BC Centre for Palliative Care

B.C. INTER-PROFESSIONAL PALLIATIVE SYMPTOM MANAGEMENT GUIDELINES

fraserhealth

Interior Health
Every person matters

First Nations Health Authority
Health through wellness

BC CANCER

island health

Providence HEALTH CARE

Vancouver CoastalHealth

northern health

OPIOID PRESCRIBING AND MANAGEMENT IN PALLIATIVE CARE

BC Centre for Palliative Care

TABLE OF CONTENTS

PURPOSE

To provide guidance, informed by evidence and endorsed by expert practice, on safe and effective opioid prescribing and management practices for healthcare providers who are prescribing strong opioids for adults with pain or dyspnea related to advanced, life-limiting illness, and healthcare providers who are caring for people receiving opioid therapy.

SCOPE

The focus of this guideline is the prescribing and management of strong opioids for adults with dyspnea and pain related to advanced, life-limiting illness. The guideline assumes the clinician has already determined that an opioid is required to manage pain or dyspnea following a thorough clinical assessment, and other pharmacological and non-pharmacological interventions.

Treatment for pain and dyspnea other than with strong opioids is outside the scope of this guideline. More thorough guidance is provided by symptom-specific guidelines through the BC Centre for Palliative Care. Refer to Pain Guideline and/or Dyspnea Guideline.

The initiation of and rotation to methadone, use of fentanyl and sufentanil injectable and sublingual, and the use of topical opioids are beyond the scope of this guideline. Consultation and use of specific practice guidelines are recommended.

DEFINITIONS

Opioids are naturally occurring, semi-synthetic, and synthetic drugs which produce their effects by combining with opioid receptors and are used to treat pain and/or dyspnea.[1,2]

Strong opioids include opioids without a ceiling effect. Examples of these include morphine, hydromorphone, oxycodone, fentanyl, and methadone.[3]

Weak opioids include those with a ceiling effect (e.g. codeine, tramadol) and mixed agonist-antagonists (e.g. buprenorphine).[3]

Opioid naïve are persons who have not taken opioids within the last 14 days.[4,5]

Opioid tolerant are persons who have been taking at least 60 mg of oral morphine (or equivalent) per day for one week or more.[6]

Breakthrough Dose (BTD) is an as-needed (PRN) medication dose used to manage a breakthrough symptom. It does not replace or delay the next scheduled dose if one has been ordered. BTD is also known as a rescue dose.[7,8]

Scheduled/Regular opioid dose is an opioid that is given at regularly scheduled intervals throughout the day ("around-the-clock" or "by the clock").[2,9]

Incident pain/dyspnea is precipitated by a movement or voluntary action (e.g. weightbearing or wound care) and is predictable or expected.[9,10]

Titration is the adjustment (up or down) of an opioid dose to improve symptom control and minimize adverse effects.[7,11]

Total Daily Dose (TDD) the total amount of a drug (scheduled and breakthrough doses combined) taken in a 24-hour period.[2,7,12]

PREVALENCE

Strong opioids are the principal treatments for pain and/or dyspnea related to advanced and progressive disease, and their use has increased significantly in the primary care setting.[13–15] People receiving palliative care who are experiencing pain and/or dyspnea frequently require strong opioid treatment, either alone or in combination with other treatments.[13]

IMPACT

All people with advanced life-limiting illness deserve symptom control, including opioids when required, regardless of healthcare setting or co-existing conditions (e.g. substance use disorder).

In British Columbia, physicians and nurse practitioners are authorized to prescribe opioids,[16,17] and it is part of their scope of practice to support people* receiving palliative care. Healthcare providers have an obligation to deliver effective symptom relief while managing opioid safety for individuals, caregivers/families,** and society.[18]

** Throughout this document, "people" and "person" refer to the recipient of care, the one who has a life-limiting condition. This includes terms such as "patient" or "client."*

*** "Family" is defined by the person and includes all who are identified by them as significant and involved.*

CONSULTATION

- Consultation is available with experienced palliative care physicians/specialists and inter-professional palliative care teams. If there are no local or regional palliative care physicians available, one can be reached via the **BC Provincial Palliative Care Consultation Line (toll-free, 24/7) at 1-877-711-5757** (accessible only for physicians and nurse practitioners).
- Consultation with an experienced palliative care physician/specialist is recommended when pain or dyspnea is not managed after applying standard opioid guidelines and interventions.
  - Consultation is specifically recommended with opioid conversions, and when pain or dyspnea is not improving with opioid titration, based on the clinician's clinical judgement.
  - Consultation is specifically recommended for prescribing and managing fentanyl and sufentanil (injectable and sublingual) and methadone.
- Consult pharmacy for clarification or concerns regarding cost and formulations available, including long-acting preparations and routes of administration.
- If the person has an opioid use disorder, consultation with an addiction medicine specialist is recommended.
- This guideline does not include pediatrics though the content may have application for children. Seek consultation from Canuck Place Children's Hospice regarding the care of a specific child, given the infrequency and specialty practice of pediatric palliative care.
  - Canuck Place Children's Hospice 24-hour line: 1-877-882-2288
  - On-call Pediatric Palliative Care physician: 1-604-875-2161

KEY RECOMMENDATIONS

Refer to the **Key Recommendations** of opioid prescribing and management for a summary of the guidelines, and the associated **IDSA-ESMO Levels of Evidence and Strength of Recommendations.**

STEP 1 | GOALS OF CARE DISCUSSION

People with advanced, life-limiting, and progressive illness who require opioids for symptom control require the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare provider(s).[19]

Before prescribing opioids and throughout the treatment, discuss goals of care and confirm the treatment with opioids aligns with the individual's wishes and preferences. Ensure people and their caregivers have adequate education and information for decision making to enable the effective and safe use of prescribed opioids.

STEP 2 | ASSESSMENT

Prior to the prescribing of strong opioids, conduct a thorough pain and/or dyspnea assessment, using a tool such as "OPQRSTUV". *Refer to the **BCCPC Symptom Management Guidelines*** for symptom-specific assessment strategies.

Identify whether a person requires a strong opioid by determining:

- The presence of ongoing dyspnea or pain related to their progressive illness, which is expected to worsen, where other strategies (e.g. optimized medical therapy, non-pharmacological techniques, non-opioid medications, or weak opioid medications) are not successful at managing the symptom in accordance with the person's goals.[9,20,21]
- Whether this symptom significantly impairs functioning and/or quality of life.[9,20]
- Whether it's anticipated that person's symptom(s) will not be adequately managed by other methods.[9,20]

Opioid Allergies & Hypersensitivity Reactions

- Determine whether there is a history of a past opioid-hypersensitivity reaction as most documented allergies are **not true allergies,** rather opioid side effects (e.g. constipation, nausea/vomiting, and sedation).[2,9]
- Refer to an Opioid Allergic Reaction resource for more information.

Opioid Risk Assessment

- Screen all people and/or caregiver(s) for any risks that opioids may present to them (i.e. opioid use disorder, diversion, or overdose), prior to prescribing and throughout opioid treatment, particularly if the person is to receive care at home.[22]
    - Treatment with an opioid is not contraindicated for a person with a history of substance use disorder but requires a comprehensive treatment plan which may include an opioid treatment agreement to ensure safe and effective prescribing. For prescribing guidance see **Appendix B: Opioid Use Disorder.**
    - This opioid treatment agreement for chronic pain is an example of an agreement and could be adapted for a palliative population.
    - This opioid diversion risk screen is an example of a diversion screening tool.
- People who are at a higher risk of **overdose** include those who:[22]
    - Are using benzodiazepines
    - Have an active or previous substance use disorder
    - Have a history of opioid overdose
    - Receive opioid prescriptions from two or more healthcare prescribers
- Screen for people who are at high risk for **using opioids other than as prescribed** as an important step in preventing opioid-related harms for people and/or caregivers.[18]
    - People at risk for using opioids other than as prescribed include:
        - People with previous personal or family history of a substance use disorder [22]
        - People with a history of post-traumatic stress disorder and/or abuse[22,23]

- Behaviours potentially indicating use of opioids other than as prescribed include:[18]
  - Observations or reports of prescription forgery.
  - Reported theft or "borrowing" of another person's opioids.
  - Medication route alteration.
- Select one of the following risk assessment tools to assess the potential for using opioids other than as prescribed. Although these tools have not been validated for people receiving palliative care, given time constraints, provider training, and practicality, the risk assessment tools recommended in this guideline include:[18,24,25]
  - CAGE-AID[26]
  - 2 Item Screen of Drug Use[24]
  - Opioid Risk Tool - Revised[27]

STEP 3 | INTERVENTIONS

Initiating Opioids

Individual & Family Education: Initiating Opioids

- Provide the rationale and indications for opioid therapy.
- Provide verbal and written instruction on how to use opioids effectively including appropriate use of scheduled and breakthrough medications.
- Address fears and misconceptions about opioids, including driving and operating machinery, and the difference between physical dependence and opioid use disorder.
- Discuss interaction between opioids and other medications or substances, and the potential for adverse effects and risks.
- Discuss safe storage and safe disposal.
- Provide information on who to contact in case of questions and support, including after-hours.
- If eligible, provide information on the BC Palliative Care Benefit Program (Plan P).
- For people in the community setting, provide an at-home medication record to keep track of doses given.

See **Educating the Individual & Family** section for more information

When to initiate opioids:[2,9]

- After assessment has been completed and it has been determined that the person is experiencing ongoing (episodic and/or consistent) pain or dyspnea and requires a strong opioid medication for symptom management.

Selecting strong opioids:

Start opioids, even for people who are opioid naïve, by initiating a low dose of strong opioid rather than a weak opioid in the context of advanced life limiting illness, with an individualized assessment and therapeutic plan.[3]

- Strong opioids can achieve quicker and more effective relief for pain and or dyspnea[3,13–15]
- Initiating strong opioids can prevent a future opioid rotation due to need for injectable formulation or reaching the maximum ceiling dose of a weak opioid.[3]
- Avoid weak opioids for the following reasons:
  - Codeine: 5-10% of people are slow metabolizers and derive little or no therapeutic benefit.[2,3,28] Additionally, the availability of codeine in combination with acetaminophen further limits the ceiling effect and concern for toxicity.[28]
  - Tramadol: high level of variability in effectiveness and side effect profile, cost, ceiling effect, numerous drug interactions, lowering of seizure threshold, and risk for significant adverse drug reactions.[3,29]
- Use buprenorphine (a weak opioid) only in special circumstances, such as with opioid use disorder or frail adults who have had significant adverse effects when taking strong opioids.[30,31] Buprenorphine is a partial agonist with complex pharmacology and therefore not a first choice for pain management.[30] It is also costly and not covered by the Palliative Care Drug Plan (Plan P) Formulary.
- Avoid initiating fentanyl and sufentanil because of their high potency for people who are not opioid tolerant.[9,32]
  - Injectable fentanyl and sufentanil administered sublingually or parenterally are very short-acting opioids used as a pre-treatment for difficult to manage incident pain and/or dyspnea.[7,9] They are quickly absorbed, much more potent and quick-acting than short-acting morphine, hydromorphone, and oxycodone, and have a shorter duration of action than other dosage forms.[7,9,30,33,34]
  - An evidence-based protocol or guideline should be used when prescribing these medications and in monitoring for effectiveness, sedation, and opioid excess.
  - Consult with an experienced palliative care physician/specialist.
- Initiate methadone only with additional guidance.[35–37]
  - Methadone has complex pharmacokinetics - a longer time to peak effect (3-5 days), delayed achievement to steady state, variable half-life, and multiple drug interactions. It may also cause a prolonged QT interval, causing cardiac rhythm abnormalities.[38]
  - Should be considered for people who are allergic, intolerant, or unresponsive to other opioids and/or with complex pain, including nerve pain.
  - Refer to College of Physicians and Surgeons of BC Guide on Methadone for Analgesia.[38]

