

Canadian guideline for safe and effective use of opioids for chronic noncancer pain

Clinical summary for family physicians. Part 1: general population

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Abstract

Objective To provide family physicians with a practical clinical summary of the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, developed by the National Opioid Use Guideline Group.

Quality of evidence Researchers for the guideline conducted a systematic review of the literature on the effectiveness and safety of opioids for chronic noncancer pain, and drafted a series of recommendations. A panel of 49 clinicians from across Canada reviewed the draft and achieved consensus on 24 recommendations.

Main message Screening for addiction risk is recommended before prescribing opioids. Weak opioids (codeine and tramadol) are recommended for mild to moderate pain that has not responded to first-line treatments. Oxycodone, hydromorphone, and morphine can be tried in patients who have not responded to weaker opioids. A low initial dose and slow upward titration is recommended, with patient education and close monitoring. Physicians should watch for the development of complications such as sleep apnea. The optimal dose is one which improves function or decreases pain ratings by at least 30%. For by far most patients, the optimal dose will be well below a 200-mg morphine equivalent dose per day. Tapering is recommended for patients who have not responded to an adequate opioid trial.

Conclusion Opioids play an important role in the management of chronic noncancer pain, but careful prescribing is needed to limit potential harms. The new Canadian guideline provides much-needed guidance to help physicians achieve a balance between optimal pain control and safety.

Opioid prescribing has increased dramatically in recent years. For example, oxycodone prescriptions among recipients of Ontario Drug Benefits rose by 850% from 1991 to 2007, from 23 prescriptions per 1000 individuals per year to 197 prescriptions per 1000 individuals per year.¹ The average amount of oxycodone per prescription increased from 1830 mg to 2280 mg. Prescriptions of other opioids, particularly fentanyl, have also increased. These increases have been accompanied by increases in opioid-related harms such as addiction and overdose.²

Guideline development

In 2008, a research group selected by the Federation of Medical Regulatory Authorities of Canada conducted a systematic literature review on the effectiveness and adverse effects of opioids.³ The researchers drafted initial recommendations that were reviewed by the National Advisory Panel, a group of 49 experts in family medicine, psychiatry, addiction medicine, and other disciplines. Through 4 rounds of review, the National Advisory Panel achieved consensus on 24 recommendations.

Quality of evidence

The research group relied on an update of a 2006 meta-analysis of controlled trials on the analgesic effectiveness of opioids for chronic noncancer pain (CNCP).⁴ In addition, several focused literature searches identified studies on

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KEY POINTS Opioid prescribing has increased in Canada, accompanied by an increase in opioid-related harms such as overdose and addiction. To date, Canadian physicians have lacked evidence-based prescribing guidelines to help them reduce these harms. This review provides a brief clinical summary of the recently released Canadian guidelines for the general population. A companion paper summarizes recommendations for special populations. Opioids play an important role in the management of chronic noncancer pain, but careful prescribing is needed. Opioid therapy should be reserved for pain conditions that have not responded to nonopioid therapies and for which opioids have been shown to be effective, and opioids should be combined with other pharmacologic and nonpharmacologic treatments.

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long-term opioid effectiveness, medical complications, problematic opioid use, and opioid use within specific populations. In total, 10798 studies were identified from the literature; 183 met inclusion criteria. The focused reviews included studies of any design that examined adult patients taking prescription opioids for CNCP. Final recommendations were graded according to level of evidence.

Main message

This paper is a brief clinical summary of the national guideline,⁵ including recommendations on opioid indications, selection, titration, precautions, and monitoring. The paper does not address other key components of CNCP treatment, such as nonopioid medications or physical and psychotherapeutic treatments. A companion paper (page 1269) summarizes the guideline's recommendations for special populations.⁶ The complete guideline is available from nationalpaincentre.mcmaster.ca.⁵

Indications. Opioids should be reserved for patients who have not responded to nonopioid treatments and who have defined somatic or neuropathic pain conditions for which opioids have been shown to be effective. There is limited evidence to support the use of opioids for common pain conditions such as fibromyalgia and low back pain (Table 1).⁵ While tramadol (considered by many to be a weak opioid) is of modest benefit for fibromyalgia pain,^{7,8} strong opioids such as oxycodone or morphine have not been tested in this condition and are not recommended.⁹ Systematic reviews have concluded that opioids should not be used routinely for low back pain and other osteoarthritic conditions because of uncertainty about their long-term effectiveness,¹⁰ risk of misuse,¹¹ and considerable side effects.^{12,13} Acetaminophen, nonsteroidal anti-inflammatory drugs, patient education, back exercises, and behavioural therapy are recommended for chronic low back pain.¹⁴

