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**Clinical Resource**

# **Palliative Care Program Symptom Guidelines**

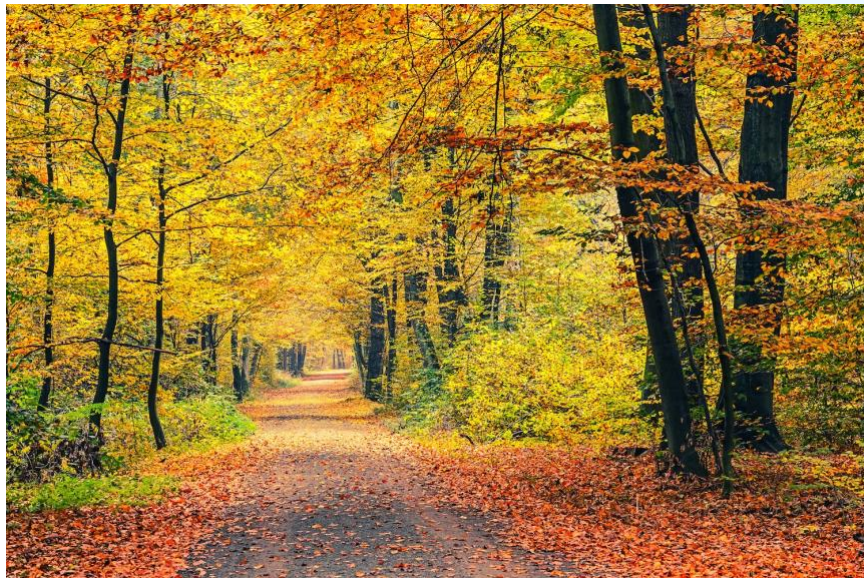
## **4th Edition**

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**Author(s): Endorsed by NH Medical Advisory Committee**  
**Revised by: Northern Health Palliative Care Consultation Team**



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# IMPORTANT NOTICE

In Northern Health there is an **interdisciplinary consult team** available for support in the management of palliative patients.

For support and education, and including:

- Patient Assessment
- Pain and Symptom Management
- End-of-Life Decision Making

**Nurse Consultants** are available Monday through Friday (excluding statutory holidays) and can be reached at:

**Northeast:** 250-795-6134

**Northwest:** 250-631-4191

**Northern Interior/Prince George:** 250-565-7318

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In the event the Nurse Consultants are unavailable, and there is urgent advice needed, **physicians** can:

1. Contact the Northern Health Palliative Care Physician on-call at **250-565-2000**. Palliative on-call physicians are available 24hrs a day to assist physicians across Northern Health manage their palliative patients.
2. Provincial Palliative Care Consultation line at **1-877-711-5757**

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## INTRODUCTION

Palliative care requires an interdisciplinary, total person approach with a goal to allow one an opportunity to achieve physical, emotional and spiritual comfort. The following definitions help us to understand Northern Health's vision and commitment to providing high quality services that are competent, compassionate and respectful of all people who are dying and their families.

Good palliative care is a continuum of services provided in accordance with a care plan developed collaboratively between the person with a life limiting illness, the person's primary care provider and members of the person's care team.<sup>(1)</sup>

**Palliative Care:** "Palliative care" means the specialized care of people who are dying - care aimed at alleviating suffering (physical, emotional, psychosocial or spiritual), rather than curing. The term "palliative care" is generally used in association with people who have an active, progressive and advanced disease, with little or no prospect of cure".<sup>(1,2)</sup>

**Hospice Palliative Care:** "Hospice palliative care" is a philosophy of care that stresses the relief of suffering and improvement of the quality of living and dying. It helps patients and families to:

- Address physical, psychological, social, spiritual and practical issues and their associated expectations, needs, hopes and fears;
- Prepare for and manage self-determined life closure and the dying process; and
- Cope with loss and grief during illness and bereavement<sup>(1,2)</sup>

**End of Life Care:** "End of life care" is associated with advanced, life-limiting illnesses, and focuses on comfort, quality of life, respect for personal health care treatment decisions, support for the family, psychological and spiritual concerns".<sup>(1,3)</sup>

**Population Needs-Based Approach to Palliative Care:** "Recognizes that individuals facing a serious illness have different needs, based on their unique health conditions, stage of disease and complexity of symptoms. Health care services and supports should therefore vary in type and intensity to most effectively meet the needs of the individual".<sup>(3)</sup>

**Palliative Care Approach:** Makes certain aspects of palliative care available to patients and families at appropriate times throughout the illness trajectory. After diagnosis and in the early stages of the illness the palliative care approach focuses primarily on:

- Open and sensitive communication about prognosis and illness trajectory;
- Advanced care planning;

- Psychosocial and spiritual support; and
- Pain and symptom management as required.

Later in the illness focuses on:

- Review of goals of care, and adjusting care strategies to reflect changes;
- On-going psychosocial support;
- Pain and symptom management; and
- Engagement of specialized palliative care providers as needed to address complex physical, psychosocial or spiritual symptoms.<sup>(1,3)</sup>

Palliative approach requires upstream orientation to care delivery, adapts specialized palliative care knowledge and expertise and embeds it in care delivery, care processes and necessitates integration of care delivery.<sup>(1,4)</sup>

## **What is Evidence-Based Palliative Care?<sup>(6)</sup>**

**Four important points are:**

- “Evidence-based practice is the conscious, explicit and judicious use of current evidence in making decisions about the care of individual patients.
- It is more difficult to measure quality of life and altered outcomes in patients and families whose illness or frailty make it difficult to collect data.
- Outcome and quality of life measures need to be sensitive to the wider aspects of palliative care, not merely mortality, function, or absence of symptoms.
- Those working in palliative care must use existing research through appropriate systematic reviews to maximize the value of data yielded in caring for patients and families”.

## **What is a Clinical Practice Guideline (CPG)?**

Clinical Practice Guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances”.<sup>(5)</sup> “Their purpose is to make explicit recommendations with a definite intent to influence what clinicians do.”<sup>(6, 7)</sup>

## **Why do we need to use Evidence-Based Clinical Practice Guidelines in Hospice Palliative Care?**

We need to use Clinical Practice Guidelines in Hospice Palliative Care to help us provide the best care possible. Hospice Palliative Care Clinical Practice Guidelines will help us to:

- Inform healthcare providers, patients and families.
- Educate healthcare providers and the public.

- Include all members of the healthcare team.
- Improve clinical decision-making.
- Reduce variation in professional practice.
- Ensure equitable allocation of resources.
- Measure the quality of our care.
- Identify opportunities for improvement.
- Improve management of the healthcare system.
- Provide a foundation for the future.

## **What are the Palliative Care Symptom Guidelines?**

These guidelines are an addition to the B.C. Inter-Professional Palliative Symptom Guidelines originally developed in 2017. The provincial guidelines included 15 symptoms and 2 guidelines on Refractory Symptoms/Palliative Sedation and Nurturing Psychosocial and Spiritual Well-Being which were added in 2019. The remaining symptoms are covered under the Northern Health Palliative Care Symptom Guidelines (Oct, 2019). These guidelines provide recommendations based on scientific evidence and expert clinical opinion. They provide practical and easy-to-follow advice to healthcare providers for effective patient care.

The NH Guidelines (Oct, 2019) are intended to be a resource for the more common symptoms that are not covered under the Provincial Guidelines, and are experienced by adult patients ( $\geq 19$  years of age) and their families who are living with advanced life threatening illness. As they are symptom guidelines only, they do not replace individual patient and family assessment and/or clinical judgment within the scope of professional practice. As these Palliative Care Symptom Guidelines are a work in progress and evidence changes, we encourage providers to be aware of this. We welcome and appreciate feedback.

## **What is the purpose of using the AGREE Instrument?**

The purpose of using the Appraisal of Guidelines and Evaluation (AGREE) Instrument is to provide a framework for assessing the quality of clinical practice guidelines. The AGREE Instrument was used to ensure a structured and rigorous development process and as a self-assessment tool to ensure that the guidelines were sound before adopting the recommendations. It is suggested that the AGREE Instrument is perceived as reflecting the current state of knowledge in the field.<sup>(4)</sup>

For guidelines adapted from the Fraser Health Hospice Palliative Care Symptom Guidelines, the number of appraisers for each of the guidelines ranged between five and eight. All Fraser Health guidelines received two external reviews by a

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physician and pharmacist at the Fraser Valley Cancer Center. Each guideline received an overall assessment based on four options:

1. 'strongly recommend'
2. 'recommend (with provisos and alterations)'
3. 'would not recommend'
4. 'unsure'

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## SYMPTOM ASSESSMENT ACRONYM

The Symptom Assessment Acronym is a tool to aid in a systematic assessment approach to whatever hospice palliative care symptom you are reviewing. Other aids are available however; in Northern Health we found this Symptom Assessment Acronym helpful. We recommend this tool for our Northern Healthcare providers to guide a consistent and comprehensive symptom assessment in hospice palliative care.

*Assessment using Acronym O, P, Q, R, S, T, U, and V (1, 2, 3, 4, 5, 6, 7, 8, 9) \**

<b>O</b> Onset	When did it begin? How long does it last? How often does it occur?
<b>P</b> Provoking/ Palliating	What brings it on? What makes it better? What makes it worse?
<b>Q</b> Quality	What does it feel like? Can you describe it?
<b>R</b> Region/ Radiation	Where is it? Does it spread anywhere?
<b>S</b> Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right now? At best? At worst? On average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom?
<b>T</b> Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
<b>U</b> Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
<b>V</b> Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

**\* also include a Physical Assessment (as appropriate for symptom)**

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October 2008**

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# ASCITES

## Rationale

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

## Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of ascites. This guideline does not address disease specific approaches in the management of ascites. Ascites may develop in 15% to 50% of patients with malignancies<sup>(1, 2)</sup> but most cases (80%) of ascites will be related to cirrhosis.<sup>(3)</sup>

## Definition of Terms

**Ascites** is the accumulation of fluid within the peritoneal cavity.<sup>(2)</sup>

## Standard of Care

1. Assessment
2. Diagnosis
3. Education
4. Treatment: Non-pharmacological
5. Treatment: Pharmacological

## RECOMMENDATION 1 - ASSESSMENT OF ASCITES

Ongoing comprehensive assessment is the foundation of effective management of ascites, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family (*see Table 1*).



**Table 1: Ascites Assessment using Acronym O, P, Q, R, S, T, U, and V\***

<b>O</b> Onset	When did it begin? How often does it occur?
<b>P</b> Provoking/ Palliating	What brings it on? What makes it better? What makes it worse?
<b>Q</b> Quality	What does it feel like? Can you describe it? Have you noticed weight gain?
<b>R</b> Region/ Radiation	Where is the pressure? Is it spreading?
<b>S</b> Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right now? At best? At worst? On average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom – nausea, loss of appetite, pain?
<b>T</b> Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
<b>U</b> Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
<b>V</b> Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

\* also include a Physical Assessment (as appropriate for symptom)

### Diagnostic Tests:

- Using abdominal radiography, ascites may demonstrate a ‘ground glass appearance’.<sup>(1)</sup>
- Ultrasound or CT scan may be required to demonstrate small volumes of free peritoneal fluid.<sup>(1)</sup>
- Diagnostic paracentesis may be required to elucidate the type of ascites and should be done on newly diagnosed cases of ascites.<sup>(1)</sup>

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## Clinical Signs and Symptoms:

- Abdominal pressure, pain.(1, 3, 4)
- Anorexia, early satiety, nausea, vomiting.(1-4)
- Dyspnea and/or orthopnea.(1-3)
- Increased abdominal girth.(2)
- Peripheral edema.(1, 2)
- Reduced mobility.(4)
- Reflux esophagitis.(1-3)
- Shifting dullness to percussion and a fluid thrill.(2,5)

## RECOMMENDATION 2 - 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 ascites is identifying underlying cause(s) and treating as appropriate (*See Causes of Ascites*). While underlying cause(s) may be evident, treatment may not be indicated, depending on the stage of the disease.

