fraserhealth
Better health.
Best in health care.

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.

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

Recommendation 1 Opioid 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 'Pain Guideline' for the assessment and management of pain.

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 'Pain Guideline' for the assessment and management of 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.

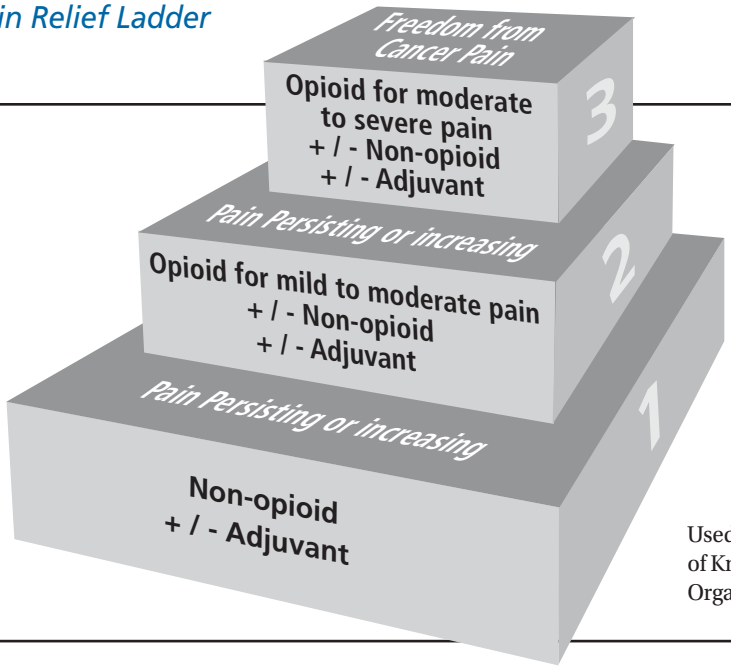
Identifying the underlying etiology of pain is essential in determining the interventions required.

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



Used with permission from the Department of Knowledge Management, World Health Organization, Geneva, Switzerland.

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	100, 200, 300, 400, 600, 800 mcg tablet
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	12 hour formulations: 3, 4.5, 6, 9, 12, 18, 24, 30 mg SR capsules 24 Hour formulations: 4, 8, 16, 32 mg	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:100 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	Not established
Opioid Class	Naturally occurring	Naturally occurring	Semi-synthetic	Semi-synthetic	Synthetic
Comments:	• Ceiling effect at 360- 600 mg • Ineffective analgesic in 10 percent of Caucasians and others lacking the enzyme to convert codeine to morphine.(1, 13, 14, 21)		• In renal failure metabolites may accumulate to toxic levels.(1)	• 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 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]

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 trans-mucosal absorption occur. If swallowed onset of action will be delayed due to slower gastrointestinal absorption rate.[1]
- Use of sublingual sufentanil requires close patient monitoring and titration - information regarding this procedure can be found in the Clinical protocol "Sufentanil - sublingual for management of incident pain in Hospice Residence and Tertiary Hospice Palliative Care Units" available from: http://fhpulse/clinical_resources/clinical_policy_office/Lists/CDST%20Library/DispForm.aspx?ID=1012

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, TCA's, 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 who are neutropenic or thrombocytopenic.[17]

Recommendation 7 Routes of Administration of Opioids continued...

  - 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 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 Bowel Care* 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 opiod 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 Twitching/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]

Recommendation 8 Adverse Effects of Opioids continued...

It is due to the accumulation of toxic metabolites and impaired renal 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 CO_2 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 effects have developed, employ a dose reduction to try and maintain adequate pain control with diminished adverse effects.[2]

Recommendation 9 Opioid Titration continued...

- Doubling the nightime dose will avoid wakening the patient in the early morning for a scheduled q4h dose, however, night loading doses should be considered only for 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 hours and three to six days respectively.[2] If transdermal 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 acetaminophen or ASA. 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]

References

Information was compiled using the CINAHL, Medline (1996 to April 2006) and Cochrane DSR, ACP Journal Club, DARE and CCTR databases, limiting to reviews / systematic reviews, clinical trials, case studies and guidelines / protocols using pain and opioid terms in conjunction with palliative / hospice / end of life / dying. Palliative care textbooks mentioned in generated articles were hand searched. Articles not written in English were excluded.

1. Black F, Downing GM. Pain - Analgesics. In: Downing GM, Wainwright W, editors. Medical Care of the Dying. 4th ed. Victoria, B.C. Canada: Victoria Hospice Society Learning Centre for Palliative Care; 2006. p. 189-251.

2. Black F, Wilde J, Downing GM. Pain - Principles and Titration. In: Downing GM, Wainwright W, editors. Medical Care of the Dying. 4th ed. Victoria, B.C. Canada: Victoria Hospice Society Learning Centre for Palliative Care; 2006. p. 159-88.

3. McLeod BE. 'Expert' nurses decision-making regarding intravenous patient controlled analgesia (Unpublished Thesis). The University of British Columbia; 2000.

4. McCaffery M, Pasero C. Assessment. In: McCaffery M, Pasero C, editors. Pain: Clinical Manual. 2nd ed. St. Louis: Mosby; 1999. p. 35-102.

5. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid Rotation in Patients with Cancer Pain. A Retrospective Comparison of Dose Ratios between Methadone, Hydromorphone and Morphine. Cancer. 1996 August 15;78(4):852-7.

6. Duquette C. Improving function and quality of life for older adults through pain assessment and management. 2002 [cited 2006 November]; Available from: http://www.medscape.com/viewarticle/443993

7. Waller A, Caroline NL. Principles and techniques of pharmacologic management. Handbook of Palliative Care in Cancer. 2nd ed. Boston, MA: Butterworth-Heinemann; 2000. p. 41-58.

8. Pain. In: Yarbro CH, Frogge MH, Goodman M, editors. Cancer Symptom Management. Sudbury, Massachusetts: Jones and Bartlett 2004. p. 83-7.

9. Gallagher R. Opioid Side Effects and Special Situations. In: Gallagher R, editor. Managing Cancer Pain The Canadian Health Care Professional's Reference. Toronto, Ontario: Healthcare & Financial Publishing, Rogers Media; 2005. p. 42-8.

10. Daeninck P, Shadd J. Non-opioid and adjuvant analgesics. In: Gallagher R, editor. Managing Cancer Pain The Canadian Health Care Professional's Reference. Toronto, Ontario: Healthcare & Financial Publishing, Rogers Media; 2005. p. 49-65.

11. Stimmel B. Symptoms of Opioid Withdrawal. Analgesia & Addiction: The Pharmacologic Treatment of Pain. New York: Raven Press 1983.

12. Bruera E, Kim HN. Cancer Pain. Journal of the American Medical Association. 2003 November 12;290(18):2476-9.

13. Gallagher R. Opioid Therapy for Cancer Pain. In: Gallagher R, editor. Managing Cancer Pain The Canadian Health Care Professional's Reference. Toronto, Ontario: Healthcare & Financial Publishing, Rogers Media; 2005. p. 29-41.

14. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny NI, Calman K, editors. Oxford Textbook of Palliative Medicine. 3rd ed. Oxford, England: Oxford University Press; 2004, paperback 2005. p. 316-41.

15. Waller A, Caroline NL. Modalities for Pain Control in Cancer. Handbook of Palliative Care in Cancer. 2nd ed. Boston, MA; 2000. p. 23-40.

16. Fine PG. Principles of effective pain management at the End of Life. [CME] 2006 [cited 2006 November]; Available from: http://www.medscape.com/viewprogram/6079

17. Miaskowski C, Cleary J, Burney R, Coyne P, Finley R, et al. Guideline for the Management of Cancer Pain in Adults and Children. Guideline for the Management of Cancer Pain in Adults and Children, APS Clinical Practice Guidelines Reprinted with permission of the American Pain Society. 3rd ed. Glenview, Il.: American Pain Society; 2005. p. 58-77.

18. World Health Organization. WHO's Pain Relief Ladder. 1986 [cited 2006 November]; Available from: http://www.who.int/cancer/palliative/painladder/en/

19. Kobierski BL. The 3 "B's" of symptom control during opioid therapy. In: Joint Fraser Health Fraser Valley Cancer Centre Symptom Guidelines Task Group, editor. Surrey, BC; 2006.

20. End of Life/Palliative Education Resource Center Medical College of Wisconsin, Pain and Palliative Care Committees. Analgesic Prescribing Guidelines. Guidelines for Physician Staff - Froedtert Hospital, Milwaukee, Wisconsin [cited 2006 November]; Available from: http://www.eperc.mcw.edu/Educational%20Materials/Clinical/Pain-AnalGuide.pdf

21. Harlos M, MacDonald L. Managing pain in palliative patients. In: MacDonald N, Oneschuk D, Hagen N, Doyle D, editors. Palliative Medicine - A case based manual. 2nd ed. New York: Oxford University Press Inc.; 2005.

22. Tayler C, McLeod B. Linking nursing pain assessment, decision-making and documentation. Canadian Journal of Oncology Nursing. 2001;11(1):28-32.

23. The Alberta Cancer Board PCN. Management of Cancer Pain. In: Pereira J, Otfinowski PB, Hagen N, Bruera E, Fainsinger R, Summers N, editors. The Alberta Palliative Care Resource. 2nd ed. Calgary, Alberta: The Alberta Cancer Board; 2001. p. 8-35.

24. Mercadante S, Arcuri E. Opioids and renal function. The Journal of Pain. 2004 February;5(1):2-19.

25. Glare P, Walsh D, Sheehan D. The adverse effects of morphine: a prospective survey of common symptoms during repeated dosing for chronic cancer pain. American Journal of Hospice and Palliative Medicine. 2006;23(3):229-35.

26. Reese TJ, Gwilliam B, Davies A. An assessment of the efficacy and tolerability of a "double dose" of normal release morphine sulphate at bedtime Palliative Medicine 2002. 16(6); 507-12.

27. Dean M, Harris JD, Regnard C, Hockley J. Using opioids. Symptom Relief in Palliative Care. Oxford, United Kingdom: Radcliffe Publishing Ltd; 2006. p. 49-52.

28. Federal Drug Administration. Decision memo-analysis and recommendations for agency action - COX-2 selective and non-selective NSAIDS. 2005 April 15, 2005 [cited 2006 November 23]; Available from http://www.fda.gov/cder/drug/infopage/cox2/NSAIDdecisionMemo.pdf

29. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. Journal of American Medical Association. 2006 October 14;296(13):1633-45.

30. Clinical Pharmacology (database online). Codeine monograph. Gold standard. 2006 November 23, 2006 cited; Available from: http://cpip.gsm.com

31. Miaskowski C, Cleary J, Burney R, Coyne P, Finley R, et al. Cancer Pain Management. Guideline for the Management of Cancer Pain in Adults and Children, APS Clinical Practice Guidelines Reprinted with permission of the American Pain Society. 3rd ed. Glenview, Il.: American Pain Society; 2005. p. 39-48.

32 Kunz K, Thiesen JA, Schroeder ME. Severe episodic pain: management with sublingual sufentanil. Journal of Pain and Symptom Management. 1993 May;8(4):189-90.

33 Donelly S, Davis MP, Walsh D, Naughton M. Morpine in cancer pain management: a practical guide. Supportive Care in Cancer. 2002;10(1):13-35.

34 Harlo M. Palliative care incident pain and incident dyspnea protocol [Online] 2002 Dec 8 [cited 2007 Jan 9] Available from: URL: http://www.palliative.info/incidentpain.htm

Fentanyl Transdermal

Principles

A. Indications For Fentanyl Transdermal Use

- Topical, non-invasive alternative to oral medications.[1,2]
- Poor absorption of oral opioids.
- To manage persistent severe pain; that is stable and controlled for at least 48 hours.
- To provide around the clock opioid treatment[3-5] and improve patient compliance.[6-7]
- To potentially lower opioid adverse effects of constipation,[8-11] nausea,[8] and histamine release.[12-14]
- Renal failure.[15]

B. Contraindications To Fentanyl Transdermal Use

- Significant patient risk of opioid toxicity including respiratory depression based on prior opioid dosing;
  - Current daily dose is less than 60 mg of oral morphine equivalent per 24 hours **and** duration of time on this dose has been inadequate to demonstrate opioid tolerance;
    - One week of stable, consecutive (uninterrupted) days of therapy is the minimum duration,[3,16-19] while up to two weeks has been suggested for chronic non-cancer patients.[20]
  - When codeine or tramadol was the prior regular opioid, due to inability to assure safe conversion to fentanyl.[20-22]
- Pain is mild, unstable or poorly controlled.[8,9]
- Acute pain management, e.g., post-operative, or during acute pain titration.[3-5,23-28]
- Patient is under 18 years of age.[3-5,23-28]
- Patients with significant respiratory depression and patients who have acute or severe bronchial asthma.[3,5]

C. Properties

- Fentanyl is suited for transdermal delivery (i.e., supply of medication for absorption through the skin into the bloodstream) because of its high potency (80 to 100 times that of morphine), low molecular weight and high lipid solubility.[6,19,29,30]
- Fentanyl blood concentrations level off between 12 to 24 hours after application.[6]
- Most commonly, full clinical effects will occur between 24 and 48 hours after a single patch application.[19]

- Steady state serum levels achieved after multiple patch dosing; by day six[31] but may be as long as twelve days due to individual variation in skin permeability, drug clearance.[3]
- After patch removal serum fentanyl concentrations decline gradually, falling about 50% in 17 hours, within a range of 13 to 22 hours.[5]
- No pharmacologic dose ceiling[30] but practical available skin coverage limits transdermal dose. In practice when required doses are 300 to 500 mcg per hour, effectiveness should be assessed with appropriate consideration of alternative means of analgesia as necessary.
- No known active metabolites, thus useful for patients with renal impairment.[32]

