PRESCRIPTION pad

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July 2013

Opioids in Chronic Non-Cancer Pain: The Basics

Chronic pain is a complex problem and opioids are just one small piece in a comprehensive pain management strategy. While opioids can provide meaningful benefit in terms of pain reduction and functional improvement for some patients, they also have the potential to cause considerable harm. Safer use of opioids begins with an awareness of the current evidence and limitations of opioid use, knowledge regarding how opioids compare to each other, and how current guidance highlights the importance of a structured approach for their use in chronic non-cancer pain (CNCP). This PAD educational session on *Opioids in CNCP* aims to provide a balanced perspective on these practice areas as well as some practical tips for developing a culture of "opioid stewardship."

Learning Objectives

During each PAD session, participants will have the opportunity to discuss:

1. The evidence (and the evidence gaps) for the benefits and harms of opioids in CNCP.
2. The importance of an initial short-term, structured opioid trial.
3. The characteristics of specific opioids and opioid formulations including:
   - how other opioids compare to morphine,
   - the evidence for using immediate-release vs. sustained-release formulations,
   - the propensity for drug interactions,
   - guidance for switching from one opioid to another, and
   - opioids best avoided in CNCP.
4. The role of opioid stewardship to improve patient and public safety.

Contents

BC's Provincial Academic Detailing (PAD) Service is offered free of charge to health care professionals. The service is provided by health authorities and supported by the Ministry of Health. A broad-based advisory committee helps identify relevant topics. All articles are peer-reviewed by clinical experts.

Evidence gaps

Consider the gaps in the evidence for the benefits and harms of opioids in chronic non-cancer pain.[1]

- Evidence for opioid efficacy is derived from short-term (majority ≤ 12 weeks) randomized, controlled clinical trials (RCTs) enrolling carefully-selected patient populations (i.e., largely without psychiatric comorbidity or apparent substance misuse risk).[1-4]
- Meta-analyses generally report efficacy as average reductions in pain, but these results are difficult to extrapolate to individual patients who "tend to have either very good or very poor pain relief."[5]
- Approximately 1/3 of patients in these short-term RCTs discontinued opioid therapy due to either an inadequate reduction in pain or due to the emergence of adverse events.[2]
- The short duration of these RCTs neither allows for a determination of longer-term efficacy nor do they reliably inform of possible treatment-emergent harms (e.g., analgesic tolerance, hyperalgesia, neuroendocrine effects, opioid addiction, or sleep apnea).[1,3,6]

Goal setting

Prior to initiating an opioid trial, highlight the importance of realistic patient expectations and establish treatment goals that include patient-centered improvements in function.[7]

- Patients should be advised that opioids are only one part of a comprehensive pain management plan.[8]
- A reasonable goal of opioid therapy is to provide a meaningful reduction in pain (i.e., not to completely eliminate pain) that safely enables sustained improvements in function within a pre-specified time period.[7,9-11]
- The SMART (Specific, Measurable, Attainable, Relevant, Time dependent) approach for structured goal setting has been suggested.[12,13]

Opioid trial

Opioids should only be initiated as a structured and short-term trial with pre-determined goals.[7,9-11]

- For all patients, consideration must be given to the risks for opioid addiction and misuse.[8,9] The 2010 Canadian guideline provides information on opioid risk screening tools.[9]
- The initial opioid trial should be short-term (e.g., 2 to 6 weeks[7] or 2 to 3 dose increases[9]) since obvious pain reduction generally occurs early in the trial.[9,14,15]
- If the opioid trial does not safely contribute to clear and meaningful gains in pain reduction or if it compromises function, it is reasonable to cautiously trial an alternate opioid or to seek pain specialist consultation.[9,10]
- If the opioid trial safely contributes clear and meaningful pain reduction and functional improvement, revisit therapy every 3 to 6 months[7] and consider if dose reductions are possible.[7,9,16]
- Opioid therapy should only be continued if there is no evidence of serious harm, misuse, or diversion.[7,16]
- This goal-setting and evaluative approach should also be applied to patients who have been receiving long-term opioid therapy but did not have an initial structured opioid trial.[9]
- The Opioid Manager is an example of a structured approach that can be used: nationalpaincentre.mcmaster.ca/opioidmanager/.

Opioid selection

Be familiar with the characteristics of specific opioids and opioid formulations suitable for CNCP.

