

Chronic Pain Management: Pharmacologic Treatments (Non-Opioids)

Canada is in the midst of an opioid crisis. Like many organizations across the country, CADTH has made addressing the opioid crisis a top priority. In the last year, we have delivered a large body of evidence to inform decisions on effectively treating opioid use disorder and how we use drug and non-drug interventions to help patients manage pain. But in doing so, we've also revealed some significant gaps in the evidence — areas where evidence is needed but where little or no high-quality evidence can be found.

Knowing where these gaps in the evidence exist can help researchers and research funding bodies to better focus their efforts on opioid research and the management of pain.

Following, you'll find a list of gaps in evidence related to the treatment of chronic pain with non-opioid pharmacologic options that we've identified while carrying out recent rapid reviews through our **Rapid Response Service**. For the treatment of chronic pain with opioids, please see the related publication on *Opioids for the Treatment of Pain*.

Other publications in this series will highlight gaps in areas also important to the opioid crisis including *Treating Opioid Use Disorder*, *Opioids for the Treatment of Pain*, *Chronic Pain Management: Non-Pharmacologic Treatments*, and *Acute Pain Management: Non-Opioid Treatments (Pharmacologic and Non-Pharmacologic)*.

For more information about the CADTH response to the opioid crisis and our evidence, please visit [cadth.ca/opioids](https://www.cadth.ca/opioids) and [cadth.ca/pain](https://www.cadth.ca/pain).

It's important to note that these gaps in evidence have been compiled from multiple CADTH reports from 2014 to the end of 2017. For more details on each identified gap, consulting the full CADTH report is highly recommended. Depending on the date of the report, additional evidence may now be available that addresses the research gaps, as well as evidence from other organizations. And because of the methods used for rapid reviews, it is possible that evidence that could potentially address the research gaps may not have been included.

Nabilone for Chronic Pain Management (2017)

Evidence Requested for Decision-Making

- Clinical effectiveness of nabilone for the treatment of chronic pain due to any disease in adults
- Recommendations from evidence-based guidelines regarding nabilone for the treatment of chronic pain due to any disease in adults

What We Found

- Low-quality evidence suggests some positive benefits and limited harms of nabilone compared with placebo or known analgesics.

Evidence Gaps

What We Did Not Find

High-quality research

Larger and longer-term studies

Recommendations from evidence-based guidelines

Viscosupplementation for Knee Osteoarthritis (2017)

Evidence Requested for Decision-Making

- Clinical effectiveness of viscosupplementation for adults with knee osteoarthritis
- Cost-effectiveness of viscosupplementation for adults with knee osteoarthritis
- Recommendations from evidence-based guidelines regarding viscosupplementation for adults with knee osteoarthritis

What We Found

- Viscosupplementation with hyaluronic acid may be superior to intra-articular placebo, corticosteroids, and NSAIDs for improving knee pain and function without increasing adverse events (however, results are inconsistent, studies had significant limitations, and clinical significance was questionable).
- Low-quality evidence suggests viscosupplementation with hyaluronic acid may be cost-effective in the treatment of knee osteoarthritis, compared with other interventions (e.g., NSAIDs, physiotherapy, weight loss, and ambulatory aid).
- The majority of guidelines did not find sufficient evidence to make a recommendation for or against the use of viscosupplementation for knee osteoarthritis.
- Two guidelines recommend **against** its use, while other guidelines recommend viscosupplementation after failure of other treatments, or in older adults with a certain osteoarthritis grade.

Evidence Gaps

What We Did Not Find

High-quality research (including examining clinical effectiveness in specific stages of osteoarthritis, in specific age groups, and for patients who have failed other therapies)

High-quality evidence on the cost-effectiveness of viscosupplementation with hyaluronic acid compared with other interventions (pharmacological and non-pharmacological)

Canadian studies

NSAID = nonsteroidal anti-inflammatory drug.

The Use of Medical Cannabis with Other Medications (2017)

Evidence Requested for Decision-Making

- Clinical evidence regarding the safety of medical cannabis when used concurrently with other medications
- Recommendations from evidence-based guidelines regarding the use of medical cannabis with other medications

What We Found

- Medical cannabis (Nabilone) may have additive depressant effects with diazepam when taken together with alcohol and codeine.
- Medical cannabis may decrease the need for opioids, NSAIDs, tricyclic antidepressants, dexamethasone and ondansetron when used concomitantly.