Baseline assessment. The physician should determine the cause and type of pain (neuropathic, nociceptive, or mixed) through a careful pain history, a physical examination, and appropriate investigations (Box 1).⁵ The physician should inquire about pain intensity (using an 11-point scale on which 0 represents no pain and 10 represents the worst possible pain), aggravating and relieving factors, and the effects of the pain on daily activities. Brief questionnaires, such as the short form of the McGill Pain Questionnaire¹⁵ or the Brief Pain Inventory (available online from www.algosresearch.org/PracticeTools/DxTestForms/index.html),¹⁶ can be useful for monitoring progress. Patients should be asked about personal and family histories of problematic substance use and about current use of alcohol, cannabis, opioids, benzodiazepines, sedating over-the-counter preparations, and street drugs. Screening questionnaires and urine drug screening can also help identify high-risk patients; additional resources and information are provided in the companion article on page 1269.⁶ Physicians should also inquire about mood and social support, as these can affect patients' perceptions of pain.

Starting opioid therapy. Physicians should review the goals of opioid therapy and common side effects with patients before starting opioid therapy (Box 2).⁵ Physicians should emphasize that elimination of pain is unlikely; a realistic goal for opioid therapy is improved function or pain reduction of 30% or more. Potential medical complications should be reviewed, including sexual dysfunction,^{17,18} opioid-induced hyperalgesia,^{17,19} and sleep apnea.²⁰⁻²² Patients should be warned to avoid alcohol and sedating drugs (particularly during titration), and to seek urgent medical attention if they experience early signs of overdose such as "nodding off" and slurred speech. Patients should also keep their opioid medication secure from friends or family. There is only

Table 1. Evidence of opioid efficacy

EXAMPLES OF CNCP CONDITIONS FOR WHICH OPIOIDS WERE SHOWN TO BE EFFECTIVE IN PLACEBO-CONTROLLED TRIALS*		EXAMPLES OF CNCP CONDITIONS THAT HAVE NOT BEEN STUDIED IN PLACEBO-CONTROLLED OPIOID TRIALS
TRAMADOL ONLY	WEAK OR STRONG OPIOID	
<ul style="list-style-type: none"> • Fibromyalgia 	<ul style="list-style-type: none"> • Diabetic neuropathy • Peripheral neuropathy • Postherpetic neuralgia • Phantom limb pain • Spinal cord injury with pain below the level of injury • Lumbar radiculopathy • Osteoarthritis • Rheumatoid arthritis • Low back pain • Neck pain 	<ul style="list-style-type: none"> • Headache • Irritable bowel syndrome • Pelvic pain • Temporomandibular joint dysfunction <ul style="list-style-type: none"> -atypical facial pain • Non-cardiac chest pain • Lyme disease • Whiplash <ul style="list-style-type: none"> -repetitive strain injury

CNCP—chronic noncancer pain.

*These trials were limited by the short duration of opioid therapy (maximum of 3 months).

Reprinted from the National Opioid Use Guideline Group.⁵

Box 1. Baseline assessment of the chronic noncancer pain patient**1. Pain condition**

Comprehensive knowledge of the patient's pain condition includes

- a thorough history and physical examination to determine the type, cause, and nature of the pain, including questions about past investigations and interventions for pain and any medication trials,
- an estimate of the pain intensity and the functional impairment that arises from it (impact of pain on work, school, home, and leisure activities), and
- diagnosis.

2. General medical and psychosocial history

Other relevant history includes

- general medical history, including questions about general physical health, emotional health, and medication use, and
- psychosocial history, including information about living arrangements, family and social support, family obligations, and work status.

3. Psychiatric status

Psychiatric status includes information regarding

- the patient's current and past history of psychiatric disorders and treatments, and
- any family history of psychiatric disorders.

4. Substance use history

Substance use history includes questions about

- current, past, and family histories of substance use, abuse, and addiction (alcohol, marijuana, tobacco, benzodiazepines, opioids, cocaine, amphetamines, barbiturates, hallucinogens, and solvents), and
- whether the patient has previously attended a treatment program for addiction.

5. Documentation

Maintain detailed records document

- patient assessment, treatment plan, discussion of risks and benefits, informed consent, opioids prescribed, and outcomes.

Reprinted from the National Opioid Use Guideline Group.⁵

Box 2. Opioid information for patients: *These messages could be used to create patient education materials.*

Opioids are a group of similar medications that are used to help with pain—there is more than 1 type of opioid and they have different names (for example, Percocet, OxyContin, Tylenol No. 2, and Tramacet).

