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“Seek simplicity, and mistrust it.”
Alfred North Whitehead



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Definitions and Abbreviations

Chronic non-cancer pain (CNCP) Chronic pain not associated with cancer that lasts more than 6 months

Severity of pain: On a 0 to 10 scale

- Mild** pain is rated 1 to 3
- Moderate** pain is rated 4 to 7
- Severe** pain is rated 8 to 10

Visual analog scale a horizontal line, 100 mm in length, anchored at each end by descriptors such as no pain and very severe pain. The patient marks on the line the point that represents their level of pain. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.¹

No pain | _____ | Very severe pain

MEQ Morphine equivalent The dose of an opioid given in terms of its potency relative to morphine. For example 12 mg of hydromorphone is 60 mg MEQ.

N-methyl-D-aspartate (NMDA) receptors are glutamate-activated receptors located in the central nervous system which play a key role in memory and learning. Prolonged firing of pain-sensing neurons leads to glutamate release, and subsequent activation of central NMDA receptors. This causes spinal cord neurons to become more responsive to all inputs, increasing sensitivity to pain stimuli and decreasing sensitivity to opioid receptor agonists. NMDA-mediated spinal sensitization may play a role in the maintenance of neuropathic pain and hyperalgesia.²⁻⁴

- ARI** absolute risk increase
- ARR** absolute risk reduction
- NNH** number needed to harm
- NNT** number needed to treat
- RR** relative risk
- RRI** relative risk increase
- RRR** relative risk reduction



Measures of treatment effect

In previous academic detailing documents we have described measures of treatment effect such as relative risk reduction, absolute risk reduction, and number needed to treat.

- Those measures are used when the outcomes are **dichotomous**, ie the event either happened or did not happen (eg the patient died or survived).
- However, sometimes outcomes are measured on **continuous** scales in which the outcome may have a range of values. Using pain as an example, a patient may rate pain intensity as being a value on a 0 to 10 scale.
- Furthermore, different studies may use different scales. Again using pain as an example, in one study pain may be measured by asking a patient to indicate the intensity of their pain on a 100 mm visual analog scale and in another study it may be measured on a 0 to 10 point scale.
- In such cases, the method used to combine results in a meta-analysis is to standardize the measures in each study.
 - This is done by subtracting the mean score on the scale in the study group (e.g., opioid group) from the mean score on the scale in the control group (eg placebo group) and dividing this result by the pooled standard deviation of the two groups.
 - This provides a measure called the **standardized mean difference**.
 - The standardized mean differences for each study are then pooled using meta-analysis to arrive at an overall pooled standardized mean difference which is sometimes referred to as the **effect size**.
 - The number so calculated is the number of standard deviations the study group differs from the control group. For example, a standardized mean difference of 1.0 means the average result of the study group differs by one standard deviation from the control group.
- It is not possible to calculate statistics like relative risk and number needed to treat from the standardized mean difference.
- However, some benchmarks cited in the Canadian Guideline⁵ are

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 visual analog scale)
0.5 to < 0.8	Medium	Mean difference 10% to 20% of the scale
≥ 0.8	Large	Mean difference >20% of the scale



SUMMARY STATEMENTS

Question 1: What are the benefits and harms of opioids in treating CNCP?

- Evidence for long-term use of opioids is limited because the longest duration of most comparisons is 13 weeks and most comparisons were against placebo.
- For pain reduction, opioids
 - Have a **medium** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
 - However weak evidence suggests that the **strong** opioids morphine and oxycodone may provide a **small** effect compared to other drugs.
- For improving function, opioids
 - Have a **small** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
- Many people cannot tolerate opioids and stop taking them with a NNH of approximately 8 over 1 to 13 weeks.
- Weak evidence suggests that patients who are able to continue taking opioids long-term experience clinically significant pain relief.
 - Whether quality of life or functioning improves is inconclusive.
- Addiction is probably rare, but aberrant behaviour occurs in an average of 11.5% of patients and in studies ranged from 0% to 44%.

Question 2: Are some weak opioids more efficacious or associated with fewer adverse events than others?

- There is **insufficient evidence** to conclude that any one weak opioid is more efficacious or associated with fewer adverse events than other weak opioids.
- There are more RCTs of tramadol vs placebo or other agents than there are of codeine or buprenorphine vs placebo or other agents.
- One of the manufacturers of tramadol, in cooperation with the United States Food and Drug Administration has notified healthcare professionals that the drug may be sought by drug abusers and people with addiction disorders. Misuse or abuse poses a significant risk that could result in overdose or death.

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



Question 3: Are some strong opioids more efficacious or associated with fewer adverse events than others?

- There is **insufficient evidence** to conclude that any one strong opioid is more efficacious or associated with fewer adverse events than other strong opioids.

Question 4: Are long-acting opioid preparations more efficacious or associated with fewer adverse events than short-acting preparations?

- There is **insufficient evidence** to conclude that long-acting opioid preparations are more efficacious or associated with fewer adverse events than short-acting preparations.

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Introduction

- This topic has been developed based on a guideline published by the National Opioid Utilization Guidelines Group.^{5,6} NOUGG was formed by the Canadian regulatory colleges which recognized a need for guidance in use of opioids for chronic non-cancer pain (CNCP).⁶
- There was no industry funding for developing the guideline.⁶
- The guideline is now based at the Michael G. DeGroot National Pain Centre at McMaster University.
- We have also used information from recent U.S. guidelines,^{7,8} Cochrane reviews,⁹⁻¹⁴ and an evidence review by the Oregon Health and Science University.¹⁵
- A telephone survey conducted by Ipsos Reid in 2004 (N = 1005; response rate 20%) found that 25% of respondents had CNCP lasting at least six months. The rate was highest in the Atlantic provinces (36%).¹⁶
- According to data from the 2005 Canadian Community Health Survey, chronic pain affected 27% of seniors living in households.¹⁷

Scope of this document

- This document focuses on the evidence for efficacy and adverse effects of oral and transdermal opioids for CNCP.
- Opioids are used for many painful conditions and we will report details of Cochrane reviews on common and frequently studied conditions.
 - Osteoarthritis^{9,11}
 - Neuropathic pain^{10,12}
 - Low back pain¹³
- While addiction and abuse are well recognized adverse effects, we will not cover their recognition and management as these are complicated topics requiring a separate document.
- Similarly, we recognize that comprehensive management of chronic pain is multi-dimensional and often considers psychosocial factors such as motivation, compensation, and family support, but will not cover these factors.
- We will also not cover the evidence for intrathecal opioids and opioids used with other medications such as anti-depressants, NSAIDs, and anticonvulsants.

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Local resources

Several provincial resources can help with managing patients with chronic pain.

