabis.
  - If considering medical cannabinoids, recommend against medical cannabis (particularly smoked) as the initial product (strong recommendation).
    - Evidence has a very high risk of bias, and long term consequences are unknown.
    - Products available can have far higher concentrations of THC and CBD than those researched.
- International Association of Pain Special Interest Group on Neuropathic Pain<sup>38</sup>:
  - **Weak recommendation against** the use of cannabinoids in neuropathic pain, due to negative results, potential misuse, diversion and long-term mental health risks of cannabis particularly in susceptible individuals.
- Canadian Pain Society Revised Consensus Statement on Management of Chronic Neuropathic Pain<sup>19</sup>
  - Cannabinoids are listed as a third-line treatment option.
  - Paucity of high quality studies with long trial duration, large sample size and large effect size to better establish their efficacy and their potential for abuse.

Academic Detailing Thoughts about Medical Cannabis

- The pharmaceutically produced cannabis oil products are becoming available before the scientific literature to inform benefits and harms.
- This creates a challenging atmosphere for physicians to provide evidence based best practice advice to patients.



- There is interest in cannabinoids as opioid sparing agents to minimize the harms associated with opioids, particularly mortality.
- While mortality may not be increased with cannabinoids, there is considerable concern for morbidity.
- It is important to be aware of the other centrally acting medications that the patient is taking when cannabinoids are initiated.
- Cannabinoids should be prescribed with the same degree of caution and regulation as any other centrally acting agent.
- Boundaries for managing cannabis should be the same as boundaries for managing opioids.
- An assessment for increased risk of harms and strategies to manage risk should always be considered when prescribing cannabinoids.
- There is a thought in the medical community that oils are better or safer than smoked cannabis due to:
  - More consistent dosage delivery
  - Avoid the harms of “smoking”
  - Easier delivery
  - Hospitalized patients can get their medication at the bedside.
- However, it can be difficult to predict the level of sedation that can occur with oils.
- Some experts suggest starting with oils that are high in CBD concentration (CBD weighted) and may suggest adding in a component of a lower concentration of THC. However, dispensaries will often make adjustment to this, further compounding the problem of not really knowing what the patient is taking or understanding potential drug interactions.
- Potency is the important factor in selecting medical cannabinoids, not the absolute amount in grams. The CFPC recommends restricting to < 9.5% THC. Many available products contain >20% THC.
- If patients self-report that cannabis works for them, explore the ways in which they state it is helpful:
  - What motivates them to use cannabis?
  - Ask them: How does cannabis help you?
  - Is it a strategy that helps them live with purpose and connection or is it a strategy that isolates and disconnects them from the people and things that matter in their lives?
  - Is it a strategy that helps them improve their function and quality of life or is it a strategy that just gets them through the day?



- Patients will often self-report cannabis use for anxiety for which there is little to no evidence to support its use. Tolerance can develop and patients will need escalating amounts to achieve the same effect.

SUMMARY for Cannabinoids:

- May be suggested as a third line option for neuropathic pain after an adequate trial of at least 3 prescribed non-opioid analgesics. Benefits are limited and there is a high risk of harms.
- In general, evidence has a very high risk of bias and the long term consequences are unknown.
- Products available can have far higher concentrations of THC and CBD than those researched.

**Combination Therapy**

- As noted in previous sections of this document, monotherapy treatment for chronic non cancer pain often has limited efficacy or the dose is limited by side effects.
  - Often **sedation** is the most common dose limiting side effect.
- There is a possibility that combining two different drugs (**with different mechanisms of action**) may improve analgesic efficacy.
- There are many trials published looking at various combinations and doses of medications for various pain states but the availability of good quality trials for any one specific combination is lacking.
  - There is evidence that two-drug combinations show superior efficacy compared to monotherapy. However, there is also high dropout rates in the two-drug combination arms due to adverse events, the most notable being CNS depression.