- Only prescribe an opioid that you are highly familiar with.[17]
- Reviews conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) did not identify therapeutic advantages for buprenorphine (transdermal), tapentadol, tramadol, or abuse-deterrent opioid formulations over other available products.[18-24]
- Consider each opioid's propensity for drug interactions, unique safety concerns, and cost to the patient.
- Evidence reviews have not identified safety or efficacy advantages for sustained release formulations and scheduled opioid dosing in comparison to immediate-release formulations or 'as needed' dosing.[1,25,26]
- For safety, immediate release opioids are preferred during the initiation phase.[8]
- Regularly scheduled dosing using sustained-release formulations may be preferred in the management of patients where there are opioid addiction concerns and then only in an intensively supervised setting.[27] The 2010 Canadian guideline provides advice on referral to expertise in addiction medicine.[9]

Opioid dosing

Evidence does not identify a specific safe or effective opioid dose that can be applied to all patients with CNCP.[28]

- Safety of a specific opioid dose is expected to vary depending on age, co-morbidity, drug interactions, and polypharmacy.[29]
- If no obvious pain reduction occurs early in the trial (i.e., after 2 to 3 dose increases), progressive dose escalations are not recommended and it is reasonable to cautiously trial an alternate opioid or to seek expert consultation.[9,10]
- Use only the lowest effective dose that safely supports meaningful functional gains.[10,16] There is increasing observational evidence of an association between opioid dose and serious harms (i.e., opioid-related overdose, opioid-related mortality).[30-34]
- A recent BC Coroner's report identified that 61% of prescription (non-illicit) opioid-related deaths between 2005 and 2010 in British Columbia were judged as accidental.[35]
- Increasing opioid misuse and opioid-related overdose reported at the population level is correlated, in part, with the increasing availability of higher opioid doses in sustained release formulations.[1,9,36,37]
- Polypharmacy is discouraged.[16] Combined use of opioids with sedative-hypnotics or alcohol increases the risk of central nervous and respiratory system depression.[38,39] The 2010 Canadian guideline provides benzodiazepine tapering recommendations.[9]
- Pharmacodynamic (e.g., antidepressants, antipsychotics, anticonvulsants, antiemetics, muscle relaxants) and pharmacokinetic (e.g., CYP450) drug interactions can also increase the risk for potential harms.[10]

Switching opioids[9]

Cautiously switching from one opioid to another may be considered for patients who have not responded meaningfully to, or who have experienced important adverse events with, one opioid. **The following recommendations do not apply when switching to methadone or transdermal fentanyl:**

1) Calculate the total 24 hour dose of the current opioid.
2) Use the opioid equivalence chart to estimate the equivalent 24 hour dose of the new opioid: nationalpaincentre.mcmaster.ca/documents/opioid_manager_switching_opioids.pdf.
3) Reduce the dose of the new opioid to help account for possible incomplete cross-tolerance between opioids.
   a) If the previous opioid dose was ≤ 75 mg oral morphine equivalents per 24 hours, reduce the dose of the new opioid to 60% to 75% of the previous opioid.[39]
   b) If previous opioid dose was > 75 mg oral morphine equivalents per 24 hours, reduce the dose of the new opioid to 50% or less of the previous opioid.[39]
4) Divide the 24 hour dose of the new opioid based on the specific drug and dosage form selected.