Evidence Gaps

What We Did Not Find

High-quality research

Additional data on the drug interactions of medical cannabis with other medications

Recommendations from evidence-based guidelines

NSAID = nonsteroidal anti-inflammatory drug.

Magnesium as an Alternative or Adjunct to Opioids for Chronic Pain(2017)

Evidence Requested for Decision-Making

- Clinical effectiveness of magnesium as an analgesic for the treatment of adult patients with migraine or chronic pain
- Recommendations from evidence-based guidelines regarding the use of magnesium as an analgesic in adult patients with migraine or chronic pain

What We Found

- There is a possible benefit of intravenous magnesium for migraine treatment and of oral magnesium for migraine prophylaxis compared with placebo but results are conflicting.
- There is a possible benefit of intramuscular magnesium for complex regional pain syndrome compared with placebo but results are conflicting.
- Intravenous magnesium followed by oral magnesium may be beneficial for refractory chronic low back pain compared with placebo (demonstrated in one RCT).
- In one guideline, magnesium was not recommended for the treatment of acute migraine.
- In two guidelines, magnesium was recommended for migraine prophylaxis.

Evidence Gaps

What We Did Not Find

High-quality research

Studies with consistent dosing and routes of administration of magnesium, and with consistent outcomes measures

Evidence evaluating more subtypes of chronic pain (studies were only available for migraine, complex regional pain syndrome, and chronic low back pain)

Evidence comparing magnesium to opioids

Canadian studies

Recommendations from evidence-based guidelines regarding the use of magnesium for chronic pain conditions other than migraine

RCT = randomized controlled trial.

Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain (2016)

Evidence Requested for Decision-Making

- Clinical effectiveness and safety of delta-9-tetrahydrocannabinol/cannabidiol for the treatment of adult patients with chronic non-cancer pain or neuropathic pain
- Recommendations from evidence-based guidelines on the use of delta-9-tetrahydrocannabinol/cannabidiol for adult patients with chronic non-cancer pain or neuropathic pain

What We Found

- Delta-9-tetrahydrocannabinol/cannabidiol buccal spray may be associated with favourable short-term patient outcomes, including reduced levels of perceived pain and good tolerability, when compared with placebo therapy.
- One guideline recommended third-line use of delta-9-tetrahydrocannabinol/cannabidiol buccal spray for patients uncontrolled on drug therapy in the management of chronic neuropathic pain.

Evidence Gaps

What We Did Not Find

High-quality research (well-designed, prospective, randomized, active comparator-controlled trials with adequate follow-up)

Studies on long-term therapy with delta-9-tetrahydrocannabinol/cannabidiol spray

Studies on long-term benefits after discontinuation of therapy with delta-9-tetrahydrocannabinol/cannabidiol buccal spray

Studies on comparative clinical effectiveness of delta-9-tetrahydrocannabinol/cannabidiol oral spray in comparison with other active comparators (e.g., pharmacologic treatments)

Canadian studies

Recommendation from evidence-based guidelines for the management of patients with other chronic non-cancer pain (other than chronic neuropathic pain)

1000 mg versus 650 mg Acetaminophen for Pain or Fever (2016)

Evidence Requested for Decision-Making

- Clinical effectiveness of 1,000 mg compared with 650 mg or 650 mg of acetaminophen for pain

What We Found

- 1,000 mg of acetaminophen may improve pain relief compared with 650 mg of acetaminophen in various acute post-operative pain conditions.
- The risk of adverse events was similar between the two doses, with no serious adverse events reported.