- Opioids are used to improve your ability to be active and to reduce pain.
 - You and your doctor will ensure that the medication helps you to achieve your goals (eg, become more active).
 - Your doctor will see you for follow-up visits to assess pain relief, any side effects, and your ability to meet your goals.
- Common side effects of opioids include nausea (28% of patients report it), constipation (26%), drowsiness (24%), dizziness (18%), dry skin or itching (15%), and vomiting (15%).
 - Side effects can be minimized by slowly increasing the dose of the drug and, if necessary, by using anti-nausea drugs and bowel stimulants.
- Your doctor will ask you questions and discuss your concerns about the risk of becoming addicted.
 - Addiction means that a person uses the drug to “get high” and cannot control the urge to take the drug.
 - Most patients do not “get high” from taking opioids and most have a low risk of addiction. Those at greatest risk have a past history of addiction with alcohol or other drugs.
- Opioids have risks—these can be managed by working cooperatively with your doctor.
 - Take the medication as your doctor prescribed it.
 - Do not drive while your dose is being gradually increased or if the medication is making you sleepy or confused.
 - Only 1 doctor should prescribe your opioid medication—it is not safe to obtain this medication from 2 different doctors.
 - Do not take opioids from someone else, and do not share them with others.
 - You may be asked for a urine sample—this will help to show all the drugs you are taking and ensure that you are not taking an unsafe combination of drugs.
 - Your doctor will give you a prescription for the amount of medication that will last until your next appointment. Keep your prescription safe and use the medications as instructed. If you run out too soon or lose your prescription your doctor will probably not provide another.
 - If you cannot follow these precautions it might not be safe for your doctor to prescribe opioid medication for you.
- If you stop taking your medication abruptly, you will experience a withdrawal reaction.
 - Withdrawal symptoms do not mean you are addicted, just that you stopped the drug too quickly. Your doctor will direct you on how to slowly stop this medication so you won't have this experience.
 - Opioid withdrawal symptoms are flulike (eg, nausea, diarrhea, and chills).
 - Withdrawal is not dangerous but it can be very uncomfortable.
 - If you interrupt your medication schedule for 3 days or more for any reason, do not resume taking the medication without consulting a doctor.
- Overdose from opioids is uncommon, but you and your family should be aware of the signs.
 - Opioids are safe over the long term, BUT they can be dangerous when starting or increasing a dose.
 - Overdose means thinking and breathing slows down—this could result in brain damage, trauma, or death.
 - Mixing opioids with alcohol or sedating drugs, such as pills to help anxiety or sleeping, greatly increases the risk of overdose.
 - Contact a doctor if you notice any of the following signs of overdose: slurred or drawling speech, becoming upset or crying easily, poor balance, or “nodding off” during conversation or activity.
- The medication the doctor prescribes for you can be very dangerous to others.
 - Your body will get used to the dose your doctor sets for you, but this same dose can be very dangerous to others.
 - You have reached your proper dose slowly, but someone who is not used to the medication could have a serious reaction, including death. Do not give your medication to anyone else—it is illegal and could harm or kill them.
 - Keep your medication securely stored at home—the bathroom medicine cabinet is not a safe place; research has shown that others, particularly teenagers might help themselves to these drugs from friends or relatives.

Reprinted from the National Opioid Use Guideline Group.⁵

weak evidence²³ to support the use of opioid treatment agreements (**Box 3**),²⁴ but they might be considered for patients who are not well known by the physician or who are at higher risk of misuse.

Benzodiazepines: Benzodiazepines are commonly implicated in opioid overdose deaths,²⁵ and they considerably lower the lethal opioid dose.²⁶ Therefore opioids should be titrated more slowly, with smaller dose increases, in patients taking benzodiazepines. Benzodiazepine tapering should be considered before initiating opioid therapy (**Box 4**),^{5,27} particularly in patients taking moderate to high daily doses (eg, 20 mg diazepam or 4 mg lorazepam or clonazepam).⁵ Benzodiazepines can be successfully tapered in the primary care setting²⁸⁻³¹; psychiatric symptoms and sleep improve or remain stable with tapering.^{30,32-34} Similar precautions should be employed for other sedating drugs.