**Tramadol – It’s an OPIOID**

*We have included tramadol even though it is an opioid. Because it is not regulated as a Narcotic, there is potential for it being prescribed with less caution and consideration for risk. In addition, in some guidelines it is listed separate from opioids which leads to mis-interpretation. There is confusion about its dual mechanism of action and potential for harmful drug interactions.*

- Tramadol is classed as an **opioid analgesic** indicated for the treatment of mild-moderate pain. However, in Canada, it is not regulated as an opioid.
- As an opioid it carries a risk of addiction, abuse and misuse.<sup>6</sup>
- It has a low binding affinity to the  $\mu$  opioid receptor.



- The opioid effects are reliant on an active metabolite (o-desmethyltramadol).
- Conversion to this metabolite is reliant on the enzyme CYP 2D6 (this is also the enzyme that converts codeine to morphine. Approximately 5 to 10% of the population are poor metabolizers).
- Tramadol is a **dual acting analgesic**: it also inhibits the reuptake of norepinephrine and serotonin.
  - This leads to a potential increased number of drug interactions and an additional risk of adverse events beyond those related to its opioid properties.
- It is unknown what percentage of tramadol's effect is due to its action on opioid receptors versus inhibiting norepinephrine and serotonin reuptake.

### **Neuropathic Pain (Tramadol)**

- Cochrane Review by Duehmke<sup>64</sup>
  - LOW quality evidence
  - Included 6 trials (N=438) tramadol vs. placebo; study duration ranged from 4-6 weeks
  - Inclusion criteria: patients with moderate or severe neuropathic pain for at least three months due to cancer, cancer treatment, postherpetic neuralgia, peripheral diabetic neuropathy, spinal cord injury, or polyneuropathy.
  - Tramadol was started at a dose of about 100mg daily and increased over one to two weeks to a maximum of 400mg daily or the maximum tolerated dose, and then maintained for the remainder of the study.
  - **Primary Outcomes**
    - Participant-reported pain relief of 30% or greater
    - Participant-reported pain relief of 50% or greater
    - PGIC much or very much improved
    - PGIC very much improved
  - **Tramadol vs Placebo**
    - ≥ 50% improvement in pain (pooled from 3 of the trials)
      - Event Rate: tramadol 53% versus placebo 30%
      - NNT 4 (95% CI 3 to 9)
    - Adverse events leading to discontinuation
      - Event Rate: tramadol 15% versus placebo 3%
      - NNH 8 (95% CI 6 to 14)
  - **Authors' comments:** The evidence of benefit for tramadol was of low or very low quality (small, largely inadequate studies, with potential risk of bias increasing the apparent benefits). It does not provide a reliable indication of the likely benefit.



➤ Guideline Placement:

- Canadian Pain Society: Tramadol is recommended as a 2nd line agent for neuropathic pain along with other opioid analgesics; after TCAs/Gabapentoids/SNRIs but before cannabinoids.

***Fibromyalgia (Tramadol)***

- There is limited evidence for use of tramadol in fibromyalgia.
  - Three randomized placebo controlled trials
    - One trial involved 12 people using IV tramadol vs. placebo.<sup>65</sup>
    - **Bennett (2003)**<sup>66</sup> compared tramadol/acetaminophen combination to placebo in patients with fibromyalgia.
      - N = 315
      - The primary outcome measure was time to discontinuation.
      - Secondary outcomes included pain and pain relief.
    - **Primary Outcome**
      - The cumulative rate of discontinuation due to lack of efficacy:
        - Event rates: Tramadol 29% versus placebo 51% (p<0.001)
        - NNT = 5 (95% CI not available)
    - Discontinuation due to adverse events
      - Event rates: Tramadol 19% versus placebo 12% (p = 0.09)
      - No statistically significant difference
  - **Russell (2000)**<sup>67</sup>
    - N = 100
    - Patients were given tramadol 50-400mg/day prior to randomization.
    - Responders (69%) were then enrolled in a double blind placebo controlled trial for 6 weeks.
    - **Primary outcome:** time to exit due to inadequate pain relief
      - Event rates: Tramadol 57% (N = 20) of patients completed the trial versus placebo 27% (N = 9).
      - NNT 3 (95% CI not available)
- Guideline Placement:
  - Canadian Guidelines: Tramadol is the only opioid that has been studied in fibromyalgia. It should be reserved for treatment of patients with moderate to severe pain that is unresponsive to other treatments.<sup>7</sup>
  - NHS Guidelines: Tramadol is not listed as a treatment option for fibromyalgia.<sup>21</sup>