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

### Causes of ascites:(1, 3)

- Cirrhosis – is the predominant cause in 80% of cases. It presents as transudative ascites (ascitic fluid protein concentration of less than 2.5g/dl).
- Malignancy – causes 10% of cases. They are mostly (80%) epithelial related ovarian, uterus, breast, colon, gastric and pancreatic however the remaining 20% have tumours of primary unknown origin. The fluid produced in malignancy is exudative (ascitic fluid protein concentration of greater than 2.5g/dl).
- Heart failure – is responsible for 3% of cases. The fluid produced is transudative.
- Renal related – 3%, tuberculosis – 2%, pancreatitis – 2% and miscellaneous – 1% or absent.(5, 9)

### Types of ascites:(6)

- Raised hydrostatic pressure – caused by cirrhosis, congestive heart failure, inferior vena cava obstruction and hepatic vein occlusion.
- Decreased osmotic pressure – caused by protein depletion (nephrotic syndrome, protein-losing enteropathy), reduced protein intake (malnutrition) or reduced protein production (cirrhosis).

- Fluid production exceeding resorptive capacity – caused by infection or neoplasms.
- Chylous – due to obstruction and leakage of the lymphatics draining the gut.

### **RECOMMENDATION 3 - EDUCATION**

Education of patient and their family should comprise discussion of treatment methods of ascites and the value of paracentesis when the patient becomes symptomatic.<sup>(3)</sup>

### **RECOMMENDATION 4 - TREATMENT: NON-PHARMACOLOGICAL**

- Observation is appropriate when the condition is asymptomatic.<sup>(3)</sup> Observation would include measuring the abdominal girth at a marked site each week<sup>(6)</sup> as well as appropriately scheduled weight measurement.
- Paracentesis is the draining of ascitic fluid via a catheter inserted through the abdominal wall. This may be achieved under ultrasound guidance or in an outpatient setting for quick relief of symptoms. Generally, upwards of 5 litres of fluid may be removed with little risk of hypotension or hypovolemic shock when patient screening is applied.<sup>(6)</sup> Intravenous hydration should be considered if the patient is hypotensive, dehydrated or known to have severe renal impairment and paracentesis is still indicated.<sup>(4)</sup> If there is leakage over the paracentesis site an ostomy bag can be applied.<sup>(2, 6)</sup> Single or repeated paracentesis in patients with advanced cancer does not significantly lower serum protein.<sup>(2)</sup>
- Peritoneal catheters (smaller bore catheter) may be useful when ascites is rapidly accumulating and requiring frequent paracentesis for symptom control. This significantly exposes the patient to the risk of peritonitis and is usually reserved for patients in the terminal phase of their illness, with a prognosis of weeks.<sup>(3, 5, 7, 8)</sup>
- Radiation therapy and chemotherapy may be useful in cases where a meaningful response to tumour growth may be expected, such as lymphoma.<sup>(1)</sup>
- Salt restriction plays an important role where fluid is transudative, but may also provide relief in patients with cancer and hepatic metastases.<sup>(1, 3)</sup>
- A low fat diet and increase in medium-chain triglyceride intake may be useful in patients with chylous ascites.<sup>(1)</sup>

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## RECOMMENDATION 5 - PHARMACOLOGICAL

### Diuretics:

- Diuretics should be considered in all patients, but has to be evaluated individually. Patients with malignant ascites due to massive hepatic metastases seem to respond better to diuretics than those with malignant ascites due to peritoneal carcinomatosis or chylous ascites.<sup>(4)</sup>
- Diuretics may help with portal hypertension (hepatic metastases, heart failure and cirrhosis)<sup>(3)</sup> and should be tried in most patients after their first abdominal paracentesis as approximately one-third of patients are shown to benefit.<sup>(9)</sup>
- Goal of diuretic therapy would be to achieve a weight loss of 0.5 to 1 kg per day.<sup>(6)</sup>
- Spironolactone 100 mg daily<sup>(2)</sup> titrated slowly to 400 mg daily – titrated to remove enough fluid for comfort.<sup>(1, 3, 6)</sup>
- Furosemide 40 to 120 mg daily may be added to spironolactone to improve the effect <sup>(2, 3, 6)</sup> and prevent hyperkalemia. Furosemide given by continuous infusion is reported to produce significant diuresis and marked relief of ascites.<sup>(2)</sup>
- When utilizing diuretics monitor electrolytes, renal function, drug interactions and blood pressure weekly.<sup>(6)</sup>

### Octreotide:

- Octreotide in doses of 200 to 600 mcg S.C. per day has shown promise in cases of ascites refractory to paracentesis.<sup>(2, 10)</sup> Dosing frequency should be in two to three divided doses per day.

### 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 ascites 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.

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**Approved by: Northern Health Hospice Palliative Care Consult Team,  
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# DEPRESSION IN THE TERMINALLY ILL

## Rationale

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

## Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of depression. This guideline does not address disease specific approaches in the management of depression.<sup>(1-12)</sup>

## Definition of Terms

**Depression** is a primary mood disorder, which, according to the DSM-IV-TR includes:

- a depressed mood and/or;
- an inability to experience pleasure in normally pleasurable acts (anhedonia).<sup>(13)</sup>

**For major depression**, the DSM-IV-TR states that one of the above symptoms must be present for a period of at least two weeks in combination with four *or more* of the following symptoms:<sup>(13)</sup>

- Feelings of overwhelming sadness and/or fear, or the seeming inability to feel emotion (emptiness).
- A decrease in the amount of interest or pleasure in all, or almost all, daily activities.
- Changing appetite and marked weight gain or loss. Note: ensure not related to disease process.
- Disturbed sleep patterns, such as insomnia, loss of rapid eye movement (REM) sleep, or excessive sleep (hypersomnia).
- Psychomotor agitation or retardation nearly every day.
- Fatigue, mental or physical, also loss of energy.
- Intense feelings of guilt, helplessness, hopelessness, worthlessness, isolation/loneliness and/or anxiety.
- Trouble concentrating, keeping focus or making decisions or a generalized slowing and obtunding (to dull or blunt, especially sensation or pain) of cognition, including memory.

- Recurrent thoughts of death (not just fear of dying), desire to just “lay down and die” or “stop breathing”, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- Feeling and/or fear of being abandoned by those close to one.

**Minor depression** is a less-used term for a subclinical depression that does not meet criteria for major depression but where there are at least two symptoms present for two weeks.

Note: do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

## Standard of Care

1. Incidence and Risk Factors
2. Assessment
3. Diagnosis
4. Education
5. Treatment: Non-pharmacological
6. Treatment: Pharmacological

## RECOMMENDATION 1 - INCIDENCE AND RISK FACTORS

### Incidence and Risk Factors

People with advanced illness have a higher incidence of clinical depression than the general population. The prevalence of depression in the general population is 6 to 10%.<sup>(9)</sup> Terminally ill patients have been found to have a higher level of both physical and emotional distress with 24% having depression.<sup>(14)</sup> Clinical depression occurs in 15 to 30 % of cancer patients.

The diagnosis of depression in people with cancer is often under-diagnosed and under-treated.<sup>(9)</sup>

### Risk factors include:

#### Non-cancer related risk factors:

- History of depression or family history of depression.<sup>(3, 4, 9, 10)</sup>
  - Two or more episodes in a lifetime.
  - First episode early or late in life.
- Lack of family or social support.<sup>(8, 10)</sup>
- Previous suicide attempts.<sup>(3, 4, 9)</sup>
- Concurrent chronic illnesses such as: stroke or myocardial infarction.<sup>(15)</sup>

- Intercurrent substance abuse

### **Cancer-related risk factors:**

- Depression at time of cancer diagnosis.(3, 4)
- Advanced stage of cancer.(4, 9, 10)
- Additional concurrent life stressors.(3, 4, 9)
- Increased physical impairment or discomfort.(4, 5, 8-10, 12)
- Being unmarried and having head and neck cancer.(10)
- Pancreatic and primary or metastatic brain cancers.(4, 8, 10)
- Medications may contribute to depression (benzodiazepines, corticosteroids, anticonvulsants, methyldopa, propranolol, chemotherapeutic agents).(4, 7, 8, 10)
- Chronic pain.(3,4,8,9,10,12)

## **RECOMMENDATION 2 - ASSESSMENT OF DEPRESSION**

Ongoing comprehensive assessment is the foundation of effective management of depression, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.(1, 2, 5, 16)

Recognition and diagnosis of depression is variable depending on the clinical setting and the diagnostic acumen of those delivering end of life care.(9)

### ***Suggested Questions for the Assessment of Depressive Symptoms in Adults with Terminal Illness***(15, 17)

<b>How well are you coping with your illness. Well? Poor?</b>	Well being
<b>How are your spirits since diagnosis? During treatment? Down? Blue?</b>	Mood
<b>Do you cry sometimes? How often? Only alone?</b>	Mood
<b>Are there things your still enjoy doing, or have you lost pleasure in things you used to do before you became ill?</b>	Anhedonia
<b>How does the future look to you? Bright? Black?</b>	Hopelessness
<b>Do you feel you can influence your care, or is your care totally under others' control?</b>	Helplessness
<b>Do you worry about being a burden to family and friends during the treatment?</b>	Worthlessness



<b>Physical symptoms (Evaluate in the context of disease related symptoms)</b>	
<b>Do you have pain that is not controlled?</b>	Pain
<b>How much time do you spend in bed?</b>	Fatigue
<b>Do you feel weak? Fatigue easily? Rested after sleep? Any relationship between how you feel and a change in treatment or how you otherwise feel physically?</b>	Fatigue
<b>How is your sleeping? Trouble going to sleep? Awake early? Often?</b>	Insomnia
<b>How is your appetite? Food tastes good? Weight loss or gain?</b>	Appetite
<b>How is your interest in sex? Extent of sexual activity?</b>	Libido
<b>Do you think or move more slowly than usual?</b>	Psychomotor slowing

Adapted from Roth, AJ, Holland JC: Psychiatric complications in cancer patient. In: Brain MC, Carbone PP, eds.: Current Therapy in Hematology-Oncology. 5th ed. St Louis, Mo: Mosby-Year Book, Inc., 1995, pp 609-618.

**Mnemonics** commonly used to remember the DSM-IV criteria are:

- **SIGECAPS** (sleep, interest (anhedonia), **g**uilt, **e**nergy, **c**oncentration, **a**ppetite, **p**sycho**m**otor, **s**uicidality)<sup>(17)</sup> and;
- **DEAD SWAMP** (**d**epressed mood, **e**nergy, **a**nhedonia, **d**eath (thoughts of), **s**leep, **w**orthlessness/guilt, **a**ppetite, **m**entation, **p**sycho**m**otor).<sup>(17)</sup>

## RECOMMENDATION 3 - DIAGNOSIS

Identifying the underlying etiology of depression is helpful in determining the interventions required.