- **Nova Scotia Prescription Monitoring Program (NSPMP)**
 - Physicians and pharmacists can access detailed information about patients' use of monitored drugs and the pharmacies at which they have filled their prescriptions.
 - Upon request the NSPMP will monitor **patient management agreements** and alert the physician should the patient breach the agreement by filling a prescription from another physician or at a pharmacy outside of the agreement. Phone **1-877-476-7767** or **496-7123** to set up this service.
 - The NSPMP will provide physicians with their own prescribing profile and how it compares to peers in their DHA and provincially. Simply call the NSPMP and request your **Prescriber Peer Comparison Report**.
 - The NSPMP's **medical consultant, Dr Peter MacDougall**, an anesthetist and pain management specialist, is available to physicians and pharmacists for advice on pain management cases. Phone **478-0546** or pcmacdou@gmail.com
 - Dr MacDougall also directs the **Nova Scotia Chronic Pain Collaborative Care Network**. This network has physician-mentors around the province with expertise in pain management. Other primary care professionals can connect with a mentor to obtain ongoing advice on managing patients in chronic pain.
 - Mentors are in the following locations
 - Amherst/Antigonish
 - New Waterford
 - Halifax
 - Windsor
 - Yarmouth
 - For information on becoming or accessing a mentor, contact
 - Michele Chappell RN 902-473-7941 michele.chappell@cdha.nshealth.ca
 - **Pain clinics** associated with local Health Districts are in the following locations
 - Halifax 473-4130/4131
 - Berwick 538-7103
 - Hants 792-2271
 - Cape Breton 567-8183
 - Yarmouth 742-3542 ext 692
 - Truro, Amherst, Antigonish, New Glasgow 1-800-270-4776 ext 3312
 - The **Regional District Drug Information Centre** operating out of Capital District Health Authority provides advice on issues such as drug interactions, adverse effects, and dosage adjustments. Phone **473-4234**

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This review will address 4 questions

1. What are the benefits and harms of opioids in treating CNCP?
2. Are some weak opioids more efficacious or associated with fewer adverse events than others?
3. Are some strong opioids more efficacious or associated with fewer adverse events than others?
4. Are long-acting opioid preparations more efficacious or associated with fewer adverse events than short-acting preparations?

Background information

Levels of Evidence and Strength of Recommendations

- The Canadian Guideline adapted the evidence-grading system used by the Canadian Task Force on Preventive Care.⁶

Canadian Guideline Recommendation Grading	
Grade A	Recommendations are supported by evidence from RCTs.
Grade B	Recommendations are supported by <ul style="list-style-type: none"> • Evidence from controlled trials without randomization, or • Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group, or • Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here.
Grade C	Recommendations are supported by consensus opinion.

- In grading the evidence, the Canadian Guideline also considered how **directly** a reference addressed a recommendation. For example, an RCT may **inform** a recommendation but its main objective may not have been the same as the guideline recommendation. In such a case, the recommendation may be assigned Grade B even though it is supported by an RCT.
- There are 24 recommendations, some consisting of more than one part. The lack of high quality evidence is reflected in the number of Grade A, B, and C recommendations:
 - Grade A 4 recommendations
 - Grade B 12 recommendations
 - Grade C 20 recommendations

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- Evidence on this topic is somewhat limited with many studies being of short duration (≤ 12 weeks), and with few subjects. The Canadian Guideline cited 65 RCTs:⁵

- Duration

- 24 weeks 1 study (Study drug was propoxyphene which is no longer recommended.)
 - 12 – 16 weeks 13 studies 20%
 - 8 – 12 weeks 5 studies 8%
 - 4 – 6 weeks 29 studies 45%
 - < 4 weeks 17 studies 26%
- } 51% of studies were ≤ 6 weeks long

- Dropouts

- $\geq 30\%$ dropouts 33 studies 51%
- 20% to 30% dropouts 14 studies 22%

- N subjects

- > 300 subjects 15 studies 23%
- 100 – 300 subjects 21 studies 32%
- < 100 subjects 29 studies 45%

- In addition, 51 studies had **placebo** for a control group. Only 14 were direct comparisons of different drugs.

- By drug the number of studies listed was

- Tramadol 24 studies 1 to 13 weeks long 37%
- Morphine 14 studies 1 to 9 weeks long 22%
- Oxycodone 11 studies 2 to 16 weeks long 17%
- Codeine 6 studies 1 to 4 weeks long 9%
- Fentanyl 3 studies 3 to 6 weeks long 5%

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Outcomes

- When evaluating the **efficacy** of therapies in CNCP it is important to consider their effect on **pain** and **function**.¹⁸
- Studies use a variety of scales to measure pain and function and Cochrane reviews take different approaches to reporting them.
 - The scales may be numeric i.e., patients select a number from 0 to 10 or 0 to 100 or
 - The scales may be “visual analogue scales” i.e., patients select a point on a 10 cm or 100 mm line to indicate the severity of their pain.
 - In such cases, Cochrane reviewers standardized results to 100.^{9,12}
 - Commonly used measures of function in low back pain are the Oswestry Disability Index and Roland Disability Questionnaire.¹⁹
- To address the problem of different scales, several Cochrane and other meta-analyses report results as “standardized mean difference” (SMD). (See page 4 for details.)
 - Standardized mean difference is calculated by dividing the differences in mean values at the end of treatment across treatment groups by the pooled standard deviation differences and can be categorized as
 - Small SMD = <0.5
 - Medium SMD = 0.5 to <0.8
 - Large SMD = ≥ 0.8
- For reduction in **pain**, a reduction of **20%**¹⁴ to **30%**⁵ on a 10-point scale is considered a minimum clinically significant difference.
 - When commenting on results from Cochrane reviews, we have generally used 30% as the minimum clinically significant difference.
 - However, some studies and Cochrane reviews report the percent of people achieving at least a **50%** reduction in pain and use this value to calculate NNT⁹⁻¹¹
- According to the Canadian Guideline, pain is categorized as **mild, moderate, or severe**. Based on a 0 to 10 scale
 - Mild pain is rated 1 to 3
 - Moderate pain is rated 4 to 7
 - Severe pain is rated 8 to 10
- For **function**, the scale varies according to the condition studied.
 - In osteoarthritis, the WOMAC scale is used.
 - It is a 24 item questionnaire containing 5 questions on pain, 2 on stiffness, and 17 on function.
 - Scales are either a 0 to 4 Likert scale or 0 to 100 visual analogue scale.
 - Minimum clinically significant differences for the two scales are:
 - Likert scale – approximately 0.7¹⁹
 - Visual analogue scale – approximately 10

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- Cochrane reviews standardize the WOMAC scale to a 10-point scale for which the minimum clinically significant difference would be approximately 1.0.⁹
- Reporting of adverse effects also varies. Cochrane reviews report adverse events as patients¹¹
 - Experiencing **any** adverse event
 - **Withdrawing** because of adverse events
 - Experiencing any **serious** adverse events e.g.,
 - Hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality or birth defect, life-threatening events, or death
 - Experiencing symptoms of opioid **dependence** such as craving or physical withdrawal symptoms.

Opioids: mechanism of action

- The following information about the mechanism of action of opioids is excerpted from Nicholson 2003.²⁰
 - Opioids mediate their actions by binding and activating endogenous opioid receptors that comprise part of a pain-modulating pathway that descends from the midbrain to the spinal cord dorsal horn.
 - Opioid receptors and endogenous opioid peptides have also been identified in the peripheral nervous system.
 - Opioid receptors consist of three subtypes: μ (mu), δ (delta) and κ (kappa).
 - Most opioid drugs, for which morphine is the prototype, are relatively selective for μ receptors.
 - These drugs are “full agonists” and through their stimulation of μ receptors
 - Produce analgesia;
 - Affect mood and rewarding behaviour; and
 - Alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine functions.
- Full agonists have no ceiling to their analgesia. Analgesia increases with increasing dose until adequate pain control is achieved or dose-limiting adverse effects occur. In practice, this requires dose titration to achieve a balance between acceptable analgesia and adverse effects.
- Table 1 summarizes the effect of selected opioids on the receptors.