How to initiate opioids:

- Register the person for the BC Palliative Care Benefit Program (Plan P) for expanded drug benefit coverage if eligibility criteria are met (BC Palliative Care Benefits Registration). If the person is not eligible for Plan P, complete/submit special authority request as applicable.
- **Initiate a scheduled short-acting (SA) opioid dose with a breakthrough dose (BTD).**[12]

  - For episodic pain and/or dyspnea related to underlying disease, initiating only a breakthrough dose, instead of a scheduled one, may be sufficient (see **Table 1**).
  - Use the oral route when possible as the safest, least costly, and least invasive administration method.[9,39,40]
  - Ensure that all doses are given at the scheduled times, including overnight dose.
- Determine whether the person is opioid tolerant.
  - For people who have been on opioids previously and now have recurrent symptoms; tolerance gained from past opioid use is not sustained. Opioid doses should be restarted at levels appropriate for an opioid naïve person if the person is not currently taking opioids and/or has NOT been taking up to 60 mg of oral morphine (or equivalent) per day for one week or more.
- Order medications to proactively cover the **3 "B's"** – Bowels, "Barfing" (nausea), and Breakthrough.[41] See **Opioid-Induced Adverse Effects**.
- Choose the medication type, dose, dosage form, route, and frequency based on individual requirements.[34,42–44]
  - Considerations include symptom severity, age, ability to swallow, presence of nausea or vomiting, diagnoses, organ dysfunction, concomitant medications, allergies, sensitivities, adverse effect profile, setting, medication cost, ability to monitor the person, ease of administration, and trajectory of disease progression.[9,39,45]
  - Note that significant variability exists between individuals regarding opioid requirements because of pharmacodynamic and pharmacokinetic differences between individuals. For example, morphine requirements may vary 1,000-fold between individuals.[45]
  - If the need for a subcutaneous route may be foreseeable, consider starting with an opioid that has the option for a subcutaneous route to potentially avoid an opioid rotation.
- Use an evidence-based source to determine initial dosing. See **Table 1** for suggested starting doses for opioid naïve.[2,9,30,39,40]
  - Start with the lowest appropriate dose and titrate to effect.[9]

How to initiate opioids in frailty and organ failure:

- When prescribing for people with frailty, heart failure, chronic lung disease, and renal or hepatic insufficiency, be aware these conditions compound the risk of opioids in unique ways.[46] Opioids **are** safe for these populations but require special prescribing and monitoring practices to achieve the goal of titration to effect effect.[9,46–53]
- Prescribe lower starting doses for the frail adult and those with advanced organ failure.[47–54]
- Prescribe opioids using the frail adult doses (see **Table 1**) for individuals who are experiencing refractory dyspnea in advanced cardiac and lung disease including heart failure[55–58] and chronic obstructive pulmonary disease[15,59–61] and pulmonary fibrosis[62] if other interventions have failed.[55–58]
  - Consider prescribing low-dose opioids for persistent breathlessness as a scheduled rather than breakthrough dosing and evaluate effectiveness.

- For severe cardiac ischemic angina, prescribe opioids using frail adult dosing.[55]
- For people with End-Stage Renal Disease (ESRD) and End-Stage Liver Disease (ESLD) dose adjustments beyond the lower starting doses may be required. For further prescribing guidance, see **Appendix A: End-Stage Renal & Liver Disease**.
    - Consider renal dosing for people with any disease with impaired renal function.[50,53,63,64]

Table 1: Starting Doses of Strong Opioids for Opioid Naïve Adults[2,9,15,19,42,65,66]

Oral Opioid (Short-Acting)	Starting Dose: Regular Adult*	Starting Dose: Dyspnea, Frail Adult & Organ Failure**
Morphine	Scheduled dose: 5 mg Q4H PO BTD: 2.5 mg Q1H PRN PO	Scheduled dose: 2.5 mg Q4H PO BTD: 1.25 mg Q1H PRN PO†
Hydromorphone	Scheduled dose: 1 mg Q4H PO BTD: 0.5 mg Q1H PRN PO	Scheduled dose: 0.5 mg Q4H PO BTD: 0.25 mg Q1H PRN PO†
Oxycodone	Scheduled dose: 2.5 mg Q4H PO BTD: 1.25 mg Q1H PRN PO†	Scheduled dose: 1.25 mg Q4H PO† BTD: 1.25 mg Q1H PRN PO†

** When clinically indicated and with adequate monitoring, higher starting doses can be used when initiating opioid therapy.*
***Heart, Lung, Renal & Liver. Further dose adjustments are required for advanced renal and liver failure (see Appendix A: End-Stage Renal & Liver Disease)*
† Doses can be adjusted based on the availability of opioid preparations.

Table 2: Opioid Equianalgesic Conversion[2,9,67]

Drug	Equivalent Oral dose	Oral:Parenteral Ratio	Equivalent Parenteral dose
Morphine*	10 mg	2:1**	5 mg
Oxycodone	5-7.5 mg†	N/A	N/A
Hydromorphone	2 mg	2:1**	1 mg

**Morphine is often used as a reference drug to measure relative potency of other opioids (morphine equivalents).[21]*
***Oral to parenteral dose ratio is generally 2:1, but there are circumstances, based on individual characteristics, which may require a 3:1 ratio.*
† Oxycodone is generally considered about 1.5 to 2 times more potent than morphine. A more conservative conversion uses the 1.5 equivalency.

Establishing Breakthrough Dose (BTD)

When to prescribe a breakthrough dose:

- If a person is ordered a scheduled opioid, they should also have an order for a BTD.[9,12,30,39,40]
    - BTDs are an important element in achieving comfort.
    - Even people with well-controlled pain and/or dyspnea may experience breakthrough symptoms.

How to calculate and prescribe a breakthrough dose:[2,9,12,30,39]

- Prescribe short-acting opioids available as-needed every hour orally or every 30 minutes to one hour subcutaneously.
  - Generally, a BTD should not be given more frequently than the BTD medication's peak analgesia time, 30 to 60 minutes (post-dose), except for methadone which is more pharmacologically complex and therefore should be available less frequently.
- Prescribe the BTD at a dose calculated generally as 10% of the **total daily opioid dose** (total drug in a 24-hour period). Adjust to a practical dose based on available formulations of the prescribed opioid and the individual response.
- When possible, use the same opioid for breakthrough and scheduled doses. This improves ease and clarity for determining future dose titrations and minimizes risk of calculation errors.

Changing the Route of Administration

Although oral (PO) administration is the preferred route, there are times when a switch to the parenteral, subcutaneous (SC) or intravenous (IV), route is needed. In palliative care, the SC route is often preferred over IV to achieve easier access, more consistent serum levels, a longer duration of route access, and the potential for self-administration. The insertion of a SC butterfly/cannula is preferred to provide ongoing access and reduce pain from repeated injections with a needle. Intramuscular (IM) is not a recommended route. Regular IM administration is painful, and many patients lack muscle mass due to cachexia.[9]

When to consider switching from an oral to parenteral route:

- When the person can no longer swallow safely and without other enteral access.
- When a more rapid medication onset is required.
- When gastrointestinal absorption is compromised (e.g. bowel obstruction, extensive ascites, inflammation).
- When the person is experiencing severe nausea or vomiting, limiting their ability to take or absorb oral medications.

How is the medication dose converted when switching routes?

- When switching the same medication from PO to SC or IV, the equianalgesic dose ratio ranges from 2-3:1.[9,67] The ratio of PO to SC is the same as PO to IV. In this guideline we recommend using a 2:1 ratio as a general guide, while considering individual characteristics.[9,67]
- If an opioid switch is occurring at the same time as a route switch, see **Table 4: Steps for Rotating Opioids.**

Ensuring Access to Adequate Medication Supply

Prescribe an adequate and rational amount of medication supply. Take into consideration variables such as cost to the person, ability of the individual to access medications in their care setting, risk of medication being used in ways other than prescribed, and chemical waste to environment.

- Prescribe enough medication for someone at home to prevent risk of running out:

- If the person has a prognosis of several months and is on a stable oral dose, continue to follow up regularly and provide sufficient medication until the follow-up appointment.
- If the person's symptom is not adequately managed, provide enough medication, including breakthrough dosing, to last until they can be reassessed.

Monitoring

Individual & Family Education: Monitoring

- Educate on potential adverse effects, what to monitor for, how to use prescribed as-needed medications, and/or when to report effects to a healthcare provider.
- Discuss the signs and symptoms of opioid withdrawal and opioid excess. Provide education on managing opioid excess and clarify that with careful prescribing and monitoring these events are unlikely to occur.
- For people in the community setting, review at-home medication record to confirm appropriate medication usage. When both long-acting and short-acting formulations are prescribed, ensure the person and/or caregiver understand how and when to use each preparation.[2]

See **Educating the Individual & Family** section for more information

Monitoring is important for assessing the effectiveness of the opioid to decrease symptom burden, as well as for adverse effects, which can range from mild to severe. Many adverse effects of opioids are predictable and manageable (e.g. constipation and nausea).[2,9] Severe adverse effects, including sedation and respiratory depression, are typically dosing related.[30,68]

Monitoring requires a team-based approach including all members of the interdisciplinary team and caregivers.

When to monitor the person:[6,9,30,68–70]

- To determine the frequency of monitoring, consider the severity of pain or dyspnea, the time to peak medication effect, the person's clinical condition, the setting, and the person's and/or caregiver's ability to follow instructions and seek help if required.
- When starting any opioid, monitor closely for **adverse effects** such as sedation and respiration depression to ensure safety.
- When initiating, titrating, or rotating opioids, monitor at frequent and regular intervals until steady state is achieved.[2,6,9,47–50,69,70] For further opioid information, see **Appendix E: Selected Properties of Opioids**.
- Following the start of any new treatment that may change a person's experience of pain and/or dyspnea (e.g. drug interactions that impact opioid effectiveness or a treatment that alters the symptom, such as radiation or surgery).
- With each report of a change or exacerbation to the symptom or with frequent use of breakthrough opioid medication in a short period of time due to poorly controlled pain and/or dyspnea.

How to monitor the person:

Monitor the **4As**: analgesia, activities of daily living, adverse effects, and atypical opioid use.[2,71]

1. **Analgesia**: assess and document the person's symptom(s) using scales such as a Likert scale (e.g. 0–10 symptom rating scale) or behavioural scales to monitor opioid effectiveness.[2,72] Document and monitor the use of both scheduled and breakthrough medication.
2. **Activities of daily living**: monitor the person's ability to sleep, typical level of daily activities, and psychosocial functioning to observe changes over time.[2]
3. **Adverse effects:** Assess for common opioid-induced adverse effects, striving for the best symptom management with the least negative effects.[2]
4. **Atypical opioid usage**:
    - Be conscious of behaviours potentially suggestive of using opioids in ways other than prescribed, such as multiple lost prescriptions, medication running out early, or unauthorized dosing escalations. Consider whether an opioid treatment agreement (see **Appendix B**) with the person would be helpful to clarify expectations.[2]
    - Monitor for adherence to medication regime, resulting in the person receiving significantly more or less opioid than prescribed, and signs of **opioid withdrawal** or **opioid excess**.[2,72]
        - For opioid withdrawal symptoms, see **Opioid Taper or Withdrawal of Opioids**.
        - For opioid excess symptoms, see **opioid excess** below.