Morphine

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 5, 10, 20, 25, 30, 40, 50, 60 mg (M.O.S.®, MS-IR®, Statex®, generic) **Liquid:** 1, 5, 20, 50 mg/mL (M.O.S.®, Statex®, generic) **Sustained-release (SR) formulations:** **Tablet (12 hour):** 15, 30, 60, 100, 200 mg (MS Contin®, generic) **Capsule (12 hour):** 10, 15, 30, 60, 100, 200 mg (M-Eslon®) **Tablet (24 hour):** 10, 20, 50, 100 mg (Kadian®)
Key features[40]	**Classification:** Opioid agonist; phenanthrene[41] **Metabolism:** mainly glucuronidation via UDP-glucuronoslytransferase[42] **Selected adverse drug reactions/Precautions unique to morphine:** Active metabolites: morphine-3-glucuronide (neuroexcitatory) and morphine-6-glucuronide (analgesic) have been shown to accumulate in renal impairment[42]; evidence does not identify a specific degree of renal impairment at which specific opioids should be avoided or when dose adjustments should necessarily occur[43] SR formulations: MS Contin® tablets and generics must be swallowed intact, and not chewed, crushed, split, or dissolved; only the 200 mg tablet is scored and may be broken in half once; M-Eslon® and Kadian® capsules should be swallowed intact or can be opened and the contents sprinkled on soft food (see official prescribing monograph for more details) **Selected drug-drug interactions (see official product monograph for additional information):** MAOIs: use within 14 days contraindicated; interaction less likely than with phenylpiperidine opioids (e.g., meperidine, tramadol, and fentanyl)[44,45] CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects CYP450: CYP450 interactions unlikely[42] **Selected populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 25% if GFR 10-50 mL/min, ↓ dose by 50% if GFR < 10 mL/min[46] Hepatic: use with caution; use lower doses and longer dosing interval Geriatrics: use with caution; use lower doses and longer dosing interval; 3 day tolerance check for sedation[9]
Recommended adult dosing[9,40]	**Immediate-release (IR) formulations:** **Initial dose:** 5-10 mg every Q4H (maximum 40 mg/day) **Titration:** Every 7 days by 5-10 mg/day **Sustained-release (SR) formulations:** **Titration:** Every 14 days by 10 mg/day
Equivalent dose to oral morphine 30 mg[9]	30 mg
PharmaCare coverage	Full Benefit ($ to $$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

** CADTH is the Canadian Agency for Drugs and Technologies in Health

Codeine

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 15, 30 mg (generic) **Liquid:** 5 mg/mL (generic) **Tablet with acetaminophen:** 8, 15, 30, 60 mg (Tylenol No. 1®, 2®, 3®, 4®; Atasol 15®, 30®, generic) **Liquid with acetaminophen:** 8 mg (with 160 mg acetaminophen) per 5 mL (Tylenol with Codeine®) **Tablet with ASA: 8, 15, 30 mg** (222®, 282®, 292®, generic) **Sustained-release (SR) formulations:** **Tablet (12 hour):** 50, 100, 150, 200 mg (Codeine Contin®)
Key features[40]	**Classification:** Opioid agonist; phenanthrene[41]; there is conflicting evidence as to whether or not codeine needs to be converted to morphine for analgesic efficacy[41] **Metabolism:** CYP2D6, CYP3A4[42,47,48] **Selected adverse drug reactions/Precautions unique to Codeine:** CYP2D6 genetic polymorphism: may affect safety and efficacy ranging from absent or reduced analgesic effect (poor metabolizers) to toxicity (ultra-rapid metabolizers)[41,42,48,49] Ultra-rapid metabolizers: may ↑ serum morphine levels; may result in toxicity even at recommended doses; widely varying prevalence estimates (1 to 10% Caucasians; 0.5 to 1% Chinese, Japanese, Hispanics; 3% African Americans; 16 to 28% North Africans, Ethiopians, Arabs) Poor metabolizers: may ↓ conversion of codeine to morphine (5 to 10% Caucasians, 1% Asians) Nursing women: maternal use of codeine may lead to serious adverse events in nursing infants if the mother is an ultra-rapid metabolizer (secondary to ↑ morphine levels)[50]; SR formulations are contraindicated Conversion from IR to SR formulation: ↓ total daily codeine dose by 25% when converting from IR (codeine phosphate) to SR (codeine base) due to differences in codeine content between salts SR formulations: must be swallowed intact and not chewed, crushed, or dissolved; all strengths may be halved once, except 50 mg Converting from codeine to other opioids: approach with additional caution given the potential for CYP2D6 polymorphism which may make the assessment of opioid tolerance more uncertain; Canadian guideline does not recommend converting from codeine to transdermal fentanyl[9] Combination products: maximum 4 g of acetaminophen or ASA per day for adults including all sources of acetaminophen or ASA; inquire about non-prescription analgesic use **Selected drug-drug interactions (see official product monograph for additional information):** MAOIs: use within 14 days contraindicated; interaction less likely than with phenylpiperidine opioids (e.g., meperidine, tramadol, and fentanyl)[44,45] CYP2D6 inducers: may ↑ morphine levels[47] CYP2D6 inhibitors: may ↓ morphine levels[47] CYP3A4 inhibitors: may ↑ codeine levels[47] CYP3A4 inducers: may ↓ codeine levels[47] CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects **Selected populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 25% if GFR 10-50 mL/min; ↓ dose by 50% if GFR < 10 mL/min[46] Hepatic: use with caution; use lower doses and longer dosing interval Geriatrics: use with caution; use lower doses and longer dosing interval; 3 day tolerance check for sedation[9]
Recommended adult dosing[9,40]	**Immediate-release (IR) formulations:** **Initial dose:** 15-30 mg codeine Q4H **Titration:** Every 7 days by 15-30 mg/day, **Maximum daily dose:** 600 mg/day **Sustained-release (SR) formulations:** **Titration:** Every 2 days by 50 mg/day, **Maximum daily dose:** 600 mg/day
Equivalent dose to oral morphine 30 mg[9]	200 mg
PharmaCare coverage	**Immediate-release (IR) formulations:** Full Benefit ($ to $$)* **Sustained-release (SR) formulations:** Requires Special Authority ($$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Hydromorphone