Weak opioids

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Table 1 Receptor activity of selected opioids

Opioid medication	Opioid receptor			Other receptors
	μ (mu)	δ (delta)	κ (kappa)	
	<ul style="list-style-type: none"> • Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritis, euphoria, anorexia, urinary retention, physical dependence 	Analgesia, spinal analgesia	<ul style="list-style-type: none"> • Analgesia • Sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea 	
Codeine	Weak agonist	Weak agonist		
Tramadol	Weak agonist			Serotonin and norepinephrine reuptake inhibitor
Buprenorphine	Agonist	Antagonist	Antagonist	
Morphine	Agonist		Weak agonist	
Hydromorphone	Agonist	Weak agonist		
Oxycodone	Agonist	Agonist	Agonist	
Fentanyl	Strong agonist			
Methadone	Agonist			NMDA receptor antagonist Serotonin and norepinephrine reuptake inhibitor

Adapted from Trescot 2008¹⁸

- Opioids can be classified as “weak” or “strong” depending on whether they are weak or strong agonists.
- Examples of **weak** opioids are
 - Codeine
 - Tramadol
 - Buprenorphine
 - Pentazocine
 - Propoxyphene
 - Meperidine
 } No longer recommended because of limited efficacy, adverse effects, or drug interactions
- Examples of **strong** opioids are
 - Morphine
 - Hydromorphone
 - Oxycodone
 - Fentanyl
 - Methadone

Weak opioids

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Opioids: features of selected opioids

- This section highlights some features of commonly used opioids. It does not include information on dosages and potential drug interactions.
- The **Regional District Drug Information Centre** operating out of Capital District Health Authority provides advice on issues such as drug interactions, adverse effects, and dosage adjustments. **Tel 473-4234.**

Codeine

- Approximately 10% of each dose is metabolized to morphine, which is responsible for most of its analgesic effect.²¹
- Patients with genetic variations in the CYP2D6 enzyme (“poor metabolizers” or “rapid metabolizers”) may be at risk of both increased side effects and poor analgesic response.²²
- Antitussive effects and some adverse effects probably come from codeine itself.²¹
- Dose ceiling: It has been reported that there is little increase in efficacy from single doses over 60 mg;²³ however, this has not been clearly demonstrated in clinical trials.
- Inexpensive

Tramadol

- Dual mechanism of action: weak opioid plus monoamine (serotonin and norepinephrine) reuptake inhibitor.²⁴
- Metabolized by the liver to active and inactive metabolites; both parent drug and metabolites are eliminated renally.²⁵
- Interacts with CYP2D6 inhibitors/inducers
- Serotonin syndrome has been reported when tramadol has been combined with selective serotonin reuptake inhibitors (SSRI’s).²⁶
- Tramadol lowers the seizure threshold; concomitant use with other medications which lower the seizure threshold (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, bupropion) is not recommended.^{25,26}
- Relatively expensive compared to codeine.
- Not legally scheduled as a narcotic; triplicate prescription forms not required. Legal status is under review by Health Canada.
- One of the manufacturers of tramadol, in cooperation with the United States Food and Drug Administration has notified healthcare professionals that the drug may be sought by drug abusers and people with addiction disorders. Misuse or abuse poses a significant risk that could result in overdose or death.²⁷

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Buprenorphine

- Buprenorphine is a mu opioid receptor agonist and a kappa opioid receptor antagonist.^{28,29}
 - Buprenorphine dissociates slowly from the mu receptor, resulting in a slow onset and long duration of analgesia.³⁰
- Buprenorphine is supplied as a transdermal patch in 5 mg, 10 mg and 20 mg strengths and provides a steady delivery of buprenorphine for **7 days**.
 - Buprenorphine should only be administered to patients who require **continuous** opioids for pain management.
- Doses higher than 5 mg should not be initiated in patients who are opioid naïve.³¹
- External heat sources (heating pads, hot water bottles, electric blankets) will increase absorption and possibly adverse effects, similar to other transdermal preparations.³¹
 - It takes 3 days after applying the first patch for levels to reach steady state.
 - After patch removal levels decrease by 50% within 12 hours.
- Following transdermal administration buprenorphine undergoes extensive hepatic metabolism to two metabolites:
 - Via glucuronidation to buprenorphine 3-o-glucuronide (inactive)
 - Via CYP3A4 to norbuprenorphine (active). Norbuprenorphine is subsequently glucuronidated to an inactive metabolite before excretion.
- Approximately 30% of buprenorphine metabolites undergo renal excretion.
 - The remainder, approximately 70%, is excreted as metabolites in the feces. This makes it a useful drug in patients with renal impairment.^{31,32}

Morphine

- “Gold standard” strong opioid medication.
- Theoretically, dose may be escalated indefinitely.
- Not metabolised by Cytochrome P450 system; lower risk of drug interactions.²²
- Generic immediate release dosage formulations are inexpensive; slow or extended release formulations are more costly, especially in higher doses.
- Morphine can cause toxicity in patients with renal dysfunction.

Hydromorphone

- Semisynthetic morphine derivative
- Approximately 5 times as potent as morphine on a mg-per-mg basis.
- Not metabolised by Cytochrome P450 system; fewer drug interactions than fentanyl or methadone.²²
- Efficacy and occurrence of adverse events appear to be similar to that of morphine, in equipotent doses.
- Similar to morphine, there is no analgesic “ceiling” effect; dose is limited by the appearance of adverse effects.
- Little evidence for use in chronic non-cancer pain; however, there is no reason to believe it would be less effective for this indication than morphine.³³

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Oxycodone

- Semisynthetic strong opioid analgesic.
- Only opioid that is a kappa agonist (which is associated with euphoria).
- Slightly more potent than morphine when given orally, due to better bioavailability.
- Formerly considered as a weak opioid, because it was available only in a low-dose formulation in combination with acetaminophen.
- Metabolised via Cytochrome P450 system to active metabolites noroxycodone and oxymorphone (>1%); therefore there is potential risk of drug-drug interactions.²²
- Oxycodone serum levels appear to be ~25% higher in women than in men at similar doses; dose may need to adjusted in female patients.²²
- Main route of elimination is renal, as a mixture of parent drug and metabolites.

Fentanyl

- Semisynthetic opioid, 50 to 80 times as potent as morphine.²¹
- Anesthetic properties in high doses.²¹
- Metabolised by Cytochrome P4503A4 system to inactive metabolites; subject to a large number of drug interactions.
- Recommended for use in renal failure^{34,35}, but uremia in end-stage renal disease can decrease hepatic clearance; important to monitor for toxicity.^{35,65}
- Available in Canada as a transdermal patch (Duragesic, generics).
 - Oral/buccal and transmucosal formulations are available in the US and Europe, but are not approved in Canada to date.³⁶
- Fentanyl transdermal patches are contraindicated in opioid-naïve patients, due to the high potency of the drug and the extended release format. Fatal respiratory depression has been reported.³⁷
- Initiation of transdermal fentanyl, recommended approach from Canadian Guideline⁵
 - Before starting fentanyl, obtain a complete history of opioid use within the last 2 weeks to ensure the patient is fully opioid tolerant.
 - Tolerance can be assumed if the patient is on a moderate, stable dose of a strong opioid, i.e., a total daily dose of at least 60–90 mg/day morphine equivalence for at least 2 weeks.
 - This dose should be scheduled rather than prn (at least bid for controlled release or qid for immediate release).
 - Do **not** switch from **codeine** to fentanyl regardless of the codeine dose, as some codeine users may have little or no opioid tolerance.
 - Maintain the initial dose for at least 6 days: use extra caution with patients at higher risk for overdose, e.g., elderly, patients on benzodiazepines.