D. Safety Precautions

- Indicated for severe pain only due to safety concerns with opioid medicines that are controlled release and extended release, such as the fentanyl transdermal patch. The indication has been removed for use of these Canadian products for moderate pain.[33]
- Elevated temperature may increase fentanyl concentrations.[3-5,34-37] Monitor patient for fevers greater than 38.9° C and report to physician.[38,39] Avoid application site exposure to heat sources such as hot tubs, heated waterbeds, heating pads, electric blankets, heat lamps, saunas, or prolonged sunbathing.[3-5,37,40]
- Do not cut the patch delivery system, as this use would be outside the product's licensed indication.[3-5,23-28] Half of a matrix patch may not equal half a dose due to uneven cutting or lower surface area.[41] The current fentanyl patch matrix system (drug-in adhesive) has been cut in anecdotal clinical use[15,42] although no studies have been completed.[41]
- Caregivers should wear gloves when handling the patch to prevent unintentional caregiver transdermal absorption.[43] If the active patch surface accidentally does touch caregiver skin, soap use might further enhance transdermal fentanyl absorption. Flush and wash skin with water only if sticky adhesive side of patch accidentally touches skin, do not use soap.[3-5]
- Drug interactions occur primarily via three major mechanisms: increased central nervous system depressive effects causing risk of sedation and respiratory impairment; altered fentanyl metabolism by cytochrome P450 3A4 liver enzymes which increase or decrease drug levels; or additive serotonergic effects. *See Appendix A, TABLE A2 – Fentanyl Drug Interactions* for listing of drug interactions and details.
- Use in renal impairment with caution and at reduced doses due to possible gradual accumulation.[1,15] However, along with methadone, fentanyl is one of the safest opioids of choice in patients with chronic kidney disease.[1,44]
- Patients are at risk of thermal skin burns when wearing transdermal patches which contain aluminum or conductive material during some procedures.[23,45,46] Presently, only one Canadian brand of fentanyl transdermal patch provides a precaution regarding its application due to metallic (aluminum) content.[23] Prior to magnetic resonance imaging (MRI), cardioversion or electrocautery, assess then remove fentanyl patches if content is metallic.[23,45]

- Transdermal fentanyl patch use in patients with systemic skin disorders such as scleroderma is limited, but has been used.[47-49] In scleroderma, subcutaneous fibrosclerosis, deformity and devascularization of capillary skin vessels may disturb systemic absorption, with diminished transdermal fentanyl absorption reported in two scleroderma patients.[49]
- Hospital inpatient pharmacy departments are recommended to use order entry sets for all the fentanyl dosing levels to standardize dosage strengths provided.
- To minimize medication selection errors, use of TALLman lettering should represent the drug name as fentaNYL, to be employed per current policy in specified situations including for narcotic registers, medication labels, medication administration records, patient medication profiles, pre-printed orders, inventory and wardstock storage areas.[147]
- Refer to fentanyl transdermal patch product monographs for complete listing of precautions.[3-5,23-28]
- Refer to comprehensive transdermal patch reviews for detailed medication safety practices to guide medication error prevention and safety practices.[45,50,51]

E. Storage and Disposal of Transdermal Patches

- Ensure safe storage of new and used patches, out of sight and away from children and pets, or others who could misuse.[3,52]
- A used patch may contain enough residual fentanyl to be potentially lethal for children or an opioid naïve adult.[53] Matrix patches on average will retain 57 to 59% of the original fentanyl content after 72 hours and 71 to 73% after 48 hours. These residual percentages are significantly greater (from 37 to 100 % higher) than the older reservoir patch system. The residual fentanyl in the patch can range widely due to interindividual differences.[53-55]
- Avoid overprescribing, and limit patch quantities prescribed. Intentional suicides and overdoses using multiple fentanyl patches have occurred with misuse or diversion by patients or family members with access.[56-60] Overprescribing medication also poses environmental concerns when unused medication requires disposal.[61]
- A patch exchange return program has been implemented in Ontario to minimize diversion of used patches where there is a concern of misuse.[62-65]
- The safe disposal of patches remains an issue of major risk management concern. Its importance has been stressed in several reports and cases of fatalities.[38,52,56-60,66-77] **Safe disposal should always occur** - select the method most suitable for the patient setting. Consider various risks such as potential caregiver or family member misuse or abuse, presence of children or pets. Flushing the patch down the toilet provides an immediate and effective disposal method to avoid unintentional poisonings and abuse[23, 24, 26, 27], although there are environmental concerns.

- Lockable medication boxes have been suggested by fentanyl patch manufacturers for temporary storage of used fentanyl patches prior to disposal.[3-5,25] Few sources exist to obtain these lockable medication boxes[78,79] so families should use alternative locked storage.

Recommendations for Disposal

Hospitals

- After removal fold patch in half – sticky side to sticky side.
- Immediate disposal should be undertaken into a sharps container by a nurse, witnessed by another nurse, and documented on the medication administration record with the initials of both nurses.[80,81]
- Dispose a used patch into a sharps container with restricted access, e.g., within nursing station, to minimize or prevent patch removal from container.
- Full sharps containers should be securely stored in a separate area designated for the storage of biomedical waste to prevent unintended access prior to collection for waste disposal and incineration.[80]
- Use of sharps containers as a suitable used fentanyl patch disposal container has been questioned for a number of reasons such as not being child-proof, single-use, and expensive, with current disposal within Fraser Health involving water sterilization and landfill final disposal.[82] Within hospitals, considered environmental waste options might include a secure specialty drug sink collection method.[83]

Hospice Residences, Licensed Care Facilities

- Follow regulations or procedures for your facility.
- Check with your community pharmacy provider for disposal assistance.
- Consider following recommendations for hospitals as noted above, with use of sharps container or alternative.

Community, e.g., patient's own home

Preferred Method

- After removal fold patch in half – sticky side to sticky side.
- Immediately place in a tamperproof, child-resistant container, *see Figure A1*.
  - A sufficiently large empty prescription vial with child-resistant lid;
    - i.e., that is 9 cm (3 ½ inches) tall; a size such as a 30 or 40 dram vial.
    - Patches from the various manufacturers vary in shape and size rectangular, square depending on the strength. The vial should accommodate the appropriate patch size – which will be to a maximum length for the longest patch, 100 mcg per hour measuring 6 to 9 cm (2 ½ - 3 ½ inches) in length.

- Ensure the tamperproof, child-resistant container with the used patches is securely stored in an out of sight location to prevent accidental removal or access by children or pets. A lockable medication box for temporary storage has been suggested.[3-5,25]
- Return the used patches within the tamperproof, child-resistant container or vial regularly to the community pharmacy. Nearly all of British Columbia pharmacies participate in a medication return take-back program.[82]

Alternative Method

*Use in situations when it is of foremost importance to assure safety; i.e., to prevent possibility **for accidental, intentional or unintended use**.

- After removal fold patch in half – sticky side to sticky side.
- Immediately flush patch down toilet.[23,24,26,27]

** This method is not recommended if there are other suitable and safe methods of disposal. This method is not recommended when the sewage system is a septic field or septic tank.[70] A medication disposal product Deterrasystem™ which is a bag with deactivation properties using carbon, may be an option for immediate neutralization for patients with a septic system; however, there is insufficient data regarding its safety and effectiveness.[84-87]

Practice

A. Converting to Fentanyl Transdermal Patch

- If patient previously on codeine or tramadol, do not convert to fentanyl transdermal patch;[21] **please seek consultation** due to significant interpatient variability in metabolism, safety and effectiveness concerns with these drugs.
- Conversion from oxycodone may require some precaution due to the potential of variable polymorphism and different active metabolites produced.[88-90] However, this is insufficiently studied to currently provide dosing adjustment advice, so consider seeking consultation.
- Assess current 24-hour opioid requirement of morphine, hydromorphone or oxycodone. For other opioids convert them to a 24 hour oral morphine equivalent dose. Based on the estimated 24-hour equivalent morphine, hydromorphone or oxycodone dose. *See Chart A1 Fentanyl Transdermal Patch Equianlagesic Conversion.*
- Use Chart A1 to perform *uni*directional conversion; i.e., to transdermal fentanyl from other opioids.[3-5,91]
- Do not reduce the morphine equivalent amount to account for a lack of complete cross tolerance[91,92] as the conversion chart is designed to be conservative, with 50% of patients requiring a dose increase after the initial patch strength application.[4]

- ***Always*** provide a breakthrough dose selecting the appropriate dose. *See Chart A2 - Approximate Breakthrough Doses Recommended for Fentanyl Transdermal Patch.* Because the conversion is conservative and approximate, provision of breakthrough (BT) doses is important. Breakthrough pain is most commonly reported within the first three days of patch treatment.[93]
- If breakthrough doses of immediate release morphine or immediate release hydromorphone are given subcutaneously, give one-half the oral dosage, typically provided every hour as needed.
- Monitor for adverse effects during initiation (and dose increases) particularly for sedation and respiratory depression.[3-5] Use the Pasero Opioid Sedation Scale for sedation monitoring.[94-96] Should opioid excess occur, refer to Clinical Protocol "Appropriate use of narcotic antagonist (naloxone) in adult hospice palliative care patients"[97] and Clinical Practice Guideline for the "prevention, recognition and management of opioid excess in adult hospice palliative care patients[96] remembering that with the prolonged effects of transdermal fentanyl, with a half-life of 13 to 22 hours after patch removal, that extended monitoring and management is needed.
- These guidelines do not recommend initiating patients on a 12 mcg per hour patch unless conditions of opioid tolerance are assured – see contraindications section above. Should a prescriber be considering starting a 12 mcg per hour patch, review product monograph advice and warnings, while exercising cautious clinical judgment and seeking consultation. When patients are not sufficiently opioid tolerant to initiate fentanyl transdermal patch, an alternative transdermal system of buprenorphine might be considered, starting only at the lowest, 5 mcg per hour strength.[127]

CHART A1 - Fentanyl Transdermal Patch Equianalgesic Conversion*†

Oral Morphine (mg per day)	SC/IV Morphine (mg per day)	Oral HYDROmorphone (mg per day)	SC/IV HYDROmorphone (mcg per day)	Oral oxyCODONE (mcg per day)	Transdermal fentaNYL (mcg per hour)
60-134	30-67	12-26	6-13	45-89	25
135-179	68-89	27-35	14-17	90-119	37
180-224	90-112	36-44	18-22	120-149	50
225-269	113-134	45-53	23-26	150-179	62
270-314	135-157	54-62	27-31	180-209	75
315-359	158-179	63-71	32-35	210-239	87
360-404	180-202	72-80	36-40	240-269	100
405-449	203-224	81-89	41-44	270-299	112
450-494	225-247	90-98	45-49	300-329	125
495-539	248-269	99-107	50-53	330-359	137
540-584	270-292	108-116	54-58	360-389	150
585-629	293-314	117-125	59-62	390-419	162
630-674	315-337	126-134	63-67	420-449	175
675-719	338-360	135-143	68-71	450-479	187
720-764	361-382	144-152	72-76	480-509	200
765-809	383-404	153-161	77-80	510-539	212
810-854	405-427	162-170	81-85	540-569	225
855-899	428-449	171-179	86-89	570-599	237
900-944	450-472	180-188	90-94	600-629	250
945-989	473-494	189-197	95-98	630-659	262
990-1034	495-517	198-206	99-103	660-689	275
1035-1079	518-539	207-215	104-107	690-719	287
1080-1124	540-562	216-224	108-112	720-749	300

SC = subcutaneous, IV = intravenous

*The conversions between fentanyl and morphine are partially taken from the Duragesic MAT monograph in the 2011 Compendium of Pharmaceuticals and Specialties.[98] The hydromorphone and oxycodone conversions are based on a morphine to hydromorphone ratio of (5:1) and a morphine to oxycodone ratio of (1.5:1).[99]

†Use Chart above ONLY to perform unidirectional conversion; i.e., **to** transdermal fentanyl **from** other opioids.

For reverse direction conversion, see Chart A4 and consult hospice palliative care physician or pharmacist.

For doses above 300 mcg per hour consult hospice palliative care physician or pharmacist.

CHART A2 – Approximate Breakthrough Doses Recommended for Fentanyl Transdermal Patch

FentaNYL Patch Strength	morphine		HYDROmorphone		OxyCODONE
	Oral Immediate Release	Subcutaneous	Oral Immediate Release	Subcutaneous	Oral Immediate Release
12 mcg per hour	5 mg	2.5 mg	1 mg	0.5 mg	2.5 mg
25 mcg per hour	10 mg	5 mg	2 mg	1 mg	5 mg
37 mcg per hour	15 mg	7.5 mg	3 mg	1.5 mg	10 mg
50 mcg per hour	20 mg	10 mg	4 mg	2 mg	12.5 mg
62 mcg per hour	25 mg	12.5 mg	5 mg	2.5 mg	15 mg
75 mcg per hour	25 mg	12.5 mg	5 mg	2.5 mg	17.5 mg
87 mcg per hour	30 mg	15 mg	6 mg	3 mg	20 mg
100 mcg per hour	35 mg	17.5 mg	7 mg	3.5 mg	25 mg
112 mcg per hour	40 mg	20.5 mg	8 mg	4 mg	27.5 mg
125 mcg per hour	45 mg	22.5 mg	9 mg	4.5 mg	30 mg
137 mcg per hour	50 mg	25 mg	10 mg	5 mg	32.5 mg
150 mcg per hour	55 mg	27.5 mg	11 mg	5.5 mg	35 mg
162 mcg per hour	60 mg	30 mg	12 mg	6 mg	40 mg
175 mcg per hour	65 mg	32.5 mg	13 mg	6.5 mg	42.5 mg
187 mcg per hour	70 mg	35 mg	14 mg	7 mg	45 mg
200 mcg per hour	70 mg	35 mg	14 mg	7 mg	47.5 mg
212 mcg per hour	75 mg	37.5 mg	15 mg	7.5 mg	50 mg
225 mcg per hour	80 mg	40 mg	16 mg	8 mg	55 mg
237 mcg per hour	85 mg	42.5 mg	17 mg	8.5 mg	57.5 mg
250 mcg per hour	90 mg	45 mg	18 mg	9 mg	60 mg
262 mcg per hour	95 mg	47.5 mg	19 mg	9.5 mg	62.5 mg
275 mcg per hour	100 mg	50 mg	20 mg	10 mg	65 mg
287 mcg per hour	105 mg	52.5 mg	21 mg	10.5 mg	70 mg
300 mcg per hour	110 mg	55 mg	22 mg	11 mg	72.5 mg

B. Initiation of Fentanyl Transdermal Patch

- During the first twelve hours after the patch has been started, utilize appropriate regular, ***AS WELL AS*** PRN (as needed) dosing during the transition. *See Chart A3 - Switch Schedule for Initiation of Fentanyl Transdermal Patch and Discontinuation of Prior Opioids.*
- Maintain patch in manufacturer's packaging until ready to apply. Place patch on a dry, non-hairy, non-inflamed, non-irradiated skin area, on chest, back, flank or upper arm without cuts or sores.[3-5,15,100] A flat surface is recommended, and locating the patch where skin movement is limited, such as the anterior chest wall, or either side of the midline on the (preferably lower) back. Avoid areas where tight clothing, straps could

rub the patch off.[41,45,100] Body hair may be clipped with scissors, but do not shave, as this could irritate skin. Avoid placing a patch over a tattoo, whenever possible. Fentanyl toxicity occurred due to increased absorption from patch on top of a five day old tattoo.[101] Data is absent regarding the effect on absorption with established tattoos.