The usual somatic symptoms of depressed patients (fatigue, loss of appetite, sleep disturbance, poor concentration, etc.) are often present in advanced cancer and terminal illness and cannot always be relied upon for diagnosis.<sup>(4, 10)</sup>

Psychological symptoms of depression that are persistent, out of character and severe are of greater diagnostic value in patients with advanced illness.<sup>(5, 18)</sup> In particular, watch for pervasive dysphoria, feelings of helplessness, hopelessness and worthlessness, guilt, loss of self-esteem, loss of interest and wishes to die. Even very mild or passive suicidal ideation is indicative of significant depression in terminally ill patients.<sup>(1, 4-6)</sup>

If the diagnosis of depression is uncertain, consider psychiatric referral and a trial of antidepressant medication or therapy. When in doubt, treat.<sup>(1, 6)</sup>

## RECOMMENDATION 4 - EDUCATION

Depression is a distressing symptom to experience and witness. It is commonly under reported as many of the signs and symptoms are a feature of terminal illness.<sup>(1, 5)</sup>

Reinforce to patient and family the importance of reporting symptoms that are causing distress, physical or psychological, as both may influence psychological well being.<sup>(1, 5, 9)</sup>

Reinforce that if depression is diagnosed it can be managed. Treatment can be effective even when life expectancy is short.<sup>(1, 5, 9)</sup>

Teach the purpose of Non-pharmacological and pharmacological measures and the goal of each.<sup>(5)</sup>

Teach that many antidepressant medications take time to become effective.<sup>(5)</sup>

## RECOMMENDATION 5 – TREATMENT: NON-PHARMACOLOGICAL

Depression in patients with advanced disease is optimally managed by utilizing a combination of supportive psychotherapy, cognitive-behavioural techniques, and antidepressant medications.<sup>(8, 12)</sup>

Always ensure that pain is well treated or alleviated. Uncontrolled pain is a major risk factor for depression and suicide among patients with cancer.<sup>(1, 2, 4)</sup>

For patient and family consider psychosocial therapies, relaxation techniques, massage therapy and therapeutic touch.<sup>(1, 4-6, 8, 12, 15)</sup>

## RECOMMENDATION 6 - TREATMENT: PHARMACOLOGICAL

**“Medication without ongoing contact is often seen as abandonment and never acceptable.”<sup>(19)</sup>**

- Start with low doses and increase slowly.<sup>(1, 5, 6, 8, 15)</sup>
- When anticipated survival time is short, consider psychostimulants due to their more immediate onset of effect.<sup>(1, 5, 6, 8, 15)</sup>
- Consider side effects and additional therapeutic benefit (tricyclic antidepressants may benefit neuropathic pain but worsen constipation; avoid tricyclics in patients with cardiac conduction delays, etc.).<sup>(1, 2, 5, 6, 8, 15)</sup>

- Withdrawal symptoms may be of significant importance in palliative patients who are unable to continue with oral medications.
- There are similar response rates when comparing antidepressant medications.<sup>(20)</sup>

### **Selective Serotonin Re-uptake Inhibitors (SSRIs)<sup>(1, 2, 5, 8, 10, 15)</sup>**

Example: **Citalopram**,<sup>(6)</sup> **Paroxetine**, **FLUoxetine**, **Sertraline** <sup>(15)</sup>

Initial and maintenance doses are specific for each of the SSRI's.

Initial dose for Citalopram: 10 to 20 mg per day to start, increasing at intervals of no less than one week. Maximum daily dose is 60 mg, although doses above 40 mg are not ordinarily recommended.<sup>(20)</sup> Usual maintenance dose is 20 to 30 mg per day.

- Have fewer side effects than tricyclic antidepressants (TCAs).
- Start SSRI at half the usual dose for the general population.
- Paroxetine and FLUoxetine are active inhibitors of the enzyme responsible for metabolizing oxyCODONE and codeine to its active analgesic form. Concurrent use of these opioids and SSRIs can therefore result in decreased pain control.
- The sudden cessation of SSRI therapy when a patient is unable to swallow can produce a withdrawal syndrome. Withdrawal risk is greater with short-half life drugs such as paroxetine, lowest with long-half life drugs such as FLUoxetine, and are of intermediate risk for other SSRI's.<sup>(20)</sup>

**FLUoxetine has less selective receptor sites and a much longer half-life than the other SSRIs and should not be the drug of choice. Switching to other antidepressants after having been on FLUoxetine can be complicated due to the extended half life.**<sup>(5)</sup>

### **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**

Example: **Venlafaxine**<sup>(10)</sup>

Initial dose: Venlafaxine XR – 37.5 to 75 mg per day then maintenance dose: 150 to 375 mg per day.

### **Atypical Antidepressants**

Example: **BuPROPion**<sup>(1, 2, 8, 15)</sup>

- Initial activating dose-related seizure-inducing potential. Contraindicated in patients with a history of seizure, in those with concomitant conditions predisposing to seizure, and in patients taking other drugs that lower seizure threshold.

- Low incidence of sedative, hypotension and anticholinergic side effects.
- Can cause over stimulation.
- Generally considered third line treatment.
- Initial: 100 mg per day then maintenance: 200 to 300 mg per day.

Example: **TraZODdone**<sup>(1, 10)</sup>

- Trazodone may cause hypotension including orthostatic hypotension and syncope; caution is required if it is given to patients receiving antihypertensive drugs and an adjustment in the dose of the antihypertensive medication may be required
- Increased serum digoxin and phenytoin levels have been reported with concurrent trazodone use.<sup>(1,10)</sup>
- Treatment should be started with low initial doses of 25 to 50 mg daily in divided doses or in an evening single dose. The dose may be increased slowly to a maximum of 300 to 400 mg daily in ambulatory patients and to 600 mg daily in hospitalized patients.

Example: **Mirtazapine**<sup>(10, 21)</sup>

- A tetracyclic antidepressant. Mirtazapine elimination is decreased in elderly persons.
- When used concomitantly with drugs that reduce the seizure threshold (e.g., phenothiazines), mirtazapine may increase the risk of seizure.
- Initial dose: 7.5 to 15 mg daily, maintenance dose: 15 to 45 mg daily.

## **Psychostimulants**<sup>(1, 2, 5, 10, 12)</sup>

Examples: **Methylphenidate and Dextroamphetamine.**

- Consider this class of medication when life expectancy may be short,<sup>(1, 5, 6, 8, 15)</sup> as these drugs work within hours to days.
- They often enhance opioid analgesia, reduce opioid sedation and improve appetite. They can improve attention, concentration and overall performance.
- Side effects include agitation, confusion, insomnia, anxiety and paranoia. Use cautiously in the elderly, avoid in delirious patients<sup>(1)</sup> and underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.<sup>(21)</sup>
- A common clinical practice is to start a psychostimulant and a SSRI together and then withdraw the stimulant while titrating the SSRI upward.
- Start methylphenidate at 5 mg PO at 8 AM and noon. Initial doses could be lower at 2.5 mg b.i.d. in very frail patients. Increase 2.5 to 5 mg every 1

or 2 days until desired effect is reached, or to a maximum daily dose of 30 mg per day.<sup>(23)</sup> Afternoon dosing can affect nighttime sleep and is generally not recommended.<sup>(5)</sup>

## Tricyclic Antidepressants (TCA)<sup>(1, 2, 5, 8, 10, 15)</sup>

Examples: **Nortriptyline, Amitriptyline, Desipramine, Imipramine and Doxepin**

- Requires a careful risk-benefit ratio analysis because the adverse effect profile may be troubling to patients in a palliative/hospice setting.<sup>(1)</sup> Effects include sedation and anticholinergic effects; dry mouth, blurred vision, urinary hesitancy, or retention, constipation.
- Avoid TCA's in patients with cardiac conduction delays,<sup>(1, 2, 5, 6, 8, 15)</sup> coronary artery disease, or history of myocardial infarction in past six months.<sup>(20)</sup>
- Adverse effects usually decrease 3 to 4 days after initiation of a TCA or after increasing the dosage.
- The secondary amines (desipramine and nortriptyline) generally have fewer side effects, such as sedation and anticholinergic effects, than the tertiary amines (imipramine, amitriptyline, and doxepin).<sup>(23)</sup>
- The specific liver enzyme cytochrome P450 metabolism pathway may affect drug levels. From 5 to 10% of Caucasians have a recessive gene that results in deficient 2D6 metabolism which would affect desipramine and nortriptyline.<sup>(20)</sup> Twenty percent of Asians are deficit in the 2C19 enzyme affecting the metabolism of TCA's such as imipramine.<sup>(20)</sup>
- Start at low doses (10 to 25 mg PO at bedtime) and increase by 10 to 25 mg PO every 4 days.
- Onset of antidepressant effect may take 2 to 4 weeks.
- May provide additional neuropathic pain benefits.

## 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 depression terms in conjunction with palliative/hospice/end of life/dying/terminally ill. Palliative care textbooks mentioned in generated articles were hand searched. Articles not written in English were excluded.

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**Approved by: Northern Health Hospice Palliative Care Consult Team,  
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# HYPERCALCEMIA IN MALIGNANT DISEASE (PALLIATIVE MANAGEMENT)

## Rationale

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

## Scope

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

Hypercalcemia is the most frequent metabolic emergency in oncology and occurs in 10% to 40% of cancer patients.<sup>(1-3)</sup> Hypercalcemia most commonly occurs in patients with advanced cancer and is an indicator of poor prognosis.<sup>(1, 2, 4-6)</sup>

## Definition of Terms

**Hypercalcemia** is defined as serum calcium (corrected) greater than 2.6 mmol/L.<sup>(3)</sup>

## Standard of Care

1. Assessment
2. Diagnosis
3. Education
4. Treatment: Non-pharmacological
5. Treatment: Pharmacological

## RECOMMENDATION 1 - HYPERCALCEMIA ASSESSMENT

Ongoing comprehensive assessment is the foundation of effective management of hypercalcemia, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.

**Table 1: Hypercalcemia Assessment using Acronym O, P, Q, R, S, T, U and V\***

<b>O</b> Onset	When did it begin? How often does it occur?
<b>P</b> Provoking/ Palliating	What brings it on? What makes it better? What makes it worse?
<b>Q</b> Quality	What does it feel like? Can you describe it?
<b>R</b> Region/ Radiation	
<b>S</b> Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right now? At best? At worst? On average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom? Nausea/vomiting, constipation, weakness, loss of appetite, confusion or agitation?
<b>T</b> Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
<b>U</b> Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
<b>V</b> Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

\* also include a Physical Assessment (as appropriate for symptom)

## Signs And Symptoms:

The severity of symptoms are not always related to the degree of hypercalcemia but often reflect the rapidity of onset.<sup>(4)</sup> Patients do not always exhibit all of the clinical features. The onset of hypercalcemia may be insidious.<sup>(3)</sup>

- **Neurological:** fatigue, lethargy, confusion, myopathy, hyporeflexia, seizures, psychosis and coma.<sup>(7)</sup> The most frequent effect of hypercalcemia is delirium.<sup>(8)</sup>
- **General:** dehydration, polydipsia, polyuria.<sup>(7, 9)</sup> Weakness and bone pain may also be present.<sup>(8)</sup>



- **GI:** anorexia, nausea and vomiting, weight loss, constipation, ileus and abdominal pain.(7-9)
- **Cardiac:** shortened Q-T interval, prolonged P-R interval, wide T waves, ventricular and atrial arrhythmias and bradycardia.(7, 9) Arrhythmias, such as bradycardia, can be fatal.(8)
- **Renal:** polyuria, polydipsia, dehydration and development of kidney stones.(8)
- **Early:** polyuria, nocturia, polydipsia, dehydration, anorexia, easy fatigability, weakness, hyporeflexia, pain may be precipitated or exacerbated by hypercalcemia.(4)
- **Late:** apathy, irritability, depression, decreased ability to concentrate, obtundation, coma, profound muscle weakness, nausea and vomiting, constipation, increased gastric acid secretion, acute pancreatitis, visual disturbances, sudden death from cardiac dysrhythmias may occur if calcium rises fast, especially in patients taking digoxin.(4)

## Laboratory Studies:

### Always relate serum calcium levels to serum albumin levels

### Method for Calculating Correction of Calcium Level to Reflect Albumin Level:

- If serum albumin is less than 40 grams per litre, increase measured calcium by 0.20 mmol per litre for every 10 grams of albumin below 40 grams per litre.
- If serum albumin is greater than 40 grams per litre, reduce measured calcium by 0.20 mmol per litre for every 10 grams of albumin over 40 grams per litre.