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- Application of a transdermal system leads to the formation of a reservoir in the skin under the patch. Therefore, it can take 17 hours or more for the fentanyl serum concentration to fall by 50% after system removal; in elderly patients, this may be further prolonged up to 34 hours.
- Increases in skin temperature can accelerate the release of drug from the patch.
 - Patients should be counseled to avoid use of external heat sources (e.g. heating pads, electric blankets, heat lamps, hot water bottles) at the site of application. Saunas and hot tubs should also be avoided.
 - Fever, especially in excess of 40°C, could theoretically increase release of fentanyl from the patch. Patients with fever wearing a fentanyl transdermal system should be monitored for signs of opioid toxicity.
- Limited data are available to estimate dosage and clinical effect of fentanyl transdermal patches in pediatric populations; therefore these systems are not recommended in patients under 18 years of age.³⁸

Methadone

- Synthetic opioid agonist.
- Complicated metabolism, considerable interaction potential.²²
- As well as activity at the opioid receptor, it inhibits serotonin and norepinephrine reuptake and also inhibits NMDA.²¹
- Dosage conversion to morphine equivalents is unreliable.⁵
- Long half-life; the only opioid with prolonged activity which does not depend on a slow-release formulation.²¹
- Best used for stable pain conditions; the long half-life and complex metabolism makes it difficult to titrate.^{21,39}
- Prescribers must be specially authorized by Health Canada.
- Relatively inexpensive compared to other high potency agents – a possible alternative for uninsured patients.

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Question 1: What are the benefits and harms of opioids in treating CNCP?

- Evidence for long-term use of opioids is limited because the longest duration of most comparisons is 13 weeks and most comparisons are against placebo.
- For pain reduction, opioids
 - Have a **medium** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
 - However weak evidence suggests that the **strong** opioids morphine and oxycodone may provide a **small** effect compared to other drugs.
- For improving function, opioids
 - Have a **small** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
- Many people cannot tolerate opioids and stop taking them with a NNH of approximately 8 over 1 to 13 weeks.
- Weak evidence suggests that patients who are able to continue taking opioids long-term experience clinically significant pain relief.
 - Whether quality of life or functioning improves is inconclusive.
- Addiction is probably rare. However aberrant behaviour occurs in an **average** of 11.5% and in studies ranged from 0% to 44%.

- This section reviews the evidence from Cochrane reviews for efficacy and safety of opioids for osteoarthritis, neuropathic pain, and low back pain.
 - Of note, studies are short, ranging from 1 to 13 weeks.
- Generally for each condition we report findings for
 - Pain control
 - Function
 - Adverse effects
- Where possible we report these outcomes compared to placebo and to other drugs.
- We also provide information from the Canadian Guideline and our own comments which are designated "**ADS Comments**".
- Because opioids tend to increase the outcomes of pain relief, function, and adverse effects, data are presented as
 - Absolute risk increase (ARI)
 - Relative risk (RR). (This is more intuitive than relative risk increase when dealing with large differences in risk as is the case with adverse effects from opioids.)

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



Osteoarthritis

- Two Cochrane reviews looked at use of opioids in osteoarthritis.
 - One considered **non-tramadol** opioids vs placebo.¹¹
 - Opioids included were codeine, morphine, oxycodone, fentanyl, and oxymorphone
 - One considered **tramadol** vs placebo and other medications. However, there were too few studies to draw conclusions about the efficacy of tramadol vs other drugs.⁹

Osteoarthritis: Pain control for non-tramadol opioids vs placebo¹¹

- 10 studies, N = 2268, 1 to 12 weeks duration (median 4 weeks)
 - Standardized mean difference = 0.36 (95% CI: 0.26 to 0.47)
 - The authors consider this is a **small to moderate** effect.

Osteoarthritis: Pain control for tramadol vs placebo⁹

- 3 studies, N=749, duration 2, 12, and 13 weeks
 - Tramadol led to a decrease of 8.5 points on a 100 point scale (95% CI: 5 to 12 points).
 - **ADS Comment:** This was a **12%** decrease from the mean baseline intensity of 69.5 units which would **not** be clinically significant.
- 4 studies (N=793) 1.5, 2, 13, 13 weeks duration
 - Tramadol increased the percent of participants reporting at least **50%** pain relief from 50% to 69%.
 - ARI 19%, NNT 6 (95% CI: 4 to 9) over approx 12 weeks.

Osteoarthritis: Function for non-tramadol opioids vs placebo¹¹

- 7 studies, N = 1894, 2 to 12 weeks duration, median 4 weeks
 - Standardized mean difference = 0.33 (95% CI: 0.12 to 0.45)
 - The authors consider this is a **small to moderate** effect.

Osteoarthritis: Any adverse events for non-tramadol opioids vs placebo¹¹

- 4 studies, N = 1080, 4, 6, 12, 13 weeks duration
 - 87% in the opioid group vs 54% in the placebo group reported any adverse events.
 - RR 1.6, NNH = 3 (95% CI: 2 to 4) over 4 to 13 weeks
(Calculations done by Dalhousie ADS from data in Cochrane review.)

Weak opioids

Codeine

Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone

Hydromorphone Fentanyl



Osteoarthritis: Adverse events leading to withdrawal from the study, non-tramadol opioids vs placebo¹¹

- 10 studies, N = 2403, 1 to 12 weeks duration (median 4 weeks)
 - 33% in the opioid group vs 8% in the placebo group withdrew from the study because of adverse events.
 - RR 4.1, NNH = 4 (95% CI: 3 to 5) over 1 to 12 weeks
(Calculations done by Dalhousie ADS from data in Cochrane review.)

Osteoarthritis: Minor adverse events, tramadol vs placebo⁹

- 4 studies, N = 953, 1.5, 2, 11, 13 weeks duration
 - Minor adverse events were defined as being of a mild nature such as mild nausea or constipation
 - 51% in the opioid group vs 18% in the placebo group reported minor adverse events.
 - RR 2.8, NNH = 5 (95% CI: 4 to 7) over 1.5 to 13 weeks
Note: NNH are those reported in Cochrane review. Event rates (51% and 18%) are those calculated by ADS using random effects model and Comprehensive Meta-analysis program. There is a slight discrepancy in NNH when reported in Cochrane compared to that calculated from 51%-18% = 33% with NNH = 3.

Osteoarthritis: Adverse events leading to stopping medication, tramadol vs placebo⁹

- 7 studies, N = 1336, 1 to 13 weeks duration (median 8 weeks)
 - 22% in the opioid group vs 8% in the placebo group stopped medication because of adverse events.
 - RR 2.8, NNH = 8 (95% CI: 7 to 12) over 1 to 13 weeks

Osteoarthritis: Conclusions of the Cochrane authors

- The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events.
 - Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe.¹¹
 - **ADS Comment:** While there is increased risk of adverse events, they are reversible with discontinuation of opioids and should not preclude a trial of opioid therapy since some patients may benefit.
- Tramadol or tramadol/acetaminophen decreases pain intensity, produces symptom relief and improves function, but these benefits are **small**.
 - Adverse events, although reversible and not life threatening, often cause participants to stop taking the medication and could limit tramadol or tramadol plus acetaminophen usefulness.
 - It is not known whether tramadol is still effective after long-term use because the duration of studies was short.⁹

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



Neuropathic Pain

- As in osteoarthritis, two Cochranes reviewed use of opioids in neuropathic pain.
 - One considered **non-tramadol** opioids vs placebo and other medications.¹²
 - Opioids included were morphine, oxycodone, methadone, and levorphanol.
 - One considered **tramadol** vs placebo and other medications. However, there were too few studies to draw conclusions about the efficacy of tramadol vs other drugs.¹⁰

Neuropathic pain: Pain control for non-tramadol opioids vs placebo¹²

- 7 studies, N = 608, 3 to 8 weeks duration (median 4 weeks)
 - Mean difference on 100 point visual analog scale = 12.8 (95% CI: 9.1 to 16.4)
 - **ADS Comment:** Assuming
 - A decrease of 30% is the minimum clinically significant difference
 - The maximum effect of 16.4 (upper confidence interval)
 - This would be clinically significant if the patient started at a pain intensity of **55** on the 100-point scale and decreased by 16 points to a score of 39.
 - This is considered **moderate** pain.
 - Patients presenting with pain scores **higher** than 55 may be **less** likely to notice a clinically significant difference in their pain when taking a non-tramadol opioid compared to placebo.