- Ensure patch is firmly adhered to skin; hold palm of hand over patch for 30 seconds to ensure complete contact, especially around the edges.[3] Fentanyl patches that have fallen off or accidentally transferred to children have resulted in deaths.[51,52,71-73,76] Do not let children see patch application, and do not call them stickers, tattoos or Band-Aids which could encourage them to mimic your actions.[71]
- Patch adherence can occasionally be problematic. Opioids such as transdermal fentanyl can cause sweating in up to 10% of patients.[102] The occlusive patch itself may induce sweating, irritation and adhesion difficulties,[103] which is more pronounced in warm weather.[104-106]
- Current product instructions do permit use of an transparent adhesive film dressing (such as Tegaderm or Bioclusive) completely over top of the fentanyl transdermal patch to keep patch adhered to skin.[3-5,23-28,107]
- In disorientated persons where there is a risk they might remove the pain patch, consider patch placement on the upper back to minimize removal risk, or covering it with an transparent film dressing overlay (such as Tegaderm or Bioclusive).[107-109] Inadvertent removal and insecure discarding of fentanyl patches poses a harm risk to others.
- Confirm patch position and that it remains adhered to the skin, by sight or touch, at a minimum of once daily, and more frequently according to nursing discretion, when factors necessitate; e.g., bathing, sweating, removal for a procedure.[39,110-113] Regular confirmation of adhesion permits determination of effectiveness.[112]
- Patch size and shape might affect adherence, though this has not been studied. Available strength sizes and dimensions are similar from most manufacturers. Some brands are sized differently. *See Table A1 below.*

TABLE A1 - Sizes of Canadian Fentanyl Transdermal Patches

Brand/Strength	12 mcg	25 mcg	37 mcg	50 mcg	75 mcg	100 mcg
Apotex[23,114]	Not available	10.7 cm^2 31.12 x 35.08 mm	Not available	21.4 cm^2 39.68 x 54.48 mm	32.1 cm^2 54.48 x 59.31 mm	42.8 cm^2 51.37 x 83.73 mm
Janssen[3,115]	5.25 cm^2 20.47 x 26.06 mm	10.5 cm^2 25.48 x 41.48 mm	Not available	21 cm^2 37.77 x 60.83 mm	31.5 cm^2 55.19 x 60.78 mm	42 cm^2 60.73 x 72.4 mm
Mylan[25,116]	3.13 cm^2 12.7x 25.48 mm	6.25 cm^2 18.3 x 35.70 mm	Not available	12.5 cm^2 39 x 42.6 mm	18.75 cm^2 41.6 x 45.8 mm	25 cm^2 41.6 x 60.8 mm
Pharmascience[26,117] & Ranbaxy[28,118]	5.25 cm^2 16.25 x 32.5 mm	10.5 cm^2 32.5 x 32.5 mm	Not available	21 cm^2 32.5 x 65 mm	31.5 cm^2 56.2 x 56.2 mm	42 cm^2 56.2 x 75 mm
Sandoz[5,119]	5.25 cm^2 16.25 x 32.5 mm	10.5 cm^2 32.5 x 32.5 mm	15.75 cm^2 32.5 x 48.5 mm	21 cm^2 32.5 x 65 mm	31.5 cm^2 56.2 x 56.2 mm	42 cm^2 56.2 x 75 mm
TEVA[28]	3.75 cm^2 20 X 20 mm	7.5 cm^2 26 X 30 mm	Not available	15 cm^2 30 x 51 mm	22.5 cm^2 47.5 x 48 mm	30 cm^2 47.5 x 64 mm

- Cachectic patients may have reduced skin permeability due to reduced subcutaneous fat tissue for reliable drug depot transfer, hence fentanyl pharmacokinetics may be altered.[3,120,121] While fentanyl plasma levels were normal at 4 and 24 hours after application in cachectic patients (BMI less than 18 kg/m^2), they were significantly lower at 48 and 72 hours than normal weight patients.[120] Monitor for adequacy of sustained pain relief and consider Q48H patch replacement if there is any wearing off effect (end of dose failure).[122,123]
- Patients with advanced cancer suffering from sweating or cachexia may have reduced absorption of transdermal fentanyl.[121] Switching to other opioids, e.g., morphine, hydromorphone, may be necessary to improve opioid delivery efficacy and tolerability. [121]
- Do not write on a fentanyl transdermal patch; e.g., with a permanent ink Sharpie marker due to risk of ink leaching or risk of puncturing the patch's surface.[45,124] Use the supplied manufacturer labels to write the date and time of patch application on them, then attach those labels to the patch. Record time, date and location of application in the medication administration record sheet.[125]
- When rotating application sites it is recommended to not reapply to the same site within seven days to help minimize irritant skin reactions.[45] Anecdotal management of skin irritation from transdermal patches has included use of steroid sprays topically prior to patch application (e.g., fluticasone or beclomethasone),[43,126-131] however, use of this practice only discussed in some detail in four transdermal fentanyl patients.[129] Use of skin creams are best avoided during patch application, but after removal steroid creams can be considered, with the suggestion to wait 6 to 12 hours post removal.[127]

CHART A3 – Switch Schedule for Initiation of Fentanyl Transdermal Patch and Discontinuation of Prior Opioids[131,132]

From other opioid to Fentanyl Transdermal (FTD) Patch	0 Hour	4 Hour	8 Hour	12 Hour
ORAL immediate release (IR) to Transdermal (FTD) Patch	Apply patch + give regular IR dose	Regular IR dose	Give last regular IR dose then stop	No IR dose
ORAL Sustained release (SR) FTD Patch	Apply Patch + give one SR Dose	No SR dose	No SR dose	No SR dose
Subcutaneous (SC) intermittent (e.g., Q4H) to FTD Patch	Apply Patch + give regular SC dose	Give full SC dose	Give last regular SC dose then stop	No SC dose
Continuous subcutaneous infusion (CSCI) to FTD Patch	Apply patch, continue full CSCI dose for 4 to 8 h, then stop the infusion			No CSCI
	** NOTE: Provide PRN Breakthrough dose throughout Conversions			

Literature provides little data regarding a scheduled switch.[91,131,132] Supervise closely during use of this suggested guideline.[131,132]

C. Dose Titration with Fentanyl Transdermal Patch

- Wait a minimum of three days after initial application for the first dosage increase.[3-5,23-28] All subsequent dosage increases should occur six days following the previous application.[3-5,23-28]
- Calculate and total the amount of breakthrough doses in the prior 24 hours to guide incremental dose increase.[91]
- Consider a 30 to 50% baseline dose increase,[133,134] usually in 12 to 25 mcg per hour dose increments, using the available patch strengths. Below is the approximate equianalgesia when titrating using the 12 mcg per hour fentanyl transdermal patch.

Oral Morphine (mg per day)	SC/IV Morphine (mg per day)	Oral HYDROmorphone (mg per day)	SC/IV HYDROmorphone (mg per day)	Oral oxyCODONE (mg per day)	Transdermal fentaNYL (mcg per HOUR)
45 - 59	22 – 30	9 - 12	4.5 - 6	30 - 40	12

- Always remove the old patch before applying a new one and rotate the sites of application.[15] Ensure patients are educated to do the same.
- When less than a full patch dose is desired, a dose-modifying method has been suggested which involves applying an occlusive dressing (such as TEGADERM) onto the skin to block the appropriate surface area portion of the patch exposed to the skin, i.e., half the patch contact surface on top of the dressing and half adhered to the skin.[135-138] The absorption from a transdermal patch is proportionate to the surface area of the patch.[31] Dose-modifying methods using a half-patch are **best avoided** or used very cautiously, as this can be error-prone due to unfamiliarity and lack of approved instructions.[139] To date, a single fatal case was reported to Health Canada in which a health care professional was using a dose-modifying method.[140]
- Patches are usually replaced every 72 hours. Early wearing off of the patch's effectiveness (end of dose failure) with emergence of pain on day 3 of patch application can indicate under-dosing and the need for the patch dose strength to be increased. Alternatively, changing patches every 48 hours is a consideration.[91,122,123] A review of cause of failure is indicated, and may include; cachectic patients, smokers, rapid metabolizers, improper application, poor therapy compliance, prolonged elevated heat or temperature and drug interactions causing increased metabolism (e.g., carbamazepine, dexamethasone, ethanol, nicotine, phenytoin, phenobarbital, rifampin and valproic acid).[122,141,142]
- Provide and appropriately adjust for a new PRN breakthrough dose.[7,19] *See Chart A2 – Approximate Breakthrough Doses Recommended for Fentanyl Transdermal Patch as a guide.*
- Increases in the dose of fentanyl patches are NOT appropriate for patients who have incident pain whose pain is otherwise well controlled. Incident pain should be managed by appropriate use of breakthrough analgesia, or sublingual sufentanil.

- With changes in fentanyl patch doses, the safest recommended practice is **to remove all prior used patches** and commence all new patches.[143,144] This will ensure that all patches have the same start date. Any other method requires clear communication involving the patient, care providers and the pharmacy.

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 17 hours of removal, 75% in 34 hours, 87.5% in 51 hours and 93.5% in 68 hours.[5,6,91]
- Ensure safe disposal of patch, see recommendations for disposal earlier in document.
- Fentanyl patches should be removed from the skin of deceased patients, preventing unintended fentanyl overdose as a 31 year old funeral home employee died from misuse.[145]
- *See Chart A4 - Switch Schedule for Discontinuation of Transdermal Fentanyl Patch and Initiation of Opioids* when discontinuing patch and initiating immediate or sustained release oral therapy, intermittent subcutaneous (SC) or Continuous Subcutaneous Infusion (CSCI) therapy.

CHART A4 – Switch Schedule for Discontinuation of Fentanyl Transdermal Patch and Initiation of Opioids[131,132]

From Fentanyl Transdermal Patch (FTD) to other opioid	0 Hour	4 Hour	8 Hour	12 Hour
FTD Patch to Oral IR	Remove Patch	No IR dose	Full IR dose	Continue IR dose
FTD Patch to Oral SR	Remove Patch	No IR dose	Full SR dose	–
FTD Patch to intermittent SC	Remove Patch	No SC dose	Full SC dose	Continue SC dose
FTD Patch to CSCI	Remove Patch	Begin full CSCI dose 4 to 8 hours after removal of patch, or start with a breakthrough dose followed by full dose at 12 hours		Full CSCI dose

**** NOTE: Provide PRN Breakthrough dose throughout Conversions**

Literature provides little data regarding a scheduled switch.[131,132] Supervise closely during use of this suggested guideline,[131,132] particularly if patient is cachectic and reporting little or no improvement with prior patch doses increases, with consideration of using the last effective patch strength upon which to base conversion calculations.[91]

Education

Patient information leaflets are available from each of the Canadian manufacturers of fentanyl transdermal patch. They are described as a Consumer Information document. Two of the manufacturers provide the leaflets directly on the firm's websites[3,146] while for others refer to the corresponding product supplier[4,5,23-28] and can be found within the final pages of the firm's product monographs accessible from Health Canada's Product Database found at: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

For general Fentanyl Transdermal information (subscription required) refer to: http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410380

Patient Disposal of Fentanyl Transdermal Patches

Provide patients the information brochure. *See Figure A1 – Fraser Health Patient Information Brochure – Safe Disposal of Used Pain Patches at Home.* Obtain brochure from Fraser Health patient education website: https://patienteduc.fraserhealth.ca/search/results/78982
Ensure patient and family comprehension, ability to perform, and ask if patient or family have any questions.

References

1) Cancer Care Ontario's Symptom Management Guides-to-Practice: Pain. Toronto: Cancer Care Ontario; 2010 Available from: https://www.cancercare.on.ca/CCO_DrugFormulary/Pages/FileContent.aspx?fileId=97481

2. NICE. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. NICE Guideline 140. Manchester: National Institute for Health and Clinical Excellence; 2012 Available from: Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. http://www.nice.org.uk/guidance/cg140

3. Duragesic Mat product monograph [Online]. 2014 Aug 5 [cited 2014 Sep 26]; Available from: http://www.janssen.ca/product/114

4. RAN-Fentanyl Transdermal system product monograph 2013 Apr 5 Ranbaxy Pharmaceuticals Canada Inc Mississauga Ontario. [cited 2013 Jul 12] Available from http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

5. Sandoz fentanyl patch product monograph [Online]. 2014 Sep 22 [cited 2014 Nov 7] Available from: http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

6. Muijsers RBR, Wagstaff AJ. Transdermal Fentanyl an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 2001;61(15):2289-307.

7. Carver AC, and Foley KM. Palliative care symptom assessment and management. Neurologic Clinics 2001 Nov; 19(4).

8. Grond S, Radbruch L, Lehmann K. Clinical pharmacokinetics of transdermal opioids. 2000 Jan; 38(1):59-89.

9. Radbruch L, Sabatowski R, Loick G, Kulbe C, Kasper M, Grond S et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. Palliative Medicine 2000;14:111-9.

10. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncology 2012;13:e58-68.

11. Tassinari D, Sartori S, Tamburini E, Scarpi E, Tombesi P, Santelmo C et al. Transdermal fentanyl as a front-line approach to moderate-severe pain: a meta-analysis of randomized clinical trials. J of Palliative Care 2009;172-80.

12. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report Expert working group of the EAPC. Journal of Clinical Oncology 2001 May 1;19(9):2542-54.

13. Analgesic options for patients with allergic-type opioid reactions, opioid intolerance decision algorithm. Pharmacists Letter Feb 2006 Vol 22 Document #200915,220201.