***Chronic Low Back Pain (Tramadol)***

- Cochrane Review by Chaparro<sup>68</sup>



- 15 trials included; 5 trials (N=1378) studied tramadol vs. placebo; duration was 90 days in 3 trials and 4 weeks in 2 trials.
  - Included male and female participants, aged 18 years or older, who had persistent pain in the low-back for at least 12 weeks, with or without radiating symptoms to the legs or prior low-back surgery (failed back surgery syndrome).
  - Low back pain was defined as pain occurring below the lower ribs and above the gluteal folds, including the buttocks.
  - Failed back surgery syndrome was defined as back pain, leg pain, or both, lasting longer than six months from the date of surgical intervention, or pain that began prior to one year from the date of intervention, after the individual had achieved symptomatic relief.
  - **Excluded** patients with cancer, infections, inflammatory arthritic conditions (including osteoarthritis) or compression fractures.
  - Also excluded trials where < 50% of participants had CLBP or study authors failed to report results separately for this specific cohort.
  - **Primary Outcomes**
    - Pain ratings: verbal rating scale, visual analog scale or final visit pain score
    - Function: Oswestry Disability Index (ODI), Roland-Morris Disability Questionnaire (RMDQ) or Quebec Back Pain Disability Scale (QBPD)
    - Global improvement: patient satisfaction or quality of life improvements
    - Proportion of patients reporting 30% or 50% pain relief
  - **Results: Tramadol vs. placebo**
    - Standardized mean difference (favouring tramadol)
      - Pain -0.55 (95% CI -0.66 to -0.44) Rated low quality evidence
      - Function -0.18 (95% CI -0.29 to -0.07) Rated moderate quality evidence
  - **Authors' comment:** There is some evidence for short term efficacy of tramadol compared to placebo for chronic low back pain.
- Guideline Placement:
  - Toward Optimized Practice: Tramadol is considered 4th line, after acetaminophen, NSAIDs, TCAs or codeine.<sup>11</sup>

### ***Osteoarthritis (Tramadol)***

- Cochrane Review by Cepeda<sup>69</sup>
  - 11 randomized control trials (N= 1939) comparing tramadol or tramadol/acetaminophen vs. placebo or active comparator
    - All but one study was industry funded.
    - Included adults with primary or secondary osteoarthritis (participants had to meet the American College of Rheumatology clinical criteria for OA).
    - Also included studies that evaluated participants with radiographic evidence of OA and studies in which authors stated that only participants with OA were included.



- The mean dose of tramadol was 200mg/day.
- **Primary Outcomes**
  - Pain
    - Patient reported pain intensity, or
    - Patient reported pain relief
  - Patient global assessment of improvement
  - Physical function
    - Self-reported, or
    - Performance-based measures of function, or
    - Any physical function scale
  - Safety of tramadol
    - Presence and degree of severity of adverse events, or
    - Total withdrawals due to adverse events
  - Joint imaging
- **Results: Tramadol vs Placebo**
  - $\geq 50\%$  improvement in pain (pooled from 4 trials); Duration 8-12weeks
    - Event rates: Tramadol or tramadol/acetaminophen 69% versus placebo 50%
    - NNT 6 (95% CI 4 to 9)
    - This outcome was also used as a surrogate marker for the outcome measure “global assessment of improvement”.
  - Physical Function outcomes
    - Evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC)
      - Reduction (improvement) in the score was larger in the tramadol group than the placebo group (-0.34; 95% CI -0.49 to -0.19).
      - Relative improvement of 8.5% in the mean baseline score of 4.
    - Authors also comment that function may improve by 0.32 more points on a scale of 0 to 10 with tramadol.
    - The clinical relevance of this improvement is questionable.
  - Adverse Events leading to discontinuation (pooled from 4 trials)
    - Event rates: Tramadol 20% versus placebo 8%
    - NNH 8 (95% CI 7 to 12)
  - The data on tramadol vs. active comparators was too limited to draw conclusions on those comparisons.
- **Authors’ conclusions:** Tramadol or tramadol/acetaminophen decreases pain intensity, produces symptom relief and improves function, but the benefits are small. Adverse events often cause participants to stop taking the medication.