#### Alternatively:

- Corrected calcium (mmol/L) =  
Measured calcium (mmol/L) + [0.02 x (40 – measured albumin g/L)].(1, 3, 8)

### Other possible abnormal results:

- Alkaline phosphatase – usually elevated, except in myeloma.(4)
- Chloride may be elevated in primary hyperparathyroidism.(4, 5)
- BUN, creatinine may be elevated from renal damage.(4)
- Electrocardiogram – prolonged PR interval, widened QRS complex, shortened QT, widened T wave, bradycardia.(4)

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## RECOMMENDATION 2 - 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 hypercalcemia is identifying underlying cause(s) and treating as appropriate. While underlying cause(s) may be evident, treatment may not be indicated, depending on the stage of disease.

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

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

### Causes:

- The majority of cases of humoral hypercalcemia of malignancy are associated with impaired gut absorption of calcium and low levels of vitamin D.<sup>(9)</sup>
- Secretion of parathyroid hormone-related protein by the tumour.<sup>(6, 8, 10)</sup> This occurs in 80% of hypercalcemia cases.<sup>(8)</sup>
- Osteolytic skeletal metastases.<sup>(4, 8)</sup> The extent of metastases does not correlate well with level of calcium.<sup>(4)</sup>
- Decreased renal clearance of calcium.<sup>(9)</sup>
- Increased gastrointestinal absorption of calcium in response to elevated levels of 1,25-dihydroxycholecalciferol (1,25 (OH)<sub>2</sub>D<sub>3</sub>, calcitriol) resulting from ectopic production of this vitamin by haematological neoplasms – this occurs rarely.<sup>(9)</sup>

### Tumours most often associated with hypercalcemia:

- Multiple myeloma – 40% to 50%.<sup>(4, 5)</sup>
- Breast – greater than 20% of cases with cancer-related hypercalcemia.<sup>(4, 5)</sup>
- Lung – 20%, usually squamous cell, sometimes adenocarcinoma, rarely small cell.<sup>(4)</sup>
- Hypernephroma.<sup>(4)</sup>
- Squamous cell cancers of the head and neck and esophagus.<sup>(4)</sup>
- Thyroid.<sup>(4)</sup>
- Rarely or never – prostate or colorectal cancer.<sup>(4)</sup>

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## RECOMMENDATION 3 - EDUCATION

Teach patients at risk and their caregivers the signs and symptoms of hypercalcemia to promote early recognition of acute rises in serum calcium.<sup>(4)</sup>

## RECOMMENDATION 4 - TREATMENT: NON-PHARMACOLOGICAL

### Re-hydration

- Hydration alone may be sufficient for asymptomatic patients with borderline serum calcium.<sup>(4)</sup>
- Adequate hydration reduces serum calcium by a median of 0.25 mmol per litre.<sup>(3)</sup>
- All hypercalcemic patients are dehydrated due to polyuria and vomiting.<sup>(4)</sup>
- Hydration is appropriate for treatable hypercalcemia.<sup>(11)</sup> Re-hydration with 2 to 3 litres per day is now the accepted practice with daily serum electrolyte measurement to prevent hypokalemia and hyponatremia for cases of severe or symptomatic hypercalcemia.<sup>(4, 9)</sup>
- Increase patient's oral fluid intake to 2 to 3 litres per day, as tolerated.<sup>(4)</sup>
- Most patients are usually 4 litres behind in their overall fluid balance when a diagnosis of hypercalcemia is made. Rehydration with normal saline should commence at 100 to 120 mL per hour I.V. or by hypodermoclysis based on patient's cardiac status (e.g., a slower rate should be used in patients prone to CHF).

### Mobilization:

- Mobilization of the patient is important, in that it slows down the loss of skeletal calcium associated with immobility.<sup>(4)</sup>

### Diet:

- Low calcium diet is needed to control hypercalcemia caused by elevated 1,25 (OH)<sub>2</sub>D<sub>3</sub> but they are unpalatable, impractical and exacerbate malnutrition and have no place in palliative therapy.<sup>(3, 4, 9)</sup>

## RECOMMENDATION 5 - TREATMENT: PHARMACOLOGICAL

### Bisphosphonates:

- Bisphosphonates are appropriate to administer when serum calcium (corrected) is greater than or equal to 3 mmol per litre or when serum calcium (corrected) is less than 3 mmol per litre when accompanied by symptoms.<sup>(3)</sup>

- Bisphosphonates cause a fall in calcium in 48 hours.<sup>(9)</sup> These agents are very useful and well tolerated but are quite expensive.<sup>(1)</sup>
- Oral bisphosphonates (like clodronate or alendronate) can be used, but in many palliative care patients are not well tolerated. Parenteral drugs including pamidronate and zoledronic acid have been used with success<sup>(8)</sup> and are better tolerated and more effective than oral.<sup>(5)</sup>
- Do not give bisphosphonates until the patient is fully re-hydrated and has an adequate urine output.<sup>(4)</sup>
- Recheck serum calcium, electrolytes, urea, and creatinine on the 3rd day after administering bisphosphonates.<sup>(1)</sup>
- Renal failure is the most serious adverse effect.<sup>(3)</sup> Bisphosphonates are contraindicated in patients with serum creatinine greater than 400 umol per litre or calculated creatinine clearance of less than 10 mL per minute.<sup>(3)</sup>
- In patients with pre-existing renal disease and a serum creatinine less than 265 umol per litre, no change in dosage, infusion time or interval of pamidronate is required for multiple myeloma patients.<sup>(12)</sup>
- Caution is required in patients receiving other drugs that may affect renal function (NSAIDS, ACE inhibitors, aminoglycosides).<sup>(3)</sup>
  - **Pamidronate** 30 to 90 mg I.V. for severely elevated calcium (over 3.5 mmol per Litre) use 90 mg I.V. bolus in 250 mL<sup>(13, 14)</sup> to 500 mL NS<sup>(4, 10)</sup> over 60<sup>(13, 14)</sup> to 90 minutes.<sup>(2, 9)</sup>
    - Pamidronate has been shown to be superior to clodronate in terms of duration of normal calcium levels achieved.<sup>(2, 9)</sup>
    - Best given with acetaminophen, 500 mg PO or rectally to prevent pamidronate fever.<sup>(4)</sup>
    - Usual expected duration of effect of pamidronate is 3 to 4 weeks.<sup>(1,3)</sup>
  - **Clodronate** 1500 mg I.V. over 4 hours in 250 or 500 mL NS<sup>(1, 3, 10)</sup> or 500 mg I.V. daily for 3 days – dilute in 500 mL NS.
    - Usual expected duration of action of clodronate is 2 weeks.<sup>(1, 3)</sup>
    - Dose adjustment for decreased renal function: if creatinine clearance is 10 to 50 mL per minute a dose reduction of 25% to 50% is recommended.<sup>(3)</sup>
  - **Zoledronic acid** 4 mg in 100 mL NS over 15 minutes I.V.<sup>(1, 2, 9, 12)</sup> Zoledronic acid has been shown to achieve normal serum calcium levels in more patients, faster and with longer duration than Pamidronate.<sup>(9)</sup>

- Usual expected duration of effect of zoledronic acid is 4 to 6 weeks.<sup>(1)</sup>
- Useful for refractory hypercalcemia treatment.<sup>(1)</sup>
- Fever is a common side effect of zoledronic acid, with renal impairment seen rarely.<sup>(5)</sup>
- Zoledronic acid has been found to be effective in reducing and delaying bone complications across a broad range of solid tumours and multiple myeloma.<sup>(2)</sup>
- Dose adjustment for decreased renal function:<sup>(3)</sup>

<b>Baseline Creatinine Clearance (mL/min)</b>	<b>Zoledronic Acid Recommended Dose</b>
<b>Greater than 60</b>	<b>4 mg</b>
<b>50 to 59</b>	<b>3.5 mg</b>
<b>40 to 49</b>	<b>3.3 mg</b>
<b>30 to 39</b>	<b>3 mg</b>

### Calcitonin:

- Calcitonin 4 to 8 international units per kg given S.C. or I.M. q12h (can titrate up to q6h).<sup>(3, 4, 16)</sup>
- Calcitonin has a rapid onset of action – approximately 4 hours<sup>(9)</sup> but has a shorter duration of action<sup>(4)</sup> and is very useful when a rapid lowering of serum calcium is required<sup>(1, 3-5, 16)</sup> but needs to be combined with bisphosphonates.<sup>(3, 5, 16)</sup>
- Possible side effects: flushing, mild nausea, crampy abdominal pain.<sup>(4)</sup> A small risk of hypersensitivity exists due to salmon derivation.<sup>(3)</sup>

### Steroids:

- Corticosteroids may lower serum calcium if they have an antineoplastic effect on the underlying malignancy.<sup>(3)</sup> They should be reserved for situations in which bisphosphonates are not easily accessible or are ineffective or in which other indication for corticosteroids (pain or nausea) exist.<sup>(3)</sup>
- PredniSONE 40 to 100 mg daily<sup>(9)</sup> for up to one week.<sup>(4)</sup>
- Hydrocortisone 100 mg I.V. q6h.<sup>(7)</sup>
- Dexamethasone 4 mg S.C. q6h for 3 to 5 days.
- Steroids are particularly useful for hypercalcemia seen with lymphomas and multiple myeloma.<sup>(5)</sup>

Drugs promoting hypercalcemia (thiazide diuretics, lithium, ranitidine, cimetidine, vitamins A and D and preparations containing calcium) should be withdrawn.(4, 9, 15)

The routine use of furosemide in conjunction with hydration to promote calcium excretion is not recommended, because of the risk of volume and electrolyte depletion.(3)

## 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 hypercalcemia 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.

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# Malignant Bowel Obstruction

## Rationale

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

## Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of bowel obstruction. This guideline does not address disease specific approaches in the management of bowel obstruction.

Obstruction occurs in 3% to 42% of malignancies, with the higher number in patients with ovarian cancer.<sup>(1-6)</sup> Most commonly seen with colorectal cancer and ovarian cancer <sup>(7, 8)</sup> but may occur with any cancer having an abdominal or pelvic presence, usually occurring in advanced stages of the disease.<sup>(1, 3, 9-12)</sup>

Obstructions may be partial or complete, acute or insidious and reversible or irreversible.<sup>(1)</sup> Obstruction usually leads to local inflammation with luminal accumulation of intestinal fluids, gases and solids producing symptoms and creating a vicious cycle of distension and secretion.<sup>(1, 5, 11)</sup> The small bowel is more commonly involved than the large bowel (61% versus 33%).<sup>(13)</sup>

## Definition of Terms

**Bowel obstruction** occurs when there is blockage of the forward flow of gastric and intestinal contents through the gastrointestinal tract and can occur in the large or small bowel.<sup>(2,14,15)</sup> It can be due to direct infiltration, intraluminal obstruction or external obstruction. This may occur due to tumour growth, adhesions, carcinomatosis, fecal impaction, pharmacotherapy and/or neuropathy.<sup>(2, 5, 9)</sup>

## Standard of Care

1. Assessment
2. Diagnosis
3. Education
4. Treatment: Non-pharmacological
5. Treatment: Pharmacological

## RECOMMENDATION 1 - ASSESSMENT OF BOWEL OBSTRUCTION

Ongoing comprehensive assessment is the foundation of effective management of bowel obstruction, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and the appropriate diagnostics (see *Table 1*). Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.<sup>(9)</sup>

**Table 1: Bowel Obstruction Assessment using Acronym O,P, Q, R, S, T, U and V\***

<b>O</b> Onset	When did it begin? Have you had this before?
<b>P</b> Provoking/ Palliating	What brings it on? What makes it better? What makes it worse?
<b>Q</b> Quality	What does it feel like? Can you describe it? Is the pain constant, colicky or crampy?
<b>R</b> Region/ Radiation	Where is it? Does it spread anywhere
<b>S</b> Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right now? At best? At worst? On average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom? Nausea/vomiting, constipation, weakness, loss of appetite, confusion or agitation?
<b>T</b> Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
<b>U</b> Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
<b>V</b> Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

**\* also include a Physical Assessment (as appropriate for symptom)**

- Plain abdominal films may demonstrate dilated loops of bowel, air and fluid levels, fecal impaction and/or the obstruction.<sup>(1, 5, 9, 11)</sup>