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 1, 2, 4, 8 mg (Dilaudid®, generic) **Liquid:** 1 mg/mL (Dilaudid®, generic) **Sustained-release (SR) formulations:** **Capsule (12 hour):** 3, 6, 12, 18, 24, 36 mg (Hydromorph Contin®) **Tablet (24 hour):** 4, 8, 16, 32, 64 mg (Jurnista®)
Key features[40]	**Classification:** Opioid agonist; phenanthrene[41] **Metabolism:** mainly glucuronidation via UDP-glucuronoslytransferase[42] **Selected adverse drug reactions/Precautions unique to hydromorphone:** Active metabolite: hydromorphone-3-glucuronide (neuroexcitatory) has been shown to accumulate in renal impairment (similar to morphine-3-glucuronide)[42]; evidence does not identify a specific degree of renal impairment at which specific opioids should be avoided or when dose adjustments should necessarily occur; the preference for hydromorphone over morphine in patients with any degree of renal impairment (e.g., all older adults) is not supported by high-quality evidence[43] SR formulations: Hydromorph Contin® capsules should be swallowed intact or can be opened and the contents sprinkled on soft food (see official product monograph for more details); Jurnista® tablets must be swallowed intact and not chewed, crushed, split, or dissolved **Selected drug-drug interactions (see official product monograph for additional information):** MAOIs: use within 14 days contraindicated; interaction less likely than with phenylpiperidine opioids (e.g., meperidine, tramadol, and fentanyl)[44,45] CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects CYP450: CYP450 interactions unlikely[42] **Selected populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 25% if GFR 10-50 mL/min, ↓ dose by 50% if GFR < 10 mL/min[46] Hepatic: use with caution; use lower doses and longer dosing interval Geriatrics: use with caution; use lower doses and longer dosing interval; 3 day tolerance check for sedation[9] **CADTH** recommendation:** Jurnista® offers no therapeutic advantage compared with other less costly SR opioid formulations.[51]
Recommended adult dosing[9,40]	**Immediate-release (IR) formulations:** **Initial dose:** 1-2 mg every Q4-6H (maximum 8 mg/day) **Titration:** Every 7 days by 1-2 mg/day **Sustained-release (SR) formulations:** **Titration:** Every 14 days by 3-4 mg/day
Equivalent dose to oral morphine 30 mg[9]	6 mg
PharmaCare coverage	**Immediate-release (IR) formulations:** Full Benefit ($)* **Sustained-release (SR) formulations:** Requires Special Authority ($$$ to $$$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Oxycodone