➤ Guideline Placement:

- American Rheumatology Society 2012: conditionally recommend that health professionals consider using tramadol as a possible first line option in hand, knee and hip OA.<sup>15</sup>

***Risks/harms***

- As an opioid tramadol carries a risk of addiction, abuse and misuse which can lead to overdose and death.
  - Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed tramadol and should be routinely monitored for signs of misuse and abuse.<sup>6</sup>
- Evidence suggests NNH 8 for the outcome of adverse events leading to discontinuation.
- Tramadol's dual mechanism of action is reflected in the listed side effects, warnings and precautions and drug interactions. Please refer to the official product monograph for complete details.
  - Serious warnings and precautions include
    - Limitations of use
    - Addiction, abuse and misuse
    - Life-threatening respiratory depression
      - Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed.
    - Administration (i.e. extended release products must be swallowed whole)
    - Accidental exposure
    - Neonatal opioid withdrawal syndrome
    - Interaction with alcohol
    - Risks from concurrent use with benzodiazepines or other CNS depressants.

SUMMARY for Tramadol

- Tramadol is an **opioid analgesic** officially indicated for the treatment of mild-moderate pain.
- In Canada, it is a prescription medication but NOT regulated as a narcotic or controlled drug.
- Tramadol
  - Has low binding affinity to the  $\mu$  opioid receptor.
  - Inhibits the reuptake of norepinephrine and serotonin.
    - This leads to a potential increased number of drug interactions and an additional risk of adverse events beyond those related to its opioid properties.



- Neuropathic pain
  - Results of a Cochrane Review rated LOW quality evidence **for tramadol versus placebo**
    - $\geq 50\%$  improvement in pain (pooled from 3 of the trials)
      - Event Rate: tramadol 53% versus placebo 30%
      - NNT 4 (95% CI 3 to 9) for 4 to 6 weeks
    - Adverse events leading to discontinuation
      - Event Rate: tramadol 15% versus placebo 3%
      - NNH 8 (95% CI 6 to 14) for 4 to 6 weeks
    - **Authors' comments:** The evidence of benefit for tramadol was of low or very low quality (small, largely inadequate studies, with potential risk of bias increasing the apparent benefits). It does not provide a reliable indication of the likely benefit.
- Fibromyalgia
  - There is limited evidence for use in fibromyalgia.
- Chronic low back pain
  - Results of a Cochrane review: Tramadol vs. placebo
    - Standardized mean difference (favouring tramadol)
      - Pain -0.55 (95% CI -0.66 to -0.44) Rated low quality evidence
      - Function -0.18 (95% CI -0.29 to -0.07) Rated moderate quality evidence
    - **Authors' comment:** There is some evidence for short term efficacy of tramadol compared to placebo for chronic low back pain.
- Osteoarthritis
  - Results of a Cochrane Review for tramadol versus placebo
    - $\geq 50\%$  improvement in pain (pooled from 4 trials); Duration 8-12weeks
      - Event rates: Tramadol or tramadol/acetaminophen 69% versus placebo 50%
      - NNT 6 (95% CI 4 to 9)
    - Adverse Events leading to discontinuation (pooled from 4 trials)
      - Event rates: Tramadol 20% versus placebo 8%
      - NNH 8 (95% CI 7 to 12)
    - **Authors' conclusions:** Tramadol or tramadol/acetaminophen decreases pain intensity, produces symptom relief and improves function, but the benefits are small. Adverse events often cause participants to stop taking the medication.
- Risks/harms
  - As an opioid tramadol carries a risk of addiction, abuse and misuse.
  - Tramadol's dual mechanism of action is reflected in the listed side effects, warnings and precautions and drug interactions. Please refer to the official product monograph for complete details.