Addressing Opioid-Induced Adverse Effects

Many adverse effects are predictable and often preventable.[2,9,21] The majority of adverse effects resolve with repeated dosing as the body develops tolerance, **except** in the case of constipation or opioid-induced neurotoxicity.[2,9,68]

- **Very common** adverse effects include constipation (particularly for frail adults), nausea and vomiting, dry mouth, drowsiness, and sedation.[2]
- **Common** adverse effects include mild cognitive impairment, urinary retention, pruritus, and syncope. [2]
- **Less common** adverse effects are sweating and postural hypotension.[2]
- Opioid-induced neurotoxicity is a rare but serious adverse reaction that can happen with opioids and can include hallucinations, delirium, myoclonus, seizure disorder, hyperalgesia.[5] See **opioid-induced neurotoxicity** below**.**
- Respiratory depression is rare with appropriate dosing,[2] however, the risk of respiratory depression because of opioids is greater for those with respiratory impairments (e.g. pneumonia, COPD), and for people taking additional sedative medications. Low-dose opioids are generally safe to prescribe for people with persistent breathlessness, including those with COPD.[73,74]

Frail adults are at a higher risk of medication-induced adverse reactions due to the physiologic changes of aging, comorbidities such as cognitive impairment, kidney and/or liver dysfunction, and/or concomitant medications. Monitor the frail adult population for adverse effects to opioids more frequently and more closely.[47,75–77] Adverse effects for frail adults may present atypically (e.g. urinary retention may present as delirium or agitation). The most common adverse effects in frail adults are constipation, nausea, dizziness, and urinary retention.[78,79]

How to manage adverse effects:

- Adhere to the principle of starting with the lowest appropriate opioid dose and titrating slowly to effect, when possible, to mitigate adverse effects.[9]
- When opioids are initiated, also initiate prescriptions and/or over-the-counter medications to prevent and manage both nausea and constipation.[9,21,80]
- If an adverse effect does not resolve and is not manageable to the person, consider if opioid rotation is indicated.[2,9]

Sedation

- Many people with advanced illness and palliative care needs have comorbidities and are using other medications, which can put them at increased risk of sedation and opioid excess.[46]
- Monitor the person regularly for sedation and respiratory depression using a standardized monitoring assessment tool. See **Pasero Opioid-Induced Sedation Scale (POSS)** in **Appendix C**.[81–84]
- People usually become sedated from opioids before experiencing respiratory depression. Less opioid is required to produce sedation than to produce respiratory depression, making it a particularly sensitive indicator of impending respiratory depression.[81]
    - Monitoring for sedation rather than waiting for reduced respiratory rate is key. A POSS score greater than 2 is an indicator for higher risk of respiratory depression.[81,82]
- When a person is actively dying (last hours to days), it is expected that their level of consciousness will naturally decrease, and respiratory rate will change. Interventions for reduced consciousness (e.g. administering naloxone or decreasing opioid dose) are not appropriate for someone who is actively dying.
    - Monitoring for comfort should continue with an approach to always use the effective opioid dose. However, during the active dying phase it is no longer appropriate to use signs of sedation and reduced respiratory rate as indicators of opioid excess.

Opioid Excess

In the rare instances where opioid excess causes respirations to be less than or equal to 8 breaths per minute, life is threatened, and treatment with an opioid antagonist is required, naloxone is the appropriate treatment. However, symptoms of withdrawal can be precipitated by using opioid antagonists. The objective is to **address the excess opioid rather than full reversal of opioid effects**.

- When assessing the person, ensure sedation and reduced respiratory rate are not due to natural, active dying.
- Avoid precipitating an opioid withdrawal syndrome (including severe pain) by diluting naloxone and administering small incremental doses to achieve a target respiratory rate.
- *Note: Caring for people in the community requires an individualized plan in relation to suspected opioid excess.*

Administering Naloxone in a Palliative Context[9,85]

1. Prepare naloxone: Add Naloxone 0.4mg (1mL of 0.4 mg/mL solution) to 9mL of normal saline to form a solution of naloxone 0.04mg/mL (total volume 10mL).

2. Administer: Administer 0.02mg–0.04mg (0.5–1 mL) IV or SC and repeat every 2–5 minutes until the respiratory rate is greater than 8 breaths/min and the level of consciousness has improved.
3. Monitor: The half-life of naloxone is only a few minutes, considerably shorter than most opioids. Following the initial treatment of opioid excess, continue to closely monitor the person (respiratory rate, level of consciousness, pupil size, and comfort) until there is no further respiratory depression, for at least two hours. Several naloxone doses may be required. Extended monitoring and extended naloxone exposure may be required (e.g. 12+ hours) if the use of long-acting opioids or methadone resulted in the opioid excess.
4. Until there is sustained improvement to respiratory rate and level of consciousness, hold the scheduled opioid, then provide an as-needed (PRN) dose at 50% of previous scheduled dosing as required.

See example Naloxone Administration Protocol in **Appendix D**.

Nausea & Vomiting

- When initiating a prescription for opioids, also write a prescription for managing nausea and vomiting. Preferred antiemetics include metoclopramide or haloperidol, depending on the person's clinical condition and concomitant medications, considering drug interactions or synergistic effects.[86]
- Refer to **Nausea & Vomiting Guideline** for a more detailed guideline on managing nausea/vomiting.

Opioid-induced Constipation

- The constipating effects of opioids are persistent. When initiating opioids, prophylactic laxatives should be prescribed and continued for the duration of opioid treatment.[68,87–89]
- Using a stepwise approach, start with stimulant (e.g. sennosides) and/or osmotic [e.g. lactulose or polyethylene glycol (PEG) laxatives as the preferred medications for opioid-induced constipation.[39,87,90–93,93–96]
  - Note that polyethylene glycol is not covered by **BC Palliative Care Benefits**.
- As the dose of opioids increases, the dose of laxative often needs to increase, with dosing twice daily or even three times daily,[93] up to the maximum recommended or tolerable dose required to achieve regular bowel movements.[39,87,94,97]
- Avoid bulk forming or psyllium fibre laxatives such as Metamucil® as it requires adequate fluid intake to be effective.[9]
- Avoid "stool softeners," such as Docusate Sodium or Docusate Calcium as they are ineffective at managing opioid-induced constipation.[98]
- Refer to **Constipation Guideline** for a more detailed guideline on managing constipation.

Opioid-Induced Neurotoxicity

- Throughout the opioid treatment, monitor the person for signs of accumulation of toxic opioid metabolites causing opioid neurotoxicity.[2,9,21,80,99] Accumulation is not dose related and is individually variable.[9]
- Signs of opioid-induced neurotoxicity effects include decreased level of consciousness, confusion/cognitive impairment, agitation, myoclonus (involuntary single or irregularly repetitive movement on one body part), hallucinations, hyperalgesia (an increased perception or experience of painful stimuli), and/or allodynia (experience of pain induced by nonpainful stimuli).[2,9,99]
- To manage opioid-induced neurotoxicity:
  - Exclude other causes for the adverse effects (example, other causes of delirium).[9]
  - Provide hydration to support clearance of toxic metabolites. The use of even short-term parenteral hydration should be considered where feasible as it can allow for quicker resolution of symptoms.[99]
  - Depending on the person's circumstance and degree of symptom control, apply an appropriate strategy including reducing the opioid dose, rotating the opioid, changing the opioid route, and treating the toxicity symptomatically short-term. If needed, consider adding an adjuvant analgesic.[2,9,99]
- Refer to **Twitching/Myoclonus/Seizures Guideline** for a detailed guideline on managing opioid neurotoxicity.

Titrating Opioids

Individual & Family Education: Titrating Opioids

- Provide rationale for change.
- Provide verbal and written instruction on potential adverse effects, what to monitor for, how to use prescribed as-needed medications, and/or when to report effects to a healthcare provider.
- Adverse effects such as drowsiness and nausea can be expected when increasing the opioid dose but should improve in 48-72 hours.

Following the initiation of an opioid, adjustments are almost always required. For onset, peak, and duration estimates for specific opioids, see **Appendix E: Selected Properties of Opioids.**

Assess the need for titration when:

- More than three breakthrough doses used in 24 hours, excluding those for incident pain.[9]
- Pain and/or dyspnea is not controlled although steady state of the scheduled medication has been reached.[9]

How to titrate:

- Adjustments to dose should typically be done after the opioid reaches steady state.[15,100]
- For dosing adjustments, assume steady state is reached at the following times, with scheduled dosing of:
  - Short-acting opioids in 24 hours,[101] titrate dosing after 24 hours.
  - Long-acting oral opioids in 72 hours,[101] titrate dosing after 72 hours.
  - Fentanyl transdermal in 72 hours,[9,102] though potentially longer due to individual variation in skin permeability and drug clearance.[33]
- Fentanyl transdermal can be titrated after 72 hours, however, patches are best suited for stable pain, therefore titration is typically no faster than after two patch changes (6 days).[33]
- The rapidity of the dose escalation should be related to the symptom severity, expected onset and duration of analgesics, and ability to monitor during dose titration.[2,9]
- A severe or crisis symptom may require more aggressive titration, including using short-acting opioids to allow for more rapid adjustments.[2,9,100] This may require consultation with an experienced palliative care physician/specialist.
- If the opioid is being switched in addition to a dose titration, see **Steps for Rotating Opioids.**
- To titrate, determine the new scheduled and breakthrough doses using a stepwise titration calculation by first converting all doses to the equivalent of one route and one opioid, calculating the total daily dose, calculating the new scheduled and breakthrough doses, and converting to the desired route of administration if different from current route.[2,9,103] See **Appendix F: Steps for Titration Opioids and Example Calculation**.

Switching an oral opioid from short-acting to long-acting

Oxycodone, morphine, and hydromorphone are all available as long-acting oral medications. They have a duration of action of approximately 12 hours and are available in a variety of dosage strengths.[2,9,30] Long-acting oral opioids must be swallowed whole (not chewed, split, dissolved, or crushed) to ensure a long-lasting effect and prevent quick medication release. If needed, long-acting morphine and hydromorphone capsules can be carefully opened, and the beads sprinkled onto a spoon or cold applesauce for ease of swallowing (without chewing or crushing the beads and ensuring that all medication is taken).

When to consider switching to a long-acting opioid

- Pain or dyspnea is well controlled after titrating the short-acting opioid dose for optimal symptom control.[2,9,30,103]
- To improve medication adherence, provide stable baseline symptom relief, and reduce medication burden (e.g. no overnight dosing required).[2,9,30]
- For individuals with cognitive impairment, dependence on caregivers for administration, and/or insecure housing who may benefit from long-acting formulations. [2,9,30]

How to switch to long-acting opioids:

- Calculate total daily dose = total regular dose + breakthrough doses
- Long-acting Q12H dose = total daily dose ÷ 2
  - Some people, due to a genetic predisposition, may metabolize rapidly and require Q8H dosing[101]
- When prescribing a long-acting opioid, also prescribe a short-acting opioid for the breakthrough dose, preferably using the same drug.[9,30]

Rotating Opioids

Individual & Family Education: Rotating Opioids

- Provide rationale for change.
- Provide verbal and written instruction on potential adverse effects, what to monitor for, how to use prescribed as-needed medications, and/or when to report effects to a healthcare provider.

