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- Hospice Palliative Care Program
Symptom Guidelines

Principles Of Opioid Management

Principles Of Opioid Management

□ Rationale

This guideline is adapted for inter-professional primary care providers working in various settings in Fraser Health, British Columbia and the Fraser Valley Cancer Centre and any other clinical practice setting in which a user may see the guidelines as applicable.

□ Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of pain and requiring the use of opioid medication to control the pain. This guideline does not address disease specific approaches in the management of pain.

□ Definition of Terms

Opioid refers to drugs with morphine like actions, both natural and synthetic. Examples of opioids are: codeine, morphine, hydromorphone, oxycodone, fentanyl and methadone.⁽¹⁾

- **Short acting opioid** medications are also called immediate release (IR). These can come in oral, suppository, gel or parenteral formulations.⁽²⁾
- **Long acting opioid** medications are also called sustained release (SR), controlled release (CR) or extended release (ER). These can come in oral or transdermal formulations.⁽¹⁾
- **Total Daily Dose (TDD)** is the 24 hour total of a drug that is taken for regular and breakthrough doses.⁽²⁾
- **Steady state** is when the rate of drug availability and elimination equal one another.⁽¹⁾
- **Breakthrough Dose (BTD)** is an additional dose used to control breakthrough pain (a transitory flare of pain that occurs on a background of relatively well controlled baseline pain). It does not replace or delay the next routine dose. BTD is also known as a rescue dose.⁽²⁾

Opioid titration has traditionally been referred to as adjusting the dosage of an opioid.^(3, 4) It requires regular assessment of the patient's pain, when and why it occurs as well as the amount of medication used in the previous 24 to 72 hour period.⁽²⁾

Opioid rotation is switching one opioid for another. It is required for patients with inadequate pain relief and / or intolerable opioid related toxicities or adverse effects.^(1, 5)

Definition of Terms continued...

Opioid withdrawal occurs when an opioid is discontinued abruptly. Withdrawal symptoms last for a few days and are generally the opposite of symptoms exhibited when the opioid was started.⁽¹⁾

Opioid naïve patient refers to an individual who has either never had an opioid or who has not received repeated opioid dosing for a 2 to 3 week period.⁽⁶⁾

Opioid tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effect over time.^(7, 8) It is a known pharmacologic effect of opioids.⁽⁸⁾ Tolerance to the analgesic effects of opioids is relatively uncommon.⁽⁷⁾

Physiologic dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and / or administration of an antagonist.⁽⁸⁾

Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving.⁽⁹⁾

Non-Opioid is a term used to describe drugs that are structurally and functionally unrelated to opioids but whose primary indication is for the treatment of pain.⁽¹⁰⁾ Examples are: acetaminophen, acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs).⁽¹⁾

Adjuvant analgesics (sometimes known as co-analgesics) are medications whose primary indication lies elsewhere, but which have been found to be beneficial in the management of some types of pain. Commonly used adjuvants are: corticosteroids, anti-psychotics, radiation, anti-convulsants and bisphosphonates. Other adjuvant therapies used include intrathecal and epidural analgesia, nerve blocks and surgery.⁽¹⁾

□ Standard of Care

- | | |
|--|--|
| 1. Opioid Principles | 7. Routes of Administration of Opioids |
| 2. Screen for Sensitivity or Allergy to Specific Opioids | 8. Adverse Effects of Opioids |
| 3. Assessment of Pain | 9. Opioid Titration |
| 4. Diagnosis | 10. Use of Long Acting Opioids |
| 5. Pain Management | 11. Opioid Rotation |
| 6. Treatment with Opioids | 12. Opioid Withdrawal |
| | 13. Treatment: Pharmacological |

Recommendation 1 Principles

- Opioids can and should be used for both cancer and non-cancer pain where other measures, including non-opioid analgesics, are insufficient to control debilitating pain.⁽¹¹⁾
- Opioids are the drugs of choice for moderate to severe pain associated with advanced illness.⁽¹²⁻¹⁶⁾
- When the pain is only mild to moderate but expected to worsen, starting a stronger opioid may avoid another drug switch.⁽¹⁾
- Long-acting or sustained-release analgesic preparations should be used for continuous pain.⁽¹⁶⁾
- Medical use of opioids for pain associated with advanced illness rarely, if ever, leads to drug abuse or opioid addiction.⁽¹³⁾
- There is no ceiling or maximal recommended dose for strong opioids.⁽¹⁵⁾ Large doses may be needed to manage pain associated with advanced illness.^(8, 17)
- Use oral route whenever possible.⁽¹⁸⁾ There is no perfect route of administration; the plan must be individualized to the patient and the setting.⁽¹⁾
- When writing opioid orders, remember to order medications to cover the 3 “B’s” – Bowels, “Barfing” and Breakthrough.^(2, 16, 17, 19)
- Consider opioid rotation if there are adverse effects from, or tolerance to, the current opioid.⁽²⁾
- It is not recommended to administer two different opioids (e.g., regular morphine with codeine or hydromorphone for breakthrough) at the same time⁽²⁰⁾ unless the duration of relief desired is not able to be achieved with one. For example, using IR opioids with fentanyl patches or sufentanil for incident pain when using long acting (SR) opioids.
- Meperidine has little use in the management of chronic pain and is rarely used in the palliative setting.^(15, 21)
- Opioid use does not shorten survival.⁽¹⁶⁾
- Documentation of the use of opioids contributes to appropriate dosing and pain control.⁽²²⁾

Recommendation 2 Screen for Sensitivity or Allergy to Specific Opioid

- Most “allergies” to morphine are not true allergies but adverse effects.⁽¹³⁾
- The only absolute contraindication to the use of an opioid is a history of a hypersensitivity reaction.⁽¹⁶⁾
- Opioids cause histamine release with subsequent itch and rash, which is sometimes mistaken for an allergic reaction.⁽¹³⁾
- Patients allergic to one opioid are not likely to be allergic to another opioid in a different structural class.

Recommendation 2 Screen for Sensitivity or Allergy to Specific Opioid continued...

- If there is a true history of allergy to codeine or morphine (natural occurring opioids), a semi-synthetic opioid (such as hydromorphone or oxycodone) or a synthetic opioid (such as fentanyl or methadone) may be cautiously tried with appropriate precautions.⁽¹⁷⁾ The prevalence of true allergic reactions to synthetic opioids may be lower.⁽¹⁶⁾
- Education of and appropriate management of possible adverse effects of opioids help to avoid situations where patients and / or families assume that they are “allergic” or can never take a drug again.⁽²⁾

Recommendation 3 Assessment of Pain

Ongoing comprehensive assessment is the foundation of effective management of pain using opioids, including interview, physical assessment, medication review, medical and surgical review, psychosocial review and review of physical environment.⁽¹⁶⁾ Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.

See *Fraser Health Hospice Palliative Care Symptom Guidelines for Pain Management Principles at the End of Life* for direction on pain assessment.

Assess patient and family fears and barriers around the use of opioids.^(7, 16, 23)

Recommendation 4 Diagnosis

Management should include treating reversible causes where possible and desirable according to the goals of care. The most significant intervention in the management of pain is identifying underlying cause(s) and treating as appropriate. While underlying cause(s) may be evident, treatment of pain is always indicated, no matter what the stage of disease or while investigations are ongoing.⁽¹⁾

See *Fraser Health Hospice Palliative Care Symptom Guidelines for Pain Management Principles at the End of Life* for direction in diagnosing pain.

Whether or not the underlying cause(s) can be relieved or treated, all patients will benefit from management of the symptom using education or medication.

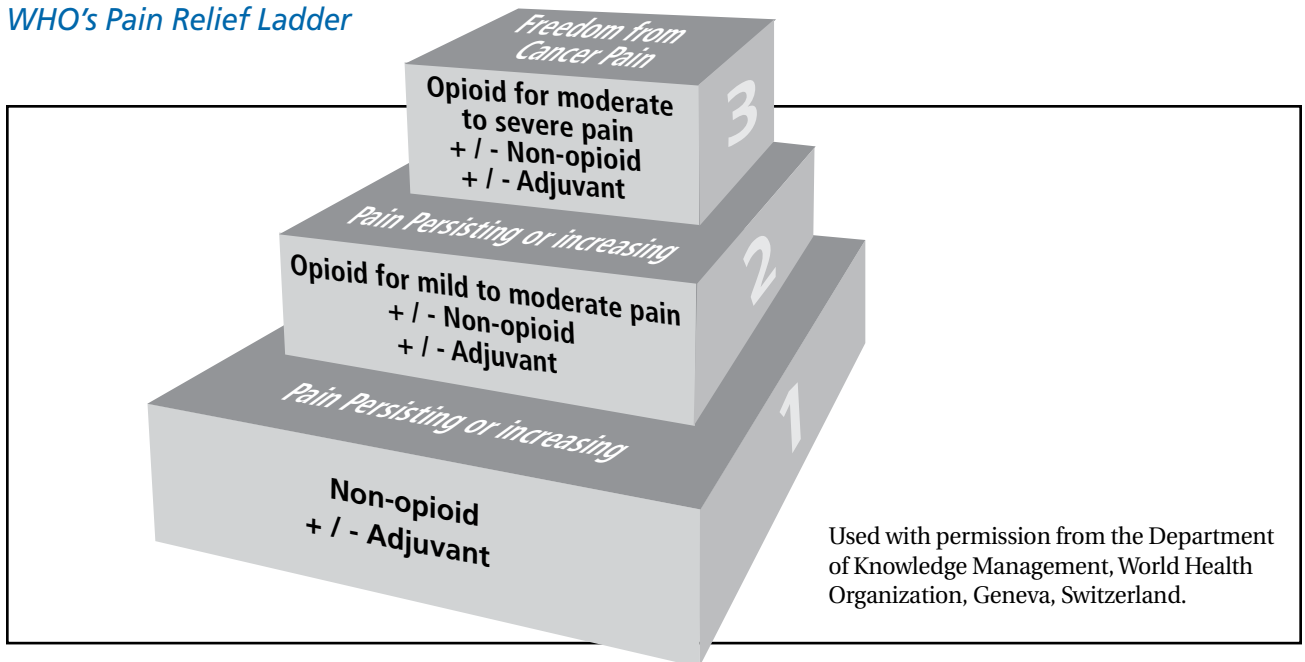
Identifying the underlying etiology of pain is essential in determining the interventions required.