Neuropathic pain: Pain control for non-tramadol opioids vs other drugs¹²

2 studies, N = 240, 5, 6 weeks duration

- The two studies compared morphine to gabapentin and morphine or methadone to nortriptyline or desimpramine.
- Neither study by itself showed a statistically significant result.
- When results were combined, opioids showed a statistically significant benefit of 6 (95% CI: 0.2 to 12) on a 100 point visual analog scale.
 - **ADS Comment:** Assuming
 - A decrease of 30% is the minimum clinically significant difference
 - The maximum effect of 12 points (upper confidence interval)
 - This would be clinically significant if the patient started at a pain intensity of **40** on the 100-point scale and decreased by 12 points to a score of 28.
 - A score of 40 is considered **moderate** pain.
 - Patients presenting with pain scores **higher** than 40 may be **less** likely to notice a clinically significant difference in their pain when taking a non-tramadol opioid compared to other drugs.

Weak opioids

Codeine

Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone

Hydromorphone Fentanyl



Neuropathic pain: Pain control for tramadol vs placebo¹⁰

- 3 studies, N = 302, 4,6,6 weeks duration
 - Tramadol **increased** the percent of participants reporting at least **50%** pain relief from 32% to 61%.
 - RR 1.7, NNT 4 (95% CI: 3 to 6) over approx 6 weeks.

Neuropathic pain: Function for non-tramadol opioids vs placebo

- One Cochrane review reported there was **no consistent reduction** in disability found comparing non-tramadol opioids to placebo.¹²

Neuropathic pain: Adverse events leading to withdrawal from the study, non-tramadol opioids vs placebo¹²

- 4 studies, N = 414, 3,4,5,6 weeks duration
 - 11% in the opioid group vs 5% in the placebo group withdrew from the study because of adverse events.
 - RR 2.8, NNH = 17 (95% CI: 9 to 100) over 3 to 6 weeks

Neuropathic pain: Adverse events leading to withdrawal from the study, tramadol vs placebo¹⁰

- 2 studies, N = 195, 4, 6 weeks duration
 - 17% in the opioid group vs 4% in the placebo group withdrew from the study because of adverse events.
 - RR 5.4, NNH = 8 (95% CI: 5 to 20) over 4 to 6 weeks

Neuropathic pain: Minor adverse events, non-tramadol opioids vs placebo¹²

- 6 studies, N = 546, 3 to 8 weeks duration (median 4.5 weeks)
 - Minor adverse events were reported and were similar to those listed in Table 2 which is from the Canadian Guideline.

Neuropathic pain: Conclusions of the Cochrane authors

- Intermediate-term studies demonstrate significant efficacy of opioids over placebo, which is likely to be clinically significant.¹²
 - **ADS Comment:** We question if the results are clinically significant since the mean difference was a decrease of 13 on a 100 mm scale. For this to be clinically significant at the 30% level, the baseline pain score would have to be ≤ 43 which is mild to moderate pain.
- Reported adverse events of opioids are common but not life threatening.¹²

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- Tramadol is an effective treatment for neuropathic pain. Its use may be limited by side effects but these are reversible and not life-threatening.¹⁰
 - **ADS Comment:** The findings are based on 3 studies with a total of about 150 subjects per group, lasting 4 to 6 weeks.

Table 2 Adverse events reported in Canadian Guideline⁵

Outcome	Event Rate		ARI	RR	NNH	95% CIs
	Placebo	Opioid				
Nausea	9%	28%	17%	3.1	6	5 to 8
Constipation	7%	26%	20%	3.7	5	4 to 7
Drowsiness	7%	24%	14%	3.4	7	6 to 10
Dizziness	5%	18%	12%	3.6	8	6 to 11
Dry skin/itching	2%	15%	10%	7.5	10	7 to 20
Vomiting	3%	15%	11%	5.0	9	6 to 14

ARI absolute risk increase; RR relative risk; NNH number needed to harm; CI confidence interval

Low Back Pain

- One Cochrane review looked at the evidence for opioids in low back pain.¹³
 - 3 studies compared tramadol to placebo.
 - 1 study compared oxycodone with or without sustained release morphine to naproxen up to 1000 mg per day.

Low back pain: Pain control for tramadol vs placebo

- 3 studies, N = 908, 4, 13, 13 weeks duration
 - Standardized mean difference = 0.71 (95% CI: 0.39 to 1.02)
 - **ADS comment:** This is considered a **medium** effect.

Low back pain: Function for tramadol vs placebo¹³

- 3 studies, N = 878, 4, 13, 13 weeks duration
 - Standardized mean difference = 0.17 (95% CI: 0.04 to 0.3)
 - **ADS comment:** This is considered a **small** effect.

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



Low back pain: Pain control and function for non-tramadol opioids vs other drugs¹³

- Only 1 small study (12 subjects per group, 16 weeks) was included in the analysis. There was no significant difference in pain control or function between oxycodone with or without sustained release morphine and naproxen up to 1000 mg per day.
 - However this study was too small to draw definite conclusions.

Low back pain: Conclusions of the Cochrane authors

- The benefits of opioids in clinical practice for the long-term management of chronic low back pain remain **questionable**.

Canadian Guideline⁵

- The Canadian Guideline did not report on low back pain specifically but did report on “widespread soft tissue pain.” It cites two RCTs of the use of tramadol for fibromyalgia.
 - The longer one lasted 13 weeks and randomized ~158 subjects to 37.5-mg tramadol/325-mg acetaminophen up to four times daily vs placebo.
 - **Pain relief**
 - Tramadol/acetaminophen
 - Decreased pain score by 12 mm on 100 mm scale (18%)
 - Increased the percent of participants reporting at least **30%** pain relief from 24% to 42%.
 - Relative risk increase 75%, NNT 6 (95% CI: 4 to 13) over 13 weeks
 - Increased the percent of participants stopping medication because of adverse events from 12% to 19% which was not statistically significant.
 - **ADS Comments**
 - A more useful comparison would have been tramadol/acetaminophen vs acetaminophen rather than vs placebo.
 - 128 subjects were excluded in a pre-randomization “screening” phase but no details are given for their exclusion e.g., intolerance to tramadol.