A significant proportion of people with advanced illness requiring opioids will encounter a need to change from one opioid to another.[104]

When to rotate someone to a different opioid:

- Symptom control is not achieved despite dose titration and an adequate dose trial. [2,9,67,105,106]
- Intolerable or dose-limiting adverse effects or opioid-induced neurotoxicity.[2,67]
- Change in the person's condition, such as renal function creating a higher risk for accumulation of toxic metabolites.[63,67]
- Change regarding safety or access to medication.
- The medication is not available in the desired formulation when switching from the oral route to parenteral (SC/IV) or transdermal.[9,67]
- To facilitate a more appropriate route of administration, dose, or to reduce oral medication burden (e.g. morphine 400 mg oral can be more easily managed with an equianalgesic dose of hydromorphone).[9]

How to rotate opioids:

- With the exception of methadone (which is not covered by this guideline), rotation is most often done by direct substitution, where the current opioid is stopped, and the new one introduced.[107]
- Complete a robust symptom assessment, clarifying the reason for rotation, the current level of symptom control, and the person's overall status.
- Determine the best choice for a new opioid based on clinical factors, personal preference, drug formulation/pharmacology, and, importantly, considering the reason the current opioid is not adequate.[2,30,67,104,107–109]
- In the presence of limiting adverse effects, switch to an opioid with fewer active metabolites (e.g. fentanyl patch instead of hydromorphone).[9]

- Following rotation, re-assess the person. Monitor for efficacy and safety, considering the care setting and level of monitoring available.
  - An individual may require dose titration following a rotation.
  - Consider breakthrough doses may need to be administered more frequently as initial rotation may lead to conservative scheduled dosing.
- Consult with an experienced palliative care physician/specialist if needed; opioid conversion is not just a mathematical calculation, it requires ongoing assessment of the person and a clear understanding of how they are using the medication.
- To calculate the scheduled and breakthrough doses for a new opioid, use a stepwise rotation calculation. Select the type and formulation of the new opioid, convert all doses to the equivalent of one route and one opioid, calculate the total daily dose, then the equianalgesic dose using opioid equianalgesic conversion dosing. Reduce the equianalgesic dose by up to 25-50% to account for incomplete cross-tolerance and any other individual factors, convert dose to desired route of administration (if different from current route), and calculate the new scheduled and breakthrough doses.[9] See **Appendix G: Steps for Rotating Opioids and Example Calculation**.

Opioid Rotation to Methadone[35–37]

- Conversion should be done in consultation with an experienced palliative care physician/specialist and usually in an acute care setting.
- Conversion should be individualized as equianalgesic dosing is variable and based on the person's current opioid use.[36]

Fentanyl Transdermal Patch Conversion

Fentanyl is a strong opioid that has multiple routes of administration. For this guideline, only the transdermal route will be discussed as it is commonly used in the palliative care setting. Transdermal fentanyl is a patch applied to the skin and is typically changed every 72 hours. Fentanyl transdermal should not be initiated in opioid naïve patients given its relative potency and extended duration of action.[110]

Individual & Family Education: Fentanyl Transdermal Patch

- Effective application of the fentanyl patch is to clean, dry, intact skin, free of hair (if needed, use clippers and not a razor) and to an area with subcutaneous fat.
- When changing patches, remove the old patch first, then apply new patch, removing plastic and holding in place for 30 seconds. Do not overlap patches. Rotate patch placement on body.[110]
- Avoid exposure to heat sources (i.e. heating pads or hot tubs) as this can increase fentanyl release and may lead to opioid excess.[110]
- For safe removal avoid touching inside of patch. If not using gloves, wash hands using only water (no soap as this can increase medication absorption). For disposal, fold patch in half, with sticky sides stuck together and place in a pharmacy approved container.[110] Return used patches to pharmacy for safe disposal.

- Used fentanyl transdermal patches can contain a significant amount of residual medication. **Safe patch disposal is important to prevent harm to individuals, caregivers, and accidental poisoning of children and pets**.[110]

Consider initiating transdermal fentanyl for people:

- With stable pain and/or dyspnea who are on an established opioid regime.
- For whom the oral route is not preferred or not possible (e.g. bowel obstruction).
- Who would benefit from infrequent dosing (Q72H) and/or around-the-clock opioid treatment.

Transdermal fentanyl is not indicated for people:

- Who have not been taking a total daily dose [TDD] of at least 60mg of oral morphine equivalent for one week.[110]
- Being treated for incident pain and/or dyspnea, acute pain, or perioperative pain.[110]
- Receiving codeine or tramadol, due to the inability to ensure safe conversion.
  - If the person is receiving these, first rotate to hydromorphone or morphine and establish them on a TDD of 60mg morphine PO equivalent for at least one week before converting to a fentanyl patch.[111]

How to initiate fentanyl transdermal patch:

- Use a conversion chart to determine the fentanyl patch dose in conjunction with clinical reasoning.[9,39,67,104] See **Table 5** below.
  - When using this table for other opioids than those listed, convert the medication to morphine equivalents.
  - The 12mcg/hr patch is best used for dose titration or adjustments, but not typically as an initial dose.[39,112]
    - Initiating someone on a 12 mcg/hr patch is not recommended unless opioid tolerance is assured.[39,112]
    - Based on clinical judgement and the individual's needs and context, a provider may consider prescribing a 12mcg fentanyl patch for someone regularly using opioids, but who is on less than the equivalent of 60 mg of oral morphine per day.[112]
- Apply the fentanyl patch and continue the previous opioid doses for first 12 hours to account for the initial delay in fentanyl patch absorption. Use scheduled and as-needed dosing during this transition.[2,9] For people taking a long-acting opioid, the patch can be started at the same time as the final long-acting dose is taken.
- Prescribe an appropriate breakthrough dose of short-acting morphine or hydromorphone.[113]
- In elderly, cachectic, or diaphoretic people, transdermal fentanyl may have altered pharmacokinetics due to poor fat stores, muscle wasting, reduced absorption, or altered clearance. Monitor the person to ensure medication effectiveness and adequate dosing.[110]
- Consider Q48H dosing if end-of-dose failure is occurring.[114]

Table 3: Unidirectional conversion: From Morphine or Hydromorphone to Fentanyl Patch*[9,39]

The table does **not** apply if converting someone **from** fentanyl **to** morphine or hydromorphone.

For doses beyond those included in the table, refer to BC Guideline link below.

Oral Morphine (mg/24hrs)	Oral Hydromorphone (mg/24hrs)	Fentanyl Patch (mcg/hr)
25-59	5-11	12**
60-134	12-26	25
135-179	27-35	37
180-224	36-44	50
225-269	45-53	62
270-314	54-62	75
315-359	63-71	87
360-404	72-80	100

**Dosing in table above is conservative as dose reductions have been made to account for incomplete cross-tolerance when rotating to fentanyl.*
*** Initiating someone on a 12 mcg/hr patch is not recommended unless opioid tolerance is assured.[39,]*

Table adapted from BC Guidelines.ca Fentanyl Patch Equianalgesic Conversion (long version)

Table 4: Approximate Breakthrough Doses Recommended for Fentanyl Patch[39]

Breakthrough should be 10% of the total daily opioid dose.[2,9,12,30,39]
For doses beyond those included in the table, refer to BC Guideline link below.

Fentanyl Patch Strength (mcg/hour)	Oral Morphine Short-Acting (mg)	Oral Hydromorphone Short-Acting (mg)
12	5	1
25	10	2
37	15	3
50	20	4
62	25	5
75	30	6
87	35	7
100	40	8

Table adapted from BC Guidelines.ca Fentanyl Patch Equianalgesic Conversion (long version)

Fentanyl transdermal patch considerations:

- Full clinical effects occur 24-48 hours after application. Steady state is achieved after multiple patch dosing, usually by day 6 but as long as day 12.[110]
- With initial application, the dose may be titrated after 3 days. With ongoing treatment, titrate dose after 6 days to ensure has reached steady state.[115]

- Monitor for adverse effects, particularly sedation and respiratory depression, during initiation and titration.[9,30] If the person has a fever, monitor for increasing serum fentanyl concentration.[110]
- For more comprehensive descriptions of transdermal fentanyl refer to health authority resources and the drug product monograph.
- If rotating to another opioid from a fentanyl patch, consult with a pharmacist or an experienced palliative care physician/specialist for dosing advice.

Opioid Taper or Withdrawal of Opioids

Individual & Family Education: Taper or Withdrawal of Opioids

- Educate the individual and family not to suddenly stop taking opioids once they have been taken regularly, but to speak to their prescriber about a plan for tapering if appropriate.
- Provide the rationale and indication(s) for the opioid taper or stopping of treatment.
- Address individual and caregiver(s) goals, questions, or concerns.
- Inform the person about what to expect. Discuss physical dependence and the signs and symptoms of opioid withdrawal and what to do if withdrawal symptoms occur.
- Outline the plan for tapering.

Physical dependence on opioids is a normal and predictable neurophysiological response to regular treatment with opioids for more than a few weeks.[2,9] For an individual with palliative care needs, reduction of opioids may be appropriate, however, seldom is the complete cessation of opioids appropriate.[2]

Opioid withdrawal occurs when an opioid is discontinued abruptly or with significant reduction in the opioid dose.[2,9,101] Symptoms can include anxiety, agitation, insomnia, lacrimation and rhinorrhea, fever, sweating, tremors, muscle aches, abdominal cramps, nausea and diarrhea.[9]

When to consider reduction or withdrawal of an opioid:

- When the person is achieving appropriate pain control by another method such as radiation, nerve block, or epidural analgesia.[2,101]
- Resolution of underlying pain and/or dyspnea.
- Individual choice to reduce opioid use.

NOTE: If a person's symptoms are fully resolved at current opioid dosing, with significant opioid side effects (e.g. somnolence):

- Reassess for other factors contributing to clinical change (e.g. renal compromise, infection).
- If respiratory rate is 8 or fewer breaths per minute (and patient is not actively dying, when a decreased respiratory rate is expected), treat opioid excess. See **Administering Naloxone in a Palliative Context**.

Consider opioid rotation, close monitoring for symptoms, withdrawal symptoms, and opioid toxicity.
- Consult with an experienced palliative care physician/specialist if needed.

How to reduce or withdraw opioids:
- If person's symptoms are resolved **fully** at current opioid dosing, **without** significant opioid adverse effects, taper slowly.[116,117]
- Use a stepwise approach, tapering gradually to prevent withdrawal.[116,117]
- Experience indicates that the usual daily dose required to prevent withdrawal is equal to 75% of the previous daily dose. Following this rule of thumb, doses can be gradually titrated down until the drug is discontinued or symptoms recur, at which point the previous lowest effective dose can be maintained.[2]
- **Taper approximately 10% every week until the treated symptom recurs, or the opioid is stopped**.[116,117]
  - Adjust the rate of tapering as needed to minimize or avoid withdrawal symptoms.
  - If the pain or dyspnea recurs, return to lowest previously effective dose
  - If withdrawal symptoms occur, return to the previous dose for 1 week, and try further reduction again slowing the taper.
- Consult with an experienced palliative care physician/specialist if needed.

10% Taper example:
For an individual taking 20 mg of morphine short-acting Q4H (total of 6 doses daily).
Doses have been adjusted based on morphine preparations (5mg short-acting tabs).
- Reduce to 17.5mg morphine (short acting) Q4H x 1 week,
- then 15mg Q4H x 1 week,
- then 12.5mg Q4H x 1 week,
- then 10mg Q4H x 1 week,
- then 7.5mg Q4H x 1 week,
- then 5mg Q4H x 1 week,
- then 2.5mg Q4H x 1 week,
- then stop regular dosing and use only as-needed (PRN)

EDUCATING THE INDIVIDUAL & FAMILY

During every stage of opioid prescribing and management, provide ongoing education to the individual and/or family to ensure effective, appropriate, and safe medication use. This education promotes understanding of opioid therapy and supports adequate symptom control.

How to provide education:
- Use a person-centered approach incorporating harm reduction and trauma-informed principles, considering the individual's history and experience.

- Provide information on who to contact in case of questions and support, including after-hours.
- Provide verbal and written information about opioids in a way that is accessible to the individual and/or caregivers and in a language they are fluent in.

Instruct about safe opioid storage and safe disposal: [65,118–120]

- Store medication in a safe place that is not visible to anyone besides the individual and/or caregiver(s) who manage the medications.
  - Keep away from children and pets.
- Keep track of number of medicines used.
- Use take-back programs in hospitals and pharmacies for unused medication. Do not give unused medications to anyone. Do not discard opioids in the garbage, toilet, or sink.
- Use an appropriate container for storing unused opioids and used fentanyl patches and return this container to pharmacy for disposal.