- Gastrograffin contrast studies may further elucidate the point of obstruction and is preferred over barium, because barium can interfere with other studies.(1)
- CT scans may be required to determine the extent of the disease and help plan appropriate further treatments.(1)
- It is difficult to differentiate between partial and complete obstruction.(1, 5, 14)
- The functional adrenal insufficiency in cancer may contribute to intestinal obstruction in patients with carcinomatosis peritonei.(16)

## RECOMMENDATION 2 - DIAGNOSIS

Identifying the underlying etiology of bowel obstruction is essential in determining the interventions required. The type of obstruction, the condition of the patient and the predicted prognosis determine the treatment plan for the obstruction.(12, 14)

### Clinical symptoms:

- Pain may be constant, crampy or colicky(1,3,11,13,16) resulting from the accumulation of secreted bowel fluid.(2,5,8) Suspect bowel strangulation if refractory to opioid analgesics.(5)
- Abdominal distension.(2, 5, 11, 16)
- Nausea and vomiting are eventually present but may vary in their intensity based on the level of the obstruction and the degree of compromise of bowel patency. In obstructions of the stomach, duodenum, pancreas or jejunum, vomiting will develop early and in large volumes.(1, 2, 5)
- Bowel sounds are usually altered and may be tympanic, high pitched, diminished or absent.(5, 9)
- Abdominal exam may demonstrate visceral or peritoneal irritation or may prove benign.(14)
- In complete obstruction there will be an absence of feces and flatus.(1, 5, 11)
- Fatigue.(11)
- Anorexia.(11)
- Diarrhea with partial obstruction (overflow diarrhea).(2, 5)

## Causes of Bowel Obstruction<sup>(9)</sup>

<b>Tumour mass</b>	Single or multiple Invasion and blockage of bowel (apple core) Extrinsic compression
<b>Constipation</b>	Impacted feces, obstipation
<b>Adhesions</b>	Post-operative Malignant Post-radiation
<b>Volvulus</b>	Around tumour Around adhesions Around fistula
<b>Ileus</b>	Infection, peritonitis Drugs
<b>Peritonitis</b>	Infection, bleeding
<b>Massive ascites</b>	

## RECOMMENDATION 3 - EDUCATION

The patient and family should be involved in discussions. Information should be reinforced so that appropriate decisions regarding disease modifying or symptom modifying therapies can be made.<sup>(3, 9, 13)</sup>

## RECOMMENDATION 4 - TREATMENT: NON PHARMACOLOGICAL

- Acute or initial treatment may include; keeping patient NPO, administering intravenous or subcutaneous fluids and performing nasogastric tube drainage. Nasogastric tube drainage should be an intermittent and temporary measure for initial treatment and decompression or while waiting to make other treatment decisions.<sup>(1, 2, 4-7, 9-14)</sup>
- Hydration should be considered in patients where dehydration causes agitated confusion or results in renal failure causing opioid metabolite accumulation leading to myoclonus or seizure<sup>(5, 6, 14)</sup> and should be considered on an individual basis.<sup>(2)</sup>
- Total parenteral nutrition should only be considered for the patient who would have clinical or life-extending benefit. It is not recommended for most terminally ill patients<sup>(5, 9)</sup> and is best used in patients with a true long term prognosis.<sup>(13)</sup>
- Good mouth care and ice chips should be given for dry mouth.<sup>(2, 9, 13)</sup>
- Nasal care should be provided to patients who have a nasogastric tube inserted.<sup>(14)</sup>
- Support should be offered to patient and family as they confront the terminal nature of the disease.<sup>(9, 13, 14)</sup>
- Give small, low residue meals for patients with controlled nausea and vomiting.<sup>(2)</sup>

## Surgical Options:

- The rate of inoperable patients ranges from 6% to 50%.<sup>(6, 10)</sup>
- While surgery is the primary treatment for malignant bowel obstruction, not every patient will be a suitable candidate because of poor prognosis or advanced disease.<sup>(1, 9)</sup>
- Surgery should be avoided in patients exhibiting: palpable abdominal and pelvic mass, ascites exceeding three litres, multiple obstructive sites and pre-operative weight loss of greater than nine kilograms.<sup>(4, 6, 12, 17)</sup>
- Interventions may include resection, bypass, stenting and venting gastric or jejunal tubes<sup>(4)</sup> and should be considered when symptoms have not been relieved after 48 to 72 hours of conservative medical management.<sup>(1, 9)</sup> Stenting and gastric or intestinal venting using percutaneous endoscopic gastrostomy tubes (PEG) are less invasive, generally well tolerated and can be done under sedation.<sup>(3-7, 12, 18-20)</sup>
- Mortality from surgery may approach 30% hence careful clinical judgment must be exercised and involving other disciplines and family is advisable.<sup>(1, 9, 17)</sup>
- Prognosis, disease progression, patient's wishes and co-morbidities must be considered.<sup>(1)</sup>

## RECOMMENDATION 5 - TREATMENT: PHARMACOLOGICAL

Treatment should always be parenteral as absorption via PO route is variable.

- Corticosteroids for inflammation - dexamethasone 4 to 16 mg S.C. daily for incomplete or small bowel obstruction.<sup>(1, 5-7, 9)</sup> These were found to work better in patient populations that were not already taking steroids prior to the obstruction<sup>(7)</sup> and should be discontinued if the patient does not respond to steroid treatment within 4 to 5 days.<sup>(13)</sup>
- Antiemetics for nausea – combinations work best.<sup>(5, 9, 17)</sup> See B.C. Inter-Professional Palliative Symptom Guidelines (Jun, 2019) *for Nausea and Vomiting*.
- Motility agents to stimulate bowel in cases of incomplete obstruction – metoclopramide 5 to 20 mg S.C. q.i.d.<sup>(5, 6, 9, 17)</sup> It is contraindicated in complete bowel obstruction.<sup>(5, 6, 13)</sup>
- Anti-motility agents may have a role in complete obstruction - hyoscine butylbromide 10 to 20 mg S.C. q.i.d.<sup>(1, 2, 11, 21, 22)</sup>
- Anti-secretory agents - octreotide 50 to 150 mcg S.C. t.i.d.<sup>(5, 9)</sup> or 300 to 900 mcg by continuous S.C. infusion.<sup>(2, 5-7, 10, 11, 21)</sup> Octreotide was found to be more effective than hyoscine butylbromide in relieving gastrointestinal symptoms of advanced cancer patients.<sup>(21)</sup> In another study, octreotide resulted in significantly reduced gastrointestinal secretions by the second day of treatment<sup>(10)</sup> and it was also shown to reduce levels of nausea and

pain when compared to scopolamine butylbromide<sup>(10)</sup> or hyoscine butylbromide.<sup>(11)</sup>

- Analgesics for pain may be given via S.C. or I.V. or transdermal route.<sup>(1, 5, 7, 9, 10, 21)</sup>
- Analgesics should not be avoided fearing aggravating an obstruction.<sup>(7)</sup>
- Cathartics via rectal route in cases of fecal impaction.<sup>(9)</sup>

## 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 bowel obstruction 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.

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# PRINCIPLES OF OPIOID MANAGEMENT

## Rationale

This guideline is adapted for inter-professional primary care providers working in various settings in Northern 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.<sup>(1)</sup>

- **Short acting opioid** medications are also called immediate release (IR). These can come in oral, suppository, gel or parenteral formulations.<sup>(2)</sup>
- **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.<sup>(1)</sup>
- **Total Daily Dose (TDD)** is the 24 hour total of a drug that is taken for regular and breakthrough doses.<sup>(2)</sup>
- **Steady state** is when the rate of drug availability and elimination equal one another.<sup>(1)</sup>
- **Breakthrough Dose (BTD)** is an additional dose used to control breakthrough pain (a transitory are 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.<sup>(2)</sup>

**Opioid titration** has traditionally been referred to as adjusting the dosage of an opioid.<sup>(3, 4)</sup> 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.<sup>(2)</sup>

**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. <sup>(1, 5)</sup>

**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.<sup>(1)</sup>

**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.<sup>(6)</sup>

**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.<sup>(7, 8)</sup> It is a known pharmacologic effect of opioids.<sup>(8)</sup> Tolerance to the analgesic effects of opioids is relatively uncommon.<sup>(7)</sup>

**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.<sup>(8)</sup>

**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.<sup>(9)</sup>

**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.<sup>(10)</sup> Examples are: acetaminophen, acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs).<sup>(1)</sup>

**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.<sup>(1)</sup>

## 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.
- 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 Northern Health Palliative Care Program Symptom Guidelines (Oct, 2019) 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 Northern Health Palliative Care Program Symptom Guidelines (Oct, 2019) 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.

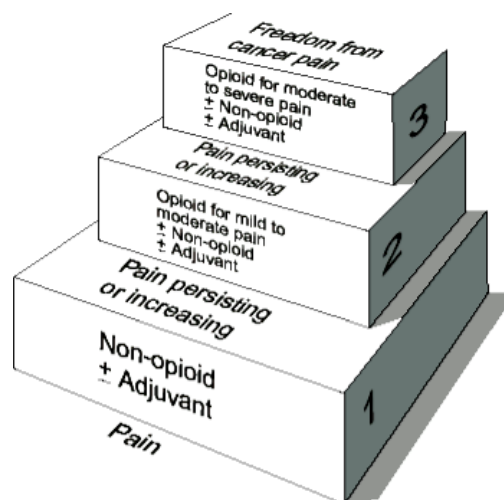
Identifying the underlying etiology of pain is essential in determining the interventions required.

## 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



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Author(s): Endorsed by NH Medical Advisory Committee

Date Issued (I), REVISED (R), reviewed (r): October 2008(I), November 2017(R), October 2019 (R)

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

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

**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.<sup>(7, 18)</sup>

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

**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. <sup>(1, 8, 16)</sup>
- Sustained release formulations have duration of analgesic effect of 8 to 12 hours. <sup>(16)</sup>
- Equianalgesic doses need to be calculated when switching from one drug to another, when changing routes of administration or both. <sup>(1)</sup>
- 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. <sup>(1)</sup>

## 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:	<ul style="list-style-type: none"> <li>• Ceiling effect at 360- 600 mg</li> <li>• Ineffective analgesic in 10 percent of Caucasians and others lacking the enzyme to convert codeine to morphine. (1, 13, 14, 21)</li> </ul>		<ul style="list-style-type: none"> <li>• In renal failure metabolites may accumulate to toxic levels. (1)</li> </ul>	<ul style="list-style-type: none"> <li>• Lower incidence of pruritus, sedation and nausea and vomiting. (1)</li> </ul>	Half-life is 2 to 4 hours with duration of analgesic action between 30 minutes and 4 hours **See Appendix A

### 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)

### 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)

Author(s): Endorsed by NH Medical Advisory Committee

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- When converting to methadone dose reduction of 75 to 90% should be considered.(16)
- See Appendix B for further methadone information.