Recommendation 5 Pain Management

World Health Organization’s (WHO) Pain Relief Ladder for Cancer Pain⁽¹⁸⁾

If pain occurs, there should be prompt oral administration of drugs in the following order: non-opioids (aspirin and acetaminophen); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. Adjuvant drugs should be used for specific pain etiologies. To maintain freedom from pain, drugs should be given “by the clock”, that is every 3 to 6 hours, rather than “on demand”. This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80 to 90% effective.⁽¹⁸⁾

WHO’s Pain Relief Ladder



Step One: for very mild pain a non-opioid analgesic (such as acetaminophen or ASA) may be adequate.^(7, 18)

Step Two: if the pain is moderately severe a weak opioid plus or minus appropriate adjuvant agent(s) may provide adequate analgesia.^(7, 18)

Step Three: for severe pain, or when it is expected that pain will become severe, it is best to start with a low dose of a strong opioid and titrate up the dose according to effect.^(7, 18)

A weak opioid is one that has a ceiling effect, which may be due to a low affinity for opioid receptor sites.⁽¹⁾

Recommendation 5 Pain Management continued...

The W.H.O Principles can be summed up as follows:⁽⁷⁾

- **By mouth** oral route is the route of administration of choice.
- **By the clock** analgesic medications for moderate to severe pain should be given on a fixed dose schedule, not on an as needed basis.
- **By the ladder** analgesics given per the W.H.O three step ladder.
- **For the individual** the dosage must be titrated against the particular patient's pain.
- **Use of adjuvants** to enhance analgesic effects, to control adverse effects of opioids and to manage symptoms that are contributing to the patient's pain (anxiety, depression or insomnia).
- **Attention to detail** determine what the patient knows, believes and fears about the pain and things that can relieve it. Give precise instructions for taking the medication.

Recommendation 6 Treatment with Opioids

Commonly used first line oral opioids include codeine, morphine, hydromorphone, and oxycodone. They share the following characteristics:

- Half-life of immediate release preparations is 2 to 4 hours with duration of analgesic effect between 4 to 5 hours when given at effective doses.^(1, 8, 16)
- Sustained release formulations have duration of analgesic effect of 8 to 12 hours.⁽¹⁶⁾
- Equianalgesic doses need to be calculated when switching from one drug to another, when changing routes of administration or both.⁽¹⁾
- An equianalgesic table should be used as a guide in dose calculation. Due to incomplete cross-tolerance clinicians should consider reducing the dose by 20 to 25% when ordering.⁽¹⁾

Principles Of Opioid Management

Comparison of Available Opioids:

Opioid	Codeine	Oxycodone	Morphine	Hydromorphone	Fentanyl
Immediate release preparations	15, 30 mg IR tablet Liquid: 5 mg per mL	5, 10, 20 mg IR tab Liquid: N/A	5, 10, 30 mg IR tab Liquid: 1, 5, 10, 20, 50 mg per mL	1, 2, 4, 8 mg IR tab Liquid: 1 mg per mL	No IR tablet ** Parenteral solution may be given as sublingual dose
Sustained release preparations	50,100,150, 200 mg SR tablets	5, 10, 20, 40, 80 mg SR tablets	12 Hour formulations: 10, 15, 30, 60, 100, 200 mg SR 24 Hour formulations: 10, 20, 50,100 mg capsule	3, 6, 12, 18, 24, 30 mg SR capsules	12, 25, 50, 75, 100 mcg patch
Rectal	No suppository	No suppository	5, 10, 20, 30 mg suppositories	3 mg suppository	No suppository
Parenteral	30,60 mg/mL	No injection	2, 10, 15, 25, 50 mg/mL injection	2, 10, 50 mg/mL injection	50 mcg/mL injection
Relative potency: compared to 10 mg PO Morphine	PO:1 mg NOTE: 10 mg morphine =100 mg codeine	PO: 6.7 mg	PO: 10 mg Parenteral: 5 mg	PO: 2 mg S.C., I.V.: 1 mg	50 to 100 mcg when administered sublingually
Opioid Class	Naturally occurring	Naturally occurring	Semi-synthetic	Semi-synthetic	Synthetic
Comments:	<ul style="list-style-type: none"> • Ceiling effect at 360- 600 mg • Ineffective analgesic in 10 percent of Caucasians as they lack an enzyme to convert codeine to morphine.^(1, 13, 14, 21) 		<ul style="list-style-type: none"> • In renal failure metabolites may accumulate to toxic levels.⁽¹⁾ 	<ul style="list-style-type: none"> • Lower incidence of pruritus, sedation and nausea and vomiting.⁽¹⁾ 	Half-life is 2 to 4 hours with duration of analgesic action between 30 minutes and 4 hours **See Appendix A

Recommendation 6 Treatment with Opioids continued...
Fentanyl Information (See Appendix A):

- Fentanyl is 80 to 100 times more potent than morphine.^(1, 14)
- A recent study reported less constipation and somnolence in patients using transdermal fentanyl compared to those using SR morphine.⁽¹⁾
- Fentanyl's high lipophilic properties provide a sufficient sublingual bioavailability of 90%, thus making it a suitable opioid for use sublingually.⁽¹⁾
- Transdermal patches may not be appropriate for patients with fever, diaphoresis, cachexia, morbid obesity, ascites or opioid-naïve patients.⁽¹⁶⁾ These conditions may have a significant effect on the absorption, blood levels and clinical effects of the drug.⁽¹⁶⁾
- Used fentanyl patches may contain enough residual drug to cause serious problems for children, opioid-naïve patients and pets.⁽¹⁾ Ensure they are disposed of properly, (needle disposal container, incineration, or flushing).

Sufentanil Information:

- Sufentanil is 5 to 10 times more potent than fentanyl.⁽¹⁾
- Injectable sufentanil (like fentanyl) is readily absorbed through the mucous membranes.⁽¹⁾
- Its early onset of action of about 5 to 10 minutes, when used sublingually, makes it ideal for incident pain control. It provides a peak analgesic effect of 15 to 30 minutes, duration of the analgesic effect of 30 to 40 minutes. Use for incident pain control, dosing 10 to 15 minutes prior to the painful event.⁽¹⁾
- Patients need to be able to hold the solution in their mouth for 2 minutes to have transmucosal absorption occur. If swallowed onset of action will be delayed due to slower gastrointestinal absorption rate.⁽¹⁾
- Initial dose titration with sufentanil should be approached cautiously in opioid naïve patients or for patients on low doses of opioids, as the dose of 6.25 mcg provides a wide range of approximate dose equivalency of 6.25 to 20 mg of oral morphine.^(32,33,34) Many patients tolerate an initial dose of 12.5 mcg. If it is felt that sufentanil may be too potent to use for patient taking low doses of opioids fentanyl could be alternatively considered.⁽¹⁾

Methadone Information (See Appendix B):

- The complexity in prescribing methadone prevent it being a first-line opioid.⁽¹⁾
- The initiation of or switch to methadone for advanced cancer-related pain should be restricted to experienced physicians to avoid inadvertent over or under dosing.⁽⁵⁾
- When converting to methadone dose reduction of 75 to 90% should be considered.⁽¹⁶⁾
- See Appendix B for further methadone information.