When initiating opioids, educate on:

- How to use opioids effectively and safely, including appropriate use of scheduled and breakthrough medications.
- In-home medication recording of opioid doses given and effect (for people in the community setting).[2] This in-home medication record is an example.
- Directions for prescribed route, dosing, and frequency.
- Anticipating increasing or reducing doses to achieve symptom control and minimize adverse effects.
- Following the planned medication regime (e.g. not stopping or starting medications prior to talking to prescriber or pharmacist).
- Common fears and misconceptions about opioids (see **Table 7**), including driving and operating machinery, and the difference between physical dependence and opioid use disorder.
- Interaction between opioids and other medications or substances, and the potential for adverse effects and risks.

When monitoring people taking opioids, educate on:

- Adverse effects, what to monitor for, how to use as-needed medications, and when to report effects to a healthcare provider. Drowsiness, nausea, and constipation commonly occur when using opioids.
  - Drowsiness and nausea may develop when opioids are started or when the dose is increased, but usually resolve within 3-5 days.
  - Constipation will always occur and needs to be anticipated, pro-actively managed, and assessed on an ongoing basis.
- Signs and symptoms of **opioid withdrawal** and **opioid excess**. Discuss managing opioid excess and clarify that with careful prescribing and monitoring these events are unlikely to occur.
- For people in the community setting, review at-home medication record to confirm appropriate medication usage.

- When both long-acting and short-acting formulations are prescribed, ensure the person and/or caregiver understand how and when to use each preparation.[2]

When titrating opioids, educate on:

- Adverse effects such as drowsiness and nausea can be expected when increasing the opioid dose but should improve in 48-72 hours.

When tapering or withdrawing opioids, educate on:

- Importance of not suddenly stopping opioids if taking them regularly but speaking to the prescriber about a plan for tapering if appropriate.

Table 5: Addressing Fears & Misconceptions around Opioids

Fear or misconception	Reality
Fear of addiction	The overwhelming majority of people taking opioids for symptom control will not become addicted. The need to increase doses over time also does not indicate addiction, but rather progression of disease and/or developing opioid tolerance. For many people, their opioid doses remain stable over long periods of time. If opioids are abruptly discontinued, a physical reaction may occur. This is a normal physiological reaction, not a sign of addiction.
Being started on an opioid means a limited life expectancy as prescribers only start these when the "end is near."	Opioids, if used with appropriate starting doses, are very safe and do not shorten a person's life. People with slowly progressing diseases may be on opioids for many months and even years without major repercussions. Optimizing symptom management can significantly improve quality of life.
Opioids are very sedating and cause "zombie-like" states or confusion.	Although mild to moderate sedation is common when initiating opioids, even with appropriate starting doses, this usually resolves spontaneously within a few (3-5) days. If sedation persists, providers could seek other causes, switch opioids, or reduce the opioid dose if the symptom is well-controlled.
Fear the opioid won't be effective at the end of life or when symptoms worsen.	Pain and/or dyspnea do not necessarily intensify in the terminal phases. Usually, these can be well controlled in the final stages if they were well controlled in earlier stages. The best way to manage pain is to control it early. Strong opioids do not have a ceiling dose, and doses may be increased over time to provide quality symptom control. Availability of a variety of opioids also allows for switching between opioids if one is no longer effective or causes intolerable side effects.

Being allergic to an opioid.	Most "allergies" to opioids are not true allergies, rather side effects such as nausea/vomiting and sedation and will resolve in 3-5 days. A detailed history is required to rule out a true allergy.
Not being able to drive again.	For non-commercial driving in Canada, taking opioids does not mean you can no longer drive. Stable and long-term opioid treatment has no significant effects on functions related to driving. For people who are experiencing drowsiness, it is not safe to drive. When first starting an opioid, switching opioids, or when doses are being increased, it is not safe to drive.

Adapted from Pallium Palliative Pocketbook ©Pallium Canada. All rights reserved.[9]

Table 6: Resources for individuals and/or families

Resource Title & Link	Source
Frequently Asked Questions & Key Considerations	
Opioids for symptom control in palliative care	Island Health
Common concerns about opioids in palliative care	Canadian Virtual Hospice
Frequently asked questions about opioid pain medicine	Fraser Health
Preventing constipation while on opioids	Fraser Health
Opioids in a Community Setting	
In-home medication monitoring record	Interior Health
Storage & disposal of opioids	Institute for Safe Medication Practices Canada
How to take long-acting opioid pain medicine	Fraser Health
How to take short-acting opioid pain medicine	Fraser Health
Fentanyl Patches	
Safe disposal of fentanyl patches	BC Pharmacists
Fentanyl patches	Institute for Safe Medication Practices Canada
Fentanyl patches: how to use safely	Fraser Health

ADDITIONAL RESOURCES

Appendix A:

End-Stage Renal Disease (ESRD):

People with ESRD have a **higher risk of opioid adverse effects** due a decrease in renal clearance of opioid metabolites, gastroparesis and delayed gastric emptying causing delayed absorption, hypoalbuminemia and fluid retention influencing volume distribution of drug, polypharmacy potentially causing drug-drug interactions, and a reduced therapeutic window for some opioid medications when on dialysis.[52,76,121] Monitor people with ESRD closely when taking opioids.[77]

Initiating opioids for people with End-Stage Renal Disease:

Choose one of the preferred opioid medications for chronic renal disease, as metabolite accumulation can cause opioid-induced neurotoxicity.[78]

Table A.1: Preferred opioid medications in chronic renal disease[122]

Recommended[122]	Use with caution[122]	Do not use[122]
Hydromorphone[i]	Oxycodone[iv]	Morphine[v]
Fentanyl[ii]		Codeine[v]
Methadone[iii]		

[i] *Hydromorphone: Less active metabolites*[63]
[ii] *Fentanyl: No known active metabolites*[63]
[iii] *Methadone: Cleared hepatically. In severe renal impairment, caution is advised - about half of the drug and its metabolites are excreted by the kidneys.*[9]
[iv] *Oxycodone: Metabolized in the liver, 7% of the population cannot metabolize. Metabolites are excreted renally. Increased adverse effects in ultra-rapid CYP2D6 metabolizers.*[63]
[v] *Morphine and codeine: Neurotoxic metabolites are renally excreted and can accumulate.*[63]

To reduce the risk of accumulation of toxic metabolites from opioids, use lower initial dosing and extended dosing intervals as reflected in initial dosing below. Adjust the starting dose based on the individual's GFR as outlined in the table below. Lower doses can also be achieved by extended dosing intervals.[52,76,121]

Table A.2: Recommended starting opioid doses for opioid naïve with renal impairment[63]

Opioid	Starting Dose	GFR (mL/min)	Renal Dosing	Adjusted starting dose
Hydromorphone	0.5 mg PO Q4H	>50	100%	0.5 mg PO Q4H
		10 to 50	75%	0.5 mg PO Q4H Or 0.25 mg PO Q6H
		<10	50%	0.25 mg PO Q6H
Oxycodone	1.25 mg PO Q4H	>50	100%	1.25 mg PO Q4H
		10 to 50	75%	1.25 mg PO Q6H
		<10	50%	1.25 mg PO Q8H Or 1.25 mg PO Q8H
Fentanyl	Not recommended for people who are opioid naïve. Dosing for people who are opioid tolerant is calculated through equianalgesic conversion.	Favourable (renal) pharmacokinetic profile.		
Methadone	Consult with Palliative Care physician/specialist	Favourable (renal) pharmacokinetic profile (pharmacokinetically smoothest opioid in ESRD). Caution in severe renal impairment, as approximately half the drug and its metabolites are excreted by the kidneys.[9]		

To determine initial opioid dosing for people on dialysis, consult with a nephrologist or an experienced palliative care physician/specialist.

Refer to **BC Renal Analgesic Brochure** for further guidance on specific medications and supplemental dosing after hemodialysis or peritoneal dialysis: http://www.bcrenal.ca/resource-gallery/Documents/Renal-Analgesic-Brochure.pdf

End-Stage Liver Disease (ESLD):
Adverse effects may occur amongst people with ESLD due to reduced clearance and accumulation of drugs, and metabolites, leading to increased risk of sedation, respiratory depression, opioid-induced neurotoxicity, and hepatic encephalopathy.[47,48,53,123] An ideal drug for people with ESLD should have a short half-life, minimal hepatic metabolism, high oral bioavailability, and low protein binding.[47,123]

Initiating opioids for people with End-Stage Liver Disease:
Prescribe opioids at lower doses and/or at extended dosing intervals and implement careful monitoring during any titration.[47,123,124] Avoid prescribing tramadol and

codeine due to decreased metabolism and increased risk of accumulation of these opioids in people with ESLD.[47,48,53]

Table A.3: Recommended starting opioid doses for opioid naïve with end-stage liver disease [48,53]

Opioid	Starting Dose	Considerations
Morphine	2.5 mg Q4-8H PO	Do not use if the person has comorbid renal dysfunction due to risk of seizures, myoclonus, respiratory depression, and hepatic encephalopathy.[53]
Hydromorphone	0.5 mg Q4-8H PO	Risk of accumulation of metabolites with concomitant renal dysfunction.[47,123]
Oxycodone	1.25 mg Q4-8H PO	
Fentanyl	Not recommended for people who are opioid naïve. Dosing for people who are opioid tolerant is calculated through equianalgesic conversion.	

Appendix B: Opioid Use Disorder (OUD)

Treatment with an opioid analgesic is not contraindicated in a someone with a history of opioid use disorder or someone receiving opioid agonist therapy, and under-treatment might increase the risk of relapse, using illicit opioids to "self-medicate" unmet pain needs. However, treatment requires a comprehensive plan and close monitoring. People receiving palliative care who are at high-risk for or who have active OUD should be assessed more frequently than low-risk individuals.[18]

If an opioid use disorder is active, collaboration with an addiction medicine physician/specialist is **strongly recommended**. A specialist may already be involved if the person is being prescribed opioid agonist therapy (OAT).

Harm Reduction & Trauma-Informed Approach:

- Use a harm reduction approach for individuals with active opioid use disorders. Conversations about safer substance use, take-home naloxone, and referral to other harm reduction services should be routinely offered as part of standard care.[24]

How to use safe prescribing practices for people with opioid use disorder:[18]

- Consider whether an opioid treatment agreement with the person would be helpful to clarify expectations.[1]
  - This opioid treatment agreement for chronic pain is an example and could be adapted for a palliative population.
- Track previously dispensed prescriptions.
- Dispense opioids daily to weekly, depending on level of risk.
- Work with an addiction medicine specialist to determine who will be the primary prescriber. Provide a detailed symptom management plan and documentation to covering physician if the primary prescriber is absent.
- Closely monitor persons with or at risk of using opioids in ways other than prescribed may include:
  - Assessing symptom(s) and medication effectiveness more frequently (e.g. weekly)
  - Reviewing the person's PharmaNet profile each time a prescription refill is ordered
  - Considering a urine screening depending on level of risk and if there is any concern for diversion
  - Involving pharmacy staff for monitoring drug adherence, including witnessed ingestion of medications
  - Ensure return of used fentanyl patches to the pharmacy at the time of receiving a new patch.
- In terms of dosing opioids for people with opioid use disorder and/or on opioid agonist therapy, people who use high doses of opioids, whether prescribed or not, have higher opioid tolerances at baseline. Treating a new source of pain (e.g. pain related to cancer) will require even higher doses to meet analgesic needs, beyond their baseline opioid requirements.[125] Consider the same general approach, using 10% of the total daily dose for dosing breakthrough opioids, but consider an individualized approach (such as using a lower dose more frequently)

if the person is on an extremely high baseline dose (e.g. >1000 morphine-equivalent daily dose)

- If appropriate, consider consulting with an addiction medicine specialist to see if splitting methadone from daily to TID dosing might help with optimizing pain control.
- Buprenorphine may be prescribed to people for opioid use disorder. It has a high affinity for the opioid receptor, but only partial activity, so it may make analgesia challenging. Discuss with addiction medicine specialist whether this medication could be discontinued or converted to methadone as it will make pain management with full opioid agonists challenging.