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 5, 10, 20 mg (Oxy-IR®, Supeudol®, generic) **Tablet with 325 mg acetaminophen:** 2.5, 5 mg (Percocet Demi®, Percocet®, generic) **Sustained-release (SR) formulations:** **Tablet (12 hour):** 5, 10, 15, 20, 30, 40, 60, 80 mg (OxyNeo®, OxyContin®, generics) **Tablet with naloxone (12 hour):** 10, 20, 40 mg (Targin®)
Key features[40]	**Classification:** Opioid agonist; phenanthrene[41] **Metabolism:** CYP2D6, CYP3A4[42] **Selected adverse drug reactions/Precautions unique to oxycodone:** OxyNeo®: The clinical relevance of reformulating OxyContin® as OxyNeo® has not been established.[24,52,53] OxyNeo® should not be taken by patients with difficulty swallowing or who have been diagnosed with narrowing of the esophagus; post-marketing reports include difficulty swallowing, choking, gagging, regurgitation, and tablets sticking in throat. OxyNeo® should not be licked or otherwise wetted. Maximum of one tablet should be swallowed at a time. SR formulations: must be swallowed intact and not be chewed, crushed, split, or dissolved Combination products: maximum 4 g of acetaminophen per day for adults including all sources of acetaminophen; inquire about non-prescription analgesic use **Selected drug-drug interactions (see official product monograph for additional information):** MAOIs: use within 14 days contraindicated; interaction less likely than with phenylpiperidine opioids (e.g., meperidine, tramadol, and fentanyl)[44,45] CYP3A4 inhibitors: may ↑ oxycodone levels[47]; combined use not recommended CYP3A4 inducers: may ↓ oxycodone levels[47] CYP2D6 inhibitors and inducers: clinical relevance uncertain[47] CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects **Selected Populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 25% if GFR 10-50 mL/min, ↓ dose by 50% if GFR < 10 mL/min[46] Hepatic: use with caution; use lower doses and longer dosing interval Geriatrics: use with caution; use lower doses and longer dosing interval; 3 day tolerance check for sedation[9] **CADTH** Recommendation:** No evidence of therapeutic advantage for Targin® compared to a less expensive opioid and an optimized laxative regimen.[54]
Recommended adult dosing[9,40]	**Immediate-release (IR) formulations:** **Initial dose:** 5-10 mg every Q6H (maximum 30 mg/day) **Titration:** Every 7 days by 5 mg/day **Sustained-release (SR) formulations:** **Titration:** Every 14 days by 10 mg/day
Equivalent dose to oral morphine 30 mg[9]	20 mg
PharmaCare coverage	**Immediate-release (IR) formulations:** Full Benefit ($ to $$)* **Sustained-release (SR) formulations:** **Oxycodone only:** Requires Special Authority ($$$)* **Oxycodone with naloxone:** Non-Benefit ($$$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Fentanyl

Dosage forms (Brand name)[40]	**Transdermal patch (72 hour):** 12, 25, 50, 75, 100 mcg/hr (Duragesic MAT®, generic)
Key features[40]	**Classification:** Opioid agonist; phenylpiperidine[41] **Health Canada indication:** persistent moderate to severe chronic pain that cannot be managed by other means, patients who require **continuous** opioid analgesia, and who are **opioid tolerant** and receiving a daily opioid dose ≥ 60 mg oral morphine equivalents per day **Metabolism:** CYP3A4[42] **Selected adverse drug reactions/Precautions unique to fentanyl transdermal:** **Opioid naive patients: use is contraindicated at any dose**; Canadian guideline defines opioid tolerant as: receiving at least 60 mg oral morphine equivalents per day on a scheduled basis for at least 2 weeks[9] Regulatory body adverse events and warnings: respiratory arrest in opioid naive adolescents[55]; fentanyl misuse in adolescents[56]; unintentional fatal adverse reactions[57]; serotonin toxicity[58]; pediatric accidental exposure[59] Switching from codeine: Canadian guideline advises against switching from codeine to transdermal fentanyl as opioid tolerance may be more difficult to assess[9] Dose conversions from oral opioids: it may be appropriate in some situations to use lower initial doses than those recommended by the conversion table to minimize the potential for overdose Steady state: reached after 2 sequential 72 hour applications (i.e., 6 days) Breakthrough dosing: use of transmucosal fentanyl products is not indicated in CNCP Subcutaneous depot: monitor for persistent effects for a minimum of 24 hours post-removal Unintentional ↑ fentanyl exposure: compromised skin, external heat sources, and febrile illness Accidental exposure: transference via hugging, sharing a bed, or moving a patient, has been reported Disposal: used patches have high residual fentanyl content; must be disposed of safely; write on prescription "pharmacist to advise of safe disposal" **Selected drug-drug interactions (see official product monograph for additional information):** Serotonin toxicity: ↑ risk with serotonergic medications such as SSRIs, SNRIs, MAOIs, tricyclics, triptans, and CYP3A4 inhibitors; symptoms include **C**ognitive, **A**utonomic, and **N**euromuscular changes[60] MAOIs: use within 14 days contraindicated; clinically-relevant serotonin reuptake inhibition[44,45] CYP3A4 inhibitors: may ↑ fentanyl levels; combined use not recommended; fatality reported[57] CYP3A4 inducers: may ↓ fentanyl levels; fentanyl levels may ↑ if inducer is subsequently discontinued CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects **Selected populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 25% if GFR 10-50 mL/min, ↓ dose by 50% if GFR < 10 mL/min[46] Hepatic: use with caution; use lower doses Elderly, cachectic, or debilitated patients: use with extreme caution due to altered pharmacokinetics as a result of poor fat stores, muscle wasting, or altered clearance; assessment may include consideration of a lower starting dose than recommended in the conversion table
Recommended adult dosing[9,40]	**Frequency:** Applied every 72 hours **Patches should not be altered (e.g., cut, covered, or folded) in any way prior to application.** **Titration:** Do not increase dose earlier than every 6 days[9] to allow time to achieve steady state **Maximum dose:** 300 mcg/hr
Equivalent dose to oral morphine 30 mg[9]	Variable – see official product monograph
PharmaCare coverage	Requires Special Authority ($$ to $$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Buprenorphine