Recommendation 6 Treatment with Opioids continued...
Tramadol Information (See Appendix C):

- Is a synthetic opioid with analgesia provided via a weak OP3 (mu) receptor effect, and via inhibition of serotonin and noradrenaline reuptake.⁽³¹⁾ Appears to provide neuropathic pain benefit.^(28,31,36)
- Has a low incidence of constipation, nausea and dizziness compared to other opioids.⁽³⁰⁾ It has no major cardiovascular or blood pressure effects^(30,31) and a low risk of respiratory depression.^(28,32) May cause seizures; use cautiously in patients with epilepsy, head trauma, brain metastases, metabolic disorders, alcohol or drug withdrawal, CNS infections and with concurrent interacting drugs, e.g. SSRI's, TCAs, other opioids.^(30,32,34,35)
- Tramadol is used for moderate pain, and is considered a step 2 analgesic on the World Health Organization 3 step ladder,^(30,35) with a ceiling effect due to increasing seizure risk when dose exceeds 400 mg daily.^(31,34,35)
- While tramadol is used in 8% of European palliative care units,⁽²⁹⁾ it's role in Canada remains to be established. Became available in Canada as a single entity product, December 2006, as a once daily extended release tablet in 150, 200, 300 and 400 mg strengths.⁽³⁴⁾
- Tramadol is also available in combination with acetaminophen, each tablet contains 37.5 mg tramadol with 325 mg acetaminophen, and is licensed for pain treatment of five days or less. Dose 1 to 2 tablets q6h to a maximum of 8 tablets daily.⁽³³⁾

Recommendation 7 Routes of Administration of Opioids

- Patients in the last days and weeks of life often require more than one route of administration.⁽¹⁶⁾
- Repeated intramuscular administration of opioids is excessively noxious to palliative care patients and should be avoided.^(14, 16-18)
- The duration of action of most drugs is approximately equal to the half-life. Effective duration of action may be shortened in the younger patient and more prolonged in the elderly.⁽¹⁾
- **The oral route is the preferred route** in most palliative care settings.^(1, 7, 13, 16, 23) Maximal analgesia is reached at 1.5 to 2 hours for IR preparations,⁽¹⁾ 3 to 4 hours for SR preparations and for methadone.⁽²⁾
- The rectal route has more rapid absorption, within about 10 minutes, and a similar pattern of duration when compared to the oral route. It is not reliable secondary to the amount and consistency of stool in the rectum.^(2, 7, 23)
 - The oral to rectal relative potency is 1:1.^(14, 17)
 - The rectal route should be avoided in patients with rectal or anal lesions^(7, 23) or

Recommendation 7 Routes of Administration of Opioids continued...

who are neutropenic or thrombocytopenic.⁽¹⁷⁾

- Opioids can be placed in colostomies if the flow of effluent is slow enough to allow absorption.⁽¹⁷⁾
- Parenteral routes:
 - Subcutaneous and intramuscular routes, have an absorption rate of 10 to 15 minutes.
 - Intravenous injection maximum provides an early immediate peak serum level, while effective analgesia can be delayed for up to 17 minutes due to a delay in drug passing across the blood brain barrier.⁽¹⁾
 - Maximum effect is reached quicker than oral.
 - S.C. starts to lose potency at 45 to 90 minutes, intramuscular medications at 30 to 60 minutes and intravenous medications by 20 minutes.⁽²⁾
 - Use a S.C. butterfly needle for intermittent subcutaneous injections.
 - Indications for use are: inability to swallow, nausea and/or vomiting, gastrointestinal obstruction or impaired absorption and uncontrolled pain where rapid titration is necessary.
 - Continuous subcutaneous infusions have been shown to be superior to continuous I.V. infusions in the palliative care setting.^(1, 23) especially if the q4h dose of an opioid is too large to give on an ongoing basis or the opioid being used has a very short duration of action (fentanyl or sufentanil).⁽¹⁾ When high doses of intravenous morphine are needed, use only preservative-free formulations.⁽¹⁷⁾
- The transdermal route is effective but should not be used in patients with advanced cachexia. Some elderly and debilitated patients as they will not absorb the medication adequately.^(13, 21) It is also not the first choice route in those with acute or rapidly changing pain and the opioid naïve.⁽¹³⁾
- The buccal route has a quick absorption rate (10 minutes).^(2, 17) Use of concentrated forms of opioids (morphine 20 to 50 mg per ml or hydromorphone 10 to 50 mg per ml) is recommended.⁽¹⁾ The volume of drug dose must be kept at or below 0.5 ml to avoid swallowing or prevent choking.^(1, 13) Bioavailability of sublingually administered morphine or hydromorphone will be higher than the same dose given orally, as less drug is initially metabolized due to a first pass effect of the liver.⁽¹⁾
- Epidural and intrathecal administration is used in difficult or refractory pain situations.⁽¹⁾ Both these routes require the use of preservative free-formulations.⁽¹⁷⁾ Intrathecal injection delivers the drug directly into the cerebral spinal fluid.⁽¹⁾
- Topical opioids have been used in managing pain of superficial decubitus or malignant skin ulcers. Morphine can be mixed with Intrasite gel for the treatment of ulcers for direct application.^(1, 13, 14)

Recommendation 8 Adverse Effects of Opioids

- **Constipation** is the only undesirable adverse effect where tolerance does not develop.^(1, 8, 9, 12) Ensure a bowel protocol is initiated. See *Fraser Health Hospice Palliative Care Symptom Guidelines on Constipation* for guidance on a suitable bowel regime.
- **Nausea/vomiting** – usually mild and rarely persistent,^(1, 9, 23) tolerance develops rapidly.^(7, 12) Antiemetics can generally be discontinued in a few days when tolerance develops.^(8, 17) See *Fraser Health Hospice Palliative Care Symptom Guidelines on Nausea and Vomiting* for guidance in choosing an antiemetic.
- **Sedation** – often transient, especially when opioid initiated or increasing doses.^(14, 17) Will generally be relieved in 2 to 4 days.^(1, 7-9, 12, 16, 23) Persistent opioid induced sedation is usually best treated by reducing the dosage and increasing the frequency of administration – this decreases peak concentrations while maintaining the same total dose.^(8, 17) The use of psychostimulants may be beneficial.^(8, 12, 14, 16, 17)
- **Delirium/restlessness** - may be seen both upon initiation of opioids (frequently in the elderly)^(1, 12) and may occur during ongoing opioid therapy when metabolite accumulation occurs.^(1, 12, 25) For treatment of true delirium see *Fraser Health Hospice Palliative Care Symptom Guidelines on Delirium / Restlessness*.
- **Urinary retention** occurs secondary to increased tone of the bladder sphincter and inattention to the stimulus for bladder emptying. This will generally decrease within one week.⁽⁹⁾ Rarely will a patient need to be catheterized.^(1, 9, 14) Urinary retention occurs more frequently in men with prostatic hypertrophy, patients with pelvic tumours, or bladder outlet obstruction.⁽¹⁷⁾
- **Pruritis** occurs secondary to the histamine release in drugs like morphine.^(7, 16) Patients may need an antihistamine or opioid rotation, if severe.^(1, 9, 16, 17)
- **Xerostomia** (dry mouth) is a common effect of morphine. Good mouth care and frequent sips are effective for most patients. For difficult cases pilocarpine 2% eye drops or 5 mg tablets by mouth three times per day have been suggested.⁽¹⁾
- **Syncope** (dizziness) occurs secondary to orthostatic hypotension caused by venous pooling following histamine release.^(1, 9) Patients prone to this effect should be instructed to change positions slowly when moving from lying to sitting or standing.⁽¹⁾
- **Myoclonus** (spontaneous jerking movements) can occur with any dose and route of opioids.^(1, 17) Myoclonus may precede the onset of opioid-induced neurotoxicity.⁽¹⁾ See *Fraser Health Hospice Palliative Care Symptom Guidelines on Myoclonus/Seizures* for guidance with this symptom.
- **Opioid-induced neurotoxicity (OIN)** includes symptoms such as: hyperalgesia (heightened sensitivity to the existing pain), allodynia (a normally non-noxious stimuli resulting in a painful sensation), agitation/delirium with hallucinations and possibly seizures.^(1, 9, 12) It is due to the accumulation of toxic metabolites and impaired renal

Recommendation 8 Adverse Effects of Opioids continued...

function, dehydration and electrolyte imbalances contribute to this condition.^(1, 9, 21) OIN occurs more frequently with high dose parenteral administration of morphine⁽¹²⁾ and has been observed in cases using high dose hydromorphone.⁽¹⁾ OIN occurs more common in the frail elderly.⁽⁹⁾ Grand mal seizure associated with high-dose parenteral opioid infusions have been reported and may be due to preservatives in the solution. Preservative free solutions should be used when administering high-dose infusions.⁽¹⁶⁾ Opioid rotation should be considered.^(1, 21)

- **Respiratory depression** occurs rarely in patients receiving opioids regularly as tolerance to the respiratory depressant effects develop rapidly.^(1, 7-9, 14, 16, 17) Opioids should not be withheld for fear of respiratory depression in this group.⁽¹⁷⁾ The risk of respiratory depression is greater in patients with respiratory impairment (pneumonia, those with CO₂ retention or chronic obstructive pulmonary disease), and when opioids are used in opioid-naïve patients, or are too rapidly titrated.^(1, 9, 17)

Recommendation 9 Opioid Titration

- When starting an opioid, use immediate release (IR) until dose is stabilized. Alternatively, some clinicians may choose to start with an oral controlled-release (CR) formulation, with an IR form available for breakthrough pain.⁽¹³⁾
- In opioid naïve patients start with 2.5 to 5 mg of morphine or 0.5 to 1 mg of hydromorphone q4h with breakthrough medication ordered at 1.25 to 2.5 mg of morphine or 0.25 to 0.5 mg hydromorphone q1h prn.
- Analgesic effectiveness can be reassessed after 24 hours as it takes five half lives to reach a steady state (5 x 4 hrs = 20 hrs).
- Total all the regular and breakthrough opioid used in the last 24 hours to get the total daily dose (TDD).
- Divide this amount by the number of doses for the next 24 hours (normally 6=q4h) and give this dose regularly q4h with 10% of the TDD given q1h p.r.n. as a breakthrough/rescue dose (BTD) for breakthrough/rescue pain.⁽²⁾
- Dose adjustments should not be made more frequently than every 24 hours.⁽²⁾ Also assess for end of dose pain, and the presence of incident pain, which may require further titration.
- Use IR opioid formulations for breakthrough doses (BTD)⁽¹³⁾ and remember to increase the breakthrough dose proportionately when the regular dose is increased.⁽²⁾
- When full pain relief is achieved, yet adverse effect have developed, employ a dose reduction to try and maintain adequate pain control with diminished adverse effects.⁽²⁾
- Doubling the nighttime dose will avoid waking the patient in the early morning for a scheduled q4h dose, however, night loading doses should be considered only for