Weak opioids

Codeine
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Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- A 2006 meta-analysis, reported overall comparisons of opioid vs placebo and other drugs (i.e., results were pooled over a variety of conditions).⁴⁰
 - Opioids vs **placebo**
 - Pain relief – Meta-analysis of 28 studies showed **benefit** with opioids
 - Standardized mean difference 0.60 (95% CI:0.50 to 0.69), a **medium** effect.
 - Function – Meta-analysis of 20 studies showed **benefit** with opioids
 - Standardized mean difference 0.31 (95% CI:0.22 to 0.41), a **small** effect.
 - Opioids vs **other drugs**
 - Pain relief – meta-analysis of 8 studies showed **no** statistically significant benefit with opioids
 - Meta-analysis of 2 studies using **strong** opioids (morphine, oxycodone) showed **benefit** with opioids.
 - Standardized mean difference 0.34 (95% CI:0.01 to 0.67), a **small** effect.
 - The 2 studies had a total of 146 subjects.
 - Function – Meta-analysis of 3 studies showed benefit with **other drugs** (diclofenac, nortriptyline)
 - Standardized mean difference 0.16 (95% CI:0.03 to 0.30), a **small** effect.
 - Of note the one study comparing a strong opioid (morphine) to nortriptyline showed **no difference** but had only 64 subjects.
- The Canadian Guideline also lists CNCP conditions that have **not been studied** in placebo-controlled trials.⁵
 - Headache
 - Irritable bowel syndrome
 - Pelvic pain
 - Temporomandibular joint pain
 - Atypical facial pain
 - Non cardiac chest pain
 - Lyme disease
 - Whiplash
 - Repetitive strain injury

Weak opioids

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Strong opioids

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Hydromorphone Fentanyl



Longer term studies

- The longest RCTs included in the above Cochrane reviews lasted 13 weeks and so may not give an accurate idea of long-term effectiveness of opioids in CNCP.
- A 2010 Cochrane review looked at long-term (at least 6 months) use of opioids in CNCP pre-post case-series studies. Many were unblinded continuation of RCTs.¹⁴
- The review consisted of 26 studies, N = 4893. The most frequent diagnoses were
 - Back pain 7 studies
 - Osteoarthritis 6 studies
 - Unspecified 5 studies
 - Neuropathic 2 studies
- For **pain relief** with **oral** agents the Cochrane authors reviewed 4 placebo-controlled studies, 3 RCTs and 1 non-randomized study that followed patients in open-label extensions.
 - At the beginning of the studies 881 patients were enrolled.
 - For the extension part of the studies 470 patients (53%) were enrolled.
 - At 6 to 7.5 months (time of Cochrane analysis) 273 patients (31%) remained.
 - The pooled result of the 4 studies in terms of standardized mean difference was 1.6 (95% CI: 0.9 to 2.3) compared to baseline pain intensity.
- For **pain relief** with **transdermal fentanyl**, two case series studies (N=744, with 668 (90%) completing study) were associated with an standardized mean difference of 7.6 (95% CI: 4.3 to 10.9).
 - This is a very large effect size and the mean scores on a 0 to 10 scale dropped from 8.6 to 1.9.
 - The Cochrane authors state these studies suggest that clinically significant pain relief is attained **on average** among patients who begin transdermal fentanyl for CNCP.
- There were no data on **function** in the studies reviewed.
- The most frequent **adverse events** were gastrointestinal effects (i.e., constipation, nausea, dyspepsia), headache, fatigue/lethargy/somnolence, and urinary complications (i.e., retention, hesitancy) but the review did not report frequencies.
- The rates for **discontinuation** due to **adverse events** were
 - Oral agents
 - Weak opioids 11% (95% CI: 7% to 18%)
 - Strong opioids 34% (95% CI: 29% to 39%)
 - Transdermal fentanyl 12% (95% CI: 5% to 27%)
- The rates for **discontinuation** due to **insufficient pain relief** were
 - Oral agents 10% (95% CI: 8% to 14%)
 - Transdermal fentanyl 6% (95% CI: 4% to 8%)

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- Among studies that reported **addiction or abuse**, the event rate was 0.27%.
 - The authors emphasize that most studies screened out potential subjects with a history of substance abuse or addiction. In studies without such screening the rate may be higher at 3.3%.
- **Conclusions of the Cochrane authors**
 - The evidence regarding the effectiveness of long-term opioid therapy in CNCP is too **sparse** to draw firm conclusions, including quantity of mean pain relief.
 - Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief.
 - However, weak evidence suggests that patients who are able to continue taking opioids long-term experience clinically significant pain relief.
 - Whether quality of life or functioning improves is inconclusive.
 - Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.

Adverse effects associated with long-term opioid therapy

- The Canadian Guideline mentions several long-term adverse effects associated with long-term opioid therapy.⁵
 - Hyperalgesia
 - Endocrine dysfunction
 - Sleep apnea
- However there is much uncertainty about the evidence for these adverse effects because
 - It comes from non-randomized studies such as case reports and observational studies.
 - Results are inconsistent.
 - Most studies do not control for other medications such as benzodiazepines and antidepressants.

Hyperalgesia

- Opioid-induced hyperalgesia should be distinguished from opioid tolerance and/or disease progression.
- It is characterized by pain sensitivity (hyperalgesia and allodynia) that extends beyond the area of initial complaint despite increased doses of opioids.
- A recent systematic review points out that evidence for opioid-induced hyperalgesia is limited and comes mostly from acute infusions of opioids in healthy people.⁴¹
- However, our content expert considers this a real entity that may respond to slowly decreasing the dose of opioids.

Weak opioids

Codeine
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Strong opioids

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Hydromorphone Fentanyl



Endocrine dysfunction

- Neuroendocrine abnormalities and sexual dysfunction can be experienced with long-term opioid therapy.
- Opioids influence at least two major hormonal systems
 - The hypothalamic–pituitary–adrenal axis and
 - The hypothalamic–pituitary–gonadal axis.^{42,43}
- Testosterone depletion has been reported in several situations of opioid use
 - Men on sustained release opioids
 - Men receiving intrathecal opioid therapy,
 - Heroin addicts and
 - Patients receiving methadone maintenance therapy.⁴²⁻⁴⁵
- A study of women on controlled release opioids for CNCP showed inhibition of ovarian sex hormone and adrenal androgen production compared to controls.⁴⁶
- One randomized trial found that the incidence of sexual dysfunction after morphine happened in 11% of subjects but this was out of a total of 28 so would amount to 3 subjects.⁴⁷
- Two other randomized trials suggested that patients taking opioid medications reported better sexual function, which was likely due to an improvement of well-being.^{48,49}
- While evidence is limited it may be that patients may experience improved sexual function from overall well-being, but over the long-term opioids may impair neuroendocrine function.

Sleep apnea

- Chronic opioid use may be associated with disordered breathing during sleep.
- Patients may have several disturbances in their respiratory patterns during sleep, including characteristics of central sleep apnea, obstructive sleep apnea, ataxic breathing, or a combination of all 3 types.⁵⁰
- There are no opioid medications free from respiratory depressant effects.⁵¹
- We found no randomized controlled trials that reported on sleep-disordered breathing as a major adverse event in patients being treated with opioids for CNCP.
- Observational studies and case series have found sleep disorders associated with opioids.⁵²⁻⁵⁸
- However these studies did not control for the effect of other medications such as benzodiazepines and antidepressants which also affect respiration.
- One observational study found that sleep problems were more closely related to pain intensity and to depression than to opioid use.⁵⁷

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- The Canadian Guideline⁵ suggests considering a sleep study for patients using
 - High-dose opioids
 - Opioids in combination with other sedating drugs
 - Elderly patients
 - Obese patients and
 - Patients with somnolence
- There is no clear consensus on the **treatment** of opioid-associated sleep disordered breathing.⁵⁰
 - Continuous positive airway pressure (CPAP) appears to be less effective in opioid-induced sleep apnea than in obstructive sleep apnea in patients who are not on opioids.^{52,50}
 - It has been suggested that bilevel positive airway pressure (BiPAP) may be more effective than CPAP in these patients,⁵³ but this has not been confirmed in clinical trials.