14. Fine PG, Yox S. Principles of effective pain management at the End of Life. [CME] 2006 [cited 2015 Apr 8]; Available from: http://www.medscape.org/viewarticle/545562

15. Guidelines on the use of transdermal fentanyl patch (version 8 8/2008) Selby & York Palliative Care Team & Pharmacy Group. North Yorkshire and York [cited 2014 Jan 6] Available from: http://www.yacpalliativecare.co.uk/documents/download62.pdf

16. Duragesic product monograph [Online]. [cited 2010 Mar 29]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/19813s039lbl.pdf

17. Fentora (fentanyl buccal/sublingual effervescent tablet) product monograph. TEVA Canada Innovation. 2013 Oct 31 [Online]. [cited 2014 Oct 24]; Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187537.pdf

18. Product information Fentora (fentanyl) Cephalon Inc. [Online]. 2010 [cited 2010 Apr 12]; Available from www.fentora.com/hcp300_default.aspx.

19. Hall T, Hardy JR. The lipophilic opioids;fentanyl, sufentanil and remifentanil. In: Davis M, Glare P, Hardy J. Opioids in cancer pain. Oxford (U.K.): Oxford University Press; 2005 p.155-171.

20. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain 2010 National Opioid Use Guideline Group (NOUGG). p 28, 31 [cited 2014 Jan 10] Available from: http://nationalpaincentre.mcmaster.ca/opioid/

21. Jensen K, Regier L, Cassidy J, Bell C. Saskatchewan Drug Information Services, College of Pharmacy, University of Saskatchewan. Switching opioids using equivalence tables 2012 May 1 [Cited 2013 Feb 14] Available from: http://druginfo.usask.ca/healthcare_professional/drug_shortages_pdfs/Switching%20opioids%20using%20equivalence%20tables.pdf

22. Palliative Pain & Symptom Management Consultation Service for Toronto October Tip [cited 2014 Jan 10] Available from: http://www.ppsmctoronto.com/en/caretips/previoustips.asp#

23. Apo-Fentanyl Matrix fentanyl transdermal system product monograph 2014 Jan 31, Apotex Canada Inc. Toronto Canada. [cited 2014 Nov 7] Available from: http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

24. Co-Fentanyl product monograph 2013 May 21, Cobalt Pharmaceuticals Co Mississauga Ontario Canada.

25. Mylan-Fentanyl Matrix Patch fentanyl transdermal system product monograph 2015 Sep 4, Mylan Pharmaceuticals ULC Etobicoke, Canada. [cited 2014 Nov 7] Available from: http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

26. pms-Fentanyl MTX product monograph 2013 Aug 20 Pharmascience Inc Montreal Canada.

27. ProDoc Fentanyl Patch transdermal (Matrix) product monograph 2013 May 21 Pro Doc Ltée Laval, Canada.

28. TEVA-Fentanyl fentanyl transdermal system product monograph 2014 Sep 11 Teva Canada Ltd, Toronto Canada. [cited 2014 Nov 7] Available from: http://hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

29. Black F, Downing GM. Pain – Analgesics In: Downing GM, Wainwright W, editors. Medical Care of the Dying. 4th ed. Victoria B.C. Canada: Victoria Hospice Learning Centre for Palliative Care; 2006. P 189-251.

30. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In Doyle D, Hanks G, Cherny NI, Calman K. editors. Oxford Textbook of Palliative Medicine. 3rd ed. Oxford, England: Oxford University Press; 2004, paperback 2005. P 316-41.

31. McLean M, Fudin J. Optimizing pain control with fentanyl patches. 2008 July 15.[cited 2013 Nov 29]; Available from: http://www.medscape.com/viewarticle/576398

32. Dean M. Opioids in renal failure and dialysis patients. J Pain and Symptom Manage 2004 Nov;28(5):497-504.

33. Health Canada. Label changes for controlled-release opioid pain medicines encourage more targeted prescribing and safer use. [Online] 2014 Aug 18. [cited 2014 Sep 4] Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/41157a-eng.php

34. Ashburn MA, Ogden LL, Zhang J, Love G, Basta SV. The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. The Journal of Pain 2003 Aug;4(6)291-7.

35. Gupta SK, Southam M, Gale R. System functionality and physiochemical model of fentanyl transdermal system. J Pain Symptom Mange 1992;7:S17-S26.

36. Newshan G. Heat-related toxicity with the fentanyl transdermal patch. J Pain Symptom Manage 1998;16(5):277-8.

37. Rose PG, Macfee MS, Boswell MV. Fentanyl transdermal system overdose secondary to cutaneous hyperthermia. Anesth Analg 1993;77(2):390-1.

38. Institute for Safe Medication Practice. Ongoing, preventable fatal events with fentanyl transdermal patches are alarming! 2007 Jun 28 [cited 2013 Feb 14] Available from: http://www.ismp.org/Newsletters/acutecare/articles/20070628.asp

39. Federal Drug Administration. FDA patient safety news: show #67 September 2007. [cited 2014 Mar 7] available from: http://www.accessdata.fda.gov/psn/printer-full.cfm?id=71

40. Sindali K, Sherry K, Sen S, Dheansa B. Life-threatening coma and full-thickness sunburn in a patient treated with transdermal fentanyl patches: a case report. Journal of Medical Case Reports 2012;6:220 4 pages. Available from: http://www.jmedicalcasereports.com/content/6/1/220

41. Characteristics of transdermal patches. Pharmacist's Letter/Prescriber's Letter August 2012 PL Detail-Document #280813 14 pages

42. Cutting fentanyl matrix patches. Newsletter.[Online] 2005 May/June [cited 2006 Nov 23] Available from: URL: http://www.palliativedrugs.com

43. Gardner-Nix J. Caregiver toxicity from transdermal fentanyl. Journal of pain and symptom management 2001 Jun;21(6):447-8.

44. Control of pain in adults with cancer 106 Scottish Intercollegiate Guidelines Network. 2008 [cited 2014 Sep 5] Available from: http://sign.ac.uk/guidelines/fulltext/106/index.html

45. Lambert A, Seiberth J, Haefeli WE, Seidling HM. A systematic review of medication administration errors with transdermal patches. Expert Opinion Drug Safety 2014;13(8);1101-14.

46. Health Canada Notice to Hospitals Health Canada endorsed important safety information on magnetic resonance imaging systems. 2005 April 26. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14350a-eng.php

47. Olsen NJ, Palmer BF. Scleroderma: the need for extreme remedies. Am J Med Sci 2011;342(5):416-421.

48. Maier M. Pulsed radio frequency energy in the treatment of painful chronic cutaneous wounds: a report of two cases.

49. Karst M, Fink M, Wagner T, Conrad I. Transdermal fentanyl:little absorption in two patients with systemic sclerosis? Pain Medicine 2001;2(3):225-27.

50. Institute for Safe Medication Practices Canada. Medication incidents related to the use of fentanyl transdermal systems; an international aggregate analysis. 2009 [cited 2014 Nov 13] Available from: http://www.intmedsafe.net/imsn-advocacy/medication-safety-issues/

51. Fentanyl patches; preventable overdose Prescrire Int 2010 Feb; 19(105):22-5.

52. Institute for Safe Medication Practices Fentanyl patch fatalities linked to "bystander apathy" We all have a role in prevention! 2013 Aug 8 [cited 2013 Nov 29]; Available from: http://www.ismp.org/newsletters/acutecare/showarticle.asp?id=55

53. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. Annals of Pharmacotherapy 1995;29(10):969-71.

54. Solassol I, Caumette L, Bressolle F,Garcia F, Thézenas S, Astre C et al. Inter-and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. Oncology Reports 2005 Oct;14(4):1029-36.

55. Wiggins SH, Mahnken J, Reed GA. Extent of variability in fentanyl plasma levels during steady-state transdermal delivery in older nursing home residents. JAGS 2012 Oct;60(10);1986-8.

56. Lyttle MD, Verma S, Isaac R. Transdermal fentanyl in deliberate overdose in pediatrics. 2012 Pediatric Emergency Care 28(5): 463-4.

57. Wiesbrock UO, Rochholz G, Franzelius C, Greliner W. Excessive use of fentanyl patches as the only means of suicide. Archiv fur Kriminologie 2008;222(102):23-30.

58. LoVecchio F, Ramos L. 2011 Case report: suicide by Duragesic transdermal fentanyl patch toxicity. American Journal of Emergency Medicine 29:131.e1-131.e2.

59. Sjöberg, Personne M, Karlson-Stiber C. Misuse and abuse of fentanyl depot transdermal patches. XXXIV International Congress of European Poisons Centres and Clinical Toxicologists-Abstract # 186.Clinical Toxicology 2014;52:375.

60. Juebner M, Fietzke M, Beike J, Rothschild MA, Bender K. Assisted suicide by fentanyl intoxication due to excessive transdermal application. Int J Legal Med 2014 Nov;126(6):949-56.

61. Daughton CG, Ruhoy IR. Lower-dose prescribing: minimizing "side effects" of pharmaceuticals on society and the environment. Science of the Total Environment 2013;443:324-37.

62. Fentanyl patch return program Peterborough County-City Health Unit. 2014 Feb 18 [cited 2014 May 14] Available from: http://www.pcchu.ca/2014/02/18/local-healthcare-providers-collaborate-to-address-misuse-of-fentanyl-in-peterborough/

63. Opioid patch exchange disposal tool. RxFiles [cited 2014 May 14] Available from: http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx (Subscription required)

64. CBC news Fentanyl patch return bill put forward by Nipissing MPP Vic Fedeli. [cited 2015 Apr 9] Available from: http://www.cbc.ca/news/canada/sudbury/fentanyl-patch-return-bill-put-forward-by-nipissing-mpp-vic-fedeli-1.2810749

65. Ontario Legislature. Bill 33 An Act to reduce the abuse of fentanyl patches and other controlled substance patches. [cited 2015 Dec 31] Available from: http://www.ontla.on.ca/bills/bills-files/41_Parliament/Session1/b033ra.pdf

66. Health Canada Reminding Canadians to safely use and dispose of fentanyl patches to prevent accidental exposure 2013 Oct 11. [cited 2013 Oct 11] Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36239a-eng.php

67. College Quarterly. College of Physicians and Surgeons of British Columbia. From the quality of medical performance committee: more on fentanyl patches 2005 Issue 48 p.6

68. Institute for Safe Medication Practices Analysis of international findings involving fentanyl transdermal patches 2009 Dec 30 [cited 2014 Mar 7] Available from: http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2009-10-AnalysisOfInternationalFindingsFromIncidentsInvolvingFentanylTransdermal.pdf

69. Greenall J, Koczmara C, Cheng R, Hyland S. Safety issues with fentanyl patches require pharmaceutical care. Canadian Journal of Hospital Practice 2008 Jan-Feb; 61(1):57-59. Available from: http://www.ismp-canada.org/download/cjhp/cjhp0802.pdf

70. College of Pharmacists of British Columbia Fentanyl/Duragesic patch Alert Bulletin May 2005 [cited 2006 Nov 24] Available from: URL: http://www.bcpharmacists.org/new/pdf/fentanyl_10.pdf

71. National Alert Network. Proper disposal of fentaNYL patches is critical to prevent accidental exposure. 2012 Apr 25 [cited 2013 Dec 5] Available from: http://www.nccmerp.org/proper-disposal-fentanyl-patches-critical-prevent-accidental-exposure

72. Hardwick Jr WE,King WD. Respiratory depression in a child unintentionally exposed to transdermal fentanyl patch. Southern Medical Journal. 1997 Sep;90(9);962-4.

73. Longo M. Canadian Adverse Reaction Newsletter Fentanyl transdermal patches and accidental child exposure. 2009;19(3):3 Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php

74. Voigt I. Fatal overdose due to confusion of an transdermal fentanyl delivery system. Case Reports in Critical Care 2013; [cited 2014 Jan 6] Available from: http://www.hindawi.com/journals/cricc/2013/154143/

75. Raymond B, Morawiecka I. Canadian Adverse Reaction Newsletter Transdermal fentanyl (Duragesic) respiratory arrest in adolescents. 2004 Oct;14(4):1-2. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php

76. Shastay A. Mom hopes son's overdose spurs preventative efforts Home Healthcare Nurse. 2014 Sep;32(8):502.

77. Teske J, Weller J, Larsch K, Tröger HD, Karst M. Int J Legal Med Fatal outcome in a child after ingestion of a transdermal fentanyl patch. 2007;121:147-51.

78. www.LockMed.com

79. Canadian supplier of Lock Med containers: http://www.wellbeings.ca/store

80. Fraser Health Pharmacy Services Policy Manual Disposal of Pharmaceutical Waste Feb 17, 2014 [cited 2014 Mar 6] Available from: http://fhpulse/clinical_support_services/pharmacy/policies_pdtm_ppos_forms/Pharmacy%20Services%20Manual/Disposal%20of%20Pharmaceutical%20Waste%20-%20Pharmacy%20Services.pdf

81. Fraser Health Narcotics and controlled drugs policy manual 2013 Oct 13. Available from: http://fhpulse/clinical_support_services/pharmacy/policies_pdtm_ppos_forms/FH Medication Manual/Narcotics and Controlled Drugs.pdf

82. Kennedy B. Safety should not be a patchy event using transdermal fentanyl. 2015 Jan 15 presentation. Peach Arch Hospital, White Rock

83. Smart Sink Pharmaceutical waste sink. Information available at www.cactusLLC.net

84. Deterrasystem website [cited 2015 Dec 9] Available from: http://deterrasystem.com/

85. Verde Environmental Technologies Inc. Product description information. [cited 2014 Jan 11] Accessed from : http://www.verdeenvirotech.com/product-descriptions/

86. Herwadkar A, Singh N, Anderson C, Korey A, Fowler W, Banga A. Development of a disposal system for deactivation of transdermal patches of fentanyl. Scientific poster presentation provided by Dr Andrew G Korey, Verde Environmental Technologies.

87. Goodhart S. Health Care Logistics. Avoid Risk: Deactivates drugs instantly. 2015 Oct 20. [cited 2015 Dec 9] Available from: http://www.healthcarelogistics.com/blog/deterra-drug-disposal-system

88. Kennedy B. Prescribing opioids in multiethnic and genetically diverse British Columbia – practice guidance 2011 Nov 4 PainBC.org Interdisciplinary Pain Education Day Burnaby [cited 2014 Jan8]Available from:https://www.painbc.ca/sites/default/files/pdf_files/Prescribing%20Opioids%20in%20Multiethnic%20%26%20Genetically%20Diverse%20BC.pdf

89. Oxycodone PharmGKB Pharmacogenomics dosing guidelines. [cited 2014 Jan 10] Available from: http://www.pharmgkb.org/drug/PA450741

90. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, Dale O, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. Pain 2011;152:1139-45.