**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)

**SUFentanil Information (See Appendix D):**

- 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](http://fhpulse/clinical_resources/clinical_policy_office/Lists/CDST%20Library/DispForm.aspx?ID=1012)

## RECOMMENDATION 7 – Routes of Administration of Opioids

- Patients in the last days and weeks of life often require more than one route of administration.<sup>(16)</sup>
- Repeated intramuscular administration of opioids is excessively noxious to palliative care patients and should be avoided. <sup>(14, 16-18)</sup>
- 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.<sup>(1)</sup>
- The oral route is the preferred route in most palliative care settings. <sup>(1, 7, 13, 16, 23)</sup> Maximal analgesia is reached at 1.5 to 2 hours for IR preparations,<sup>(1)</sup> 3 to 4 hours for SR preparations and for methadone.<sup>(2)</sup>
- 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. <sup>(2, 7, 23)</sup>
  - The oral to rectal relative potency is 1:1. <sup>(14, 17)</sup>
  - The rectal route should be avoided in patients with rectal or anal lesions <sup>(7, 23)</sup> or who are neutropenic or thrombocytopenic.<sup>(17)</sup>
  - Opioids can be placed in colostomies if the flow of effluent is slow enough to allow absorption. <sup>(17)</sup>
- 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.<sup>(1)</sup>
  - 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.<sup>(2)</sup> 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. <sup>(1, 23)</sup> 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). <sup>(1)</sup> When high doses of intravenous morphine are needed, use only preservative-free formulations. <sup>(17)</sup>
- 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.<sup>(13, 21)</sup> It is also not the first choice route in those with acute or rapidly changing pain and the opioid naïve.<sup>(13)</sup>
- The buccal route has a quick absorption rate (10 minutes).<sup>(2, 17)</sup> Use of concentrated forms of opioids (morphine 20 to 50 mg per ml or HYDRomorphone 10 to 50 mg per ml) is recommended.<sup>(1)</sup> The volume of drug

dose must be kept at or below 0.5 ml to avoid swallowing or prevent choking.<sup>(1, 13)</sup> 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.<sup>(1)</sup>

- Epidural and intrathecal administration is used in difficult or refractory pain situations.<sup>(1)</sup> Both these routes require the use of preservative free-formulations.<sup>(17)</sup>
- Intrathecal injection delivers the drug directly into the cerebral spinal fluid.<sup>(1)</sup>
- 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.<sup>(1, 13, 14)</sup>

## RECOMMENDATION 8 – Adverse Effects of Opioids

- **Constipation** is the only undesirable adverse effect where tolerance does not develop.<sup>(1, 8, 9, 12)</sup> Ensure a bowel protocol is initiated. See B.C. Inter-Professional Palliative Symptom Guidelines (Jun, 2019) on Bowel Care for guidance on a suitable bowel regime.
- **Nausea/vomiting** – usually mild and rarely persistent,<sup>(1, 9, 23)</sup> tolerance develops rapidly.<sup>(7, 12)</sup> Antiemetics can generally be discontinued in a few days when tolerance develops.<sup>(8, 17)</sup> See B.C. Inter-Professional Palliative Symptom Guidelines (Jun, 2019) on Nausea and Vomiting for guidance in choosing an antiemetic.
- **Sedation** – often transient, especially when opioid initiated or increasing doses.<sup>(14, 17)</sup> Will generally be relieved in 2 to 4 days. <sup>(1, 7-9, 12, 16, 23)</sup> 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. <sup>(8, 17)</sup> The use of psychostimulants may be beneficial. <sup>(8, 12, 14, 16, 17)</sup>
- **Delirium/restlessness** - may be seen both upon initiation of opioids (frequently in the elderly) <sup>(1, 12)</sup> and may occur during ongoing opioid therapy when metabolite accumulation occurs. <sup>(1, 12, 25)</sup> For treatment of true delirium see B.C. Inter-Professional Palliative Symptom Guidelines (Jun, 2019) 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.<sup>(9)</sup> Rarely will a patient need to be catheterized.<sup>(1, 9, 14)</sup> Urinary retention occurs more frequently in men with prostatic hypertrophy, patients with pelvic tumors, or bladder outlet obstruction.<sup>(17)</sup>
- **Pruritis** occurs secondary to the histamine release in drugs like morphine. <sup>(7, 16)</sup> Patients may need an antihistamine or opioid rotation, if severe. <sup>(1, 9, 16, 17)</sup>
- **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.<sup>(1)</sup>
- **Syncope** (dizziness) occurs secondary to orthostatic hypotension caused by venous pooling following histamine release.<sup>(1, 9)</sup> Patients prone to this effect should be instructed to change positions slowly when moving from lying to sitting or standing.<sup>(1)</sup>
  - **Myoclonus** (spontaneous jerking movements) can occur with any dose and route of opioids.<sup>(1, 17)</sup> Myoclonus may precede the onset of opioid-induced neurotoxicity.<sup>(1)</sup> See B.C. Inter-Professional Palliative Symptom Guidelines (Jun, 2019) 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.<sup>(1, 9, 12)</sup> It is due to the accumulation of toxic metabolites and impaired renal function, dehydration and electrolyte imbalances contribute to this condition.<sup>(1, 9, 21)</sup> OIN occurs more frequently with high dose parenteral administration of morphine<sup>(12)</sup> and has been observed in cases using high dose HYDROmorphine.<sup>(1)</sup> OIN occurs more common in the frail elderly.<sup>(9)</sup> 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.<sup>(16)</sup> Opioid rotation should be considered.<sup>(1, 21)</sup>
  - **Respiratory depression** occurs rarely in patients receiving opioids regularly as tolerance to the respiratory depressant effects develop rapidly. <sup>(1, 7-9, 14, 16, 17)</sup> Opioids should not be withheld for fear of respiratory depression in this group.<sup>(17)</sup> The risk of respiratory depression is greater in patients with respiratory impairment (pneumonia, those with CO<sub>2</sub> retention or chronic obstructive pulmonary disease), and when opioids are used in opioid-naïve patients, or are too rapidly titrated.<sup>(1, 9, 17)</sup>

## 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.<sup>(13)</sup>
- In opioid naïve patients start with 2.5 to 5 mg of morphine or 0.5 to 1 mg of HYDROmorphine q4h with breakthrough medication ordered at 1.25 to 2.5 mg of morphine or 0.25 to 0.5 mg HYDROmorphine 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.<sup>(2)</sup>



- 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)<sup>(13)</sup> and remember to increase the breakthrough dose proportionately when the regular dose is increased.<sup>(2)</sup>
- 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. <sup>(2)</sup>
- Doubling the nighttime dose will avoid waking the patient in the early morning for a scheduled q4h dose, however, night loading doses should be considered only for patients with good pain control.<sup>(2,22)</sup> The use of sustained release opioids appears to be a better dosing strategy, as shown in a study with SR morphine.<sup>(26)</sup>
- 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.<sup>(2)</sup>
- 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.<sup>(2)</sup> 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.<sup>(2, 9)</sup>
- For severe pain the rate of titration may need to be more aggressive. <sup>(14)</sup>

## 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.<sup>(1,21,23)</sup>
- 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.<sup>(1, 17, 23)</sup>
- Drugs available in long acting formulations include; codeine, oxyCODONE, morphine, HYDROmorphine and fentaNYL. Methadone is considered a long acting opioid.<sup>(1)</sup>
- Before conversion to a long acting opioid, use immediate release preparations to titrate to the appropriate 24 hour dose (TDD).<sup>(1, 14, 17)</sup>

- Steady state when using morphine or HYDROmorphine sustained release is achieved after 48 to 72 hours. Dosage adjustments for these drugs should be made only every 2 or 3 days.<sup>(1, 2)</sup>
- Never prescribe sustained release oral formulations more frequently than q8h.<sup>(1)</sup>
- 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.<sup>(1, 15)</sup>
- 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.).<sup>(1, 7, 8, 12, 13, 17)</sup> Preferably use the same drug.<sup>(1, 14)</sup>
- FentaNYL transdermal patches require changing q72h but some patients may require changing q48h.<sup>(1, 21)</sup> 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:<sup>(1)</sup>
  - 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.<sup>(2, 14)</sup> The dose should only be reduced if the pain was controlled on the previous medication dosage or if there was opioid-induced neuroexcitation pain. <sup>(1, 7, 8)</sup>
- 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.<sup>(1, 13, 14, 23)</sup> The need to switch occurs in 10 to 30% of patients on oral morphine.<sup>(2)</sup>

## 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.<sup>(1, 7, 8, 14)</sup>
- If the patient has been on opioids for only a short time, abrupt discontinuation should not incur withdrawal symptoms.<sup>(1)</sup>

- 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.<sup>(8)</sup> 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.<sup>(7)</sup>
- 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.<sup>(11, 13)</sup>

## 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.<sup>(1)</sup>

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.<sup>(1, 27)</sup>

- 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).
- 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.<sup>(28)</sup> Cardiovascular risk with these agents are minimized by using the lowest effective dose, for the shortest period of time.<sup>(31)</sup> Recently, cardiovascular risk has been shown to be less with traditional NSAIDS ibuprofen and naproxen, than with other NSAIDS such as indomethacin and diclofenac.<sup>(29)</sup>

- 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 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)

### **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)
- 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.<sup>(1)</sup>

### 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.<sup>(31)</sup> 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.<sup>(31)</sup>

“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.”<sup>(16)</sup> In these cases, **refer when pain persists**.<sup>(2)</sup>

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**Approved by: Northern Health Hospice Palliative Care Consult Team, October 2019**

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# APPENDIX A: FENTAANYL TRANSDERMAL

## Principles

### Indications For FentaANYL Transdermal Use

- Topical, non-invasive alternative to oral medications.<sup>(1,2)</sup>
- 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<sup>(3-5)</sup> and improve patient compliance.<sup>(6-7)</sup>
- To potentially lower opioid adverse effects of constipation,<sup>(8-11)</sup> nausea,<sup>(8)</sup> and histamine release.<sup>(12-14)</sup>
- Renal failure.<sup>(15)</sup>

### Contraindications To FentaANYL 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,<sup>(3,16-19)</sup> while up to two weeks has been suggested for chronic non-cancer patients.<sup>(20)</sup>
  - When codeine or tramadol was the prior regular opioid, due to inability to assure safe conversion to fentaANYL.<sup>(20-22)</sup>
- Pain is mild, unstable or poorly controlled.<sup>(8,9)</sup>
- Acute pain management, e.g., post-operative, or during acute pain titration.<sup>(3-5,23-28)</sup>
- Patient is under 18 years of age.<sup>(3-5,23-28)</sup>
- Patients with significant respiratory depression and patients who have acute or severe bronchial asthma.<sup>(3,5)</sup>



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## 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.<sup>(6,19,29,30)</sup>
- FentaNYL blood concentrations level off between 12 to 24 hours after application.<sup>(6)</sup>
- Most commonly, full clinical effects will occur between 24 and 48 hours after a single patch application.<sup>(19)</sup>
- Steady state serum levels achieved after multiple patch dosing; by day six<sup>(31)</sup> but may be as long as twelve days due to individual variation in skin permeability, drug clearance.<sup>(3)</sup>
- After patch removal serum fentaNYL concentrations decline gradually, falling about 50% in 17 hours, within a range of 13 to 22 hours.<sup>(5)</sup>
- No pharmacologic dose ceiling<sup>(30)</sup> 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.<sup>(32)</sup>

## 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.<sup>(33)</sup>
- Elevated temperature may increase fentaNYL concentrations.<sup>(3-5,34-37)</sup> Monitor patient for fevers greater than 38.9° C and report to physician.<sup>(38,39)</sup> Avoid application site exposure to heat sources such as hot tubs, heated waterbeds, heating pads, electric blankets, heat lamps, saunas, or prolonged sunbathing.<sup>(3-5,37,40)</sup>
- Do not cut the patch delivery system, as this use would be outside the product's licensed indication.<sup>(3-5,23-28)</sup> Half of a matrix patch may not equal half a dose due to uneven cutting or lower surface area.<sup>(41)</sup> The current fentaNYL patch matrix system (drug-in adhesive) has been cut in anecdotal clinical use<sup>(15,42)</sup> although no studies have been completed.<sup>(41)</sup>

- Caregivers should wear gloves when handling the patch to prevent unintentional caregiver transdermal absorption.<sup>(43)</sup> 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.<sup>(3-5)</sup>
- 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.<sup>(1,15)</sup> However, along with methadone, fentaNYL is one of the safest opioids of choice in patients with chronic kidney disease.<sup>(1,44)</sup>
- Patients are at risk of thermal skin burns when wearing transdermal patches which contain aluminum or conductive material during some procedures.<sup>(23,45,46)</sup> Presently, only one Canadian brand of fentaNYL transdermal patch provides a precaution regarding its application due to metallic (aluminum) content.<sup>(23)</sup> Prior to magnetic resonance imaging (MRI), cardioversion or electrocautery, assess then remove fentaNYL patches if content is metallic.<sup>(23,45)</sup>
- Transdermal fentaNYL patch use in patients with systemic skin disorders such as scleroderma is limited, but has been used.<sup>(47-49)</sup> 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.<sup>(49)</sup>
- 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.<sup>(147)</sup>
- Refer to fentaNYL transdermal patch product monographs for complete listing of precautions.<sup>(3-5,23-28)</sup>