## Non-opioids compared to Opioids

- The focus of this document is on non-opioids in CNCP. The evidence for non-opioids suggests a trial of several agents is warranted depending on the condition. The next question would be “Are the opioids better and by how much?”
- For the recently published Canadian Guidelines for Opioids for Chronic Non-Cancer Pain, a systematic review evaluating the evidence for opioids versus non-opioids in CNCP was conducted.
  - The full systematic review has yet to be published; however, tables with results are included in the guidelines.
  - Full guidelines are available at [http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ\\_01may2017.pdf](http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf)
  - A summary of results adapted from the guidelines for first and second line therapy is provided in appendix 3 and 4.
- A recently published study of patients with chronic back pain or hip/knee osteoarthritis pain provides further comparative evidence.
- The SPACE trial<sup>73</sup> compared the effect of opioids vs non-opioids on pain-related function, pain intensity and adverse effects over 12 months.
  - Pragmatic, randomized trial with blinded outcome assessment, N = 240
  - Analgesia managed with structured symptom monitoring and a 3 step, treat to target approach, primarily by a single pharmacist
  - Study population:
    - Veterans Affairs primary care clinic patients
    - Moderate to severe chronic back pain or hip or knee osteoarthritis pain for ≥ 6 months despite analgesic use
    - 87% male, 86-88% white, mean age 58 years
    - Excluded: Long term opioid users, patients with substance use disorder or contraindications to study drugs, and conditions that could interfere with outcome assessment
  - Intervention
    - Step 1: morphine sulfate IR, hydrocodone/acetaminophen, or oxycodone IR
    - Step 2: morphine sulfate SR or oxycodone SR
    - Step 3: transdermal fentanyl
    - Dose titrated to maximum of 100 mg ME/day and opioid rotation considered when dose exceeded 60 mg ME/day without clinical response
  - Comparison:
    - Step 1: acetaminophen or NSAID
    - Step 2: adjuvant oral analgesics (nortriptyline, amitriptyline, gabapentin, topical capsaicin, topical lidocaine)
    - Step 3: duloxetine, pregabalin, tramadol



- Drug selection determined based on patient preference and comorbidities
- Subsequent changes made by titrating dosage, replacing or adding drugs
- Outcomes: Reported at baseline, 3, 6, 9, and 12 months
  - **Pain-related function** (measured with BPI interference scale, MCID = 1): No statistically significant difference between groups over 12 months (overall P = 0.58)
    - Mean (SD) 12 month BPI interference:
      - 3.4 (2.5) opioid group
      - 3.3 (2.6) non-opioid group
      - Difference, 0.1 [95% CI -0.5 to 0.7]
    - ≥ 30 % improvement in BPI interference:
      - 59% opioid group
      - 60.7% non-opioid group
      - Difference -1.7% (95% CI -14.4 to 11), P = 0.79
  - **Pain intensity** (measured with BPI severity scale, MCID = 1): Statistically significant advantage in non-opioid group over 12 months (overall P = 0.03)
    - Mean (SD) 12 month BPI severity:
      - 4.0 (2.0) opioid group
      - 3.5 (1.9) non-opioid group
      - Difference 0.5 [95% CI 0.0-1.0]
    - ≥ 30% improvement in BPI severity:
      - 41% opioid group
      - 53.9% non-opioid group
      - Difference -12.8% (95% CI -25.6 to 0), P = 0.05
  - On average, all patients achieved MCID of 1 point (moderate improvement) on the BPI interference and severity scales for pain-related function and intensity, respectively, from baseline to 12 months.
  - **Adverse effects** more common in opioid group over 12 months (overall P = 0.03), as reported by patients using a 0-19 point medication related symptom checklist
    - Mean (SD) medication-related symptoms at 12 months
      - 1.8 (2.6) opioid group
      - 0.9 (1.8) non-opioid group
      - Difference 0.9 [95% CI 0.3 to 1.5]
  - Secondary outcomes assessed but not reported here
  - Post-Hoc analysis showed no change in results whether patient treating back or osteoarthritic pain.
- Limitations:
  - Neither patients nor clinicians blinded to randomization due to complexity of intervention (risk of bias)
  - Unknown which drug had greatest effect on results in either group
  - Adverse effects measured using a non-validated tool