91. McPherson M. Demystifying opioid conversion calculations; transdermal and parenteral fentanyl dosage calculations and conversions [Online] 2009;(5):84-105 [cited 2001 Oct 7] Available from: http://www.ashp.org/DocLibrary/Bookstore/P1985SampleChapter.aspx

92. Fine PG, Portenoy RK. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage 2009 Sept;38(3):418-25.

93. Ljuca D, Husic S. Treatment of severe cancer pain by transdermal fentanyl. Bosnian Journal of Basic Medical Sciences 2010;10(2):158-64.

94. Pasero C. Assessment of sedation during opioid administration for pain management. Journal of PeriAnesthesia Nursing 2009;24(3):186-190.

95. Nisbet AT, Mooney-Cotter F. Comparison of selected sedation scales for reporting opioid-induced sedation assessment. Pain Management Nursing 2009;10(3): 154-164.

96. Fraser Health End of Life Care Practice Council and Clinical Policy Office. Clinical Practice Guideline for the prevention, recognition and management of opioid excess in adult hospice palliative care patients. Fraser Health 2013 Aug 21. Available from: http://fhpulse/clinical_resources/clinical_policy_office/Lists/CDST%20Library/DispForm.aspx?ID=80

97. Fraser Health End of Life Care Practice Council and Clinical Policy Office. Clinical Protocol Appropriate use of narcotic antagonist (naloxone) in adult hospice palliative care patients. 2013 Aug 21. Available from: http://fhpulse/clinical_resources/clinical_policy_office/Lists/CDST%20Library/DispForm.aspx?ID=913

98. Duragesic MAT monograph. 2011 Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association.

99. Fraser Health Palliative Care Pharmacy Team. Analgesic Approximate Equivalence Charts 2005 May 30. Available from: http://fhpulse/clinical_programs/end_of_life/resources/Documents/Analgesic%20Approximate%20Equivalence%20Charts.pdf

100. Institute for Safe Medication Practices Fentanyl Patch patient information [cited 2014 May 15] Available from: http://www.consumermedsafety.org/tools-and-resources/medication-safety-tools-and-resources/high-alert-medications/fentanyl-patch-duragesic

101. Borg R, Ashton A. A case of overdose via tattoo. J of the Intensive Care Society. 2015;16(3):253-6. Available from: http://inc.sagepub.com/content/16/3/253

102. Mystakidou K, Parpa E, Tsilika E, Katsouda E, Kouloulias V, Kouvaris J, et al. Pain management of cancer patients with transdermal fentanyl: a study of 1828 Step I,II & III transfers. The Journal of Pain 2004 March; 5(2):119-32.

103. Murphy M, Carmichael AJ. Transdermal drug delivery systems and skin sensitivity reactions; incidence and management. Am J Clin Dermatol 2000 Nov-Dec;1(6):361-8.

104. Skaer T. Practice guidelines for transdermal opioids in malignant pain. Drugs 2004;64(23):2629-38.

105. Skaer T. Transdermal opioids for cancer pain. Health and Quality of Life Outcomes 2006;4:24 9 pages Available from: http://www.hqlo.com/content/4/1/24

106. Cachia E, Ahmedzai SH. Transdermal opioids for cancer pain. Current Opinion in Supportive and Palliative Care 2011;5:15-19.

107. Beaton K. Senior medical information associate Janssen-Ortho Canada. Letter to Bruce Kennedy regarding adhesion problems with reservoir formulation and use of overlay on top of fentanyl patch. 2009 Dec 15.

108. Pain Management Fentanyl handling 2013 Jan 24 Alberta Health Services Calgary Zone Long Term Care Formulary [cited 2014 May 13] Available from: www.albertahealthservices.ca/hp/if-hp-ltc-e-06a-fentanyl-handling.pdf

109. Fentanyl patch can be deadly to children U.S. Food and Drug Administration 2013 Sep. [cited 2014 May 15] Available from: http://www.fda.gov/forconsumers/consumerupdates/ucm300803.htm

110. US Food and Drug Administration. FDA requiring color changes to Duragesic (Fentanyl) patches to aid safety- emphasizing that accidental exposure to used patches can cause death. 2013 Sep 23 [cited 2013 Mar 7] Available from: http://www.fda.gov/downloads/drugs/drugsafety/ucm368911.pdf

111. Health Canada Reminding Canadians to safely use and dispose of fentanyl patches to prevent accidental exposure 2013 Oct 11 [cited 2013 Mar 7] Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/36239a-eng.php

112. Fraser Health Clinical Protocol: Medication Practice – medication prescribing, directive/order processing, administration and documentation Oct 31, 2013 Available from: http://fhpulse/clinical_resources/clinical_policy_office/Lists/CDST%20Library/DispForm.aspx?ID=417

113. Facility disposal of used fentanyl patches Government of Kentucky [cited 2014 May 15] Available from: http://chfs.ky.gov/nr/rdonlyres/883bfe47-0e0a-4381-9740-107d87f5623d/0/facilitydisposalofusedfentanylpatches.pdf

114. Dorval Marie. Dispedia Drug Information Associate, Apotex Toronto ON. Email November 12, 2014 to Bruce Kennedy

115. Banks Brian Medical Information Associate Janssen Toronto ON. Email November 10, 2014 to Bruce Kennedy

116. Freeman Kilauren. Regional Sales Associate Mylan Etobicoke ON, Email November 17, 2014 to Bruce Kennedy

117. Lefkir Amel. Medical & Scientific Information Associate. Pharmascience Montreal QC Email November 11, 2014 to Bruce Kennedy

118. Katia Alloun Drug Safety and QA Specialist, Ranbaxy Mississauga ON. Email November 12, 2014 to Bruce Kennedy

119. Yousef Benattia. Medical Information and Pharmacovigilance Specialist. Sandoz Canada Boucherville QC Verbal communication November 12, 2014 to Bruce Kennedy

120. Heiskanen T, Matzke S, Haakana S, Gergov M, Vuori E, Kalso E. Transdermal fentanyl in cachectic cancer patients. Pain 2008;144:218-22.

121. Clemens KE, Klaschik E. Clinical experience with transdermal and orally administered opioids in palliative care patients – a retrospective study. Jpn J Clin Oncol 2007;37(4):302-9.

122. Fudin J. Can fentanyl patches be replaced sooner to improve pain control? Medscape Today 2008 Jul 11 Cited 2013 Feb 14] Available from: www.medscape.com/viewarticle/566115

123. Woodroffe MA, Hays H. Fentanyl transdermal system. Canadian Family Physician 1997;43:268-72.

124. Kennedy B. Clinical Pharmacist Specialist hospice palliative care, Fraser Health. Is it okay to write the application date on a fentanyl transdermal patch with a permanent ink Sharpie marker? 2012 Nov 1

125. Institute for Safe Medication Practices Canada. Report on medication system safety review of three Ontario homes to MOHLTC Task Force on medication management 2009 April [cited 2014 Jan 10] Available from: http://www.ismp-canada.org/education/webinars/20100324_LTCReport/downloads/Final_Home_Review_Report_Appendix_3.pdf

126. Greenspoon J, Herrmann N, Adam DN. Transdermal rivastigmine; management of cutaneous adverse events and review of the literature. CNS Drugs 2011;25(7):575-83.

127. RxFiles BuTrans Q and A. RxFiles [cited 2016 Feb 12]
Available from http://www.rxfiles.ca/rxfiles/uploads/documents/BuTrans-QandA.pdf

128. Musel AL, Warshaw EM. Cutaneous reactions to transdermal therapeutic systems. Dermatitis 2006 Sept;17(3):109-22.

129. Salvi FJ. Steroid spray to control skin inflammation related to transdermal fentanyl. Poster 158 Arch Phys Med Rehabil 2002 Nov;83:1670.

130. Institute for Safe Medication Practices Requirement #1 Stick to patient! 2007 June [cited 2015 Apr 16] Available from: http://www.ismp.org/newsletters/ambulatory/archives/200706_1.asp

131. Néron A. ed. Pharmacy specialty group on palliative care. Care Beyond Cure A Pharmacotherapeutic Guide to Palliative Care. Montréal (Canada): Canadian Society of Hospital Pharmacists; 2009. p.48.

132. Néron A. ed. Pharmacy specialty group on palliative care. Care Beyond Cure A Pharmacotherapeutic Guide to Palliative Care. Montréal (Canada): Canadian Society of Hospital Pharmacists; 2000. p.18.

133. Black F, Downing GM. Pain - Analgesics. In: Downing GM, Wainwright W, editors. Medical Care of the Dying. 4th ed. Victoria, B.C. Canada: Victoria Hospice Society Learning Centre for Palliative Care; 2006. p. 189-251.

134. National Patient Safety Agency Reducing dosing errors with opioid medicines Rapid Response Report. 2008 Jul [Online] [cited 2014 Oct 10] Available from: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59888

135. Fentanyl transdermal patch safety concern. Drug and therapeutics newsletter. [Online]. 2005 Dec 12(4); [cited 2006 Nov 24] Available from: URL: http://www.vhpharmsci.com/Newsletters/2005-NEWS/Dec05_news.pdf

136. Peng Y-R, Sun W-Z, Mok MS. Mini-dose titration of the transdermal fentanyl patch – a novel approach by adjusting the area of absorption. J Pain Symptom Manage 2005 July;30(1):7-8.

137. Kokubun H, Matoba M, Okazaki M, Hoka S, Yago K. Evaluation of the 2.5 mg fentanyl patch, applied using the half-side application procedure in patients with cancer pain. Yakugaku Zasshi. 2008;128:447-50.

138. Belanger D. Can you give a patient a partial dose from a transdermal patch? Medication Forum Pharmacy Practice 1998 Sep.

139. Kennedy B. Question and Answer regarding half patch fentanyl. 2014 October 2. Available from: http://fhpulse/clinical_support_services/pharmacy/admin/Documents/Half-patch%20enquiry%20response%20Oct%203%202014%20by%20Bruce%20Kennedy.pdf

140. McMorran M, Longo M, Fentanyl transdermal patch and fatal adverse reactions. Canadian Adverse Reaction Newsletter 2008(3):447-50.

141. Takane H, Nosaka A, Wakushima H, Hosokawa K.Ieiri I. Rifampin reduces the analgesic effect of transdermal fentanyl. The Annals of Pharmacotherapy 2005;39:2139-40.

142. Hall LM, O'Lenic K, Treatment strategies to overcome end-of-dose failure with oral and transdermal opioids. Pharmacy Practice 2012;25:503.

143. Institute for Safe Medication Practices Canada. Transdermal Fentanyl: a misunderstood dosage form. 2006 Aug 14, [cited 2015 Mar 2] Available from: http://www.acclaimhealth.ca/wp-content/uploads/2013/11/Fentanyl-Patches-ISMP-Canada-Safety-Bulletin.pdf

144. Health Quality & Safety Commission New Zealand. Medication alert – transdermal patches. 2014 Sep. [cited 2015 Mar 2] Available from: http://www.hqsc.govt.nz/assets/Medication-Safety/Alerts-PR/Transdermal-patch-alert-organisational-Sep-2014.pdf

145. Flanagan LM, Butts JS, Anderson WH. Fentanyl patches left on dead bodies: potential source of drug for abusers. J Forensic Sci 1996;41:320-1.

146. Apo-Fentanyl Matrix fentanyl transdermal system Consumer information. [cited 2014 Mar 24] Available from: http://www.apotex.com/ca/en/products/consumer/search.asp?qt=A2Z&qs=F&t=Search

147. TALLman lettering Policy. Lower Mainland Pharmacy Services 2014 Nov 25. Available from: http://fhpulse/lmc/pharmacy/policies/Policies/Tall%20Man%20Lettering%20-%20LMPS.pdf

TABLE A2 - Fentanyl Drug Interactions

For drug interactions known to occur with fentanyl, see table below. Consult current sources such as Lexicomp http://online.lexi.com/lco/action/home (subscription required) for further and recent drug interaction listings.

Primarily three major types of drug interactions can occur with fentanyl:

1. Increased central nervous system depressive effects with risk of sedation and respiratory impairment. For example with alcohol or benzodiazepines,
2. Modified metabolism via cytochrome P450 3A4 liver enzymes resulting in decreased or increased serum levels of fentanyl, or the other interacting drug. For example, macrolides like clarithromycin significantly elevate fentanyl serum levels,
3. An increase in risk of serotonin syndrome. For example, with selective serotonin reuptake inhibitors like citalopram.

How to use this Drug Interaction Table

1. Locate the drug that the patient is concurrently using with fentanyl. Drugs are listed alphabetically with the generic drug name **bolded** for major interactions, *italicized* for moderate.
2. Determine the general significance of the interaction, and then assess importance to your individual patient. Multiple potentially interacting medications will alter the significance.
3. Be aware of the mechanism of the drug interaction especially when the patient is taking multiple drugs to assess for possible change in fentanyl drug levels or the concurrent drug.
4. Review suggestions for monitoring parameters to follow and clinically assess need to appropriately withhold or adjust the dose of fentanyl or the interacting drugs. Use the Pasero Opioid Sedation Scale[106,107] and guidelines[108-9] when opioid excess is suspected.
5. Consult indicated references if necessary for further interaction details, or consult a healthcare professional such as a pharmacist for assistance.