Evidence Gaps

What We Did Not Find

High-quality research on the comparative efficacy and safety of 1,000 mg versus 650 mg of acetaminophen

Evidence specific to various pain conditions (included studies were limited to post-surgical pain conditions, only)

More studies evaluating the currently recommended maximum daily dose of acetaminophen (4 g) and the long-term use of acetaminophen

Gabapentin for HIV-associated Neuropathic Pain (2016)

Evidence Requested for Decision-Making

- Clinical effectiveness of gabapentin for the treatment of HIV-associated neuropathic pain

What We Found

- Low-quality studies suggest that gabapentin may improve pain and related sleep disturbances caused by HIV-associated sensory neuropathy.
- Gabapentin appeared to be well-tolerated, with somnolence being the most frequently reported side effect.

Evidence Gaps

What We Did Not Find

High-quality research (including larger sample size) on the effectiveness of gabapentin for patients with HIV-associated neuropathy

Gabapentin for Adults With Neuropathic Pain (2015)

Evidence Requested for Decision-Making

- Clinical efficacy and safety of gabapentin compared with placebo for adults with neuropathic pain
- Clinical efficacy and safety of gabapentin compared with placebo in adults with diabetic peripheral neuropathy

What We Found

- Overall, studies suggest a greater reduction in neuropathic pain with gabapentin compared with placebo in adults with a variety of conditions including diabetic peripheral neuropathy.
- However, only a moderate proportion (13% to 38%) of patients experienced substantial pain relief (assessed as 50% reduction or more in pain intensity).
- Adverse events were numerically higher with gabapentin compared with placebo.

Evidence Gaps

What We Did Not Find

High-quality research (including longer-term studies)

Studies assessing dose-effect relationship

Effectiveness in conditions other than postherpetic neuralgia and diabetic peripheral neuropathy

Systematic reviews, specifically on diabetic peripheral neuropathy

Canadian studies

Long-term Use of Cyclobenzaprine for Pain (2015)

Evidence Requested for Decision-Making

- Clinical effectiveness of long-term cyclobenzaprine for treating pain
- Clinical effectiveness of long-term cyclobenzaprine as an adjunct to other pain medication
- Cost-effectiveness of cyclobenzaprine alone or as an adjunct to other medications for treating pain
- Recommendations from evidence-based guidelines regarding the use of cyclobenzaprine for treating pain

What We Found

- Cyclobenzaprine may be more effective than placebo for patients with fibromyalgia and back pain (based on studies of limited duration).
- Comparative studies found similar outcomes for cyclobenzaprine compared with amitriptyline for fibromyalgia; and for cyclobenzaprine compared with diazepam, NSAIDs, or other muscle relaxants for musculoskeletal pain.
- There is no evidence of benefit of cyclobenzaprine for neck pain or myofascial pain.
- Adverse effects including drowsiness, dizziness, and dry mouth occur frequently.

Evidence Gaps

What We Did Not Find

Higher-quality studies

Longer-term studies with larger sample sizes

Economic evaluations

Recommendations from evidence-based guidelines (including cyclobenzaprine dosing, duration, and place in therapy relative to other available treatments)

NSAID = nonsteroidal anti-inflammatory drug.

Gabapentin for Adults with Neuropathic Pain (2014)

Evidence Requested for Decision-Making

- Clinical effectiveness of gabapentin compared with tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or pregabalin for treating neuropathic pain
- Clinical evidence regarding the misuse potential of gabapentin, pregabalin, tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors
- Recommendations from evidence-based guidelines regarding the use of gabapentin for neuropathic pain

*For more information on gabapentin misuse, see the related **Rapid Response Report**.*

What We Found

- Indirect evidence suggests similar short-term pain relief with gabapentin compared with pregabalin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors in patients with painful diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia.
- There is the potential for misuse of gabapentin, but the prevalence of misuse is unknown.
- UK guidelines support the use of gabapentin as one of the first-line treatment options for the management of neuropathic pain.
- US guidelines recommend gabapentin as an option for diabetic neuropathy.

Evidence Gaps

What We Did Not Find

Higher-quality research (including head-to-head studies comparing gabapentin with pregabalin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors)

Longer-term studies

Evidence specific to other neuropathic pain conditions

High-quality research on the potential misuse of gabapentin and pregabalin

Evidence on the prevalence of misuse and risk of misuse among patients prescribed drugs to manage neuropathic pain

Evidence assessing the potential misuse of tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors

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ABOUT CADTH

CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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CADTH Evidence
Driven.

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