First-line opioids: If the physician decides to start opioid therapy, codeine or tramadol are suggested as first-line options for mild to moderate CNCP, as they have lower rates of overdose, misuse, and addiction than more potent opioids do,^{1,35-37} and controlled trials⁴ have shown that they are effective for CNCP (**Figure 1**).⁵

Second-line opioids: If an adequate trial of codeine or tramadol fails to produce substantial pain relief or generates considerable side effects, then morphine, oxycodone, and hydromorphone are recommended as second-line treatments. Morphine should be used with caution in patients with renal impairment³⁸ (**Table 2**).^{5,27} Oxycodone and hydromorphone should be used with caution in patients at high risk of opioid misuse and addiction (see companion paper on **page 1269**).⁶ The starting dose of transdermal fentanyl (25 µg/h) can cause overdose in patients who are not fully tolerant to opioids. Therefore fentanyl should only be used in patients who have taken an opioid dosage of at least a 60- to 100-mg morphine equivalent dose (MED) daily for at least 2 weeks. Patients should not be switched directly from codeine to fentanyl, as up to 10% of white patients lack the enzyme P450 2D6 (CYP 2D6) that converts codeine to morphine and, therefore, they

might not have developed a tolerance to opioids.³⁹⁻⁴¹ Methadone has a high risk of overdose because of

Box 4. Benzodiazepine tapering

1. Benefits of benzodiazepine tapering

- Lower risk of future adverse events, such as falls
- Increased alertness and energy

2. Approach to tapering

- Taper slowly (slow tapers are more likely to be successful than rapid tapers)
- Use scheduled rather than as-needed doses
- Halt or reverse the taper if severe anxiety or depression result
- Schedule follow-up visits every 1 to 4 weeks, depending on the patient's response to the taper
- At each visit, ask the patient about the benefits of tapering (eg, increased energy, alertness)

3. Protocol

- Insufficient evidence to support use of one benzodiazepine over another; you can taper with a longer-acting agent, such as diazepam or clonazepam, or with the agent that the patient is taking (Caution: diazepam can cause prolonged sedation in the elderly and in those with liver impairment)
- Convert to equivalent dose in divided doses (see equivalence table in the *Compendium of Pharmaceuticals and Specialties*²⁷)
- Adjust the initial dose according to symptoms (equivalence table is approximate)
- Taper by no more than 5 mg of diazepam or equivalent per week
- Adjust the rate of the taper according to symptoms
- Slow the taper when the dose is <20 mg of diazepam or equivalent (eg, 1 to 2 mg a week)
- Dispense daily, twice weekly, or weekly, depending on patient reliability
- Tapers can usually be completed in between 2 to 3 weeks and 3 to 4 months
- If the taper becomes difficult, the patient can be maintained at the lower dose

Reprinted from the National Opioid Use Guideline Group.⁵

Box 3. Sample opioid medication treatment agreement

I understand that I am receiving opioid medication from Dr _____ to treat my pain condition. I agree to the following:

1. I will not seek opioid medications from another physician. Only Dr _____ will prescribe opioids for me.
2. I will not take opioid medications in larger amounts or more frequently than is prescribed by Dr _____.
3. I will not give or sell my medication to anyone else, including family members; nor will I accept any opioid medication from anyone else.
4. I will not use over-the-counter opioid medications, such as 222s and Tylenol No. 1.
5. I understand that if my prescription runs out early for any reason (for example, if I lose the medication or take more than prescribed), Dr _____ will not prescribe extra medications for me; I will have to wait until the next prescription is due.

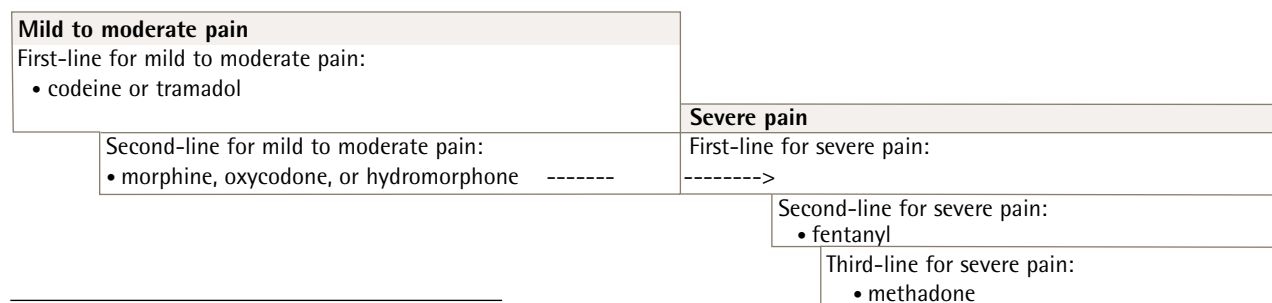
I understand that if I break these conditions, Dr _____ might choose to cease writing opiate prescriptions for me.