Recommendation 9 Opioid Titration continued...

patients with good pain control.^(2,22) The use of sustained release opioids appears to be a better dosing strategy, as shown in a study with SR morphine.⁽²⁶⁾

- When good pain control is achieved with a stable dose with an immediate release formulation, consider use of a long acting product to improve compliance.⁽²⁾
- When the patient is on sustained release opioids or fentanyl patches it is usual to titrate the dose every 48 and 72 hours respectively.⁽²⁾ If fentanyl is used, total the amount of breakthrough opioid analgesic given in the last 24 hours and convert that amount to an additional equivalent size fentanyl patch. If titration is done frequently switch to a short acting preparation.
- If pain is rapidly escalating or pain is requiring frequent titration use short acting opioids q4h until pain is controlled and opioid needs are stabilized. Consider development of tolerance (which may require opioid rotation) or reassessment for a new or progressive medical problem.
- When patients are elderly or frail, titrate over a number of days rather than rapidly over 1 to 2 days.^(2, 9)
- For severe pain the rate of titration may need to be more aggressive.⁽¹⁴⁾

Recommendation 10 Use of Long Acting Or Sustained Release Opioids

- Although there are a variety of approaches, these medications are usually used for stable (well controlled) pain only.^(1,21,23)
- Sustained release formulations should not be used to manage uncontrolled pain. Consider a switch to immediate release formulations that provide an improved titration response time. Reevaluate pain control prior to restarting the sustained release formulation.^(1, 17, 23)
- Drugs available in long acting formulations include; codeine, oxycodone, morphine, hydromorphone and fentanyl. Methadone is considered a long acting opioid.⁽¹⁾
- Before conversion to a long acting opioid, use immediate release preparations to titrate to the appropriate 24 hour dose(TDD).^(1, 14, 17)
- Steady state when using morphine or hydromorphone sustained release is achieved after 48 to 72 hours. Dosage adjustments for these drugs should be made only every 2 or 3 days.^(1, 2)
- Never prescribe sustained release oral formulations more frequently than q8h.⁽¹⁾
- SR tablet forms must be swallowed whole. Capsule forms may be opened up and the contents sprinkled onto food or put down a feeding tube but should not be crushed or chewed.^(1, 15)

Recommendation 10 Use of Long Acting Or Sustained Release Opioids continued...

- When using long-acting preparations, always give a short-acting opioid (solution or tablets) using the 10% TDD equivalency q1h p.r.n. for breakthrough pain (e.g., if the patient is on morphine sustained release 60 mg q12h PO give a breakthrough dose of morphine 10 to 15 mg PO q1h p.r.n.).^(1, 7, 8, 12, 13, 17) Preferably use the same drug.^(1, 14)
- Fentanyl transdermal patches require changing q72h but some patients may require changing q48h.^(1, 21) The full clinical effects of the fentanyl patch will occur between 24 and 48 hours after application.

Recommendation 11 Opioid Rotation

- Opioid rotation can be performed using the following methods:⁽¹⁾
 - Direct substitution – is used with weaker opioids or in severe opioid-induced neurotoxicity. The offending opioid is stopped and the new one started.
 - Gradual substitution – is used when switching between more potent opioids especially when there are already adverse effects or if the patient has anxiety about the new drug. Over the course of a few days the original analgesic is replaced by the new one.
- Conversions between opioids:
 - Due to in-complete cross-tolerance between opioids use 66% of the calculated equivalent dose.^(2, 14) The dose should only be reduced if the pain was controlled on the previous medication dosage or if there was opioid-induced neuroexcitation pain.^(1, 7, 8)
- The most common reasons opioids are switched are inadequate pain control or an unacceptable level of adverse effects from a specific opioid which limits dose escalation.^(1, 13, 14, 23) The need to switch occurs in 10 to 30% of patients on oral morphine.⁽²⁾

Recommendation 12 Opioid Withdrawal

- Rationale for discontinuing an opioid would include patient achieving appropriate pain control by another method, such as radiation therapy, nerve block or epidural.^(1, 7, 8, 14)
- If the patient has been on opioids for only a short time, abrupt discontinuation should not incur withdrawal symptoms.⁽¹⁾
- If a patient has been on opioids for greater than one week it is suggested to taper the dose by 20 to 30% every 2 to 3 days until discontinued to prevent a withdrawal syndrome.⁽⁸⁾

Recommendation 12 Opioid Withdrawal continued...

An alternative method is; for the first 2 days, give half of the previous daily dosage. Then reduce the daily dosage by approximately 25% every 2 days, until a daily dosage of 30 mg of morphine has been reached. After 2 more days on 30 mg per day of morphine, discontinue use.⁽⁷⁾

- Early symptoms include anxiety and restlessness, sweating, rapid short respirations, slight rhinorrhea and lacrimation and dilated reactive pupils.
- Late symptoms include marked rhinorrhea and lacrimation, tachypnea, tremor, yawning, pilo-erection, nausea and vomiting, diarrhea, abdominal pain, fever, leucocytosis and diffuse muscle spasms.
- Prolonged symptoms include irritability, fatigue, bradycardia and decreased body temperature.
- Withdrawal syndrome can also be precipitated by the use of opioid antagonists like naloxone. In the rare instance where this drug needs to be used, it should be mixed with 10 ml of saline and administered slowly in 1 ml increments to antagonize the respiratory depressant effects without precipitating an acute episode of withdrawal syndrome.^(11, 13)

Recommendation 13 Treatment: Pharmacological

There are three simple goals for pain management;

- A good night's sleep,
- Pain control during the day while at rest and
- Pain control when they are active and ambulatory.⁽¹⁾

Where there is no previous history of opioid intake, the starting dose is calculated by assessing the severity of the pain, patient's age, weight, sex and general physical condition.

MILD PAIN (Initial Pain Assessment between 1/10 and 4/10):

If pain is expected to remain mild for a significant length of time (weeks to months), use non-opioid or weak opioid analgesics. Go slow and go low.^(1, 27)

- Acetaminophen 325 to 650 mg PO q4h and q1h p.r.n for BTD (maximum 4 g per day, but reduce to a maximum of 2.4 g daily in the elderly and patients with history of liver dysfunction or alcoholism).⁽²³⁾
- ASA 325 to 650 mg PO q4h. Use of enteric coated form can minimize GI discomfort.
- Non-Steroidal Agents (NSAIDs) are indicated for short term use.⁽²⁸⁾ Cardiovascular

Recommendation 13 Treatment: Pharmacological continued...

risk with these agents are minimized by using the lowest effective dose, for the shortest period of time.⁽³¹⁾ Recently, cardiovascular risk has been shown to be less with traditional NSAIDs ibuprofen and naproxen, than with other NSAIDs such as indomethacin and diclofenac.⁽²⁹⁾

- Codeine maybe added in combination with or without ASA or acetaminophen to control pain. Dosing suggestion: 30 to 60 mg PO q4h and q1h PO p.r.n for BTD.⁽²³⁾ Usual maximal dose is 360 to 600 mg per day.⁽³⁰⁾

If the pain is not well controlled with these medications proceed to next step but only if doses have been taken appropriately (e.g., q4h around the clock).

MODERATE PAIN (Initial Pain Assessment of 5/10 or 6/10):

If pain has progressed, change to stronger opioids. Oxycodone can be used alone or combined with ASA or acetaminophen. For moderate pain, also use single entity opioids such as morphine, hydromorphone, fentanyl or methadone and cancel analgesic orders for mild pain. Increasing doses of opioids combined with acetaminophen runs the risk of giving toxic doses of acetaminophen to the patient.^(2, 31)

- If opioid naïve, start on morphine 5 to 10 mg oral q4h with 10% of total daily dose (TDD) q1h p.r.n.⁽³¹⁾ After 24 hours, if more than three breakthrough doses are needed, increase the regular dose – see opioid titration.⁽¹⁾
- If currently on a weak opioid, discontinue it, start morphine PO q4h at the appropriate equianalgesic dose (taking into consideration the partial cross-tolerance between opioids) with 10% TDD q1h p.r.n. for breakthrough pain.⁽¹⁾ If more than three breakthrough doses are required over 24 hours, increase the morphine dose (as per above).

SEVERE PAIN (Initial Pain Assessment between 7/10 and 10/10):

Initial worst pain intensity between 7 and 10 should be considered a pain emergency and requires rapid titration using oral, subcutaneous or intravenous routes.^(2, 31) ‘When pain is high, go high and come down quickly’.⁽¹⁾ Use morphine, hydromorphone, or oxycodone.

Acute severe pain initially requires parenteral control with a switch to oral or rectal medication once the pain is relieved. If pain is sudden, acute and severe (i.e., fracture, hemorrhage), then both quick response and high doses are necessary. Once relief is obtained, dose can be reduced. The regimen assumes that usual breakthrough dosing has been ineffective.

- Opioid naïve:
 - Give standard dose of morphine 5 to 10 mg PO⁽³¹⁾ or 5 mg S.C. or 2 to 5 mg I.V.⁽³¹⁾ STAT and repeat every 20 minutes for S.C. or every 10 minutes for I.V. until pain breaks (significantly lessens).⁽¹⁾

Recommendation 13 Treatment: Pharmacological continued...