- External validity limited by predominantly male population
- Underpowered to detect potential risk of death, opioid use disorder, and other serious opioid related harms



Appendix 1: Comparison of Canada, US and UK Low Back Pain<sup>11,12,70</sup>

Comparison of Chronic Back Pain Guidelines in Canada, United States and the United Kingdom												
Canada	United States											
<p>Toward Optimized Practice- Alberta 3<sup>rd</sup> Edition Dec 2015 (minor update 2017) Evidence Informed Primary Care Management of Low Back Pain</p> <table border="1"> <thead> <tr> <th>Pain Type</th> <th>Medication</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Acute and sub-acute low back pain or flare-up of chronic low back/spinal pain</td> <td><b>1st line</b> NSAIDs (consider PPI if &gt;45 years of age)</td> </tr> <tr> <td><b>2nd line</b> Acetaminophen Ibuprofen Diclofenac</td> </tr> <tr> <td rowspan="2">Chronic low back/spinal pain</td> <td><b>1st and 2nd lines</b> See acute pain, above</td> </tr> <tr> <td><b>3rd line</b> Tricyclics (TCAs)</td> </tr> <tr> <td rowspan="2">Neuropathic pain if co-emergent with musculoskeletal complaints</td> <td><b>1st line</b> Anticonvulsants (Gabapentin or Pregabalin)</td> </tr> <tr> <td><b>2<sup>nd</sup> line</b> - Add opioids including Tramadol</td> </tr> </tbody> </table>	Pain Type	Medication	Acute and sub-acute low back pain or flare-up of chronic low back/spinal pain	<b>1st line</b> NSAIDs (consider PPI if >45 years of age)	<b>2nd line</b> Acetaminophen Ibuprofen Diclofenac	Chronic low back/spinal pain	<b>1st and 2nd lines</b> See acute pain, above	<b>3rd line</b> Tricyclics (TCAs)	Neuropathic pain if co-emergent with musculoskeletal complaints	<b>1st line</b> Anticonvulsants (Gabapentin or Pregabalin)	<b>2<sup>nd</sup> line</b> - Add opioids including Tramadol	<p>Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: Clinical Practice Guideline American College of Physicians 2017</p> <p>In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment:</p> <ul style="list-style-type: none"> <li>Nonsteroidal anti-inflammatory drugs as first-line therapy</li> <li>Tramadol or duloxetine as second-line therapy.</li> <li>Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)</li> </ul>
Pain Type	Medication											
Acute and sub-acute low back pain or flare-up of chronic low back/spinal pain	<b>1st line</b> NSAIDs (consider PPI if >45 years of age)											
	<b>2nd line</b> Acetaminophen Ibuprofen Diclofenac											
Chronic low back/spinal pain	<b>1st and 2nd lines</b> See acute pain, above											
	<b>3rd line</b> Tricyclics (TCAs)											
Neuropathic pain if co-emergent with musculoskeletal complaints	<b>1st line</b> Anticonvulsants (Gabapentin or Pregabalin)											
	<b>2<sup>nd</sup> line</b> - Add opioids including Tramadol											
<p>United Kingdom</p> <p>National Institute of Health and Care Excellence: Low back pain and sciatica: assessment and management 2016</p> <ul style="list-style-type: none"> <li>Consider oral non-steroidal anti-inflammatory drugs (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.</li> <li>When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.</li> <li>Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.</li> <li>Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.</li> <li>Do not offer paracetamol alone for managing low back pain.</li> <li>Do not routinely offer opioids for managing acute low back pain.</li> <li>Do not offer opioids for managing chronic low back pain.</li> <li>Do not offer selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain.</li> <li>Do not offer anticonvulsants for managing low back pain.</li> </ul>	<p>All three of these guidelines have robust, high quality evidence based methodologies however they all have differing recommendations in terms of appropriate pharmacologic options</p>											