- Refer to comprehensive transdermal patch reviews for detailed medication safety practices to guide medication error prevention and safety practices.<sup>(45,50,51)</sup>

### 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.<sup>(3,52)</sup>
- A used patch may contain enough residual fentaNYL to be potentially lethal for children or an opioid naïve adult.<sup>(53)</sup> 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.<sup>(53-55)</sup>
- 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.<sup>(56-60)</sup> Overprescribing medication also poses environmental concerns when unused medication requires disposal.<sup>(61)</sup>
- A patch exchange return program has been implemented in Ontario to minimize diversion of used patches where there is a concern of misuse.<sup>(62-65)</sup>
- 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.<sup>(38,52,56-60,66-77)</sup> **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<sup>(23, 24, 26, 27)</sup>, 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.<sup>(3-5,25)</sup> Few sources exist to obtain these lockable medication boxes<sup>(78,79)</sup> 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

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nurse, witnessed by another nurse, and documented on the medication administration record with the initials of both nurses.<sup>(80,81)</sup>

- 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.<sup>(80)</sup>
- 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.<sup>(82)</sup> Within hospitals, considered environmental waste options might include a secure specialty drug sink collection method.<sup>(83)</sup>

### **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.
  - 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

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temporary storage has been suggested.<sup>(3-5,25)</sup>

- 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.<sup>(82)</sup>

## 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.<sup>(23,24,26,27)</sup>

\*\* 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.<sup>(70)</sup> A medication disposal product Deterra System™ 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.<sup>(84-87)</sup>

## Practice

### A. Converting to FentaNYL Transdermal Patch

- If patient previously on codeine or tramadol, do not convert to fentaNYL transdermal patch;<sup>(21)</sup> **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.<sup>(88-90)</sup> 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 *unidirectional* conversion; i.e., to transdermal fentaNYL from other opioids.<sup>(3-5,91)</sup>
- Do not reduce the morphine equivalent amount to account for a lack of complete cross tolerance<sup>(91,92)</sup> as the conversion chart is designed to be conservative, with 50% of patients requiring a dose increase after the initial patch strength application.<sup>(4)</sup>

- **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.<sup>(93)</sup>
- If breakthrough doses of immediate release morphine or immediate release HYDROmorphine 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.<sup>(3-5)</sup> Use the Pasero Opioid Sedation Scale for sedation monitoring.<sup>(94-96)</sup> If a mild opioid overdosing occurs (respiratory rate greater than 8 breaths per minute) hydration and reduction in opioid dose is often sufficient. If a severe opioid overdosing occurs (respiratory rate less than or equal to 8 breaths per minute) consider treatment with small doses of naloxone. Avoid precipitating an opioid withdrawal syndrome (including severe pain) when treating with naloxone. Remember that with the prolonged effects of transdermal fentaNYL, with a half-life of 13 to 22 hours after patch removal, an 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.<sup>(127)</sup>

**CHART A1 – FentaNYL Transdermal Patch Equianalgesic Conversion\*†**

Oral Morphine (mg per day)	SC/IV Morphine (mg per day)	Oral HYDROmorphine (mg per day)	SC/IV HYDROmorphine (mg per day)	Oral oxyCODONE (mg 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.<sup>(98)</sup> The HYDROmorphine and oxyCODONE conversions are based on a morphine to HYDROmorphine ratio of (5:1) and a morphine to oxyCODONE ratio of (1.5:1).<sup>(99)</sup>

†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	Subcutaneous	Oral Immediate	Subcutaneous	Oral Immediate
	Release		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.<sup>(3-5,15,100)</sup> A flat surface is recommended, and locating the

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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. 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.<sup>(101)</sup> 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.<sup>(3)</sup> FentaNYL patches that have fallen off or accidentally transferred to children have resulted in deaths.<sup>(51,52,71-73,76)</sup> 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.<sup>(71)</sup>
- Patch adherence can occasionally be problematic. Opioids such as transdermal fentaNYL can cause sweating in up to 10% of patients.<sup>(102)</sup> The occlusive patch itself may induce sweating, irritation and adhesion difficulties,<sup>(103)</sup> which is more pronounced in warm weather.<sup>(104-106)</sup>
- 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.<sup>(3-5,23-28,107)</sup>
- 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).<sup>(107-109)</sup> 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.<sup>(39,110-113)</sup> Regular confirmation of adhesion permits determination of effectiveness.<sup>(112)</sup>
- 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 <sup>(23,114)</sup>	Not available	10.7 cm <sup>2</sup> 31.12 x 35.08 mm	Not available	21.4 cm <sup>2</sup> 39.68 x 54.48 mm	32.1 cm <sup>2</sup> 54.48 x 59.31 mm	42.8 cm <sup>2</sup> 51.37 x 83.73 mm
Janssen <sup>(3,115)</sup>	5.25 cm <sup>2</sup> 20.47 x 26.06 mm	10.5 cm <sup>2</sup> 25.48 x 41.48 mm	Not available	21 cm <sup>2</sup> 37.77 x 60.83 mm	31.5 cm <sup>2</sup> 55.19 x 60.78 mm	42 cm <sup>2</sup> 60.73 x 72.4 mm
Mylan <sup>(25,116)</sup>	3.13 cm <sup>2</sup> 12.7x 25.48 mm	6.25 cm <sup>2</sup> 18.3 x 35.70 mm	Not available	12.5 cm <sup>2</sup> 39 x 42.6 mm	18.75 cm <sup>2</sup> 41.6 x 45.8 mm	25 cm <sup>2</sup> 41.6 x 60.8 mm
Pharmascience <sup>(26,117)</sup> & Ranbaxy <sup>(28,118)</sup>	5.25 cm <sup>2</sup> 16.25 x 32.5 mm	10.5 cm <sup>2</sup> 32.5 x 32.5 mm	Not available	21 cm <sup>2</sup> 32.5 x 65 mm	31.5 cm <sup>2</sup> 56.2 x 56.2 mm	42 cm <sup>2</sup> 56.2 x 75 mm
Sandoz <sup>(5,119)</sup>	5.25 cm <sup>2</sup> 16.25 x 32.5 mm	10.5 cm <sup>2</sup> 32.5 x 32.5 mm	15.75 cm <sup>2</sup> 32.5 x 48.5 mm	21 cm <sup>2</sup> 32.5 x 65 mm	31.5 cm <sup>2</sup> 56.2 x 56.2 mm	42 cm <sup>2</sup> 56.2 x 75 mm
TEVA <sup>(28)</sup>	3.75 cm <sup>2</sup> 20 X 20 mm	7.5 cm <sup>2</sup> 26 X 30 mm	Not available	15 cm <sup>2</sup> 30 x 51 mm	22.5 cm <sup>2</sup> 47.5 x 48 mm	30 cm <sup>2</sup> 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.<sup>(3,120,121)</sup> While fentaNYL plasma levels were normal at 4 and 24 hours after application in cachectic patients (BMI less than 18 kg/m<sup>2</sup>), they were significantly lower at 48 and 72 hours than normal weight patients.<sup>(120)</sup> Monitor for adequacy of sustained pain relief and consider Q48H patch replacement if there is any wearing off effect (end of dose failure).<sup>(122,123)</sup>
- Patients with advanced cancer suffering from sweating or cachexia may have reduced absorption of transdermal fentaNYL.<sup>(121)</sup> Switching to other opioids, e.g., morphine, HYDROmorphone, may be necessary to improve opioid delivery efficacy and tolerability.<sup>(121)</sup>
- 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.<sup>(45,124)</sup> 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.<sup>(125)</sup>
- When rotating application sites it is recommended to not reapply to the same site within seven days to help minimize irritant skin reactions.<sup>(45)</sup> Anecdotal management of skin irritation from transdermal patches has included use of steroid sprays topically prior to patch application (e.g., fluticasone or beclomethasone),<sup>(43,126-131)</sup> however, use of this practice only discussed in some detail in four transdermal fentaNYL patients.<sup>(129)</sup> 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.<sup>(127)</sup>

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### CHART A3 – Switch Schedule for Initiation of FentaNYL Transdermal Patch and Discontinuation of Prior Opioids<sup>(131,132)</sup>

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
<b>**NOTE: Provide PRN Breakthrough dose throughout Conversions</b>				

Literature provides little data regarding a scheduled switch.<sup>(91,131,132)</sup>  
 Supervise closely during use of this suggested guideline.<sup>(131,132)</sup>

#### C. Dose Titration with FentaNYL Transdermal Patch

- Wait a minimum of three days after initial application for the first dosage increase.<sup>(3-5,23-28)</sup> All subsequent dosage increases should occur six days following the previous application.<sup>(3-5,23-28)</sup>
- Calculate and total the amount of breakthrough doses in the prior 24 hours to guide incremental dose increase.<sup>(91)</sup>
- Consider a 30 to 50% baseline dose increase,<sup>(133,134)</sup> 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 HYDROmorphine (mg per day)	SC/IV HYDROmorphine (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.<sup>(15)</sup> 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.<sup>(135-138)</sup> The absorption from a transdermal patch is proportionate to the surface area of the patch.<sup>(31)</sup> Dose-modifying methods using

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a half-patch are **best avoided** or used very cautiously, as this can be error-prone due to unfamiliarity and lack of approved instructions.<sup>(139)</sup> To date, a single fatal case was reported to Health Canada in which a health care professional was using a dose-modifying method.<sup>(140)</sup>

- 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.<sup>(91,122,123)</sup> 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).<sup>(122,141,142)</sup>
- Provide and appropriately adjust for a new PRN breakthrough dose.<sup>(7,19)</sup> 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.<sup>(143,144)</sup> 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.<sup>(5,6,91)</sup>
- 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.<sup>(145)</sup>
- 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<sup>(131,132)</sup>

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
<b>** NOTE: Provide PRN Breakthrough dose throughout Conversions</b>				

Literature provides little data regarding a scheduled switch.<sup>(131,132)</sup> Supervise closely during use of this suggested guideline,<sup>(131,132)</sup> 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.<sup>(91)</sup>

### 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<sup>(3,146)</sup> while for others refer to the corresponding product supplier<sup>(4,5,23-28)</sup> 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](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410380)

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## 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<sup>(106,107)</sup> and guidelines<sup>(108-9)</sup> 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)

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**TABLE A2 – FentaNYL Drug Interactions**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
<b>Abiraterone</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 1,4
<i>Adalimumab</i>	<i>Moderate</i>	CYP3A4 induction	Decrease levels	Analgesia reduction	Theoretical <sup>1</sup> , Fair <sup>2</sup> 1,2
<b>Alcohol</b>	<b>Major</b>	Additive CNS depression		Sedation, respiratory depression, hypotension	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-5
<b>ALfentanil</b>	<b>Major</b>	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical <sup>1</sup> , 1,6
<b>ALPRAZolam</b>	<b>Major</b>	Additive CNS depression		CNS & respiratory depression	Theoretical <sup>1</sup> , 1
<b>Amiodarone</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	FentaNYL toxicity, low cardiac output, bradycardia	Probable <sup>1</sup> , Good <sup>2</sup> , 1-5,7
<b>Amitriptyline</b>	<b>Major</b>	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical <sup>1</sup> , 1,3
<b>amLODdipine</b>	<b>Major</b>	Additive hypotensive effect & CYP3A4 inhibition		Risk of hypotension and/or bradycardia & fentaNYL toxicity	Theoretical <sup>1</sup> , 1,3,8
Ammonium Chloride		Excretion enhanced	Decrease levels	Analgesia reduction	4
<b>Amphetamines</b>	<b>Major</b>	Additive analgesia & additive serotonergic effect		Monitor for enhanced fentaNYL analgesia, & risk of serotonin syndrome	Theoretical <sup>1</sup> , 1,4
<b>Amprenavir</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Potentiate CNS depression, effects of fentaNYL on respiration, sedation	Theoretical <sup>1</sup> , 1,3,5
Anesthetics (General)		Additive CNS depression		Sedation, CNS depression	5
Anxiolytics		Additive CNS depression		Sedation, CNS depression	3
Anticholinergics		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