Reprinted from Kahan et al.²⁴

its long half-life^{42,43}; it can be prescribed for pain only by physicians with a special exemption from Health Canada. Meperidine does not have a role in CNCP

management; it has poor oral bioavailability, and parenteral meperidine can cause seizures and other neurologic events.⁴⁴

Figure 1. Stepped-care approach to opioid selection



Reprinted from the National Opioid Use Guideline Group.⁵

Table 2. Safety issues to consider when selecting opioids

AGENT	SAFETY ISSUES*
Codeine	Prescribe for no more than 4 days in breastfeeding women: some women rapidly convert codeine to morphine, causing neonatal toxicity Overall lower risk of overdose and addiction than with stronger opioids
Tramadol	Associated with seizures in patients at high risk of seizure or when combined with medications that increase serotonin levels (eg, SSRIs) Lower risk of overdose and addiction than with stronger opioids
Morphine	A metabolite of morphine can accumulate to toxic levels in patients with renal impairment
Oxycodone, hydromorphone	Use with caution for patients at higher risk of opioid misuse and addiction
Fentanyl	Before prescribing fentanyl, ask about opioid use within the past 2 weeks; to ensure full tolerance, the patient should be taking a daily, scheduled dose of at least a 60- to 90-mg MED for at least 2 weeks, at least twice daily for CR opioids and at least 4 times daily for IR opioids Do not switch from codeine to fentanyl, regardless of the codeine dose; some patients have little or no opioid tolerance even with regular codeine use Maintain the initial dose for at least 6 days; use extra caution with patients at higher risk of overdose (eg, elderly patients, those taking benzodiazepines) Advise the patient as follows: • Apply the patches as prescribed; do not apply more than 1 patch at a time • Avoid heat sources such as heating pads • Dispose of patches securely
Methadone	Use methadone to treat pain only if you hold a written Health Canada exemption Titration is hazardous because of its very long half-life, which leads to bioaccumulation
Meperidine	Not recommended for CNCP: • Oral meperidine has poor bioavailability and is less effective than codeine • Normeperidine, a toxic metabolite, can accumulate with frequent use of meperidine
Acetaminophen-opioid combinations	Use with caution to avoid acetaminophen toxicity: no more than 3.2 g of acetaminophen for adults, which is equal to 10 tablets a day for codeine-acetaminophen or oxycodone-acetaminophen combinations; no more than 8 tablets a day for tramadol-acetaminophen combinations Warn heavy drinkers to not mix alcohol use with acetaminophen
CR formulations	Titrate with caution; CR tablets contain higher opioid doses than IR formulations do and can easily be converted to IR by biting or crushing the tablet
Parenteral opioids	Not recommended for CNCP: • High risk of overdose, addiction, and infection

CNCP—chronic noncancer pain, CR—controlled release, IR—immediate release, MED—morphine equivalent dose, SSRI—selective serotonin reuptake inhibitor.

*Refer to individual drug monographs for comprehensive safety information.²⁷

Adapted from the National Opioid Use Guideline Group.⁵

Immediate-release (IR) opioids: Immediate-release opioids are used for initial titration and for breakthrough pain. They can also be used instead of controlled-release (CR) opioids for recurrent pain that lasts a few hours or less and for activity-related pain.

Controlled-release opioids: For patients who experience pain throughout the day, CR opioids might provide more constant pain relief than IR opioids do. Caution is required with CR tablets, as they contain much higher opioid doses than acetaminophen-opioid combinations do (eg, 1 80-mg OxyContin tablet is the equivalent of 16 Percocet tablets). Opioid euphoria, sedation, and overdose are dose-related.⁴⁵⁻⁴⁷

Initial titration: Opioids should be titrated slowly in CNCP patients in order to minimize the risk of acute toxicity (**Table 3**).⁵ An initial dosage of no more than a 5- to 10-mg MED 4 times daily is suggested, with dose increases of no more than a 5- to 10-mg MED per week. Elderly patients should be titrated more slowly than younger patients because they are at higher risk of acute toxicity (see companion paper on **page 1269**).⁶

Breakthrough doses: In most cases daily breakthrough doses should be no more than 10% to 20% of the total daily dose. The CR opioid can be increased if

the patient consistently uses breakthrough doses multiple times during the day. Multiple daily breakthrough doses are usually not necessary unless the patient has severe neuropathic pain with unpredictable exacerbations. Additionally, IR opioids can be used just before activities that predictably cause severe exacerbations of pain; activity modification and pacing should also be employed.