Dosage forms (Brand name)[40]	**Transdermal patch (7 day):** 5, 10, 20 mcg/hr (BuTrans®)
Key features[40]	**Classification:** Opioid agonist (mu), antagonist (kappa, delta); phenanthrene[41,48] **Health Canada indication:** Persistent pain when **continuous** opioid analgesia is indicated for an **extended period of time**. **Metabolism:** glucuronidation via UDP-glucuronoslytransferase, CYP3A4[41,48] **Selected adverse drug reactions/Precautions unique to buprenorphine transdermal:** Opioid withdrawal: may precipitate withdrawal when switching from other opioids; FDA recommends tapering prior opioid dose down to ≤ 30 mg oral morphine equivalents per day before switching to buprenorphine transdermal from another opioid[61] Steady state: reached in ~ 3 days Subcutaneous depot: monitor for persistent effects for 24 hours post-removal Unintentional ↑ drug exposure: compromised skin, external heat sources, and febrile illness Accidental exposure: transference via hugging, sharing a bed, or moving a patient, has been reported QTc prolongation: observed at doses greater than the maximum dose (i.e., > 20 mcg/hr) Reversal of overdose: naloxone may not be effective in reversing respiratory depression resulting from overdose or may require much higher naloxone doses than other opioids; onset of naloxone activity may be delayed[18,61] Disposal: used patches have high residual buprenorphine content; must be disposed of safely; write on prescription: "pharmacist to advise of safe disposal" **Selected drug-drug interactions (see official product monograph for additional information):** MAOIs: use within 14 days contraindicated as per official prescribing monograph; interaction less likely than with phenylpiperdine opioids (e.g., meperidine, tramadol, and fentanyl)[44,45] CYP3A4 inhibitors: may ↑ buprenorphine levels CYP3A4 inducers: may ↓ buprenorphine levels; clinical relevance uncertain CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects **Selected populations:** Renal: no dose adjustment currently recommended Hepatic: contraindicated in severe hepatic impairment Geriatrics: use with caution; may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance; initiate at lowest available dose; do not use in individuals weighing < 40 kg; safety and efficacy evidence is limited in patients > 75 years of age[18] **CADTH** recommendation:** No statistically significant greater reductions in pain and is more costly compared to oral opioids.[18]
Recommended adult dosing[40]	**Frequency:** Applied every 7 days **Patches should not be altered (e.g., cut, covered, or folded) in any way prior to application.** **Initial dose:** **Opioid naive:** 5 mcg/hr patch once weekly; do not initiate at higher doses **Opioid tolerant:** **< 30 mg oral morphine equivalent/day:** 5 mcg/hr patch once weekly **30-80 mg oral morphine equivalent/day**: taper current opioid dose to < 30 mg oral morphine equivalent before converting, then initiate 10 mcg/hour patch once weekly[61] **> 80 mg oral morphine equivalent/day:** use has not been studied in patients taking > 80 mg oral morphine equivalent/day **Titration:** Dose increases generally separated by 7 days, but no more frequently than every 3 days. **Maximum dose:** 20 mcg/hr
Equivalent dose to oral morphine 30 mg[9]	Variable – see official product monograph
PharmaCare coverage	Non-Benefit ($$$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Tramadol