**Appendix 2:**

**Six Step Approach to Chronic Pain\***

STEP 1: LISTEN to the patient's pain story

STEP 2: ACKNOWLEDGE suffering

STEP 3: EXAM carefully for any new pathology or progression of a pre-existing disease.

STEP 4: MAXIMIZE non-opioid and non-cannabinoid therapies

STEP 5: RISK STRATIFY for harm if opioids or cannabinoids are used to manage pain

STEP 6: MANAGE the risk by MAPing out an approach to opioids and cannabinoids

**MAPing**

STEP 1: MONITOR for aberrant behaviour (Urine drug testing, check prescription monitoring, check for double doctoring)

STEP 2: ADJUST immediately if aberrancy present

STEP 3: PRESCRIBE using principles of harm reduction (Dispense bi-weekly, weekly, or daily)

\*Allen MA. Opioid Analgesics: Is it time for risk stratification prior to use? CJEM. September 2017



**Appendix 3: First line therapy for chronic non-cancer pain: Opioids versus Non-opioids<sup>74</sup>**

Outcome (Measurement Tool)	Study Details & Timeframe	Absolute Effect Estimates		Quality of Evidence	Author's Summary
		Trial of Opioids	Optimized Non- Opioid Therapy		
		Opioids	NSAIDs		
Pain (10 cm VAS)*	13 RCTs N = 2250 1 – 6 months	MD 0.49 fewer** (95% CI 1.24 fewer – 0.26 more)		<b>Low</b> Due to serious inconsistency & imprecision	Opioids may result in little or no difference in pain compared to NSAIDs
Physical Function (SF-36)***	8 RCTs N = 1972 4 – 16 weeks	MD 1.5 fewer (95% CI 3.08 fewer – 0.08 more)		<b>Moderate</b> Due to serious imprecision	Opioids likely result in little or no difference in physical function compared to NSAIDs
Gastrointestinal side effects	7 RCTs N = 3675 6 – 26 weeks	93 per 1000	37 per 1000	<b>High</b>	Opioids result in a small increase in gastrointestinal side effects
		Difference: 56 more per 1000 (95% CI 20 more – 116 more) [RR 2.52 (95% CI 1.54 – 4.13)]			
		Opioids	Anticonvulsants		
Pain (10 cm VAS)*	3 RCTs N = 303 4 – 6 weeks	MD 0.9 fewer (95% CI 1.65 fewer – 0.14 fewer)		<b>Low</b> Due to serious risk of bias & imprecision	Opioids may result in a small but important improvement in pain compared to anticonvulsants
Pain (Difference in patients who achieve ≥ MCID on 10 cm VAS)		779 per 1000	618 per 1000		
		Difference: 161 more per 1000 (95% CI 31 more – 260 more) [RR 1.26 (95% CI 1.05 – 1.42)]			
Physical Function (SF-36)***		MD 0.45 more (95% CI 5.77 fewer – 6.66 more)			
Gastrointestinal side effects	3 RCTs N = 342 4 – 6 weeks	64 per 1000	6 per 1000	<b>Low</b>	Opioids may result in an increase in gastrointestinal side effects compared to anticonvulsants
		Difference: 58 more per 1000 (95% CI 6 more – 331 more) [RR 10.64 (95% CI 2.01 – 56.24)]			
		Opioids	TCAs		
Pain (10 cm VAS)*	3 RCTs N = 183 5 – 8 weeks	MD 0.15 fewer (95% CI 1.04 fewer – 0.74 more)		<b>Low</b> Due to serious risk of bias & imprecision	Opioids may result in little to no difference in pain compared to tricyclic antidepressants
Physical Function (SF-36)***	2 RCTs N = 107 5 – 6 weeks	MD 5.29 fewer (95% CI 13.7 fewer – 3.12 more)			
		Opioids	Nabilone		
Pain (10 cm VAS)*	1 RCT N = 73 6 weeks	MD 0.13 fewer (95% CI 1.04 fewer – 0.77 more)		<b>Low</b> Due to serious risk of bias & imprecision	Opioids may result in little to no difference in pain compared to nabilone
Physical Function (SF-36)***	1 RCT N = 71 6 weeks	MD 1.2 fewer (95% CI 4.5 fewer – 2.1 more)			
Data on addiction, fatal overdose, non-fatal overdose, and diversion also reported for NSAIDs, anticonvulsants, and TCAs in the guidelines. Systematic reviews of data compiled pending publication.					