Office visits: At each office visit during titration, pain intensity should be assessed using the 11-point (0 to 10) numeric rating scale. Opioids show a graded analgesic response, so if the pain is opioid-responsive, the patient will experience a small reduction in pain intensity with each dose increase. For nociceptive pain, the pain intensity should be recorded at rest and with activity. The physician should also inquire at each visit about side effects, compliance, and changes in mood and daily activities. The Brief Pain Inventory can help in the assessment.¹⁶

Optimal dose: The optimal dose is reached when the patient experiences improved function or at least a 30% pain reduction (about 2 points on the 11-point scale), with minimal analgesic benefit from 1 or 2 additional dose increases and no serious side effects or complications.⁴⁸

Table 3. Suggested initial opioid dose and titration based on oral dosing for CNCP

OPIOID	INITIAL DOSE	RECOMMENDED TIME INTERVAL FOR INCREASE	SUGGESTED DOSE INCREASE	MINIMUM DAILY DOSE BEFORE CONVERTING IR TO CR
Codeine	15-30 mg every 6 h	7 d	15-30 mg/d up to 600 mg/d	100 mg
CR codeine	50 mg every 12 h	2 d	50 mg/d up to maximum of 300 mg every 12 h	NA
Tramadol-acetaminophen	<ul style="list-style-type: none"> • 37.5/325 mg • 1 tablet every 4-6 h up to 4/d 	7 d	1 tablet every 4-6 h up to 8 tablets/d	3 tablets
CR tramadol				
• Zytram	150 mg every 24 h	7 d	400 mg/d maximum	NA
• Tridural	100 mg every 24 h	2 d	300 mg/d maximum	NA
• Ralivia	100 mg every 24 h	5 d	300 mg/d maximum	NA
IR morphine	<ul style="list-style-type: none"> • 5-10 mg every 4-6 h • maximum 40 mg/d 	7 d	5-10 mg/d	20-30 mg
CR morphine	<ul style="list-style-type: none"> • 10-20 mg: once, twice, or 3 times daily • maximum 40 mg/d 	14 d	5-10 mg/d	NA
IR oxycodone	<ul style="list-style-type: none"> • 5 mg every 4-6 h • maximum 30 mg/d 	7 d	5 mg/d	20 mg
CR oxycodone	<ul style="list-style-type: none"> • 10 mg 2-3 times daily • maximum 30 mg/d 	14 d	10 mg/d	NA
IR hydromorphone	<ul style="list-style-type: none"> • 1-2 mg every 4-6 h • maximum 8 mg/d 	7 d	1-2 mg/d	6 mg
CR hydromorphone (Hydromorph Contin)	<ul style="list-style-type: none"> • 3 mg 2-3 times daily • maximum 9 mg/d 	14 d	2-4 mg/d	NA

CNCP—chronic noncancer pain, CR—controlled release, IR—immediate release, NA—not applicable. Adapted from the National Opioid Use Guideline Group.⁵

For by far most CNCP patients, the optimal dosage will be well below a 200-mg MED daily (Table 4).^{5,27,49}

Doses above a 200-mg MED: The guideline suggests a careful reassessment if the dose approaches a 200-mg MED (the “watchful dose”). The physician should

Table 4. Oral opioid analgesic conversion table based on oral dosing for chronic noncancer pain: A) Equivalence to 30 mg of oral morphine; B) Equivalence between oral morphine and transdermal fentanyl.

A)			
OPIOID	EQUIVALENCE TO 30 MG ORAL MORPHINE	TO CONVERT TO ORAL MORPHINE EQUIVALENT MULTIPLY BY ...	TO CONVERT FROM ORAL MORPHINE MULTIPLY BY ...
Morphine	30 mg	1	1
Codeine	200 mg	0.15	6.67
Oxycodone	20 mg	1.5	0.667
Hydromorphone	6 mg	5	0.2
Meperidine	300 mg	0.1	10
Methadone and tramadol	Morphine dose equivalence not reliably established		
B) TRANSDERMAL FENTANYL*		MORPHINE	
25 µg/h	60-134 mg		
37 µg/h	135-179 mg		
50 µg/h	180-224 mg		
62 µg/h	225-269 mg		
75 µg/h	270-314 mg		
87 µg/h	315-359 mg		
100 µg/h	360-404 mg		

*Formulations include 12-, 25-, 50-, 75-, and 100-µg/h patches, but the 12-µg/h patch is generally used for dose adjustment rather than initiation of fentanyl treatment.