SEVERE PAIN (Initial Pain Assessment between 7/10 and 10/10) continued...:

- If on an opioid already:

Using the Subcutaneous Route:

- Give one-half of the regular PO dose by the S.C. route STAT and if necessary, give this again in 20 minutes, until pain breaks. Double stacking (doubling each dose) may be required if the initial dose is very low – usually doubled only 1 to 3 times.⁽¹⁾

Using the I.V. Route:

- If an I.V. bolus is warranted, give 10 to 20 % of the daily IV morphine equivalent. Reassess at 15 minutes.⁽³¹⁾ The effectiveness of the analgesic should be reassessed after 15 minutes. If the pain intensity is unchanged the dose of the opioid should be doubled. If the rating has decreased by less than 50 %, the same dose should be repeated. Once the pain intensity has decreased by more than 50 % then calculate the total dose of opioid given over 4 hours and consider this dose the “effective” one to be given.⁽³¹⁾

“Many painful conditions can be readily managed by generalist physicians, nurses and allied staff. Reality is such, however, that some pain problems are complex and require added expertise.”⁽¹⁶⁾ In these cases, **refer when pain persists.**⁽²⁾

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Fentanyl Transdermal

Principles

A. Indications For Fentanyl Transdermal Use

- Non-invasive alternative to oral medications.
- Poor absorption of oral opioids.
- Pain that is stable;⁽¹⁾ pain controlled for at least 48 hours.
- To provide around the clock opioid treatment^(1,2) and improve patient compliance.^(3,4)
- To potentially lower opioid adverse side effects of constipation,^(5,6) nausea,⁽⁵⁾ and histamine release.^(7,8)

B. Contraindications To Fentanyl Transdermal Use

- Opioid naïve.^(1,2,9)
- Unstable or poorly controlled pain.^(4,5)
- Acute pain management, e.g. post-operative, or acute pain titration.^(1,2)
- Previous opioid dose is less than 45 to 134 mg of oral morphine equivalent per 24 hours.⁽¹⁾

C. Precautions

- Elevated temperature may increase fentanyl concentrations.^(1,2,10) Monitor.
- Avoid application site exposure to heat sources such as hot tubs, waterbeds, etc.^(1,2)
- Cachectic patients, may have reduced subcutaneous fat tissue for reliable drug depot release hence fentanyl pharmacokinetics may be altered.^(1,2)
- Do not cut the reservoir membrane-controlled patch delivery system.^(1,2) This patch type, if cut, may affect the rate the drug is released, and risk a toxic skin reaction and overdose.^(1,2,11)
- The newest fentanyl patch matrix system (drug-in adhesive) has been cut in successful clinical use although no studies have been completed.⁽¹²⁾
- Fold used patches in half then place in needle disposal container, or place in tamperproof container and return to a community pharmacy, to prevent misuse.⁽¹³⁾
- Caregivers should wear gloves when handling the patch.⁽¹⁴⁾ Flush skin with water only if patch drug reservoir gel accidentally touches skin, do not use soap.^(1,2)
- Refer to fentanyl transdermal patch product monographs for complete precaution listing.

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D. Properties

- Fentanyl blood concentrations level off between 12 to 24 hours.⁽³⁾
- Most commonly, full clinical effects will occur between 24 and 48 hours after patch application.⁽⁹⁾
- Fentanyl is suited for transdermal delivery because of its low molecular weight, lipid solubility and high potency.^(3,9)
- No pharmacologic dose ceiling, but practical available skin coverage limits dose.
- No known active metabolites, thus useful for patients with renal impairment.⁽¹⁵⁾
- Silicone contact adhesive, alcohol and hydroxyethyl cellulose drug reservoir.^(1,2,5)

Fentanyl Transdermal Equianalgesic Conversion Chart*

Morphine PO (mg per day)	Hydromorphone PO (mg per day)	Oxycodone PO (mg per day)	Fentanyl Patch (mcg per day)
45-134	9-26	30-89	25
135-224	27-44	90-149	50
225-314	45-62	150-209	75
315-404	63-80	210-269	100
405-494	81-98	270-329	125
495-584	99-116	330-389	150
585-674	117-134	390-449	175
675-764	135-152	450-509	200
765-854	153-170	510-569	225
855-944	171-188	570-629	250
945-1034	189-206	630-689	275
1035-1124	207-224	690-749	300

*The conversions between fentanyl and morphine are taken from the 2004 Compendium of Pharmaceuticals and Specialties.⁽¹⁶⁾ The hydromorphone and oxycodone conversion are based on a morphine to hydromorphone ratio of (5:1) and a morphine to oxycodone ratio of (1.5:1)

Approximate Breakthrough Doses Recommended for Fentanyl Transdermal Patch

Patch Strength	Oral Morphine Immediate Release ⁽¹⁷⁾	Oral Hydromorphone Immediate Release ⁽¹⁷⁾	Oral Oxycodone Immediate Release
12 mcg per hour	5 mg	1 mg	2.5 to 3.75 mg
25 mcg per hour	10 mg	2 mg	5 to 7.5 mg
50 mcg per hour	20 mg	4 mg	10 to 15 mg
75 mcg per hour	30 mg	6 mg	15 to 25 mg
100 mcg per hour	40 mg	8 mg	20 to 30 mg

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Conversion Guidelines Between Fentanyl Transdermal Patch and Oral and Subcutaneous Opioids Over First 12 Hours⁽¹⁸⁾

	0 Hour	4 Hour	8 Hour	12 Hour
Immediate release oral to TD Patch	Apply Patch Give one IR Dose	One IR Dose	One IR Dose	-
Sustained release to TD Patch	Apply Patch Give one SR Dose	-	-	-
Subcutaneous to TD Patch	Apply Patch Give full S.C. Dose	2/3 S.C. dose	1/3 S.C. dose	Stop S.C.
CSCI to TD Patch	Apply Patch, 2/3 CSCI dose for 6 hours, then 1/3 CSCI dose for 6 Hours			Stop CSCI
TD Patch to sustained release oral	Remove Patch	-	Full SR dose	-
TD Patch to intermittent S.C.	Remove Patch	1/4 S.C. dose	1/2 S.C. dose	Full S.C. dose
TD Patch to CSCI	Remove Patch	1/4 CSCI dose	1/2 CSCI dose	Full CSCI dose
** NOTE: Provide p.r.n. Breakthrough dose throughout Conversions				

Abbreviations: TD - Transdermal, IR - Immediate Release, SR - Sustained Release, S.C. - Subcutaneous, CSCI - Continuous Subcutaneous Infusion, p.r.n. - as needed

Practice

A. Converting To Fentanyl Transdermal Patch

- Calculate the total daily dose of current opioid.
- Convert this into oral equivalent for morphine, hydromorphone or oxycodone.
- Use Fentanyl Transdermal Equianalgesic Conversion Chart to determine the equivalent dose of transdermal fentanyl.
- **Always** provide a breakthrough dose selecting the appropriate dose from the Approximate Breakthrough Doses Recommended for Fentanyl Transdermal Patch chart. Provision of breakthrough doses is important, as the conversion chart is conservative,⁽¹⁹⁾ and approximate. Individualize patient treatment, for in clinical trials, 50% of patients required a dose increase after the initial patch strength application.⁽³⁾

If breakthrough doses are given S.C. give one-half the oral dosage.

B. Initiation Of Fentanyl Transdermal Patch

- Apply patch to a non-hairy skin area, on chest, back, flank or upper arm.^(1,2)

Note or record placement location to ensure removal in 72 hours time, prior to next dose replacement.

Practice

A. Converting To Fentanyl Transdermal Patch

- Calculate the total daily dose of current opioid.
- Convert this into oral equivalent for morphine, hydromorphone or oxycodone.
- Use Fentanyl Transdermal Equianalgesic Conversion Chart to determine the equivalent dose of transdermal fentanyl.
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If breakthrough doses are given S.C. give one-half the oral dosage.

B. Initiation Of Fentanyl Transdermal Patch

- Apply patch to a non-hairy skin area, on chest, back, flank or upper arm.^(1,2)
Note or record placement location to ensure removal in 72 hours time, prior to next dose replacement.
- During the first twelve hours after the patch has been started, utilize appropriate regular dosing during the transition, **AS WELL AS** p.r.n. dosing; refer to Conversion Guidelines Between Fentanyl Transdermal Patch and Oral and Subcutaneous Opioids Over First 12 Hours chart.
- Consider applying the first patch at bedtime, as lower pain requirements may occur at night,^(20,21,22) permitting peak levels to occur during the day.

C. Dose Titration With Fentanyl Transdermal Patch

- Wait a minimum of three days between dose changes.⁽¹⁵⁾
- Total amount of breakthrough doses in prior 24 hours to guide incremental dose increase.⁽¹⁹⁾
- Consider a 30 to 50% baseline dose increase,⁽²³⁾ while using the available patch strengths. Thus after a patient was successfully initiated on a 12 mcg per hour patch, consider the following progressive steps:
12 » 25 » 37 » 50 » 75 » 100 » 150 » 200 mcg per hour etc.
- When less than a full patch dose is desired, a successfully used method is to apply an occlusive dressing (such as TEGADERM) onto the skin to block the appropriate surface area portion of the patch exposed to the skin., e.g. half the patch on the dressing and half on the skin.⁽²⁴⁾

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- Rarely do patients require patches to be replaced more frequently than every three days. Early wearing off of the patch's effectiveness (end of dose failure) can indicate under-dosing and the need for the patch dose strength to be increased.
- Provide and appropriately adjust for a new p.r.n. breakthrough dose.^(4,9)

D. Discontinuation Of Fentanyl Transdermal Patch

- Upon removal of the patch, the depot of medication within the subcutaneous skin tissue and drug elimination will diminish by 50% within seventeen hours of removal.⁽³⁾
- Refer to Conversion Guidelines Between Fentanyl Transdermal Patch and Oral and Subcutaneous Opioids Over First 12 Hours, when discontinuing patch and initiating sustained release oral therapy, intermittent S.C. or CSCI therapy.