Table Abbreviations:

CNS = Central Nervous System

CYP3A4 = Cytochrome P 450 liver (drug metabolizing) enzyme 3A4

FD = Fair documentation (Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug)

GD = Good documentation (Documentation strongly suggest the interaction exists, but well-controlled studies are lacking)

TABLE A2 – Fentanyl Drug Interactions

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Abiraterone	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 1,4
Adalimumab	*Moderate*	CYP3A4 induction	Decrease levels	Analgesia reduction	Theoretical[1], Fair[2] 1,2
Alcohol	**Major**	Additive CNS depression		Sedation, respiratory depression, hypotension	Theoretical[1], Fair[2], 1-5
ALfentanil	**Major**	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], 1,6
ALPRAZolam	**Major**	Additive CNS depression		CNS & respiratory depression	Theoretical[1], 1
Amiodarone	**Major**	Strong CYP3A4 inhibition	Increase levels	Fentanyl toxicity, low cardiac output, bradycardia	Probable[1], Good[2], 1-5,7
Amitriptyline	**Major**	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], 1,3
amLODdipine	**Major**	Additive hypotensive effect & CYP3A4 inhibition		Risk of hypotension and/or bradycardia & fentanyl toxicity	Theoretical[1], 1,3,8
Ammonium Chloride		Excretion enhanced	Decrease levels	Analgesia reduction	4
Amphetamines	**Major**	Additive analgesia & additive serotonergic effect		Monitor for enhanced fentanyl analgesia, & risk of serotonin syndrome	Theoretical[1], 1,4
Amprenavir	**Major**	Strong CYP3A4 inhibition	Increase levels	Potentiate CNS depression, effects of fentanyl on respiration, sedation	Theoretical[1], 1,3,5
Anesthetics (General)		Additive CNS depression		Sedation, CNS depression	5
Anxiolytics		Additive CNS depression		Sedation, CNS depression	3
Anticholingerics		Additive GI tract slowing		Risk of severe constipation & urinary retention	3,4
Antidiarrheals		Additive GI tract slowing		Risk of severe constipation	3
Antihistamines (sedating) e.g., chlorpheniramine, brompheniramine		Additive CNS depression		Risk of hypotension, sedation, respiratory depression	3,5

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Antipsychotics		Additive hypotensive effect		May enhance hypotensive effect of fentanyl	4
Aprepitant	**Major**	Strong CYP3A4 inhibition	Increase levels	Increase in CNS depression and increased risk for fatal respiratory depression	Theoretical[1], Fair[2], 1-3,8
ARIPiprazole	**Major**	Weak CYP3A4 inhibition, co-substrate & additive CNS depression		May increase aripiprazole levels, monitor for increased effects & CNS depression	Theoretical[1], 1,8
Asenapine	**Major**	Additive CNS depression		Sedation, CNS depression	Theoretical[1], 1
Atazanavir	**Major-Avoid**	Strong CYP3A4 inhibition	Increase levels	Increase in CNS depression and increased risk for fatal respiratory depression	Theoretical[1], 1,3
Atorvastatin	**Major**	CYP3A4 inhibition		Sedation, CNS depression	Theoretical[1], 1
azithroMYCIN	*Moderate*	CYP3A4 inhibition	Increase levels	CNS & respiratory depression	Probable[1], Good[2], 1,2
Baclofen	**Major**	Additive CNS depression		Sedation, CNS depression	Theoretical[1], 1,7
Barbiturates	**Major**	CYP3A4 induction, & additive CNS depression	Decrease levels	Reduced analgesia, and/or CNS depression Could vary	Theoretical[1], Fair[2], 1-3,5
Benzodiazepines	**Major**	Additive CNS depression		Hypotension, sedation, respiratory depression	Theoretical[1], 1,7
Beta-blockers		Additive hypotensive effect		Hypotension and/or bradycardia	3,4
Bicalutamide	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 1
Boceprevir	**Major-Avoid**	Strong CYP3A4 inhibition	Increase levels	Increase in CNS depression and increased risk for fatal respiratory depression	Theoretical[1], 1
Bosentan		CYP3A4 induction	Decrease levels	Reduction of analgesia	3
Bromazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 1
Bromocriptine		Additive serotonergic effect		Increased serotonin syndrome risk	6,10

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Buprenorphine	**Major**	Opioid antagonism, additive CNS depression and CYP3A4 Co-substrate	Likely decrease levels	Mixed agonist/ antagonist may partially block effects of fentanyl or cause additive CNS effects. Reduced 3A4 fentanyl metabolism	Theoretical[1], 1,3
busPIRone	**Major**	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], Fair[2] 1,2,8
Butorphanol	**Major**	Opioid antagonism & additive CNS depression	Likely decrease levels	Mixed agonist/antagonist may partially block effects of fentanyl or cause additive CNS effects	Theoretical[1], 1,3
Calcium channel blockers		Additive hypotensive effect		Risk of hypotension and/or bradycardia	3,4
Cannabinoids		Additive CNS depression		Potentiate CNS depression	4
Carbamazepine	**Major**	CYP3A4 induction & additive serotonergic effect	Decrease levels	Reduction of analgesia, & increased risk of serotonin syndrome	Theoretical[1], Fair[2], 1,2,3,7,8
Chloral Hydrate	**Major**	Additive CNS depression		Potentiate CNS depression	Theoretical[1]
ChlordiazePOXIDE	**Major**	Additive CNS depression		Potentiate CNS depression	Theoretical[1]
ChlorproMAZINE	**Major**	Additive CNS depression		Potentiate CNS depression	Theoretical[1]
Chlorzoxazone	**Major**	Additive CNS depression		Potentiate CNS depression	Theoretical[1]
Cigarette smoking		CYP3A4 induction	Decrease levels	Reduction of analgesia	5,13
Cimetidine	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 3,4,7,8
Ciprofloxacin	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Citalopram	**Major**	Additive serotonergic effect		Increased risk of serotonin syndrome	Probable[1], Good[2], 1,2
Clarithromycin	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 1,3,7,8
Clobazam	**Major**	Additive CNS depression		Respiratory depression, hypotension	Theoretical[1]
ClomiPRAMINE		Additive CNS depression		Potentiate CNS depression	3

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
ClonazePAM	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Clorazepate	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Clotrimazole (systemic)	*Moderate*	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Good[1], 1,2,4
CloZAPpine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3
CNS depressants	**Major**	Additive CNS depression		Potentiate CNS depression	Theoretical[1], Fair[2], 4
Codeine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Crizotinib	**Avoid[4]**	CYP3A4 inhibition	Increase levels	Risk of fentanyl toxicity	Theoretical[1], 4
Cyclobenzaprine	**Major**	Additive serotonergic effect & additive CNS depression		CNS depression and increased risk of serotonin syndrome	Theoretical[1], Fair[2]
CycloSPORINE	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
CYP3A4 inhibitors	**Avoid**	CYP3A4 inhibition	Increase levels	Risk of fentanyl toxicity. Sedation, CNS & respiratory depression	Fair[2], 3,4
CYP3A4 inducers	**Major (with strong inducers)**	CYP3A4 induction	Decrease levels	Reduction of analgesia	Fair[2]
Dabrafenib	**Major**	Strong CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], Fair[2]
Dantrolene	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	1, 4
Darunavir	**Major**	CYP3A4 inhibition	Increase levels	Risk of fentanyl toxicity	Theoretical[1]
Dasatinib	*Moderate*	CYP3A4 inhibition	Increase levels	Risk of fentanyl toxicity Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1,2,4
Deferasirox	*Moderate*	Strong CYP3A4 induction	May decrease	Reduction of analgesia	Theoretical[1], Fair[2]
Delavirdine	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 3,8

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Desipramine	**Major**	Additive serotonergic effect & CYP3A4 inhibition, & CNS depression	Increase levels	Increased risk of serotonin syndrome, sedation, CNS & respiratory depression	Theoretical[1], 1,4,6
Desmopressin		Unclear mechanism		Enhanced toxicity of desmopressin	4
Desvenlafaxine	**Major**	Additive serotonergic effect		Increased risk of serotonin syndrome	Theoretical[1], Fair[2]
Dexamethasone		CYP3A4 induction	Decrease levels	Reduction of analgesia	7,12
Dexmedetomidine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Dextroamphetamine	**Major**	Additive serotonergic effect		Increased risk of serotonin syndrome	Theoretical[1]
Dextromethorphan	**Major**	Additive serotonergic effect		Increased risk of serotonin syndrome	Theoretical[1], 9
Diazepam	**Major**	Additive CNS depression		Risk of hypotension, sedation, respiratory depression	Theoretical[1], 6
Dihydroergotamine		Additive serotonergic effect		Increased risk of serotonin syndrome	9
Diltiazem	**Major**	CYP3A4 inhibition, & additive hypotensive effect	Increase levels	Fentanyl toxicity. Also additive hypotensive effect, risk of bradycardia	Theoretical[1], Fair[2], 1-3,8
DiphenhydrAMINE	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Diphenoxylate	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Diuretics		Not provided by reference		Opioid analgesics may enhance the adverse/ toxic effect of diuretics	4
Doxepin	**Major**	Additive serotonergic effect, & additive CNS depression		Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical[1], Fair[2], 3
Doxylamine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 4
Dronedarone		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	4
Droperidol	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3,4

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Drospirenone	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-4
DULoxetine	**Major**	Additive serotonergic effect		Increased risk of serotonin toxicity	Theoretical[1], Fair[2], 9
Efavirenz		CYP3A4 induction, co-substrate	up or down	Higher or lower fentanyl effects	4,8
Eletriptan	**Major**	Additive serotonergic effect		Increased risk of serotonin toxicity Consider replacing serotonergic opioids with non-serotonergic opioids	Theoretical[1], Fair[2]
Entacapone		Additive CNS depression		Sedation, CNS & respiratory depression	3
Enzalutamide	**Major**	Strong CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], Fair[2], 4
Erythromycin	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-6
Escitalopram	**Major**	Additive serotonergic effect		Increased risk of serotonin toxicity	Theoretical[1], Fair[2]
Estradiol	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Ethanol	**Major**	Additive CNS depression		Sedation, respiratory depression, hypotension	Theoretical[1], Fair[2], 1-4
Everolimus		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	4
Fluconazole	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-5,7
FLUoxetine	**Major**	CYP3A4 inhibition & additive serotonergic effect	Increase levels	Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical[1], Fair[2], 1-3
FluPHENazine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Flurazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
FluvoxaMINE	**Major**	CYP3A4 inhibition & additive serotonergic effect	Increase levels	Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical[1], Fair[2], 1-3,8
Fosamprenavir	**Major**	Potent CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-3

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Fosaprepitant	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Dosage reduction of fentanyl may be warranted	Theoretical[1], Fair[2], 1-4
Fosphenytoin	**Major**	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], Fair[2], 1-3
Frovatriptan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Ginkgo Biloba	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Ginseng, Chinese	*Moderate*	Not specified by reference		Reduction of analgesia	Theoretical[1]
Goldenseal		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Grapefruit Juice	**Major (oral fentanyl) Minor (patch)**	Potent CYP3A4 inhibition	Increase levels	Potent CYP3A4 inhibitor present in liver and intestinal mucosa of fentanyl given orally or sublingually. Oral consumption of grapefruit is a warning for patch use in product monographs but clinically relevant interactions with fentanyl patch have not yet been established.	Theoretical[1], Fair[2], 8
Haloperidol		Additive CNS depression		Sedation, CNS & respiratory depression	3
HYDROcodone	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 4
HYDROmorphone	**Major**	Additive CNS depression		Potentiate CNS depression, effects of fentanyl on respiration, sedation	Theoretical[1], Fair[2], 4
HydrOXYzine	**Major**	Additive CNS depression		Increased CNS depression	Theoretical[1], Fair[2], 4
Imatinib	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-3,8
Imipramine	**Major**	Additive CNS depression & additive serotonergic effect		Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical[1], Fair[2], 1-3
Indinavir	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-3

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
InFLIXimab	*Moderate*	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], Fair[2]
Isoniazid	**Major**	Reduced CYP3A4 metabolism, CYP3A4 Co-substrate	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Ivacaftor		CYP3A4 Co-substrate, substrate metabolism competition	Increase levels	Sedation, CNS & respiratory depression	4
Itraconazole	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 5
Kava	*Moderate*	Additive CNS depression		Sedation, increased CNS depression	Theoretical[1], Fair[2], 4
Ketamine	**Major**	Additive CNS depression		Analgesia potentiation, sedation, increased CNS depression	Theoretical[1], 10
Ketoconazole	**Major**	Potent CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-5,7
Lapatinib	*Moderate*	Weak CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Levonorgestrel	**Major**	CYP3A4 inhibition	Increase levels	Increased risk of fentanyl toxicity	Theoretical[1], Fair[2]
Lidocaine		Additive CNS depression		Increased risk of respiratory depression	7
Linezolid	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2], 9
Lithium	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Loperamide		Additive serotonergic effect		Increased risk of serotonin syndrome	6
Lopinavir	**Avoid**	Strong CYP3A4 inhibition		Significant risk of fentanyl toxicity	Theoretical[1], Fair[2]
LORazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 6
Loxapine	*Moderate*	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
LSD (Lysergic acid diethylamide)		Additive serotonergic effect		Increased serotonin syndrome risk	9
Magnesium sulfate		Additive CNS depression		Increased CNS depression, more so with magnesium via intravenous, intrathecal routes & higher doses	4, 6

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Maprotiline		Additive CNS depression		Sedation, CNS & respiratory depression	3
MDMA "Ecstasy" 3,4-methylenedixy-methamphetamine		Additive serotonergic effect		Increased serotonin syndrome risk	9
Meclizine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Meperidine	**Major**	Additive serotonergic effect and additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical[1], Fair[2],6,9
Methadone	**Major**	Additive serotonergic effect & additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical[1], Fair[2]
Methocarbamol	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Methotrimeprazine	**Major**	Additive hypotensive effect, & additive CNS depression		Hypotension, CNS sedation, respiratory depression	Theoretical[1], Fair[2], 4
Methylene Blue	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Miconazole (systemic)	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Midazolam	**Major**	Additive CNS depression		Risk of hypotension, sedation, respiratory depression	Theoretical[1], Fair[2], 7
Mirtazapine		Additive CNS depression		Sedation, CNS & respiratory depression	3
Mitotane	**Major**	Strong CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], Fair[2]
Monamine Oxidase (MAO) inhibitors	**Avoid**	Additive serotonergic effect, & additive hypotensive effect		Potentiate opioid effects, (e.g., hypo-tension) can be severe and unpredictable. Avoid concurrent use for 14 days. Fentanyl may enhance serotonerigic effect of MAOI's	Theoretical[1], Fair[2], 5,7
Morphine	**Major**	Additive CNS depression		Increased risk of CNS depression	Theoretical[1], Fair[2]
Skeletal Muscle Relaxants		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3,5