Refer to: A Guideline for the Clinical Management of Opioid Use Disorder by the BC Centre on Substance Use for more information.

Appendix C: Monitoring for Opioid-Induced Sedation

Pasero Opioid-induced Sedation Scale (POSS) with Interventions*
*Appropriate action is given in italics, below the table, for each level of sedation.

***Note**: Interventions for reduced consciousness are not appropriate for individuals receiving opioids who are actively dying (last hours to days), as the level of consciousness will naturally decrease with dying.*

S	Sleep, easy to arouse	Acceptable; no action necessary; may increase opioid dose if needed.
1	Awake and alert	Acceptable; no action necessary; may increase opioid dose if needed
2	Slightly drowsy, easily aroused	Acceptable; no action necessary; may increase opioid dose if needed
3	Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50%** or notify prescriber † or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or a NSAID, if not contraindicated.
4	Somnolent, minimal or no response to verbal and physical stimulation	Unacceptable; stop opioid; consider administering naloxone**;** †† notify prescriber † or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

*** Opioid analgesic orders or a hospital protocol should include the expectation that a nurse will decrease the opioid dose if a patient is excessively sedated.*

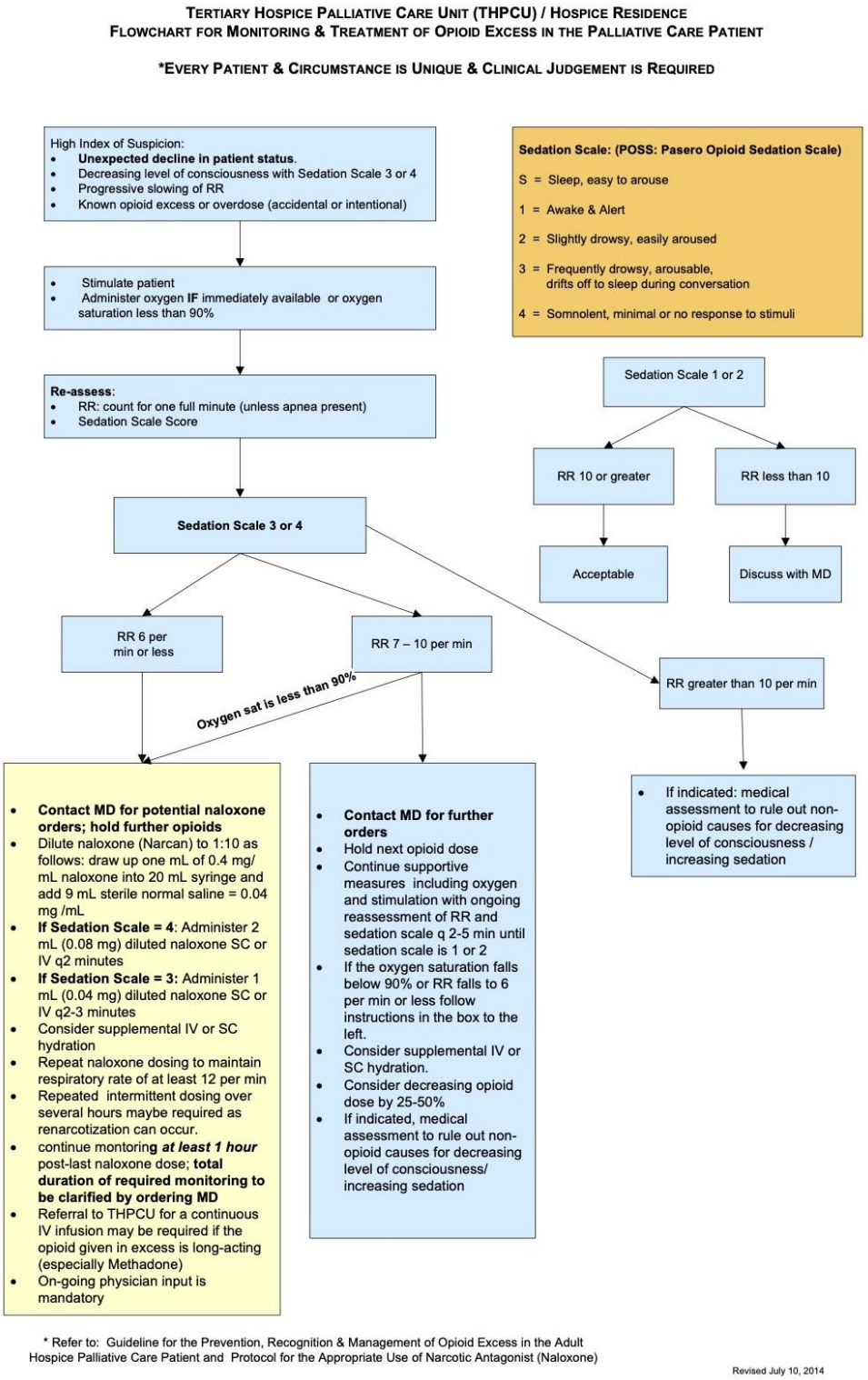
† *For example, the physician, nurse practitioner, advanced practice nurse, or physician assistant responsible for the pain management prescription.*

†† *See **Administering Naloxone in a Palliative Context** for instructions on preparing and administering naloxone.*

Resource adapted from Assessment and Management of Pain (3rd edition) by the Registered Nurses' Association of Ontario (RNAO)[81,126]

Appendix D: Administering Naloxone in an Inpatient Palliative Context

Sample Monitoring and Naloxone Administration Protocol for Opioid Excess in a Palliative Care Patient



Included with permission from Fraser Health Authority, Palliative Care Network, 2014

Appendix E: Selected Properties of Opioids

The information provided below is based on pharmacokinetic data and clinician experience. The onset, peak, and duration estimates are based on measures of drug in the system and/or analgesic effect and have wide inter-subject variability. The onset, peak, and duration of adverse consequences to therapy, such as respiratory depression, may not be reflected in these estimates and have wide inter-subject variability.

Duration of the effect is dependent on the formulation of opioid use:

- Typically, short-acting (SA) formulations have a duration of 4-5 hours when given at effective doses, as listed below in **Table E.1**.
- Long-acting (LA) formulations typically have a duration of 12 hours except long-acting morphine (Kadian) which has a duration of 24 hours.
- These durations may be adjusted when considering person-specific factors.

Individual factors that might affect properties of opioids:

- For oral route: co-administration with other medications; gastrointestinal functioning (stasis, short-gut syndrome).
  - Long-acting formulations require an intact gut for optimal absorption.
- General factors: renal function, hepatic function, drug interactions, genetic polymorphisms that influence absorption and metabolism, and opioid tolerance or opioid naivety.

Table E.1: Selected Properties of Opioids for Single, As-Needed Doses[9,127]

Route	Drug	Onset of action	Peak effect
Oral	Morphine (SA) Hydromorphone (SA) Oxycodone (SA)	15 – 30 min	30 – 60 min
	Methadone	30 – 60 min	
SC	Morphine Hydromorphone	10 – 30 min	30 – 60 min
IV	Morphine Hydromorphone	1 – 10 min	10 – 20 min
Rectal	Morphine	15 – 30 min	20 – 60 min
	Methadone	10 – 30 min	1 – 4 hours
Buccal/sublingual/intranasal	Sufentanil Fentanyl	5 – 10 min	50 min

Adapted from Pharmacokinetics of Opioids – single as needed dose, Donna K. Buna (2020) and Appendix 4, Pallium Palliative Pocketbook ©Pallium Canada. All rights reserved.

Appendix F: Steps for Titrating Opioids

Steps	Example Calculation
Steps for titration.	Example calculation for a new long-acting (LA) scheduled and subcutaneous (SC) breakthrough doses (BTD). **Current dosing:** Scheduled: morphine LA 100mg PO Q12H Breakthrough: morphine 10mg SC Q1H PRN Used 6 SC morphine BTDs in past 24 hours. *Example illustrates titration considerations.*
1. Convert all doses to the equivalent of **one route** (e.g. PO).	Scheduled: morphine LA 100mg PO BTD: morphine 10mg SC is equivalent to morphine 20mg PO.
2. Calculate the total daily dose (TDD) for the past 24 hours adding all scheduled and breakthrough doses.	Scheduled doses (Q12H): 100mg x 2 = 200mg of PO morphine/24 hrs BTD (6 in last 24hrs): 20mg x 6 = 120mg of PO morphine/24 hrs **Total Daily Dose** 200mg + 120mg = morphine 320mg PO TDD
3. Calculate the new scheduled opioid dose* by dividing the number of doses within a 24H period based on dosage form and frequency selected.**	**New** Scheduled LA dose (Q12H): morphine 320mg PO (TDD) ÷ 2 = morphine LA 160mg PO Q12H
4. Increase the BTD proportionately when the scheduled dose is increased. Determine the new short-acting BTD (10% of TDD).*	BTD PO equivalent dose: morphine 320mg PO (TDD) x 0.1 = morphine 32mg PO
5. Convert dose to desired route of administration, if different from current route.	**New** BTD SC dose: morphine 32mg PO is equivalent† to morphine 16mg SC Q1H
6. New Dosing	**New dosing**: Scheduled: morphine LA 160mg PO Q12H BTD: morphine 15mg SC Q1H PRN *BTD adjusted considering available parenteral morphine preparations.*

** Dosing will need to be adjusted based on the availability of opioid preparations.*
*** See **Appendix A: End-Stage Renal & Liver Disease** for suggested dosing frequency due to organ failure.*
† Oral to parenteral dose ratio is generally 2:1, but there are circumstances, based on individual characteristics, which may require a 3:1 ratio.

Appendix G: Steps for Rotating Opioids[9]

Steps	Example Calculation
Example calculation: Rotation from long-acting (LA) oxycodone PO to hydromorphone SC. **Current dosing:** Scheduled: oxycodone LA 75mg PO Q12H BTD: oxycodone SA 15mg PO Q1H PRN Used 2 short-acting (SA) oxycodone breakthrough doses (BTDs) in past 24 hours.	
1. Determine the type and formulation of the new opioid.	New opioid: hydromorphone SC
2. Convert all current doses to the equivalent of **one route** (e.g. PO).	*Not applicable*
3. Calculate the total daily dose (TDD) for the past 24 hours adding all scheduled and breakthrough doses.	Scheduled doses (Q12H): 75mg x 2 = 150mg of PO oxycodone/24 hrs BTD (2 in last 24hrs): 15mg x 2 = 30mg of PO oxycodone/24 hrs **Total Daily Dose** 150mg + 30mg = oxycodone 180mg PO
4. Convert the TDD to the morphine equivalent using an equianalgesic conversion table.	TDD oxycodone 180 mg PO x 1.5 = morphine 270mg PO (TDD)
5. Calculate the equianalgesic dose of the new opioid using an equianalgesic conversion table.	*Using Table 2: Opioid Equianalgesic Conversion* morphine 270mg PO (TDD) ÷ 5 = hydromorphone 54mg PO (TDD)
6. **Reduce the equianalgesic dose by up to 25-50%** to account for incomplete cross-tolerance and other individual factors.* • Dose **conservatively** (e.g. 25-50% reduction) for factors increasing the person's frailty and risk of adverse effects. • Dose **more aggressively** (i.e. no reduction) in cases of symptom crisis.	*Using a conservative dose reduction of 25%.* 25% dose reduction: hydromorphone 54mg PO (TDD) x 0.75 = hydromorphone 40mg PO (TDD) *Note:* Dose reduction is **not** required when converting to fentanyl using **Table 5** as doses have already been reduced to account for incomplete cross tolerance.
7. Convert dose to desired route, if different from current route.	Oral to SC: hydromorphone 40mg PO (TDD) equivalent** to = hydromorphone 20mg SC (TDD)
8. Calculate the scheduled opioid dose† by dividing the number of doses within a 24H period based on dosage form and frequency.††	**New** Scheduled SC dose (Q4H): hydromorphone 20mg SC (TDD) ÷ 6 = hydromorphone 3.5mg SC Q4H
9. Determine the new short-acting BTD (10% of TDD).†	**New** BTD SC dose: hydromorphone 20mg SC (TDD) x 0.1 = hydromorphone 2mg SC
10. New dosing	**New dosing**: Scheduled: hydromorphone 3.5mg SC Q4H BTD: hydromorphone 2mg SC Q1H PRN