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Methadone

Principles

A. Characteristics

Of all the medications used in Palliative Medicine, methadone should command the greatest respect. Only physicians experienced in methadone use should initiate methadone treatment.⁽¹⁻⁶⁾ Its use is highly individualized, and demands finesse, skill and knowledge for use in carefully supervised settings.

Methadone is a potent analgesic utilizing OP3 (mu)⁽⁷⁾ and OP1 (delta)⁽⁷⁾ opioid receptor agonist with N-methyl-d-aspartate (NMDA)^(2,4) receptor antagonist actions. It is used for neuropathic pain management in clinical practice;⁽⁸⁻¹⁰⁾ controlled studies have yet to confirm its role in neuropathic pain of malignant origins.^(11,12)

Its prolonged and variable half-life makes titration difficult.^(8,13-15) Liver metabolism produces no active metabolites,^(1,2,4,6,11,14,16-20) making it useful in renal impairment and for use in dialysis patients.^(2,4,12,16,19) Excretion occurs via feces and urine.^(14,16, 21,22)

The potency of methadone has been underestimated in the past, and controversy exists over the equianalgesic dose.⁽²¹⁾ The higher the dose of the previous opioid, the more powerful methadone appears.^(1,4,23) Older equianalgesic tables based equivalency on single dose studies (suggested a 1 mg methadone = 1 mg morphine ratio), and not long-term dosing.^(3,14,16,21,24) Pain control conversions have occurred where the dose of methadone has been as little as 1/240th of the previous high dose of morphine.⁽¹⁷⁾ Methadone's effect on the NMDA receptor may be part of the reason why the conversion ratio changes in chronic use.⁽⁸⁾ Antagonism of NMDA may produce a reversal of tolerance,^(1,8,13,21) reduce the tolerance of morphine, and improve pain control.⁽⁸⁾ A low incidence of dose escalation has been shown in chronic treatment.^(2,11,20)

1. **Side Effects:** The side effects of nausea,^(12,16) constipation,^(3,4,6,12,16,25) and confusion^(6,16) are often less than for other opioids. Additional side effects include sedation, dizziness, pruritus, sweating, vomiting, risk of urinary retention, dry mouth, and insomnia.^(2,3,12,14,22) Several reports have been published of prolonged QTc (corrected QT interval), torsades de pointes and syncope in patients taking high doses of methadone, greater than 200 mg per 24 hours.^(6,22,26-28) Prolonged QT interval is associated with torsades de pointes (TdP) (a type of paroxysmal ventricular tachycardia), ventricular fibrillation and sudden cardiac death.^(1,9,22,29-31) Palliative care patients are at risk in the presence of heart disease,^(22,29) abnormal liver function, low potassium and calcium, and while using selected drugs.^(7,29,32,33) Refer to Table 2 for a list of drugs associated with prolonged QT interval and torsades des pointes.

Suppositories can be pharmaceutically compounded for rectal route use.^(3,5,14,23)

Commercially, methadone is available in oral formulations of tablets of 1 mg, 5 mg, 10 mg, 25 mg and standard strengths of liquid 1 mg per mL and 10 mg per mL. Its

bitter taste can be made more palatable by adding to liquids such as fruit juice⁽⁵⁵⁾ or chocolate milk.⁽⁵⁾ Applesauce or a candy taken after a dose may alleviate the bitterness.⁽¹⁴⁾ Methadone has been used intravenously^(7,8) subcutaneously,^(35,36) and intramuscularly,⁽¹⁴⁾ although obtaining this form of the drug requires importation via Health Canada's Special Access Program.

B. Properties

- OP3 (Mu)^(2,7,37) agonist, OP1 (delta)^(7,37) and OP2 (kappa)^(7,37) agonist and NMDA receptor^(2,4) antagonist.
- Serotonin and norepinephrine uptake inhibitor.^(2,25)
- High bioavailability 80% orally,^(1-4,8,12,16,23) 34% when liquid given sublingually.^(25,38)
- Rapid onset of pain relief due to good absorption within 30 minutes,^(5,14,21-23) peak levels occur 2 to 4 hours after ingestion.⁽¹⁴⁾
- Large initial volume of distribution.^(8,16,23)
- Has a 2 to 3 hour initial phase,^(4,18,21) then a 15 to 60 hour elimination phase.^(2,18,39)
- Long half life varies from 15 to 60 hours,⁽²⁵⁾ up to 120 hours in cancer patients.^(21,22)
- Dosing frequency of q6h, q8h or q12h⁽¹³⁾ does not necessarily reflect half life.
- Metabolized in liver, mainly by CYP3A4 and to a lesser extent by CYP1A2 and CYP2D6.^(2,16,21) Other minor enzymes involved are CYP2B6, CYP2C9, CYP2C19 and⁽²⁵⁾
- Inexpensive^(3,4,12,16,18,20,24) and easily manufactured synthetic opioid.⁽³⁴⁾
- Effects can be reversed with use of naloxone.^(4,7,10,14,56)
- The relative analgesic potency ratio of oral to parenteral methadone is 2:1.^(7,16,25)
- The relative conversion from oral to rectal is 1:1,^(16,25) some clinical experience suggests that 50 % greater rectal doses may be required when switching from oral dosing.⁽⁴⁰⁾

C. Indications

- Opioid neurotoxicity.^(4,11,14,16,17)
- Opioid tolerance.^(2,11,14,16)
- Uncontrolled neuropathic pain.^(1,4,17,21)
- True morphine allergy.
- Treatment of cancer pain in patients on chronic methadone maintenance therapy.⁽¹³⁾

D. Disadvantages (Challenges)

- Wide, unpredictable variable interpatient pharmacokinetics.^(1,3,4,10,14,16,18,21,23-25)
- Poorly defined equianalgesic potency.^(1,9,12,23)
- Potency ratio changes with higher doses.^(1,4,23)
- Deposition in tissues can occur as a result of the dissociation between half-life and analgesic duration and poses the risk of delayed toxicity.^(5,6,23,41)
- Risk of respiratory depression, greatest at the start of therapy.^(3,13,25)
- Rotation best done as an inpatient, particularly when rapid opioid rotation desired.^(3,4,15,23,42) Successful titration in the community has been done with daily health care contact (phone call) and frequent and regular assessment by the family until titration is complete.⁽²³⁾ Time to steady state is 48 to 240 hours,⁽⁶⁾ and requires ongoing monitoring for up to 10 days after dose change to follow for drowsiness, risk of respiratory depression.
- Several drug interactions.^(4,18) (*see Table 1*)
- Auto-induction of metabolism by CYP3A4 increases clearance in chronic dosing.^(2,16)
- Requires a special license to prescribe for pain.^(2,3,5,15,43)
- Requires skilled prescriber.⁽⁴¹⁾
- No randomized controlled trials to support its role in cancer^(15,34) and non-cancer.⁽⁴⁴⁾ pain management.
- No comparative studies regarding the effectiveness of the different methadone switching methods.^(1,4,5,9,11,34)
- No comparative studies to provide an optimum titration strategy.^(34,45,46)
- Choice of breakthrough (rescue) drug not established in literature and clinical practice.⁽¹⁴⁾
- Requires safeguards for use by patient only, to avoid accidental ingestion, as a 10 mg dose can be fatal for a child, or 40 mg for a non-tolerant adult.⁽¹⁴⁾ Store in a childproof container within a locked box.^(14,15)

E. Contraindications

- Methadone allergy.⁽¹⁶⁾
- Concurrent monoamine oxidase inhibitor therapy.⁽¹⁶⁾
- Concurrent pentazocine, nalbuphine, butorphanol – may precipitate withdrawal symptoms.⁽¹⁴⁾
- A setting of respiratory depression.^(16,22)
- **Relative Contraindication:** prolonged QTc defined as greater than 450 milliseconds for males and greater than 470 milliseconds for females.⁽⁴⁷⁾ Particular risk occurs with an uncorrected QT greater than 500 milliseconds.⁽⁴⁷⁾

Practice

- Consultation with the Hospice Palliative Consultation Team/Physician/Pharmacist is recommended because of the complexities of methadone use.
- For a physician to obtain the necessary prescribing or inpatient reordering authority, contact the College of Physicians and Surgeons 604-733-7758 extension 2246 or 1-800-461-3008.⁽⁵⁾

QTc should be measured before embarking on methadone treatment and when the dose approaches 200 mg per 24 hours.^(6,15,47) Risk of torsades de pointes grows as QTc increases, particularly greater than 500 milliseconds.⁽⁴⁷⁾ Whenever a drug increases the QTc by 30 to 60 milliseconds in an individual, this should raise a concern.^(30,33,47) When possible, electrocardiograms should be performed during peak drug concentration.