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 50 mg (Ultram®) **Tablet with 325 mg acetaminophen:** 37.5 mg (Tramacet®, generic) **Sustained-release (SR) formulations:** **Tablet:** 75, 100, 150, 200, 300, 400 mg (Durela®, Ralivia®, Tridural®, Zytram XL®)
Key features[40]	**Classification:** Opioid agonist, norepinephrine reuptake inhibitor, serotonin reuptake inhibitor; phenylpiperidine[41] **Metabolism**: CYP2D6, CYP3A4[42] **Selected adverse drug reactions/Precautions unique to tramadol:** Seizures: reported in recommended dosage range; ↑ risk in doses above the recommended range (maximum dose 400 mg/day); ↑ risk with concomitant SSRIs, tricyclics, MAOIs, other opioids, neuroleptics, and other medications that ↓ seizure threshold; risk ↑ in patients with a history of seizure disorder, head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections, or ↑ intracranial or cerebrospinal pressure Poor CYP2D6 metabolizers: possible ↓ analgesia secondary to ↓ metabolism of tramadol to opioid agonist metabolite[62] Reversal in overdose: non-opioid, monoaminergic effects not reversible by naloxone SR formulations: not interchangeable; differences in time to reach peak levels; must be swallowed intact and not chewed, crushed, split, or dissolved[63] Combination products: maximum 4 g of acetaminophen per day for adults; inquire about non-prescription analgesic use **Selected drug-drug interactions (see official product monograph for additional information):** Serotonin toxicity: ↑ risk with serotonergic medications such as SSRIs, SNRIs, MAOIs, tricyclics, and triptans; CYP2D6 inhibitors; CYP3A4 inhibitors; symptoms include **C**ognitive, **A**utonomic, and **N**euromuscular changes[60] MAOIs: use within 14 days contraindicated; clinically-relevant serotonergic reuptake inhibition[44,45] CYP2D6 inhibitors: may ↑ risk of seizures and serotonin toxicity by ↑ tramadol; may ↓ analgesic efficacy secondary to ↓ metabolism to metabolite responsible for opioid agonist activity[47] CYP3A4 inhibitors: may ↑ risk of seizures and serotonin toxicity by ↑ tramadol[47] CYP2D6 and CYP3A4 inducers: may alter analgesia[47] CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects **Selected populations:** Renal (non-dialysis): BC Renal Agency guidance suggests ↓ dose by 50% if GFR < 50 mL/min[46]; SR products officially contraindicated if CrCl < 30 mL/min Hepatic: use with caution; use lower doses and longer dosing interval; contraindicated Child-Pugh Class C Geriatrics: use with caution; use lower doses and longer dosing interval; 3 day tolerance check for sedation[9] **CADTH** recommendation:** Insufficient evidence that any tramadol SR or tramadol/acetaminophen formulation reviewed provided a therapeutic advantage over less expensive analgesics.[20-23]
Recommended adult dosing[9,40]	**Immediate-release (IR) formulations:** **Initial:** 25 mg/day **Titration:** Every 3 days by 25-50 mg /day (maximum 400 mg/day) **Tablet with acetaminophen:** **Initial:** 1 tablet Q4-6H (maximum 4 tablets/day) **Titration:** Every 7 days (maximum 8 tablets/day) **Sustained-release (SR) formulations:** **Titration:** See official product monograph for dosing recommendations for specific products **Maximum daily dose:** 400 mg/day
Equivalent dose to oral morphine 30 mg[9]	Not reliably established
PharmaCare coverage	Non-Benefit ($$$ to $$$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, $$: $30.00 to $59.99, $$$: $60.00 to $89.99, $$$$: ≥$90.00