Adapted from the National Opioid Use Guideline Group.⁵ Data from the *Compendium of Pharmaceutical and Specialties*²⁷ and Pereira et al.⁴⁹ Wide ranges have been reported in the literature. These equivalences refer to analgesic strength of oral opioids and not psychoactive effects or effectiveness in relieving withdrawal symptoms.

review the underlying diagnoses, the need for further investigation or consultation, the patient's response to opioids, and dose-related medical complications. The 200-mg MED threshold was chosen because most patients require doses substantially below this; the average opioid dose used in controlled trials⁴ was 66 mg for oxycodone and 57 mg for morphine in nociceptive pain, and 81 mg for oxycodone and 92 mg for morphine in neuropathic pain (Table 5).⁵ Also, evidence suggests that dose-response relationships exist for medical complications of opioid therapy, including sexual dysfunction,⁵⁰ sleep apnea,⁵¹⁻⁵³ opioid-induced hyperalgesia,⁵⁴ and falls and fractures.^{55,56} Recent evidence has identified a strong relationship between prescribed dose

and risk of nonfatal and fatal overdoses.⁴⁷ Among Ontario public drug plan recipients between 2003 and 2008, 2-year opioid-related mortality rates were 1.6, 7.9, and 9.9 per 1000 population for those prescribed less than a 200-mg MED, a 200- to 400-mg MED, and a greater than 400-mg MED, respectively.⁵⁷

Furthermore, long-term observational studies found that patients taking high opioid doses tended to have greater disability and higher pain ratings than patients taking lower doses did, even after controlling for the severity of the underlying pain condition.^{58,59} Recent literature also suggests that physicians prescribe higher opioid doses to patients in greater psychological distress.^{60,61} These studies raise concerns about the safety and effectiveness of long-term, high-dose opioid therapy.

Switching opioids: Patients who have not responded to or who have had side effects with one opioid will sometimes benefit from switching to a different opioid.⁶² Because of unpredictable and incomplete cross-tolerance, the initial opioid dose of the new opioid should be no more than 50% of the previous dose if the latter is higher (ie, above a 75-mg MED), or 60% to 75% of the previous dose if the dose of the previous opioid was moderate (ie, below a 75-mg MED). There is no evidence to support the practice of combining different types of opioids.

Tapering. Patients whose pain has not responded to an adequate trial of several different opioids should have their doses tapered and discontinued. Observational studies have demonstrated that patients in severe pain despite high opioid doses experience reduced pain and improved mood with opioid tapering.⁶³⁻⁶⁸ It is not known why tapering might improve pain perception. Tapering might work by relieving hyperalgesia and withdrawal symptoms (withdrawal at the end of a dosing interval is more severe with high doses than low doses). Tapering might also improve mood by reducing opioid-induced sedation and dysphoria.⁶¹ Additionally, some of the benefits of tapering could be due to psychological countermeasures that accompanied tapering in these studies. Both physician and patient should approach the taper with positive expectations, as tapering is associated with improved mood and pain. Tapering is also indicated

Table 5. Morphine equivalents for strong opioids used in randomized trials

DRUG	PAIN TYPE	MEQ MINIMUM	MEQ AVERAGE	MEQ MAXIMUM	NO. OF STUDIES
CR oxycodone	Nociceptive	20 mg	65.7 mg	146.7 mg	6
	Neuropathic	40 mg	81.3 mg	173.3 mg	3
CR morphine	Nociceptive	25 mg	56.8 mg	120 mg	2
	Neuropathic	28.75 mg	91.7 mg	202.5 mg	5

CR—controlled release, MEQ—morphine equivalent.

Adapted from the National Opioid Use Guideline Group.⁵

for patients experiencing side effects or dose-related medical complications. **Box 5** outlines a tapering protocol.⁵

Consultation with specialists. Although evidence is weak, patients with severe pain and pain-related disability appear to have better outcomes when managed by multidisciplinary pain clinics.⁶⁵ Access to multidisciplinary pain programs is limited in most parts of Canada.⁶⁹ Pain clinics vary greatly in philosophy and treatment approaches, and family physicians should carefully select the clinics and practitioners to whom they refer their patients. Family physicians should let consultants know if they have specific concerns about patients' opioid use. Family physicians are not obliged to prescribe opioids according to consultants' recommendations. They should do so only if, in their clinical judgment, the consultants' recommendations are safe, likely to be beneficial for the patients in question, and consistent with the guideline.

Opioid patients transferred from other clinics. Family physicians should carefully explain their opioid-prescribing policies to CNCP patients who are new to their practices but who are already taking long-term opioid therapy prescribed by their previous physicians. Patients taking inappropriate doses should be advised that the dose will be tapered in the near future. Patients who are unwilling to comply with the taper should be encouraged to seek medical care elsewhere. Currently, prescribing practices vary widely among family physicians and pain physicians. Therefore physicians must prescribe opioids according to their best judgment, even if this goes against the wishes of patients, the recommendations of consultants, or the practices of patients' previous physicians.