A. Dosages

Various methods are used to initiate methadone in patients. Suggested methods follow:

1. Opioid Naïve Patients: (Twycross)⁽⁴⁸⁾

“start low go slow”

- Start with 5 mg q4h p.r.n.
- On day 4 summate doses and calculate q8h.
- 10% Total Daily Dose (TDD) for rescue.
- Alternate Regimen: (palliatedrugs.com newsletter Feb 2001).⁽⁴⁹⁾
- Start methadone 5 mg q12h and 5 mg q3h p.r.n.
- If pain control inadequate increase to 10 mg q12h after 1 to 2 days; preference is not to change regular dose for 1 week.
- Can titrate up by 1/3 to 1/2 once a week.
- With higher regular doses increase the rescue dose to 1/8.

2. Dosing Guide For Opioid Tolerant Patients

Daily oral Morphine equivalents ⁽¹⁾	Conversion ratio Morphine to Methadone ⁽¹⁾
<100 mg	3:1
101 – 300 mg	5:1
301 – 600 mg	10:1
601 – 800 mg	12:1
801 – 1000 mg	15:1
>1000 mg	20:1

Due to incomplete cross-tolerance reduce initial calculated dose by 50%

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3. Schedule (modified after Bruera, E and Newman C)⁽⁵⁰⁾

Calculate methadone total daily dose equivalent according to the table on the previous page.

Day 1: reduce original analgesic by 1/3
 add 1/3 as calculated methadone dose
 use original analgesic for rescue

Day 2: reduce original analgesic by 2/3
 add 2/3 as calculated methadone dose
 use original analgesic for rescue

Day 3: give total dose as methadone
 use methadone for rescue – 10% TDD q3h p.r.n.

- Use of methadone for breakthrough dosing may be preferred as patients on methadone may be at least partially refractory to the effects of other opioids. Some clinicians recommend only starting methadone for breakthrough doses once a regular methadone dose is established.⁽³⁾
- Patients 65 years and older may have a decreased clearance of methadone.⁽¹⁾
- In patients with stable chronic liver disease, no dosage adjustments appear to be necessary.^(21,25) Methadone's half-life may be prolonged in patients with severe cirrhosis.⁽⁵¹⁾
- Dosing frequency is normally q8h.^(5,52) Intervals of 12 hours may be attempted when patients are stable at q8h dosing.⁽⁷⁾ A dosing frequency of every 6 to 12 hours is recommended for pain control in patients previously on once daily methadone maintenance for heroin addiction.⁽¹³⁾
- Should a patient need to be rotated off methadone, the residual methadone analgesia may directly interfere with the new opioid for days after methadone's discontinuation due to its long half life.⁽¹³⁾

4. Monitoring

- Monitor for sedation, lethargy, confusion and respiratory depression q6h for 3 to 6 days after initiation or dose change, then daily until at least day 10. Respiratory depression risk reported greatest from day 4 to day 6.⁽⁵²⁾ Pulse may slow and blood pressure lower in overdoses.⁽⁵⁾
- Individualized patient dosing and evaluation is the best way to ensure the safe use of methadone.^(5,23)

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Drug Interactions: For drug interactions known to occur with methadone, see below. Consult current sources for further and recent drug listings.

Table 1 – Methadone Drug Interactions^(14,16,22,53)

Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
Abacavir	Decrease	Enzyme Induction	
Alcohol	Decrease	Enzyme Induction-chronic use	Early, additive CNS depressant effect
Alfentanil	Unpredictable	Common enzyme pathway	May increase or decrease
Amiodarone	Increase	CYP3A4 & CYP2D6	
Amitriptyline	Increase	Reduced clearance	Additive euphoria
Ammonium Chloride	Decrease		
Amprenavir	Decrease		Methadone may also decrease amprenavir
Ascorbic Acid	Decrease	Decreased renal reabsorption	In high doses that acidify urine
Antacids	Decrease	Reduced absorption	
Barbiturates	Decrease	Enzyme Induction	
Benzodiazepines		Additive toxicity	Risk of Respiratory depression, sedation
Buprenorphine			Contraindicated, opioid withdrawal risk
Bosentan	Decrease	CYP3A4	
Butorphanol	Decrease	Receptor antagonist	Contraindicated, opioid withdrawal risk
Cannabis	Unpredictable	Common enzyme pathway	May increase or decrease
Carbamazepine	Decrease	Enzyme Induction of CYP3A4	Risk of methadone withdrawal
Chloral Hydrate			Report of single fatal additive effects with methadone
Cimetidine	Increase	CYP1A2& CYP2D6	
Ciprofloxacin	Increase	CYP1A2 & CYP3A4	
Clarithromycin	Increase	CYP3A4	
Cocaine	Decrease	Methadone elimination accelerated	
Delavirdine	Increase	CYP2D6	
Desipramine	Unpredictable		Possible increased TCA toxicity, uncertain effect on methadone
Dexamethasone	Decrease	CYP450 induction	
Dextromethorphan		CYP450 induction	May increase levels of Dextromethorphan

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Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
Diazepam	Increase	CYP3A4	
Dihydroergotamine	Increase	Enzyme inhibition, CYP3A4	
Diltiazem	Increase	CYP3A4	
Efavirenz	Decrease	CYP3A4	
Erythromycin	Increase	CYP3A4	
Ethanol (acute use)	Increase	CYP450 competition or inhibition	
Fentanyl	Unpredictable	Common CYP450 pathway	Possible additive effects
Fluconazole	Increase	CYP3A4	
Fluoxetine	Increase	CYP2D6 & CYP3A4	
Fluvoxamine	Increase	CYP1A2 & CYP3A4	
Fusidic acid	Decrease	Enzyme Induction CYP3A4	
Grapefruit Juice	Increase	CYP3A4	
Heroin	Decrease	Methadone free fraction lessened	
Imipramine			Possible increased TCA toxicity, uncertain effect on methadone
Isoniazid	Increase	CYP 1A2	
Itraconazole	Increase	CYP3A4	
Ketoconazole	Increase	CYP3A4	
Meclizine	Unpredictable		Increased sedative effects if abused
Meperidine	Unpredictable		Possible opioid additive effects
Methylphenidate	Unpredictable	Possible CYP450 enzyme inhibition	
Metronidazole	Increase	CYP3A4	Proposed in literature, but unverified
Moclobemide	Increase	CYP2D6, CYP1A2	
Nalbuphine	Decrease	Receptor displacement	Contraindicated, opioid withdrawal risk
Naloxone	Decrease	Enzyme Induction	
Naltrexone	Decrease	Receptor displacement	Contraindicated, opioid withdrawal risk
Nifedipine			Nifedipine increase proposed
Nelfinavir	Decrease	CYP3A4 Enzyme Induction	
Nevirapine	Decrease	CYP450 Enzyme Induction	Methadone withdrawal cases
Octreotide	Decrease		
Omeprazole	Increase	Methadone absorption	Occurred in animal studies
Paroxetine	Increase	CYP2D6	
Pentazocine	Decrease	Receptor antagonist	Can cause opioid withdrawal

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Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
Pentobarbital	Decrease	CYP340 enzyme induction	
Phenobarbital	Decrease	CYP340 enzyme induction	Can cause sharp decrease in methadone
Phenytoin	Decrease	Enzyme Induction, CYP3A4, CYP2B6	
Primidone	Decrease	Enzyme Induction	
Promethazine	Unpredictable		Possible increased sedation or methadone effects
Propafenone	Increase	CYP2D6	
Propoxyphene	Increase	CYP3A4	
Quinidine	Increase	CYP2D6	
Rifampin	Decrease	Enzyme Induction	Cases of severe withdrawal reported
Risperidone	Decrease	Mechanism unclear	
Ritonavir	Decrease	CYP3A4	
Sertraline	Increase	CYP340 enzyme inhibition	
Sodium Bicarbonate	Increase	Decreased urinary excretion of methadone	
Spironolactone	Decrease	Enzyme Induction, CYP3A4	
Stavudine	Unpredictable		Decreased stavudine concentration
St. John's Wort	Decrease	CYP3A4	Can cause significant decrease
Tramadol			Potential withdrawal risk. Avoid concurrent use with methadone
Trimipramine	Unpredictable		Possible increased TCA toxicity, uncertain effect on methadone
Verapamil	Increase	CYP3A4	
Zafirlukast	Increase	CYP3A4	
Zidovudine	Unpredictable		Zidovudine concentration increase
Zopiclone	Unpredictable		Potential interaction, additive CNS depression

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Table 2 – Drugs that may predispose to QT interval prolongation or torsades de pointes ^(29,30,33,54)

adenosine	domperidone	lithium	quinine
amantadine	doxepin	losartan	risperidone
amiodarone	droperidol	maprotiline	rizatriptan
amitriptyline	enflurane	mefloquine	salbutamol
azithromycin	erythromycin	meperidine	salmeterol
bupropion	famotidine	methadone	sertraline
cetirizine	fentanyl	mexiletine	sevoflurane
chloral hydrate	fexofenadine	moxifloxacin	sildenafil
chloroquine	flecainide	naratriptan	sotalol
chlorpheniramine	Fluconazole	nicardipine	spiramycin
chlorpromazine	fluoxetine	Nortriptyline	sufentanil
ciprofloxacin	foscarnet	octreotide	sumatriptan
citalopram	fosphenytoin	ofloxacin	tacrolimus
clarithromycin	gatifloxacin	olanzepine	tamoxifen
clemastine	Glyburide	ondansetron	telithromycin
clindamycin	granisetron	paroxetine	terfenadine
clomipramine	haloperidol	pentamidine	thiopental
clozapine	halothane	pentobarbital	thioridazine
cocaine	hydroxyzine	pimozide	tizanidine
cotrimoxazole	ibutilide	probucol	trazodone
cyproheptadine	imipramine	procainamide	triamterene
desipramine	indapamide	prochlorperazine	trifluoperazine
diltiazem	isoflurane	promethazine	vasopressin
dimenhydrinate	isoproterenol	propafenone	venlafaxine
diphenhydramine	ketamine	propofol	verapamil
disopyramide	ketoconazole	quetiapine	voriconazole
dolasetron	levofloxacin	quinidine	zolmitriptan

The potential each of these drugs has to predispose to QT prolongation and torsades de pointes varies, but the extent is specific to the drug. Concomitant drug use in susceptible patients should be evaluated alongside other medical risk factors. Consult current sources for further and recent drug listings.