Risks of addiction and aberrant drug-related behaviour

- One of the major concerns with prescribing long-term opioids is the potential for addiction and aberrant behaviour such as drug seeking, losing medications, and early refills.
- RCTs generally have not been long enough or specifically designed to measure rates of addiction and aberrant behaviour. Also, patients at high risk of addiction or aberrant behaviour are usually excluded from such studies.
- The Cochrane review on long-term use of opioids found the risk of addiction or aberrant behaviour was 0.27%. The authors emphasize that most studies screened out potential subjects with a history of substance abuse or addiction.¹⁴
- A recent systematic review of 67 studies estimated the overall rate of addiction to be 3.3%.⁴¹
 - In studies where patients with a current or previous history of addiction or abuse were excluded, the rate was much lower at 0.19%.
 - The rate of aberrant behaviour was 11.5% (range 0% to 44%).
 - The Canadian Guideline points out limitations of this study⁵
 - The diagnosis of addiction depends on the clinician's judgement.
 - Aberrant behaviour may indicate addiction but may also indicate inadequately controlled pain.
- **The 2009 Canadian Alcohol and Drug Use Monitoring Survey** found that among users of opioid pain relievers, 2.3% reported using them to get high.⁵⁹
- Our content expert notes that merely possessing opioids may put people at risk of assault and robbery.
 - Patients should return any unused opioids to their pharmacy for disposal.

Weak opioids

Codeine
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Strong opioids

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Summary of question 1

- Evidence for long-term use of opioids is limited because the longest duration of most comparisons is 13 weeks and most comparisons were against placebo.
- For pain reduction, opioids
 - Have a **medium** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
 - However weak evidence suggests that the **strong** opioids morphine and oxycodone may provide a **small** effect compared to other drugs.
- For improving function, opioids
 - Have a **small** average effect compared to **placebo**.
 - Have **not** been shown to be superior to **other drugs**.
- Many people cannot tolerate opioids and stop taking them with a NNH of approximately 8 over 1 to 13 weeks.
- Weak evidence suggests that patients who are able to continue taking opioids long-term experience clinically significant pain relief.
 - Whether quality of life or functioning improves is inconclusive.
- Addiction is probably rare, but aberrant behaviour occurs in an average of 11.5% of patients and in studies ranged from 0% to 44%.

Weak opioids

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Strong opioids

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Question 2: Are some weak opioids more efficacious or associated with fewer adverse events than others?

- There is insufficient evidence to conclude that any one weak opioid is more efficacious or associated with fewer adverse events than other weak opioids.
- There are more RCTs of tramadol vs placebo or other agents than there are of codeine or buprenorphine vs placebo or other agents.
- One of the manufacturers of tramadol, in cooperation with the United States Food and Drug Administration has notified healthcare professionals that the drug may be sought by drug abusers and people with addiction disorders. Misuse or abuse poses a significant risk that could result in overdose or death.

- The three currently available weak opioids are codeine, tramadol, and buprenorphine.
- We found only one RCT comparing **codeine** and **tramadol** in CNCP.⁶⁰
 - Duration 4 weeks; patients with osteoarthritis or low back pain received either
 - Tramadol 37.5 mg plus acetaminophen 325 gm N=309 or
 - Codeine 30 mg plus acetaminophen 300 mg N=153
 - There was **no** statistically significant difference in **pain relief** as assessed by patients or clinicians.
 - There was **no** statistically significant difference in **overall adverse events** (~ 73% each group). However codeine was associated with a higher rate of
 - Constipation 21% vs 11%, p<0.01 and
 - Somnolence 24% vs 17%, p =0.05
 - There was **no** statistically significant difference in **withdrawals** for adverse events (~13% each group).
- Another study involved cancer patients.⁶¹
 - Duration 3 weeks; patients with gastric, breast, prostate, or lung cancer received either
 - Tramadol 200 mg N=56
 - Codeine 150 mg plus acetaminophen 2500 mg N=59
 - Hydrocodone 25 mg plus acetaminophen 2500 mg N=62
 - All patients received bisacodyl 5 mg daily to prevent constipation.
 - There were **no** significant **differences** in **pain relief** among the three groups.

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- The only significant differences in adverse events were more frequent with tramadol.

	<u>Tramadol</u>	<u>Codeine</u>	<u>Hydrocodone</u>	
• Vomiting	36%	24%	16%	P=0.047
• Anorexia	21%	2%	7%	P=0.001
• Weakness	13%	0%	2%	P=0.002
• Dizziness	41%	24%	19%	P=0.022

- The Canadian Guideline cites RCTs of codeine and tramadol vs placebo and other agents.⁵
 - Codeine vs placebo, 3 RCTs, 1 to 4 weeks duration – benefit in pain relief (1 study 4 weeks duration showed benefit in function.)
 - Codeine vs diclofenac, 1 RCT, 1 week duration – no difference in pain relief or function.
 - Tramadol vs placebo, 14 RCTs, 2 to 13 weeks duration – benefit in pain relief (4 studies, 6 to 12 weeks showed benefit in function).
 - Tramadol vs diclofenac or clomipramine, 3 RCTs, 4 to 6 weeks duration – no difference in pain relief or function.
- In March 2010, in cooperation with the United States Food and Drug Administration, the manufacturer of Ultram (tramadol) mailed a letter to healthcare professionals in the United States which is excerpted below.
 - Tramadol has mu-opioid agonist activity. ULTRAM can be sought by drug abusers and people with addiction disorders and may be subject to criminal diversion.
 - The possibility of illegal or illicit use should be considered when prescribing or dispensing ULTRAM in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
 - Misuse or abuse poses a significant risk to the abuser that could result in overdose and death.²⁷
- The Canadian Guideline does not mention **buprenorphine** for pain because BuTrans was not available in Canada while the guideline was being developed.
- We found 3 studies at least 4 weeks long comparing **buprenorphine to placebo and tramadol**.
 - Buprenorphine vs placebo, N=79, 4 weeks duration⁶²
 - Patients had a variety of CNCP diagnoses.
 - Pain control**
 - Mean difference on a 100 mm pain scale = 7.1 mm which is statistically significant but not clinically significant.
 - Function**
 - No statistically significant difference between buprenorphine and placebo.

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- **Adverse events considered severe by subjects**
 - 53% in buprenorphine group vs 42% in placebo group which was not statistically significant.
- **Withdrew because of adverse events**
 - 25% in buprenorphine group vs 9% in placebo group
 - RRI 200%, ARI 9%, NNH 6 (95% CI: 4 to 30)
- Buprenorphine patch vs placebo: N = 315, 28 days duration⁶³
 - Patients with OA of hip or knee and inadequate analgesia with ibuprofen.
 - 7 day run-in, followed by 21 day titration, 7 day maintenance period
 - Outcome evaluated on day 28 of treatment
 - 51% withdrawal rate
 - Proportion of patients achieving **"treatment success"**, defined as a patient satisfaction score of good, very good, or excellent (≥ 2 on a 0 to 4-point scale), at day 28:
 - 44% treatment vs 32% placebo
 - Odds ratio = 1.66, $p = 0.036$, NNT = 8 (95% CI: 4 to 78)
 - There was **no** statistically significant **difference** in mean pain score between buprenorphine and placebo.
 - There was a statistically significant benefit in overall satisfaction score (1.0 vs 1.3 on the 0 to 4-point scale, $p=0.046$)
 - **ADS comment:** The **clinical** significance of this difference is **questionable**.
 - **Withdrawals for adverse events**
 - 26% in buprenorphine group vs 14% in placebo group
 - Relative risk 1.85, NNH = 9 (95% CI: 5 to 24)
 - Most common adverse events in buprenorphine-treated subjects:
 - Nausea/vomiting
 - Headache
 - Dizziness
 - Somnolence
 - Application site reactions (erythema, pruritis, rash)
- Buprenorphine vs tramadol, N=134, 12 weeks duration⁶⁴
 - This open-label study was designed to see if buprenorphine was non-inferior to tramadol (BID dosing) in patients with osteoarthritis.
 - There were **no** statistically significant **differences** in **pain relief, function** or **quality of sleep**.