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Nalbuphine	**Major**	Opioid antagonism, &/ or additive CNS depression	May decrease levels	Mixed agonist/ antagonist may partially block effects of fentanyl or cause additive CNS effects	Theoretical[1], Fair[2], 3
Naltrexone	**Avoid**	Opioid mu receptor antagonist	Decrease levels	Decreases opioid effectiveness, may precipitate opioid withdrawal	Good[1], Probable[2], 1-4
Naloxone		Opioid mu receptor antagonist	Decrease levels	Decreases opioid effectiveness, may precipitate opioid withdrawal	3
Naratriptan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Nelfinavir	**Avoid**	Strong CYP3A4 inhibition	Increase levels	Increased risk of fentanyl toxicity	Theoretical[1], Fair[2], 1-3,5,7,8
Nevirapine	*Moderate*	Strong CYP3A4 induction	Decrease levels	Reduction of analgesia	Probable[1], Good[2], 1-4
Nicotine		CYP3A4 induction & additive serotonergic effect		Reduction of analgesia. Increased serotonin syndrome risk	6,8,13
NIFEdipine	**Major**	Additive hypotensive effect		Risk of severe hypotension	Probable[1], Good[2]
Nilotinib	**Major**	CYP3A4 inhibition	Increase levels	Increased risk of fentanyl toxicity	Theoretical[1], Fair[2]
Nitrazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Nitrous oxide	**Major**	CNS & cardiovascular depression		Sedation, CNS & respiratory depression. Cardiovascular depression at high doses of nitrous oxide, esp. patients with left ventricular dysfunction	Theoretical[1], 3
NORfloxacin		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	4,8
Nortriptyline	**Major**	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression. Increased serotonin syndrome risk	Theoretical[1], 3

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Octreotide		Unknown		Octreotide may enhance the analgesic effect of fentanyl. Monitor for possible decreased dose requirements if octreotide is added/ dose increased or increased requirements if octreotide is discontinued/dose decreased	4
OLANZapine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3
Opioids	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3
Orphenadrine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Oxazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
OxyCODONE	**Major**	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical[1], 6
Paraldehyde		Additive CNS depression		Sedation, CNS & respiratory depression	4
PARoxetine	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
Pazopanib	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Pegvisomant		Not provided by reference		May diminish therapeutic effect of pegvisomant	4
Pentazocine	**Major**	Opioid antagonism, & additive serotonergic effect	Likely decrease levels	Mixed agonist/ antagonist may partially block effects of fentanyl or cause additive CNS effects, some increased serotonin syndrome risk	Theoretical[1], 3,6
Perampanel		Additive CNS depression		Sedation, CNS & respiratory depression	4
Perphenazine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Phenelzine (MOA inhibitor)	**Major**	Additive serotonergic effect, additive hypotensive effect		Potentiation of opioid effects, (e.g., hypo-tension) can be severe and unpredictable. Avoid concurrent use for 14 days. Fentanyl may enhance serotonerigic effect of MAOI's	Theoretical[1], 3,6
Phenobarbital	**Major**	Strong CYP3A4 induction, & additive CNS depression	Decrease levels	Enzyme metabolism induction will lower fentanyl levels & may reduce analgesia. Yet may also increase sedation, CNS & respiratory depression	Theoretical[1], Fair[2], 1-4,8
Phenothiazines		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
Phenytoin	**Major**	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], 3,7,8
Pimozide	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression May increase pimozide levels	Theoretical[1], 3,4
Pipotiazine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Posaconazole	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Pramipexole		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
Pregabalin		Additive CNS depression		Sedation, CNS & respiratory depression	3
Primidone	**Major**	CYP3A4 induction	Decrease levels	Reduction of analgesia Sedation, CNS & respiratory depression	Theoretical[1], 4,7
Procarbazine (MAO inhibitor)	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], 9
Prochlorperazine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3,4
Promethazine		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3,4,7
ProPOFol		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 8

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
QUEtiapine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 3
Ranitidine	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Rasagiline	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
Regorafenib	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
REMifentanil	**Major**	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], 6
RifaBUTin	**Major**	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1], 3,4
RifaMPin	**Major**	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical[1] 3,4,7,
Risperidone		Additive CNS depression		Sedation, CNS & respiratory depression	3
Ritonavir	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Increased risk of fentanyl toxicity. **Avoid concurrent use if possible**	Theoretical[1], 3,4,5,
Rizatriptan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
rOPINIRole		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
Rotigotine		Additive CNS depression		May enhance sedative effect of rotigotine	4
Saquinavir	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Increased risk of fentanyl toxicity. **Avoid concurrent use if possible**	Theoretical[1], 3,4,7,8,
Sedatives & Hypnotics		Additive CNS depression		Potentiate CNS depression, effects of fentanyl on respiration, sedation	3
Selective Serotonin Re-uptake inhibitors	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2], 1,2,4

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Selegiline (MOA inhibitor)	**Major**	Additive serotonergic effect, additive hypotensive effect		Potentiate opioid effects, (e.g., hypotension) can be severe and unpredictable. Avoid concurrent use for 14 days. Fentanyl may enhance serotonerigic effect of MAOI's	Theoretical[1], 3,4,9
Simeprevir		CYP3A4 inhibition (more with oral fentanyl)	Increase levels	Sedation, CNS & respiratory depression	4
Sertraline	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Sodium Oxybate	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], Fair[2]
Spiramycin	*Moderate*	CYP3A4 inhibition	Increase levels	May increase or prolong opioid effects - sedation, CNS & respiratory depression	Probable[1], Good[2]
St John's Wort	**Major**	CYP3A4 induction, & additive serotonergic effect	Decrease levels	Reduction of fentanyl levels, analgesia & increased serotonin syndrome risk	Theoretical[1], Fair[2], 3
Succinylcholine		Enhance bradycardia		Monitor for enhanced bradycardia	4
SUFentanil	**Major**	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], 6
SUMAtriptan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
Tapentadol	**Major**	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical[1], Fair[2], 4
Telaprevir	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Temazepam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Tetrahydrocannabinol		Additive CNS depression		Sedation, CNS & respiratory depression	3
Thalidomide		Additive CNS depression		Sedation, CNS & respiratory depression	4

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Ticagrelor	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Tipranavir	**Major**	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1]
Tizanidine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Tobacco smoking		CYP3A4 induction	Decrease levels	May increase fentanyl clearance, lower analgesia	7,13
Tocilizumab	*Moderate*	Increase of CYP450 enzymes	Potentially decrease	Lower fentanyl levels & analgesia	Theoretical[1], Fair[2]
Topiramate	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
TraMADol	**Major**	Additive serotonergic effect & additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical[1], Fair[2], 1-4
Tranylcypromine (MOA inhibitor)	**Major**	Additive serotonergic effect, & additive hypotensive effect		Potentiate opioid effects, (e.g., hypotension) can be severe and unpredictable. Avoid concurrent use for 14 days. Fentanyl may enhance serotonerigic effect of MAOI's	Theoretical[1], 1,3,4
TraZODone	**Major**	Additive CNS depression & additive serotonergic effect		Increased serotonin syndrome risk, sedation, CNS & respiratory depression	Theoretical[1], 3,4,7
Triazolam	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Trifluoperazine	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
TrimEPRAZINE	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]
Tryptophan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]
Valerian	*Moderate*	Additive CNS depression		Additive CNS depression	Theoretical[1], Fair[2]
Valproic Acid	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
Venlafaxine	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1], Fair[2]

TABLE A2 – Fentanyl Drug Interactions continued

Interacting Drug	Interaction Severity[2]	Mechanism of Interaction	Effect on Fentanyl Level	Monitor For	Substantiation[1], Documentation[2], References
Verapamil	**Major**	Strong CYP3A4 inhibition, & additive hypotensive effect	Increase levels	Sedation, CNS & respiratory depression. Hypotension, bradycardia	Theoretical[1], 1,3,5
Voriconazole	**Major**	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical[1], 3,8
Zafirlukast		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	3
Ziprasidone		Additive CNS depression		Sedation, CNS & respiratory depression	4
ZOLMitriptan	**Major**	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical[1]
Zolpidem	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1], 4,8
Zopiclone	**Major**	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical[1]

☐ References for Drug Interaction Table A2:

1. Fentanyl Drugdex evaluations. Micromedex [On-line] [cited 2014 Sep 2] Available from: http://www.micromedexsolutions.com/home/dispatch Subscription required.

2. Fentanyl drug interactions. Micromedex [On-line] [cited 2014 Sep 2] Available from: http://www.micromedexsolutions.com/home/dispatch Subscription required.

3. Fentanyl monograph. Clinical Pharmacology [On-line] [cited 2006 Mar 26] Available from: https://www.clinicalpharmacology.com/ Subscription required.

4. Lexicomp. Fentanyl [On-line] [cited 2014 Mar 1] Available from: http://online.lexi.com/lco/action/home/switch Subscription required.

5. Mylan-Fentanyl Matrix Patch fentanyl transdermal system product monograph 2013 Nov 15, Mylan Pharmaceuticals ULC Etobicoke, Canada.

6. Hall Ryan CW, Hall Richard CW, Chapman MJ. Central serotonin syndrome I- causative agents, presentation, and differential diagnosis. Clinical Geriatrics 2008 Jan. Available from: http://www.drrichardhall.com/Articles/central_serotonin_syndrome-1.pdf

7. Baxer K editor. Stockleys Drug Interactions 8th ed. London (UK): Pharmaceutical Press 2008.

8. Flockhart DA. Cytochrome P450 Drug Interaction Chart Version 5.0 2009 Jan 12 [cited 2014 Apr 4] Available from: http://medicine.iupui.edu/clinpharm/ddis/

9. Gillman PK. A review of serotonin toxicity data:implications for the mechanisms of antidepressant drug action. Biol Psychiatry 2006;59:1046-51.

10. Tucker AP, Kim YI, Nadeson R, Goodchild CS. Investigation of the potentiation of the analgesic effects of fentanyl by ketamine in humans: a double-blinded, randomised, placebo controlled, crossover study of experimental pain. BMC Anesthesiology 2005;5:2.

11. Kirschner R, Donovan JW. Serotonin syndrome precipitated by fentanyl during procedural sedation. J Emerg Med 2010;38(4):477-80.

12. Wilcock A, Thomas J, Frisby J, Webster M, Keeley V, Finn G et al. Potential for drug interactions involving cytochrome P450 in patients attending palliative day care centres: a multicentre audit. British Journal of Clinical Pharmacology. 2005;60(3):326-9.

13. NHS 2012 Aug [cited 2015 Feb 2] Which medicines need dose adjustment when a patient stops smoking? Available from: http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/NW%20QA136.4%20Smoking%20and%20drug%20interactions.doc

FIGURE A1 – Fraser Health Patient Education Brochure – Safe Disposal of Used Pain Patches at Home

fraserhealth

Safe Disposal of Used Pain Patches at Home

Pain patches are placed on the skin to help relieve pain. After you remove it, there is still a lot of medicine left in the patch. To reduce the chances of the used patch hurting other people, always remove and get rid of used pain patches safely.

If used by accident or misused by others, used pain patches can cause harm or death to adults, children, and pets.

There is also a growing concern about medicine in our waste and water systems.

STOP **Never** place used pain patches in the garbage.

How to safely remove your patch

1. Remove the patch from your skin.
2. Fold the used patch in half, sticky side to sticky side.

3. Safely dispose of patch – see instructions on 'How to safely get rid of a used patch'.
4. Clean your hands **with water only.**

   Do not use soap. If the sticky surface of the patch touches your hands, the soap can make it easier for the medicine to pass through your skin.

How to safely get rid of a used patch

There are 2 ways to get rid of your used patch.

1. Store the used patch in a childproof, hard to open container.

   You could get a large medicine bottle with a childproof lid from your pharmacy. Ask the pharmacy to add a sticker: 'Keep out of reach of children'

   Label the container: 'Used patches to take back to the pharmacy'.

   Store the container out of sight and out of reach of others, including children and pets.

   Return it to the pharmacy as soon as you can.

2. Flush the patch down the toilet.

   Only use this method if you need to get rid of the patch right away when you need to keep it from being reused, misused, stolen, or abused. Whenever possible, do not to choose this way unless you have to. We want keep medicines out of our waste and water system.

   If you have a septic tank or septic field, **do not** flush patches down the toilet.

For more information, go to
British Columbia Medication Returns Program
www.healthsteward.ca

www.fraserhealth.ca

This information does not replace the advice given to you by your health care provider.

Catalogue #264650 (December 2015)
To order: https://patienteduc.fraserhealth.ca

Appendix A - Transdermal Fentanyl Systematic Search Strategies Utilized

Prior draft of Fentanyl Transdermal (Nov 24, 2006) reviewed and suitable current references maintained. http://www.fraserhealth.ca/EN/hospice_palliative_care_symptom_guidelines/

Published literature search was performed.

Databases searched: Ovid (Medline), Embase, Pubmed, International Pharmaceutical Abstracts, CINAHL (via Ebsco), All Evidence-based Medicine Reviews (OVID)

Excluded: non-English, non-human

Date range: Jan 1 2006 to May 14, 2014

Terms: fentanyl guidelines, fentanyl disposal, transdermal patch, fentanyl transdermal, fentanyl safety, palliative, end of life

Search method: use of medical subject (MeSH term) headings. Utilized "similar to" search at times when primary search article provided possibility of further search resources by this method.

Additionally, fee-free services of the Canadian Agency for Drugs and Technologies in Health (CADTH) were utilized to provide a Rapid Response Report entitled Fentanyl transdermal patches in palliative care: clinical effectiveness, safety, and guidelines. Ottawa: the Agency; 2014 May 29. (Rapid response report: summary of abstracts). Available from: www.cadth.ca

Their report identified:

- Two evidence-based guidelines
- No literature within in Health Technology assessments, systematic reviews and meta-analyses, no randomized controlled trials, and no randomized studies
- 24 other publications of further information

  CADTH search method was "a limited literature search conduced on key resources, including PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused internet search." No methodological filters applied, limited to human population, and English language for documents published between January 1, 2009 and May 14, 2014."

Internet search strategies provided references utilizing a focused search using specific terms such as fentanyl guidelines, fentanyl disposal, transdermal patch, fentanyl transdermal, fentanyl safety, and palliative. Ongoing Google Scholar alerts using terms of transdermal with fentanyl were also used.

Appendix A – Transdermal Fentanyl Development

Author: Bruce Kennedy Fraser Health Clinical Pharmacy Specialist Palliative Care.

Development Review:

Outstanding reviewer input provided by Judy Lett Fraser Health Hospice Palliative Care Clinical Nurse Specialist.