** Incomplete cross-tolerance: People who have been tolerant to morphine, for example, will be more sensitive/less tolerant when changed to hydromorphone particularly with initial dosing.[101]*
*** Oral to parenteral dose ratio is generally 2:1, but based on the individual, may require a 3:1 ratio.*
† Dosing will need to be adjusted based on the availability of opioid preparations.
*†† See **Appendix A: End-Stage Renal & Liver Disease** for suggested dosing frequency due to organ failure.*

REFERENCES

1. Government of Canada. Opioids, https://www.canada.ca/en/health-canada/services/opioids.html (2023).
2. Cherny N, Fallon M. Opioid therapy: Optimizing analgesic outcomes. In: Cherny N, Fallon M, Kaasa S, et al. (eds) Oxford Textbook of Palliative Medicine, 6th ed. Oxford: Oxford University Press, 2021.
3. Crush J, Levy N, Knaggs RD, et al. Misappropriation of the 1986 WHO analgesic ladder: the pitfalls of labelling opioids as weak or strong. Br J Anaesth 2022; 129: 137–142.
4. Lee C, Ye M, Weaver O, et al. Defining opioid naïve and implications for monitoring opioid use: A population-based study in Alberta, Canada. Pharmacoepidemiol Drug Saf; 33. Epub ahead of print 7 January 2024. DOI: 10.1002/pds.5693.
5. Lail S, Sequeira K, Lieu J, et al. Prescription of Opioids for Opioid-Naive Medical Inpatients. Can J Hosp Pharm; 67. Epub ahead of print 30 October 2014. DOI: 10.4212/cjhp.v67i5.1387.
6. Swarm RA, Paice JA, Anghelescu DL, et al. Adult Cancer Pain. Journal of the National Comprehensive Cancer Network 2019; 17: 977–1007.
7. Doulton B. Pharmacologic management of adult breakthrough cancer pain. Can Fam Physician 2014; 60: 1111–4, e585-9.
8. Tanaka R, Ishikawa H, Sato T, et al. Safety profile of prophylactic rescue dosing of immediate-release oral opioids in cancer patients. J Pharm Health Care Sci 2018; 4: 25.
9. Pallium Canada. Chapter 5: Pain. In: Pereira J (ed) Pallium Palliative Pocketbook. Ottawa, Canada: Pallium Canada, https://www.pallium.ca/mobile-app-pocketbook/ (2020).
10. Scottish Intercollegiate Guidelines Network. Scottish Intercollegiate Guidelines Network SIGN Control of pain in adults with cancer, www.sign.ac.uk/guidelines/published/numlist.html. (2008).
11. Mercadante S. Opioid titration in cancer pain: A critical review. European Journal of Pain 2007; 11: 823–830.
12. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol 2018; 29: iv166-91.
13. Dalal S, Bruera E. Pain Management for Patients With Advanced Cancer in the Opioid Epidemic Era. American Society of Clinical Oncology Educational Book 2019; 24–35.
14. Bramati PS, Bruera E. The end of the second step of the World Health Organization analgesic ladder? Annals of oncology 2022; 33: 1212–1213.
15. Johnson MJ, Currow DC. Opioids for breathlessness: a narrative review. BMJ Support Palliat Care 2020; 10: 287–295.
16. College of Physicians and Surgeons of BC. Drug programs, https://www.cpsbc.ca/registrants/programs/drug-programs (2024).
17. BC College of Nurses and Midwives. F: Prescribing Drugs. Scope of practice, https://www.bccnm.ca/NP/ScopePractice/part2/prescribing/Pages/Default.aspx (2024).
18. Lau J, Mazzotta P, Fazelzad R, et al. Assessment tools for problematic opioid use in palliative care: A scoping review. Palliat Med 2021; 35: 1295–1322.
19. National Institute for Health and Care Excellence. Palliative care for adults: strong opioids for pain relief. National Institute for Health and Care Excellence, https://www.nice.org.uk/guidance/cg140 (2016).

20. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA 1995; 274: 1870–3.
21. Wiffen PJ, Wee B, Derry S, et al. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev 2017; 7: CD012592.
22. Lau J, Mazzotta P, Whelan C, et al. Opioid safety recommendations in adult palliative medicine: a North American Delphi expert consensus. BMJ Support Palliat Care 2022; 12: 81–90.
23. Webster LR, Webster RM. Predicting Aberrant Behaviors in Opioid-Treated Patients: Preliminary Validation of the Opioid Risk Tool. Pain Medicine 2005; 6: 432–442.
24. British Columbia Centre on Substance Use (BCCSU). A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver, https://www.bccsu.ca/wp-content/uploads/2023/12/BC-OUD-Treatment-Guideline_2023-Update.pdf (2023).
25. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 2014; 160: 38–47.
26. Hinkin CH, Castellon SA, Dickson-Fuhrman E, et al. Screening for Drug and Alcohol Abuse Among Older Adults Using a Modified Version of the CAGE. Am J Addict 2001; 10: 319–326.
27. Cheatle MD, Compton PA, Dhingra L, et al. Development of the Revised Opioid Risk Tool to Predict Opioid Use Disorder in Patients with Chronic Nonmalignant Pain. J Pain 2019; 20: 842–851.
28. Straube C, Derry S, Jackson KC, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. Cochrane Database of Systematic Reviews; 2018. Epub ahead of print 19 September 2014. DOI: 10.1002/14651858.CD006601.pub4.
29. Pruskowski J, Arnold RM, Greenfield A. Tramadol in palliative care. American Medical Association, https://www.mypcnow.org/fast-fact/tramadol-in-palliative-care/ (1 February 2019).
30. Portenoy R, Mehta Z, Ahmed E. Cancer pain management with opioids: Optimizing analgesia. UptoDate, https://www.uptodate.com/contents/cancer-pain-management-with-opioids-optimizing-analgesia?topicRef=2792&source=see_link (2023).
31. Jones KF. Buprenorphine Use in Palliative Care. Journal of Hospice and Palliative Nursing 2019; 21: 540–547.
32. World Health Organization. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Place of publication not identified: World Health Organization, https://www.who.int/publications/i/item/9789241550390 (2018).
33. UpToDate. Fentanyl: Drug information, https://www.uptodate.com/contents/fentanyl-drug-information?search=transdermal%20fentanyl&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2#F170570 (2024).
34. Brant J, Rodgers B, Gallagher E, et al. Breakthrough Cancer Pain: A Systematic Review of Pharmacologic Management
. Clin J Oncol Nurs 2017; 21: 71–80.
35. Mercadante S. Switching methadone: a 10-year experience of 345 patients in an acute palliative care unit. Pain Medicine. Epub ahead of print 2012. DOI: 10.1111/j.1526-4637.2012.01334.x.
36. Sugiyama Y, Sakamoto N, Ohsawa M, et al. A Retrospective Study on the Effectiveness of Switching to Oral Methadone for Relieving Severe Cancer-Related Neuropathic Pain and Limiting Adjuvant Analgesic Use in Japan. J Palliat Med 2016; 19: 1051–1059.
37. González-Barboteo J, Porta-Sales J, Nabal-Vicuña M, et al. Switching Ratio from Parenteral to Oral Methadone 1:1.2 Is Safer Compared with Ratio 1:2 in Patients with Controlled Cancer Pain: A Multicenter Randomized-Controlled Trial (RATIOMTD-010810). J Palliat Med 2021; 24: 382–390.
38. College of Physicians and Surgeons of British Columbia. Methadone for Analgesia. 2022.

39. BC Guidelines, BC Cancer Agency. Palliative Care for the Patient with Incurable Cancer or Advanced Disease - Part 2: Pain and Symptom Management. Province of British Columbia, https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/palliative-pain-management?keyword=palliative&keyword=care&keyword=guideline#pain-scope (2017).
40. Branford R, Wighton E, Ross J. Principles of opioid therapy: Focus on opioids. In: Cherny N, Fallon M, Kaasa S, et al. (eds) Oxford Textbook of Palliative Medicine, 5th ed. Oxford: Oxford University Press, https://academic.oup.com/book/37029 (2015).
41. Kobierski B. The 3 "B's" of symptom control during opioid therapy. Surrey, BC, 2006.
42. Schmidt-Hansen M, Bennett MI, Arnold S, et al. Oxycodone for cancer-related pain. Cochrane Database Syst Rev; 8. Epub ahead of print 22 August 2017. DOI: 10.1002/14651858.CD003870.PUB6.
43. Li Y, Ma J, Lu G, et al. Hydromorphone for cancer pain. Cochrane Database of Systematic Reviews; 2021. Epub ahead of print 5 August 2021. DOI: 10.1002/14651858.CD011108.pub3.
44. Guo KK, Deng CQ, Lu GJ, et al. Comparison of analgesic effect of oxycodone and morphine on patients with moderate and advanced cancer pain: A meta-analysis. BMC Anesthesiol; 18. Epub ahead of print 24 September 2018. DOI: 10.1186/s12871-018-0583-8.
45. Davis MP, Lasheen W, Gamier P. Practical guide to opioids and their complications in managing cancer pain. What oncologists need to know. Oncology (Williston Park) 2007; 21: 1229–1238.
46. College of Physicians and Surgeons of British Columbia. Practice Standard: Safe Prescribing of Opioids and Sedatives, https://www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf (2022).
47. Waterman BL, Ramsey SU, Whitsett MP, et al. Top Ten Tips Palliative Care Clinicians Should Know About End-Stage Liver Disease. J Palliat Med 2021; 24: 924–931.
48. Soleimanpour H, Safari S, Nia KS, et al. Opioid Drugs in Patients With Liver Disease: A Systematic Review. Hepat Mon; 16. Epub ahead of print 6 March 2016. DOI: 10.5812/HEPATMON.32636.
49. Hughes LT, Raftery D, Coulter P, et al. Use of opioids in patients with cancer with hepatic impairment—a systematic review. BMJ Support Palliat Care 2022; 12: 152–157.
50. Sande TA, Laird BJA, Fallon MT. The use of opioids in cancer patients with renal impairment—a systematic review. Supportive Care in Cancer 2017; 25: 661–675.
51. Lee KA, Ganta N, Horton JR, et al. Evidence for neurotoxicity due to morphine or hydromorphone use in renal impairment: A systematic review. J Palliat Med 2016; 19: 1179–1187.
52. Owsiany MT, Hawley CE, Triantafylidis LK, et al. Opioid Management in Older Adults with Chronic Kidney Disease: A Review. American Journal of Medicine 2019; 132: 1386–1393.
53. Brecher DB, West TL. Pain management in a patient with renal and hepatic dysfunction. J Palliat Med 2014; 17: 249–252.
54. Fine PG. Treatment Guidelines for the Pharmacological Management of Pain in Older Persons. Pain Medicine 2012; 13: S57–S66.
55. Sobanski PZ, Alt-Epping B, Currow DC, et al. Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement. Cardiovasc Res 2020; 116: 12–27.
56. Kawaguchi J, Hamatani Y, Hirayama A, et al. Experience of morphine therapy for refractory dyspnea as palliative care in advanced heart failure patients. J Cardiol 2020; 75: 682–688.
57. Nakamura T, Nakamura M, Kai M, et al. Clinical Use of Oral Opioid Therapy for Dyspnea in Patients With Advanced Heart Failure - A Single-Center Retrospective Study. Circ Rep 2023; 5: 351–357.