Acute care settings. Physicians in acute care settings such as walk-in clinics or emergency departments should reach consensus on opioid prescribing policies for CNCP patients. One option is to simply refuse to prescribe in these settings; patients have a responsibility to ensure that they do not run out, and it is unsafe to prescribe opioids without knowing a patient's full medical history. Another option is to prescribe a supply that will last until the family physician is available. If the latter policy is chosen, the clinic should institute the safeguards listed in **Box 6**.

Box 5. Opioid tapering

1. Indications for opioid tapering

- Severe pain despite an adequate trial of several different opioids
- Opioid-related complications (eg, sleep apnea, falls)
- As a component of "structured opioid therapy" for addicted patients with a pain condition who do not access opioids from other sources or alter the route of delivery

1.1. Precautions for outpatient opioid tapering

- Pregnancy: acute withdrawal can cause premature labour and spontaneous abortion
- Unstable medical and psychiatric conditions: while opioid withdrawal does not have serious medical consequences, it can cause considerable anxiety and insomnia that might exacerbate severe, acute medical or psychiatric conditions
- Opioid addiction: outpatient tapering is unlikely to be successful if the patient regularly accesses opioids from other doctors or the street; methadone or buprenorphine treatment is advised
- Concurrent medications: avoid sedative-hypnotic drugs, especially benzodiazepines, during the taper

2. Opioid tapering protocol

2.1. Before initiation

- Emphasize that the goal of tapering is to make the patient feel better: to reduce pain intensity and to improve mood and function
- Have a detailed treatment agreement
- Be prepared to provide frequent follow-up visits and supportive counseling

2.2. Type of opioid, schedule, dispensing interval

- Use controlled-release morphine if feasible (see 2.3 below)
- Prescribe scheduled doses (not as needed)
- Prescribe at frequent dispensing intervals (daily, alternate days, or weekly, depending on patient's control over opioid use); do not refill the prescription if the patient runs out
- Keep daily schedule the same for as long as possible (eg, 3 times daily)

2.3. Rate of taper

- Can vary from 10% of the total daily dose every day to 5% every 1 to 4 weeks
- Slower tapers are recommended for patients who are anxious about tapering, those who might be psychologically dependent on opioids, and those who have cardiorespiratory conditions
- Once a third of the original dose is reached, slow the taper to half of the previous rate
- Hold or increase the dose if the patient experiences severe withdrawal symptoms or worsening of pain or mood

2.4. Switching to morphine

- Consider switching patients to morphine if the patient is addicted to oxycodone or hydromorphone
- Calculate equivalent dose of morphine
- Start patient on half this dose (tolerance to one opioid is not fully transferred to another opioid)
- Adjust dose up or down as necessary to relieve withdrawal symptoms without inducing sedation

2.5. Monitoring during taper

- See patient frequently; at each visit, ask about benefits of taper (eg, improved pain, mood, alertness)
- Use urine drug screening to ensure compliance

2.6. Completion of taper

- Taper can usually be completed in between 2 to 3 weeks and 3 to 4 months
- Patients who are unable to complete the taper may be maintained at a lower opioid dose if they are compliant with the treatment agreement

Adapted from the National Opioid Use Guideline Group.⁵


Box 6. Precautions for prescribing opioids to CNCP patients in acute care settings

Keep the following precautions in mind when prescribing opioids for CNCP in emergency departments or walk-in clinics:

- Contact patient's pharmacy or drug prescribing database before prescribing; do not prescribe if you are unable to access database or pharmacy records, or if the patient's history is inconsistent with this information
- Inform the patient that this is a 1-time-only prescription, and document this in the chart
- Prescribe a reasonable daily dose that you are comfortable with, even if that dose is lower than the family physician's usual prescription
- Prescribe only enough to last until the next working day
- Send a record of the visit to the family physician

CNCP—chronic noncancer pain.

Conclusion

Opioids play an important role in the management of CNCP, but careful prescribing is needed to limit potential harms. Opioid therapy should be reserved for pain conditions that have not responded to nonopioid therapies and for which opioids have been shown to be effective. Opioids should be combined with other pharmacologic and nonpharmacologic treatments. The dose should be titrated slowly and with close monitoring, particularly for patients at high risk of overdose and misuse. The optimal dose is one which improves function or decreases pain ratings by at least 30%. For by far most patients, this dose will be well below a 200-mg MED. Tapering is recommended for patients who have not responded to an adequate opioid trial. 

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Contributors

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Competing interests

Three of the authors were members of the core guideline research group. However, all statements in this article are the sole responsibility of the authors, and the summary was not reviewed by the National Opioid Use Guideline Group.

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