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Tapentadol

Dosage forms (Brand name)[40]	**Immediate-release (IR) formulations:** **Tablet:** 50, 75, 100 mg, (Nucynta IR®) **Sustained-release (SR) formulations:** **Tablet (12 hour):** 50, 100, 150, 200, 250 mg (Nucynta CR®)
Key features[40]	**Classification:** Opioid agonist, norepinephrine reuptake inhibitor, weak serotonin reuptake inhibitor[64-66]; clinical relevance of monoaminergic activity unclear **Metabolism:** glucuronidation via UDP-glucuronoslytransferase (major); CYP2C9, CYP2C19, CYP2D6 (minor)[48] **Selected adverse drug reactions/Precautions unique to tapentadol:** Seizures: reported in recommended dosage range; risk may be ↑ with concomitant SSRIs, tricyclics, MAOIs, other opioids, neuroleptics, and other medications that ↓ seizure threshold; ↑ risk in those with a history of seizure disorder, head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections, or ↑ intracranial or cerebrospinal pressure[64,65] Hypertension: clinically important in 1.5-1.7% study participants[66] Reversal in overdose: non-opioid, monoaminergic effects not reversible by naloxone SR formulations: must be swallowed intact and not chewed, crushed, split, or dissolved **Selected drug-drug interactions (see official product monograph for additional information):** Serotonin toxicity: ↑ risk with serotonergic medications such as SSRIs, SNRIs, MAOIs, tricyclics, and triptans; symptoms include **C**ognitive, **A**utonomic, and **N**euromuscular changes[60] MAOIs: use within 14 days contraindicated CNS depressants, respiratory depressants, alcohol: ↑ sedative and depressant effects CYP450: no clinically-relevant CYP450 interactions identified[48] **Selected populations:** Renal: pharmacokinetics altered in severe impairment; reduce dose; contraindicated if CrCl < 30 mL/min Hepatic: pharmacokinetics altered in severe impairment; reduce dose; contraindicated in Child-Pugh Class C Geriatrics: use with caution; use lower doses and longer interval; 3 day tolerance check for sedation[9] **CADTH** recommendation:** Insufficient information to determine relative efficacy of the tapentadol SR compared to oxycodone SR formulations.[19]
Recommended adult dosing[40]	**Immediate-release (IR) formulations:** **Initial dose:** 50-100 mg every Q4-6H **Titration:** See official product monograph for dosing recommendations **Maximum daily dose:** 600 mg **12 hour sustained-release (SR) formulations:** **Opioid tolerant:** See official product monograph for dosing recommendations **Titration:** Every 3 days by 50 mg/day **Maximum daily dose:** 500 mg/day
Equivalent dose to oral morphine 30 mg[9]	Not established (no direct conversion factor to morphine available)
PharmaCare coverage	Non-Benefit ($$$$)*

* Relative drug cost based on a 30 day supply of medication equivalent to 60 mg morphine per day.
$: ≤$29.99, **$$**: $30.00 to $59.99, **$$$**: $60.00 to $89.99, **$$$$**: ≥$90.00

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Opioid Stewardship – Practical Tips with a Focus on Safety

Stewardship is defined as "*the careful and responsible management of something entrusted to one's care.*"[67]
Opioid stewardship is the responsibility of all health care professionals involved in the prescribing and dispensing of opioids. Ongoing prescriber-pharmacist communication, clear prescription writing, and education of the patient, are critical to the safety of the patient, family, and community.

1. **Communication and collaboration with patient's community pharmacist is essential**[9]
   - Opioid prescriptions should be filled at the same pharmacy; identify and document which pharmacy.
   - Confirm prescription history using PharmaNet before an opioid prescription is issued (or contact the patient's community pharmacist to verify use).
   - Keep the patient's pharmacist advised of the therapeutic plan especially when adjusting doses or switching opioids.
   - Have a firm position on requests for early refills and communicate that plan with the patient's pharmacist.
   - The patient's pharmacist should alert the patient's prescriber of behaviours consistent with opioid misuse or diversion.
2. **Opioids are high-alert medications, write clear and specific prescriptions**
   - Specify exact quantity and exact time interval between part-fills of opioid prescriptions.
   - Draw lines through unused portions of the prescription.[9]
   - Avoid error-prone abbreviations, symbols, and dose designations.[68,69]
3. **To minimize harms from opioid use, educate patients regarding possible adverse events and toxicity as well as appropriate opioid storage and disposal**
   - Download the following patient handout from SafeMedicationUse.ca: www.safemedicationuse.ca/newsletter/downloads/201303NewsletterV4N1PreventHarmFromOpioids.pdf
   - Revisit the adverse event section of the handout (common, concerning, dangerous) when initiating an opioid or when increasing the dose.
   - Used opioid patches (fentanyl, buprenorphine) have significant residual drug and must be removed and disposed of in a specific manner. Write on the opioid prescription "Pharmacist to advise on safe storage and disposal."
   - Advise patients that it is unsafe to have large quantities of opioids prescribed; therefore prescribing and dispensing amounts should be conservative.

Direction on the management of opioid overdose or unintentional opioid exposure: Specialists in poison information at the British Columbia Drug and Poison Information Centre (BC DPIC) can provide immediate advice to health care providers and patients (24 Hour Line: 1 800 567-8911 or 604 682-5050).
Pharmacists at BC DPIC can also provide **non-emergency, medication advice to health care professionals** from 9-4 pm Mon-Fri (e.g., opioid conversions, opioid dosing): 1 866 298-5909 or 604 707-2787.

References are available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by PAD pharmacists. For more information, or to schedule an academic detailing session, please contact:

BC Provincial Academic Detailing Service
Phone: 604 660-1978
Fax: 604 660-2108