58. Connolly M, Ryder M. Consideration of Symptom Management in Advanced Heart Failure. Int J Environ Res Public Health 2022; 19: 15160.
59. Mahler DA, Selecky PA, Harrod CG. Management of dyspnea in patients with advanced lung or heart disease: practical guidance from the American college of chest physicians consensus statement. Pol Arch Med Wewn 2010; 120: 160–166.
60. Marciniuk DD, Goodridge D, Hernandez P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. Can Respir J 2011; 18: 69–78.
61. Rajnoveanu R-M, Harangus A, Todea DA, et al. Opioids in Treatment of Refractory Dyspnea in Chronic Obstructive Pulmonary Disease: Yes, No or Maybe. J Pers Med 2024; 14: 318.
62. López-Saca JM, Guzmán JL, Centeno C. A systematic review of the influence of opioids on advanced cancer patient survival. Curr Opin Support Palliat Care 2013; 7: 424–430.
63. BC Renal. Renal Analgesic Brochure, http://www.bcrenal.ca/resource-gallery/Documents/Renal-Analgesic-Brochure.pdf (2011).
64. Smith GL, Lichtman JH, Bracken MB, et al. Renal Impairment and Outcomes in Heart Failure. J Am Coll Cardiol 2006; 47: 1987–1996.
65. Bennett MI, Graham J, Schmidt-Hansen M, et al. Prescribing strong opioids for pain in adult palliative care: summary of NICE guidance. BMJ 2012; 344: e2806–e2806.
66. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database Syst Rev; 4. Epub ahead of print 22 April 2016. DOI: 10.1002/14651858.CD003868.PUB4.
67. Treillet E, Laurent S, Hadjat Y. Practical management of opioid rotation and equianalgesia. J Pain Res 2018; Volume 11: 2587–2601.
68. Portenoy RK, Mehta Z, Ahmed E. Prevention and management of side effects in patients receiving opioids for chronic pain. UpToDate, https://www.uptodate.com/contents/prevention-and-management-of-side-effects-in-patients-receiving-opioids-for-chronic-pain (2024).
69. Smith A, Farrington M, Matthews G. Monitoring sedation in patients receiving opioids for pain management. J Nurs Care Qual 2014; 29: 345–353.
70. Portenoy RK, Ahmed E. Principles of Opioid Use in Cancer Pain. Journal of Clinical Oncology 2014; 32: 1662–1670.
71. Federation of State Medical Boards. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain, https://pcssnow.org/wp-content/uploads/2013/10/FSMB-Model-Pain-Policy_July-2013.pdf (2013).
72. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies Comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for Assessment of Pain Intensity in Adults: A Systematic Literature Review. J Pain Symptom Manage 2011; 41: 1073–1093.
73. Vozoris NT. Opioid utility for dyspnea in chronic obstructive pulmonary disease: A complicated and controversial story. Annals of Cardiothoracic Surgery 2020; 9: 571–578.
74. Tsukuura H, Nishimura K, Taniguchi H, et al. Opioid use in end-of-life care in patients with interstitial pneumonia associated with respiratory worsening. J Pain Palliat Care Pharmacother 2013; 27: 214–219.
75. Lee MO, Lee M, Silverman S, et al. A Comprehensive Review of Opioid-Induced Hyperalgesia. Pain Physician 2011; 14: 145–161.
76. Lu E, Schell JO, Koncicki HM. Opioid Management in CKD. American Journal of Kidney Diseases 2021; 77: 786–795.

77. Zhuo M, Triantafylidis LK, Li J, et al. Opioid Use in the Nondialysis Chronic Kidney Disease Population. Seminars in Nephrology 2021; 41: 33–41.
78. Naples JG, Gellad WF, Hanlon JT. The Role of Opioid Analgesics in Geriatric Pain Management. Clin Geriatr Med 2016; 32: 725–735.
79. Pruskowski J, Wright R, Pharmd NS, et al. Safety Considerations When Using Opioids for Older Adults, https://www.mypcnow.org/fast-fact/safety-considerations-when-using-opioids-for-older-adults/ (2018).
80. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane Reviews. Cochrane Database of Systematic Reviews; 2017. Epub ahead of print 30 October 2017. DOI: 10.1002/14651858.CD012509.pub2.
81. Pasero C. Assessment of sedation during opioid administration for pain management. J Perianesth Nurs 2009; 24: 186–190.
82. Hall KR, Stanley AY. Literature Review: Assessment of Opioid-related Sedation and the Pasero Opioid Sedation Scale. J Perianesth Nurs 2019; 34: 132–142.
83. Nisbet AT, Mooney-Cotter F. Comparison of selected sedation scales for reporting opioid-induced sedation assessment. Pain Manag Nurs 2009; 10: 154–164.
84. Davis C, Geik C, Arthur K, et al. A Multisite Retrospective Study Evaluating the Implementation of the Pasero Opioid-Induced Sedation Scale (POSS) and Its Effect on Patient Safety Outcomes. Pain Management Nursing 2017; 18: 193–201.
85. Dunwoody C, Arnold R. Using Naloxone. Fast Facts: Palliative Care Network of Wisconsin, https://www.mypcnow.org/fast-fact/using-naloxne/ (2019).
86. Vignaroli E, Bennett MI, Nekolaichuk C, et al. Strategic pain management: the identification and development of the IAHPC opioid essential prescription package. J Palliat Med 2012; 15: 186–191.
87. Cheng CW, Kwok AOL, Bian ZX, et al. A cross-sectional study of constipation and laxative use in advanced cancer patients: insights for revision of current practice. Support Care Cancer 2013; 21: 149–156.
88. Clemens KE, Faust M, Jaspers B, et al. Pharmacological treatment of constipation in palliative care. Curr Opin Support Palliat Care 2013; 7: 183–191.
89. Larkin P, Sykes N, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med 2008; 22: 796–807.
90. Sykes N. Emerging evidence on docusate: commentary on Tarumi et al. J Pain Symptom Manage 2013; 45: 1.
91. Portenoy RK, Mehta Z, Ahmen E. Cancer pain management: General principles and risk management for patients receiving opioids. UptoDate, https://www.uptodate.com/contents/cancer-pain-management-general-principles-and-risk-management-for-patients-receiving-opioids#! (2023).
92. Larkin P. Constipation and diarrhoea. In: Cherny N, Fallon M, Kaasa S, et al. (eds) Oxford Textbook of Palliative Medicine, 6th ed. Oxford: Oxford University Press, https://doi.org/10.1093/med/9780198821328.003.0054 (2021).
93. Caraccia Economou D. Bowel management: Constipation, diarrhea, obstruction, and ascites. In: Oxford Textbook of Palliative Nursing. Oxford University Press, 2015, pp. 217–236.
94. Wiffen P. Palliative Care Formulary, 5th edition. European Journal of Hospital Pharmacy 2015; 22: 182–182.
95. Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med 2008; 22: 796–807.

96. Clemens KE, Faust M, Jaspers B, et al. Pharmacological treatment of constipation in palliative care. Curr Opin Support Palliat Care 2013; 7: 183–191.
97. Droney J, Ross J, Gretton S, et al. Constipation in cancer patients on morphine. Supportive Care in Cancer 2008; 16: 453–459.
98. Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association Technical Review on Constipation. Gastroenterology 2013; 144: 218–238.
99. Godwin B, Frank C, Molnar F, et al. Identification and management of opioid-induced neurotoxicity in older adults. Can Fam Physician 2022; 68: 269–270.
100. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain; 10. Epub ahead of print 2009. DOI: 10.1016/J.JPAIN.2008.10.008.
101. Downing M, Wainwright W. Medical care of the dying. 4th ed. Victoria Hospice Society, 2006.
102. Grond S, Radbruch L, Lehmann KA. Clinical Pharmacokinetics of Transdermal Opioids. Clin Pharmacokinet 2000; 38: 59–89.
103. Paice JA, Bohlke K, Barton D, et al. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. Journal of Clinical Oncology 2023; 41: 914–930.
104. Reddy A, Yennurajalingam S, Reddy S, et al. The Opioid Rotation Ratio From Transdermal Fentanyl to “Strong” Opioids in Patients With Cancer Pain. J Pain Symptom Manage 2016; 51: 1040–1045.
105. Reddy A, Yennurajalingam S, Pulivarthi K, et al. Frequency, Outcome, and Predictors of Success Within 6 Weeks of an Opioid Rotation Among Outpatients with Cancer Receiving Strong Opioids. Oncologist 2013; 18: 212–220.
106. Fine PG, Portenoy RK. Establishing “Best Practices” for Opioid Rotation: Conclusions of an Expert Panel. J Pain Symptom Manage 2009; 38: 418–425.
107. Schuster M, Bayer O, Heid F, et al. Opioid rotation in cancer pain treatment - A systematic review. Dtsch Arztebl Int 2018; 115: 135–142.
108. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database of Systematic Reviews 2004; 3: CD004847.
109. Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. Palliat Med 2011; 25: 504–515.
110. Sandoz Canada Inc. Product Monograph Sandoz Fentanyl Patch, https://pdf.hres.ca/dpd_pm/00055220.PDF (2020).
111. Davis MP, Glare P, Hardy J. Opioids in cancer pain. 1st ed. New York;Oxford; Oxford University Press, 2005.
112. Sandoz Canada Inc. Product Monograph Sandoz Fentanyl Patch, https://pdf.hres.ca/dpd_pm/00055220.PDF (2020).
113. Ljuca D, Husić S. Treatment of severe cancer pain by transdermal fentanyl. Biomolecules & biomedicine 2010; 10: 158–164.
114. Adams D, Bhakta B, Gunyea I. Retrospective Assessment of Frequency of Dosing of Sustained Release Opiate Preparations in Chronic Pain Patients. Pain Med 2002; 3: 185.
115. UpToDate. Fentanyl: Drug information, https://www.uptodate.com/contents/fentanyl-drug-information?search=transdermal%20fentanyl&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2#F170570 (2024).
116. Jones W, Junkins S, Rosielle D. Tapering Opioids in Patients With Serious Illness: How To Taper. Palliative Care Network of Wisconsin, https://www.mypcnow.org/wp-content/uploads/2021/01/FF-414-How-to-taper-opioids.pdf (2021).

117. RXFiles. Opioid Tapering Template, https://www.rxfiles.ca/rxfiles/uploads/documents/opioid-taper-template.pdf (2017).
118. Lau J, Zimmermann C, Selby P, et al. Opioid Disposal Practices of Patients With Life-Limiting Cancers in an Outpatient Palliative Care Clinic: A Cross-Sectional Study. J Palliat Med 2023; 26: 816–825.
119. Reddy A, de la Cruz M. Safe Opioid Use, Storage, and Disposal Strategies in Cancer Pain Management. Oncologist 2019; 24: 1410–1415.
120. Nathan S, Deamant CD. Medication disposal #286. J Palliat Med 2015; 18: 82–83.
121. Davison SN. Clinical pharmacology considerations in pain management in patients with advanced kidney failure. Clinical Journal of the American Society of Nephrology 2019; 14: 917–931.
122. BC Renal. Preferred Medications in Chronic Kidney Disease, http://www.bcrenal.ca/resource-gallery/Documents/Preferred-Medications.pdf.
123. Wilcock A, Charlesworth S, Prentice W, et al. Prescribing in Chronic Severe Hepatic Impairment. J Pain Symptom Manage 2019; 58: 515–537.
124. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of Opioids in Liver Disease. Clin Pharmacokinet 1999; 37: 17–40.
125. Carr D. Management of acute pain in adults with opioid use disorder. UpToDate, https://www.uptodate.com/contents/management-of-acute-pain-in-adults-with-opioid-use-disorder (2023).
126. Registered Nurses' Association of Ontario. Assessment and Management of Pain. 3rd edition. 2013.
127. Buna D. Pharmacokinetics of Opioids – single as needed dose. 2020.