Additional valuable reviewer contributions included input from each of the following;

Dr Mary-Jane O'Leary HPC EOL Palliative Care Consultant, Nicole Wikjord Fraser Health Hospice Palliative Care Clinical Nurse Specialist, Kathy Scarborough Fraser Health Clinical Practice Consultant Professional Practice and Integration and Carol Wilson Fraser Health Patient Education Project Coordinator.

Stakeholder Guideline review graciously provided by: Brian Banks, Nicole Dahlen, Dr Mervyn Dean, Donna Goring, Brenda Hearson, Dr. Melanie Johnson, Dr. Marylene Kyriazis, Annie Leong, Dr. Gina Louise, Dr. Nicola MacPherson, Michele Martin, Dr Douglas McGregor, Sue North, Eve Sample, Brian Shouldice, Sally Tierney, and Ruth Topolnicky.

Final review provided by Barbara McLeod Fraser Health Hospice Palliative Care Clinical Nurse Specialist.

This guideline was developed without external funding. Guideline authors have no conflict of interest.

Appendix A - Transdermal Fentanyl Review

The guideline will be due for review three years following its implementation. Review will be informed by changes in the literature, as well as relevant current practice experience that would include Patient and Safety Learning Systems reports and clinician's input.

Appendix A - Transdermal Fentanyl Approval

Approved by: End of Life Care, Practice Advisory Council, June 29, 2015

End of Life Care, Program Network Team, September 10, 2015

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] *See 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 norephinephrine uptake inhibitor.[2,25]
- High bioavailablity 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 equinanalgesic 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: (palliativedrugs.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%

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]

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

Table B1 – 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	

Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
Dextromethorphan		CYP450 induction	May increase levels of Dextromethorphan
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	

Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
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
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

Table B2 – Drugs that may predispose to QT interval prolongation or torsades de pointes [29,30,33,54]

adenosoine	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.

Appendix B - References

1) Gazelle G, Fine PG. Fast fact and concept #075 Methadone for Pain. End-of-Life physician resource center [Online]. Sep 2002 [cited 2005 Nov 12]; Available from: URL: http://www.eperc.mcw.edu

2) Lister D. The case for methadone an alternative to other opioids in the management of severe pain. Pharmacy Practice 2002 Sep;18(9):59-64.

3) Taube AW. Methadone: what is its role in cancer pain control? The Canadian Journal of CME 2003 Sep;90-9

4) Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. Journal of Palliative Medicine 2002; 5(1):127-38.

5) College of Physicians and Surgeons of BC. Recommendations for the use of methadone for pain; 2005 March.

6) Black F, Downing GM. Pain – Analgesics. In: Downing GM, Wainwright W, editors. Medical Care of the Dying. 4th ed. Victoria, B.C. Canada: Victoria Hospice Society Learning Centre for Palliative Care; 2006. p. 189-251.

7) Methadone Clinical Pharmacology [Online]. 2006 Gold Standard [cited 2006 June 30];Available from: URL:http://www.clinicalpharmacology.com/Default.asp

8) Fitzgibbon D, Ready LB. Intravenous high-dose methadone administered by patient controlled analgesia and continuous infusion for the treatment of cancer pain refractory to high-dose morphine. Pain 1997;(73): 259-61.

9) Gan B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. Pain Research and Management 2003; 8(3):149-54.

10) Oneschuk D, Bruera E. Respiratory depression during methadone rotation in a patient with advanced cancer. Journal of Palliative Care 2000;16(2):50-4.

11) Moryl N, Santiago-Palma J, Kornick C, Derby S, Fischer D, Payne R et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. Pain 2002;96:325-8.

12) Mercadante S, Casuccio A, Fulfaro F, Groff L, Boffi R, Villari P et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. Journal of Clinical Oncology 2001;19(11):2898-904.

13) Manfredi PL, Gonzales GR, Cheville AL, Kornick C, Payne R. Methadone analgesia in cancer patients on chronic methadone maintenance therapy. Journal of Pain and Symptom Management 2001 Feb;21(2):169-74.

14) Brands, J Janecek E. Methadone maintenance: a pharmacist's guide to treatment. Centre for Addiction and Mental Health, Toronto Ontario;2000.

15) College of Physicians and Surgeons of Ontario. Methadone for pain guidelines 2004 Nov [cited 2005 Dec 17] Available from: URL: http://www. cpso.on.ca/publications/publications.htm

16) Davis MP, Walsh C. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols for administration. Supportive Care in Cancer 2001;9:73-83.

17) Downing, MP. Opioid rotation, neurotoxicity and paradoxical pain. Victoria Hospice Society palliative care medical intensive course November 2004 p. 1-6.

18) von Gunten CF. Fast fact and concept #086:Methadone:starting dose information 2003 Mar [cited 2005 Jan 3]; Available from:URL: http://eperc.mcw.edu/fastFactff_86.htm

19) Dean, M. Opioids in renal failure and dialysis patients. Journal of Pain and Symptom Management 2004 Nov; 28(5):497-504.

20) Ripamonti C, Bianchi M, Bruera E. Methadone: an orphan drug? Letter to the editor. Journal of Palliative Medicine 2004;7(1):73-4.

21) Layson-Wolf C, Goode JV, Small RE. Clinical Use of Methadone. Journal of Pain and Palliative care Pharmacology 2002;16(1);29-59.

22) Methadone monograph [Online]. 2005 [cited 2005 Jan 3]; Available from URL: http://www.clinicalpharmacology.com/Default.asp

23) Hagen NA, Wasylenki E. Methadone:outpatient titration and monitoring strategies in cancer patients. Journal of Pain and Symptom Management 1999;18(5):369-75.

24) Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and methadone in patients with cancer pain. Cancer 1998;82(6):1167-73.

25) Davis M. Methadone In: Davis M, Glare P, Hardy J. editors. Opioids in cancer pain. Oxford (U.K.): Oxford University Press; 2005 p.173-198.

26) Walker PW, Klein D, Kasza L. High dose methadone and ventricular arrhythmias: a report of three cases. Pain 2003;103:321-4.

27) Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose related effects of methadone on QT prolongation in a series of patients with torsades de pointes. Pharmacotherapy 2003 June;23(6):802-5.

28) Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsades de pointes associated with very high dose methadone. Annals of Internal Medicine 2002 Sep;137(6):501-4.

29) Appendix 3:prolongation of the QT interval in palliative care. [Online]. 2003 May [cited 2005 Nov 3]; Available from: URL:http://www.palliativedrugs.com/book.php?Appendix3

30) Leavitt, SB, Krantz MJ. Cardiac considerations during methadone maintenance treatment. Addiction Treatment Forum. Clinico Communications Inc. Jan 2004 [cited 2005 Mar 15] Available from: URL:http://www.atforum.com/SiteRoot/pages/rxmethadone/cardiacmmt.shtml

31) Gil M, Sala M, Anguera I, Chapinal O, Cervantes M, Guma JR, Segura F. QT Prolongation and torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. American journal of cardiology 2003 June;92(8):995-7.

32) Walker G, Wilcock A, Carey AM, Manderson C, Weller R, Crosby V. Prolongation of the QT interval in palliative care patients. Journal of Pain and Symptom Management 2003 Sep;26(3):855-9.

33) De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of Non-antiarrhythmic drugs that prolong the QT interval or induce torsades de pointes. Drug Safety 2002; 24(4):263-86.

34) Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C et al. Methadone versus morphine as a first-line strong opioid for cancer pain : a randomized, double-blind study. Journal of Clinical Oncology 2004 Jan 1; 22(1):185-92.

35) Mathew P, Storey P. Subcutaneous methadone in terminally ill patients:manageable local toxicity. Journal of Pain and Symptom Management 1999 July;18(1):49-52.

36) Centeno C, Vara F. Intermittent subcutaneous methadone administration in the management of cancer pain. Journal of Pain and Palliative Care Pharmacotherapy 2005;19(2):7-12.

37) Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, et al. Pharmacological Reviews. International Union of Pharmacology. XII. Classification of opioid receptors. 1196;48:567-92.

38) Weinberg, DS, Inturrisi, CE, Reidenberg, B, Moulin, DE, Nip, TJ, Wallenstein, S, Houde, RW, Foley, KM. Sublingual absorption of selected opioid analgesics. Clinical Pharmacology & Therapeutics Sep 1988;44:355-42.

39) Manfredi PL, Borsook D, Chandler SW, Payne R. Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: clinical observations. Pain 1997;70:99-101.

40) Bruera, E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer. Cancer 1996 Aug 15;78(4):852-7.

41) Dart RC, Woody GE, Kleber HD. Prescribing methadone as an analgesic. Annals of Internal Medicine 2005 Oct;143(8):620.

42) Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. Pain 1993;70:109-115.

43) Tips for methadone pain management. ReadLinks Newsletter College of Pharmacists of British Columbia 2005 Jan/Feb;30(1):9

44) Sandoval JA, Furlan AD, Mailis-Gagnon A. Oral methadone for chronic noncancer pain. Systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects. Clinical Journal of Pain 2005;21:503-12.

45) Mercadante S. Switching to methadone: "ad libitum" or fixed dose ratio? Letter to the editor. Palliative Medicine 2004;18:71.

46) Tse DMW, Sham MMK, Ng DKH, Ma HM. A reply to Dr. Mercadante Letters to the editor. Palliative Medicine 2004;18:72-3.

47) Anonymous (1996) Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. European Agency for the Evaluation of Medicinal Products: Committee for Proprietary Medicinal Products (EMEA); Committee for Proprietary Medicinal Products:CPMP/986/96

48) Twycross R. Switching to methadone. American Journal of Hospice Palliative Care 2001;5:359.

49) Anon. Newsletter [Online]. 2001 Feb [cited 2005 Nov 3]; Available from: URL:http://www.palliativedrugs.com

50) Bruera E, Newman C. Role of methadone in the management of pain in cancer patients. Oncology 1999;13(9) 1275-82; discussion 1285-8,1291.

51) Micromedex methadone monograph [Online]. [cited 2006 June 30]; Available from: URL: http://www.thomhc.com

52) Lipman AG Editor. Methadone:effective analgesia, confusion, and risk Editorial. Journal of Pain and Palliative Care Pharmacotherapy 2005;19(2);3-5.

53) Leavitt, SB Methadone-Drug* Interactions 3rd edition (* medications, illicit drugs, and other substances). Addiction Treatment Forum [cited 2006 Nov 28]; Available from: URL: www.atforum/SiteRoot/pages/rxmethadone/rxmethadone.shtml

54) Woosley, RL. Drugs that prolong the QT interval and/or induce torsades de pointes. 2004 Dec 17 [cited 2005 Nov 3]; University of Arizona for Education and Research on Therapeutics Available at: URL: http://www.QTDrugs.org

55) Rheaume C, Aubin N, Gagnon B. Using methadone for pain control Information for you and your family. 2002 McGill University Health Centre Brochure.

56) Watanabe S. Methadone:the renaissance. Journal of Palliative Care 2001;17(2):117-20.

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]
- Available as immediate release 50 mg tablets, and sustained release 75, 100, 150, 200, 300, 400 mg tablets.
- 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

- Oral potency ratio of tramadol to morphine is considered to be 10:1, [16] meaning that to calculate the equivalent morphine dose from existing tramadol dose, divide the 24 hour tramadol dose by ten – for example, 400 mg of oral tramadol per 24 hours is approximately equivalent to 40 mg of oral morphine per 24 hours. Different CYP2D6 genotypes in patients could also introduce equianalgesia variation from this potency ratio.[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, Cmax is 16% higher and AUC 36% higher than after a single 100 mg dose, indicating that oral bioavailablity 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 Cmax 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 monoadmine 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).

Appendix C References

1) Leppert W, Luczak J. The role of tramadol in cancer pain treatment – a review. Supportive Care Cancer 2005;13:5-17.

2) Klepstad P, Kaasa S, Cherny N, Hanks G, de Conno F. Pain and pain treatments in European palliative care units A cross sectional survey from the European Association for Palliative CareResearch Network. Palliative Medicine 2005;19:477-84.

3) Shipton EA. Tramadol – present and future. Anaesthesia and Intensive Care 2000;28:353-74.

4) Grond S, Sablotski A. Clinical pharmacology of tramadol. Clinical Pharmacokinetics 2004;43(13):879-923.

5) Tramadol monograph Palliativedrugs.com[Online] [cited 2005 November 13] Available from: URL: http://www.palliativedrugs.com/pdi.html

6) Tramacet product monograph [Online] July 14 2005 [cited 2005 November 13] Available from: URL: http://www.janssen-ortho.com/JOI/en/

7) Zytram XL product monograph [Online] October 10 2006 [cited 2006 December 29] Available from: URL: http://www.purdue.ca/products/products.asp

8) Bamigbade TA, Langford. The clinical use of tramadol hydrochloride. Pain Reviews 1998;5:155-82.

9) Arbaiza D, Vidal O. Tramadol in the treatment of neuropathic cancer pain: a double-blind placebo-controlled study. Clinical Drug Investigation 2007;1:75-83.

10) Duhmke RM, Cornblath DD, Hollingshead JRF. Tramadol for neuropathic pain [Review]. The Cochrane Database of Systematic Reviews 2005 Aug 24;4:1-29.

11) McDiarmid T, Mackler L, Schneider DM. Clinical inquiries. What is the addiction risk with Tramadol? Journal of Family Practice 2005 Jan;54(1):72-3.

12) Adis International Ltd. Tramadol-Biovail Corporation Drugs in R&D 2004;5(3):182-3.

13) Close B. Tramadol:does it have a role in emergency medicine? Emergency Medicine Australasia 2005;17:73-83.

14) Tramadol monograph. Clinical pharmacology 2006 [Online]. [cited 2005 November 8] Available from: URL: http://cpip.gsm.com

15) Lang ES, Andruchow JE. What is the preferred first line therapy for status epilepticus? Annals of Emergency Medicine 2006; 58:98-100.

16) Tramadol David MP In: Davis MP, Glare P, Hardy J editors. Opioids in cancer pain Toronto: Oxford University Press; 2005. p. 69-82.

17) Bandolier [Online] July 1999 Oral tramadol in postoperative pain. [cited 2006 Nov 13] Available from: URL: http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/AP003.html

Appendix C approved by: Hospice Palliative Care, Clinical Practice Committee, November 24, 2006