\*MCID = Reduction of 1 cm on VAS

\*\*MD = Mean difference in change in VAS (or SF-36) scores in opioid group compared to non-opioid group

\*\*\*MCID = Increase of 5 points on a 100 point SF-36 physical component summary score

Adapted from the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain:

[http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ\\_01may2017.pdf](http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf)

**Appendix 4: Second line therapy for chronic non-cancer pain<sup>74</sup>**

Outcome (Measurement Tool)	Study Details & Timeframe	Absolute Effect Estimates		Quality of Evidence	Author's Summary	Notes
		Trial of Opioids	Continue Established Therapy without Opioids			
Pain (10 cm VAS)*	27 RCTs N= 13 876 3 – 6 months	MD 0.64 fewer** (95% CI 0.76 fewer – 0.53 fewer)		<b>High</b>	Opioid therapy results in a small but important improvement in pain	MD observed is less than MCID
Pain (difference in patients who achieve ≥ MCID on 10 cm VAS)		560 per 1000	448 per 1000			
		Difference: 112 more per 1000 (95% CI 94 more – 130 more) [RR 1.25 (95% CI 1.21 – 1.29)]				
Physical function (SF-36)***	33 RCTs N = 12 058 1 – 6 months	MD 2.16 more (95% CI 1.56 more – 2.76 more)		<b>High</b>	Opioid therapy results in a small but important improvement in physical function	MD observed is less than MCID
Physical function (difference in patients who achieve ≥ MCID on SF-36)		526 per 1000	424 per 1000			
		Difference: 102 more per 1000 (95% CI 72 more – 127 more) [RR 1.24 (95% CI 1.17 – 1.3)]				
Gastrointestinal side effects	36 RCTs N = 14 449 4 – 26 weeks	86 per 1000	28 per 1000	<b>High</b>	Opioid therapy results in an increase in gastrointestinal side effects	NNH = 18 (95% CI 13 – 24)
		Difference: 58 more per 1000 (95% CI 43 more – 77 more) [RR 3.08 (95% CI 2.53 – 3.75)]				
Study population limited to patients without current or past substance use disorder & without other current serious psychiatric disorders, who have persistent problematic pain despite optimized non-opioid therapy. Data on addiction, fatal overdose, non-fatal overdose, and diversion also reported in the guidelines. Systematic reviews of data compiled pending publication.						

\*MCID = Reduction of 1 cm on VAS

\*\*MD = Mean difference in change in VAS (or SF-36) scores in opioid group compared to non-opioid group

\*\*\*MCID = Increase of 5 points on a 100 point SF-36 physical component summary score

Adapted from the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain:

[http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ\\_01may2017.pdf](http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf)



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