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Tramadol

An Overview

Tramadol briefly:

- Is a synthetic opioid with analgesia provided via a weak OP3 (mu) receptor effect, and via inhibition of serotonin and noradrenaline reuptake.⁽⁴⁾ Appears to provide neuropathic pain benefit.^(1,4,9,10)
- Has a low incidence of constipation, nausea and dizziness compared to other opioids.⁽³⁾ It has no major cardiovascular or blood pressure effects^(3,4) and a low risk of respiratory depression.^(1,5,16) May cause seizures; use cautiously in patients with epilepsy, head trauma, brain metastases, metabolic disorders, alcohol or drug withdrawal, CNS infections and with concurrent interacting drugs, e.g. SSRI's, TCA's, other opioids.^(3,5,7,8)
- Tramadol is used for moderate pain, and is considered a step 2 analgesic on the World Health Organization 3 step ladder,^(3,8,13,16) with a ceiling effect due to increasing seizure risk when dose exceeds 400 mg daily.^(4,7,8,16)
- While tramadol is used in 8% of European palliative care units,⁽²⁾ it's role in Canada remains to be established. Not available in Canada as a single entity product, until December 2006, as a once daily extended release tablet in 150, 200, 300 and 400 mg strengths.⁽⁷⁾
- Tramadol is also available in combination with acetaminophen, each tablet contains 37.5 mg tramadol with 325 mg acetaminophen, and is licensed for pain treatment of five days or less. Dose 1 to 2 tablets q6h to a maximum of 8 tablets daily.⁽⁶⁾

Tramadol more in depth:

History

- Developed in 1962, first used in 1977 (West Germany), introduced into Poland in 1992, USA in 1995 and the U.K in 1997.⁽¹⁾
- Worldwide over 50 million patients have received tramadol, as estimated by Bamigbade and Langford in 1998.⁽⁸⁾

Market Size

- US market size for tramadol estimated to be \$US11.3 billion in June 2002 by the Canadian company Biovail.⁽¹²⁾ So roughly, the Canadian market could be 1/10th the amount, or approximately \$C1.4 billion.

Potency

- Tramadol is twice as potent as codeine orally according to palliativedrugs.com.⁽⁵⁾ But another review reference states potency as 1:1.⁽¹⁾
- Oral potency ratio of tramadol to morphine shown to be 1:4⁽⁸⁾ but in a larger study involving cancer patients it was 1:10⁽¹⁶⁾ CYP2D6 genotypes in patients might explain variation in equianalgesia in studies.⁽¹⁶⁾
- Tramadol 75 mg with 650 mg acetaminophen is equivalent to 400 mg ibuprofen for postoperative pain.⁽¹⁶⁾
- A single tablet of 100 mg oral tramadol is equivalent to 1000 mg acetaminophen for postoperative pain.⁽¹⁷⁾
- Sustained release morphine was shown to be more effective in severe cancer pain.⁽⁸⁾

In Combination

- May be safely combined with NSAIDs.⁽⁸⁾ Tramadol has no effect on prostaglandin synthesis and hence no ability to induce GI bleeding or reduced platelet activity.⁽¹³⁾
- Does not cause a withdrawal reaction when given to patients receiving morphine or methadone, yet similarly it does not prevent a withdrawal when substituted for potent opioids.⁽¹⁶⁾

Metabolism and Excretion and Absorption

- Mainly excreted by the kidneys (90%).^(4,8,16)
- Following multiple oral administration of tramadol 100 mg four times daily, C_{max} is 16% higher and AUC 36% higher than after a single 100 mg dose, indicating that oral bioavailability increases to approximately 90-100% on multiple administration, possibly due to saturated first-pass hepatic administration.⁽⁴⁾
- Has a total of 23 metabolites, all metabolites are almost completely excreted via the kidneys.⁽⁴⁾
- 7% of the population are poor metabolizers (due to the lack of the CYP2D6 enzyme) hence tramadol has little or no analgesic effect in these patients.⁽⁵⁾ It was suggested that tramadol may have some efficacy in patients in which codeine is not effective and are CYP2D6 deficient,⁽¹³⁾ although this has not been studied and is unknown. Africans (Nigerian's studied) with the CYP2D6 #17 gene or Orientals with the CYP2D6 #10 gene may have altered tramadol metabolism, and reduce it's ability to act as an analgesic.⁽¹⁶⁾
- Tramadol has not been well studied in renal and hepatic impairment, although some dosing suggestions appear.⁽¹⁶⁾ It is contraindicated in severe hepatic failure and or severe renal failure (creatinine clearance less than 30 mL per minute).^(7,14)
- High fat breakfast results in a 17% higher C_{max} and 10% higher AUC.⁽⁴⁾
- Normal half life of 5 to 7 hours, is extended with age. The maximum dose in patients 75 years or older with good renal and hepatic function is 300 mg daily.⁽¹⁶⁾

Adverse Effects

- 15% of patients have side effects. Dizziness 5%, nausea 5%, dry mouth 3%, sedation 2%, vomiting 1%.⁽¹⁶⁾ Start with low doses to improve tolerance to side effects.⁽¹⁶⁾
- Nausea and vomiting respond to metoclopramide, phenothiazines and dexamethasone.⁽¹⁶⁾ Anaphylactic reactions estimated incidence is 1 in 700,000⁽⁸⁾ with an estimated fatality of one in 3.5 million.⁽⁸⁾
- Does not cause histamine release, so has a lower risk of pruritus.^(13,16)
- Provides more acceptable side effects than tricyclic antidepressants or antiepileptics.⁽¹⁰⁾
- Dependency has occurred (range of 1 in 6000 to 1 in 100,000).⁽¹³⁾ Most tramadol abuse is associated with polysubstance use and only 4.3% of the abuse is due to tramadol as a single agent.⁽¹⁶⁾ Screen for previous history of substance abuse, as Dr Schneider's clinical commentary is to prescribe it cautiously in patients with a history of abuse or addiction.⁽¹¹⁾
- Low abuse potential has been suggested^(1,8) and is reflected in the drug scheduling worldwide and not subject to the same prescribing formalities as morphine.⁽⁸⁾ Tramacet drug schedule permits a verbal prescription in Canada. Similarly, Zytram XL, is a prescription product, permitting prescribing as a verbal prescription.
- Potential interactions with ondansetron, (lowered tramadol efficacy) antipsychotics (including atypical), flecainide, quinidine, dextromethorphan.⁽¹³⁾ Tramadol can cause additive CNS depression and respiratory depression when used with other agents that are CNS depressants e.g. alcohol, other opioids.⁽¹⁴⁾
- Tramadol may affect other drugs, causing increased digoxin and warfarin levels, or reduced carbamazepine levels.⁽¹⁴⁾

Seizure Risk

- Higher incidence of serotonin syndrome and convulsions when tramadol combined with interacting drugs. These include SSRI's, TCA'S, MAO inhibitors, reversible inhibitors of monoamine oxidase, other opioids, buspirone, LSD, cocaine, ecstasy, amphetamines, cyclobenzaprine, St. John's wort, olanzepine, respiridone.^(13,14,16)
- Activity of tramadol only partially reversed with naloxone (about 30%).⁽³⁾ In tramadol overdose, naloxone administration may increase the risk of seizure.^(7,14)
- Treatment of seizure in Zytram XL product monograph suggests the use of diazepam.⁽⁷⁾ However in conversation with Ruth Hsu at Purdue medical information Jan 2, 2007, she stated that diazepam was considered representative as a class effect drug and that lorazepam would be a better choice, as has been suggested.⁽¹⁵⁾
- Seizure risk is much higher than other opioids. Occurs in one of 7000 patients,⁽¹⁶⁾ median onset of 2 days.⁽¹³⁾
- Deaths – 12 in the USA associated with convulsions and tramadol use. In two, tramadol was used solely.⁽¹³⁾

Additional Dosing Information

- Has been studied in 40 opioid naïve patients successfully.⁽¹⁾
- Best to withdraw drug slowly and not stop abruptly.⁽¹⁴⁾ There is a risk of withdrawal symptoms, anxiety, sweating, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, panic attacks, severe anxiety, paresthesias, and hallucinations (rarely).⁽¹⁴⁾ Possibly problematic in palliative patients, no longer able to swallow.
- Not recommended in Canada in patients under age 18.^(6,7)
- Tolerance appears to develop to a lesser extent in chronic use compared with other opioids.⁽¹³⁾
- B.C. Pharmacare palliative care non-benefit drug (Zytram XL and Tramacet).
- Don't confuse TRAMADOL with TORADOL (ketorolac).

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