- **Adverse events** were frequent with both drugs, reported by 88% of patients taking buprenorphine and 79% of patients taking tramadol.
 - Withdrawals because of adverse events were more frequent with buprenorphine than tramadol (29% vs 15%, P=0.038).
 - The most common adverse effects with buprenorphine were
 - Nausea 30%
 - Constipation 19%
 - Dizziness 16%
 - Pain 15%
 - Hyperhidrosis 15%

Question 3: Are some strong opioids more efficacious or associated with fewer adverse events than others?

- There is insufficient evidence to conclude that any one strong opioid is more efficacious or associated with fewer adverse events than other strong opioids.

- To address this question we did not search for primary publications reporting RCTs comparing strong opioids to each other. Instead we report comments from the Cochrane reviews and guidelines and an extensive review of long-acting opioid preparations conducted by the Oregon Evidence-based Practice Center of the Oregon Health and Science University.¹⁵
- The Oregon review provides a thorough review of long-acting opioid preparations, most of which are strong opioids.
 - Seven studies directly compared the **efficacy** of one controlled release opioid to another in CNCP.¹⁵
 - Transdermal fentanyl vs morphine 3 studies
 - Oxymorphone vs oxycodone 2 studies
 - Oxycodone vs morphine 2 studies
 - Five trials found **no difference** between long-acting opioid preparations.
 - The 2 which found a significant difference (1 trial of transdermal fentanyl vs oral controlled release morphine and one trial of extended-release morphine vs sustained-release oxycodone) were both open label, rated poor quality, and were inconsistent with higher quality trials evaluating the same comparison that found no differences.

Weak opioids

Codeine
Tramadol Buprenorphine

Strong opioids

Morphine Oxycodone Methadone
Hydromorphone Fentanyl



- Six studies provided data comparing **adverse effects** of long-acting opioid preparations.¹⁵
 - Transdermal fentanyl vs morphine 2 studies
 - Oxycodone vs oxymorphone 2 studies
 - Oxycodone vs morphine 2 studies
- All studies excluded patients at high risk for addiction or abuse and none adequately assessed these adverse events.
- Two studies found transdermal fentanyl associated with slight trends towards less constipation but more withdrawals due to any adverse event compared to morphine.
- There were **no clear or consistent differences** in studies comparing oxycodone and oxymorphone or oxycodone and morphine.
- The authors conclude that there is **insufficient evidence** to suggest that one controlled release opioid is superior to another in terms of efficacy or associated with fewer adverse events in adult patients with CNCP.
- The Cochrane review on non-tramadol opioids found no difference in effect on pain or function with different opioids.¹¹
- The Canadian Guideline⁵ does not differentiate between morphine, hydromorphone, and oxycodone.
 - All 3 are recommended for
 - Second line therapy for mild to moderate pain AND
 - First line therapy for severe pain.
- However, the guideline does recommend⁵
 - Fentanyl for second line therapy for severe pain AND
 - Methadone for third line therapy for severe pain

These recommendations are **Grade C, consensus.**

Weak opioids

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Question 4: Are long-acting opioid preparations more efficacious or associated with fewer adverse events than short-acting preparations?

- There is insufficient evidence to conclude that long-acting opioid preparations are more efficacious or associated with fewer adverse events than short-acting preparations.
- The Oregon review also reviewed the evidence for long-acting and short-acting opioid preparations.¹⁵
 - Seven randomized clinical trials directly compared long-acting opioid preparations to short-acting preparations in patients with CNCP.
 - Oxycodone 3 studies
 - Dihydrocodeine 2 studies
 - Morphine 1 study
 - Codeine 1 study
 - Studies were rated as poor to fair quality, lasted 5 days to 16 weeks, and enrolled 36 to 107 subjects.¹⁵
 - None of the studies were designed to assess rates of addiction or abuse.
 - There were no consistent trends demonstrating significant differences in efficacy between long-acting opioid preparations and short-acting preparations.¹⁵
 - There is no convincing evidence to suggest lower adverse event rates with long-acting opioid preparations as a class compared with short-acting preparations for all assessed adverse events.
 - There were no data comparing rates of addiction or abuse of long-acting opioid preparations to short-acting preparations.¹⁵
- The Canadian Guideline suggests controlled-release opioids for the elderly to improve adherence:
 - “Controlled-release formulations are recommended for the elderly for reasons of compliance even though there is **no evidence** controlled release formulations are more effective than immediate-release formulations.”⁵

Weak opioids

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Opioid-Induced Constipation

- Constipation is an almost-universal side effect of chronic opioid therapy.⁶⁵
- Up to one third of patients experiencing opioid-induced constipation respond by reducing their opioid dose, sometimes leading to a return or increase in pain.⁶⁵
- The constellation of gastrointestinal effects known collectively as opioid bowel dysfunction comprises a number of symptoms:
 - Constipation (hard, dry stools, straining, and incomplete evacuation)
 - Abdominal cramping
 - Bloating/abdominal distension
 - Gastroesophageal reflux
- Patients rarely develop tolerance to opioid-induced constipation.⁶⁶
- Mechanism of opioid-induced constipation
 - Thought to be stimulation of peripheral μ opioid receptors in the GI tract.
 - A number of GI functions are mediated through these μ receptors, such as motility, secretion, absorption, and blood flow.
 - Centrally mediated opioid effects may also contribute to bowel dysfunction by altering autonomic outflow to the gut.⁶⁶
- Complications associated with uncontrolled constipation:⁶⁶
 - Fecal impaction
 - Pseudo-obstruction of the bowel
 - Alterations in the absorption of orally-administered medications
- Prevention/treatment of opioid bowel dysfunction:
 - Aim of treatment should be to achieve comfortable defecation, not a specific frequency of evacuation.⁶⁵
 - Prevention of constipation through prophylactic laxative administration is considered the first line choice to manage OBD.
 - Cancer Care Nova Scotia has developed guidelines for the management of opioid-induced constipation, as presented below.

Prevention of opioid-induced constipation

- Begin all patients taking around-the-clock opioids on a laxative bowel regimen:
 - Sennosides 8.6mg (e.g., Senokot) 1-2 tablets PO QHS

OR

 - Sennosides (as above) plus Docusate Sodium 100mg (e.g., Colace) 1-2 capsules PO BID

OR

 - Docusate-Senna combination product (e.g. Senokot-S) 1-2 capsules PO QHS

Weak opioids

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Strong opioids

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Management of opioid-induced constipation

- If no bowel movement in any 48 hour period, add **one or two** of the following:
 - Sennosides 2 tabs PO HS to 4 tabs PO TID
 - Bisacodyl 5 mg PO HS to 15 mg PO TID
 - Milk of Magnesia PO 30-60 mL once or twice daily
 - Lactulose PO 15 to 60 mL once or twice daily
- If no BM after 72 hours, consider rectal examination to rule out impaction.
- If **not** impacted, try one of the following:
 - Bisacodyl (Dulcolax) suppository 10 mg
 - Magnesium citrate 8 oz PO
 - Mineral oil 30 to 60 ml PO
 - Milk of magnesia 25 mL + cascara 5 mL
- Adapted from CCNS Best Practice Guidelines for the Management of Cancer-Related Pain in Adults.

- Our content expert suggests 2 tablespoons of ground flax seed accompanied by 8 glasses of water per day is effective for prevention of opioid-induced constipation.
- Patients can buy whole seeds and grind them in a coffee grinder, blender, or food processor.

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Weak opioids

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Strong opioids

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