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**TABLE A2 – Fentanyl Drug Interactions continued**

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

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**TABLE A2 – FentaNYL Drug Interactions continued**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
<b>Fosaprepitant</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Dosage reduction of fentaNYL may be warranted	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-4
<b>Fosphenytoin</b>	<b>Major</b>	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-3
<b>Frovatriptan</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Ginkgo Biloba</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<i>Ginseng, Chinese</i>	<i>Moderate</i>	Not specified by reference		Reduction of analgesia	Theoretical <sup>1</sup>
Goldenseal		CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Grapefruit Juice</b>	<b>Major (oral fentaNYL) Minor (patch)</b>	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 <sup>1</sup> , Fair <sup>2</sup> , 8
Haloperidol		Additive CNS depression		Sedation, CNS & respiratory depression	3
<b>HYDROcodone</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>HYDROmorphine</b>	<b>Major</b>	Additive CNS depression		Potentiate CNS depression, effects of fentaNYL on respiration, sedation	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>HydroXYzine</b>	<b>Major</b>	Additive CNS depression		Increased CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>Imatinib</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-3,8
<b>Imipramine</b>	<b>Major</b>	Additive CNS depression & additive serotonergic effect		Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-3
<b>Indinavir</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-3

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**TABLE A2 – FentaNYL Drug Interactions continued**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
<i>InFLIXimab</i>	<i>Moderate</i>	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Isoniazid</b>	<b>Major</b>	Reduced CYP3A4 metabolism, CYP3A4 Co-substrate	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
Ivacaftor		CYP3A4 Co-substrate, substrate metabolism competition	Increase levels	Sedation, CNS & respiratory depression	4
<b>Itraconazole</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 5
<i>Kava</i>	<i>Moderate</i>	Additive CNS depression		Sedation, increased CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>Ketamine</b>	<b>Major</b>	Additive CNS depression		Analgesia potentiation, sedation, increased CNS depression	Theoretical <sup>1</sup> , 10
<b>Ketoconazole</b>	<b>Major</b>	Potent CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-5,7
<i>Lapatinib</i>	<i>Moderate</i>	Weak CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Levonorgestrel</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Increased risk of fentaNYL toxicity	Theoretical <sup>1</sup> , Fair <sup>2</sup>
Lidocaine		Additive CNS depression		Increased risk of respiratory depression	7
<b>Linezolid</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 9
<b>Lithium</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>
Loperamide		Additive serotonergic effect		Increased risk of serotonin syndrome	6
<b>Lopinavir</b>	<b>Avoid</b>	Strong CYP3A4 inhibition		Significant risk of fentaNYL toxicity	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>LORazepam</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 6
<i>Loxapine</i>	<i>Moderate</i>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
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

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**TABLE A2 – FentaNYL Drug Interactions continued**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
Maprotiline		Additive CNS depression		Sedation, CNS & respiratory depression	3
MDMA “Ecstasy” 3,4-methylenedixy-methamphetamine		Additive serotonergic effect		Increased serotonin syndrome risk	9
<b>Meclizine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Meperidine</b>	<b>Major</b>	Additive serotonergic effect and additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 6,9
<b>Methadone</b>	<b>Major</b>	Additive serotonergic effect & additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Methocarbamol</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Methotrimeprazine</b>	<b>Major</b>	Additive hypotensive effect, & additive CNS depression		Hypotension, CNS sedation, respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>Methylene Blue</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Miconazole (systemic)</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Midazolam</b>	<b>Major</b>	Additive CNS depression		Risk of hypotension, sedation, respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 7
Mirtazapine		Additive CNS depression		Sedation, CNS & respiratory depression	3
<b>Mitotane</b>	<b>Major</b>	Strong CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Monamine Oxidase (MAO) inhibitors</b>	<b>Avoid</b>	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 serotonergic effect of MAOI’s	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 5,7
<b>Morphine</b>	<b>Major</b>	Additive CNS depression		Increased risk of CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
Skeletal Muscle Relaxants		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3,5

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**TABLE A2 – FentaNYL Drug Interactions continued**

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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
<b>OLANzapine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3
<b>Opioids</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3
<b>Orphenadrine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Oxazepam</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>OxyCODONE</b>	<b>Major</b>	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression. Increased risk of serotonin syndrome	Theoretical <sup>1</sup> , 6
Paraldehyde		Additive CNS depression		Sedation, CNS & respiratory depression	4
<b>PARoxetine</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup>
<b>Pazopanib</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
Pegvisomant		Not provided by reference		May diminish therapeutic effect of pegvisomant	4
<b>Pentazocine</b>	<b>Major</b>	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 <sup>1</sup> , 3,6
Perampanel		Additive CNS depression		Sedation, CNS & respiratory depression	4
<b>Perphenazine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>

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**TABLE A2 – FentaNYL Drug Interactions continued**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
<b>Phenelzine (MOA inhibitor)</b>	<b>Major</b>	Additive serotonergic effect, additive hypotensive effect		Potential of opioid effects, (e.g., hypotension) can be severe and unpredictable. Avoid concurrent use for 14 days. FentaNYL may enhance serotonergic effect of MAOI's	Theoretical <sup>1</sup> , 3,6
<b>PHENobarbital</b>	<b>Major</b>	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 <sup>1</sup> , Fair <sup>2</sup> , 1-4,8
Phenothiazines		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
<b>Phenytoin</b>	<b>Major</b>	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> , 3,7,8
<b>Pimozide</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression May increase pimozide levels	Theoretical <sup>1</sup> , 3,4
<b>Pipotiazine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Posaconazole</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
Pramipexole		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
Pregabalin		Additive CNS depression		Sedation, CNS & respiratory depression	3
<b>Primidone</b>	<b>Major</b>	CYP3A4 induction	Decrease levels	Reduction of analgesia Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 4,7
<b>Procarbazine (MAO inhibitor)</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , 9
<b>Prochlorperazine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3,4
Promethazine		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3,4,7
ProPOFol		Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 8

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**TABLE A2 – FentaNYL Drug Interactions continued**

Interacting Drug	Interaction Severity <sup>2</sup>	Mechanism of Interaction	Effect on FentaNYL Level	Monitor For	Substantiation <sup>1</sup> , Documentation <sup>2</sup> , References
<b>QU</b> etiapine	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3
<b>Ranitidine</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Rasagiline</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup>
<b>Regorafenib</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>REM</b> ifentanil	<b>Major</b>	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical <sup>1</sup> , 6
<b>Rifa</b> BUTin	<b>Major</b>	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> , 3,4
<b>Rif</b> AMPin	<b>Major</b>	CYP3A4 induction	Decrease levels	Reduction of analgesia	Theoretical <sup>1</sup> 3,4,7,
Risperi <b>DONE</b>		Additive CNS depression		Sedation, CNS & respiratory depression	3
<b>Ritonavir</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Increased risk of fentaNYL toxicity. <b>Avoid concurrent use if possible</b>	Theoretical <sup>1</sup> , 3,4,5,
<b>Rizatriptan</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup>
r <b>OPIN</b> IRole		Additive CNS depression		Sedation, CNS & respiratory depression	3,4
Rotigotine		Additive CNS depression		May enhance sedative effect of rotigotine	4
<b>Saquinavir</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression. Increased risk of fentaNYL toxicity. <b>Avoid concurrent use if possible</b>	Theoretical <sup>1</sup> , 3,4,7,8,
Sedatives & Hypnotics		Additive CNS depression		Potentiate CNS depression, effects of fentaNYL on respiration, sedation	3
<b>Selective Serotonin Re-uptake inhibitors</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1,2,4

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**TABLE A2 – FentaNYL Drug Interactions continued**

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<b>Selegiline (MOA inhibitor)</b>	<b>Major</b>	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 serotonergic effect of MAOI's	Theoretical <sup>1</sup> , 3,4,9
Simeprevir		CYP3A4 inhibition (more with oral fentaNYL)	Increase levels	Sedation, CNS & respiratory depression	4
<b>Sertraline</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Sodium Oxybate</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<i>Spiramycin</i>	<i>Moderate</i>	CYP3A4 inhibition	Increase levels	May increase or prolong opioid effects - sedation, CNS & respiratory depression	Probable <sup>1</sup> , Good <sup>2</sup>
<b>St John's Wort</b>	<b>Major</b>	CYP3A4 induction, & additive serotonergic effect	Decrease levels	Reduction of fentaNYL levels, analgesia & increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 3
Succinylcholine		Enhance bradycardia		Monitor for enhanced bradycardia	4
<b>SUFentanil</b>	<b>Major</b>	Additive CNS depression, & additive serotonergic effect		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical <sup>1</sup> , 6
<b>SUMatriptan</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup>
<b>Tapentadol</b>	<b>Major</b>	Additive serotonergic effect & additive CNS depression		Sedation, CNS & respiratory depression, increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 4
<b>Telaprevir</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Temazepam</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
Tetrahydrocannabinol		Additive CNS depression		Sedation, CNS & respiratory depression	3
Thalidomide		Additive CNS depression		Sedation, CNS & respiratory depression	4

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**TABLE A2 – FentaNYL Drug Interactions continued**

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<b>Ticagrelor</b>	<b>Major</b>	CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Tipranavir</b>	<b>Major</b>	Strong CYP3A4 inhibition	Increase levels	Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>TiZANidine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
Tobacco smoking		CYP3A4 induction	Decrease levels	May increase fentaNYL clearance, lower analgesia	7,13
<i>Tocilizumab</i>	<i>Moderate</i>	Increase of CYP450 enzymes	Potentially decrease	Lower fentaNYL levels & analgesia	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Topiramate</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>TraMADol</b>	<b>Major</b>	Additive serotonergic effect & additive CNS depression		Increased risk of serotonin syndrome and increased risk of CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup> , 1-4
<b>Tranlycypromine (MOA inhibitor)</b>	<b>Major</b>	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 serotonergic effect of MAOI's	Theoretical <sup>1</sup> , 1,3,4
<b>TraZODone</b>	<b>Major</b>	Additive CNS depression & additive serotonergic effect		Increased serotonin syndrome risk, sedation, CNS & respiratory depression	Theoretical <sup>1</sup> , 3,4,7
<b>Triazolam</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Trifluoperazine</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>TrimEPRAZINE</b>	<b>Major</b>	Additive CNS depression		Sedation, CNS & respiratory depression	Theoretical <sup>1</sup>
<b>Tryptophan</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<i>Valerian</i>	<i>Moderate</i>	Additive CNS depression		Additive CNS depression	Theoretical <sup>1</sup> , Fair <sup>2</sup>
<b>Valproic Acid</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup>
<b>Venlafaxine</b>	<b>Major</b>	Additive serotonergic effect		Increased serotonin syndrome risk	Theoretical <sup>1</sup> , Fair <sup>2</sup>

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**TABLE A2 – FentaNYL Drug Interactions continued**

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

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**Approved by: Northern Health Hospice Palliative Care Consult Team, October 2019**

# APPENDIX B: 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.<sup>(1-6)</sup>

<sup>6)</sup> Its use is highly individualized, and demands finesse, skill and knowledge for use in carefully supervised settings.

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

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

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

1. **Side Effects:** The side effects of nausea,<sup>(12,16)</sup> constipation,<sup>(3,4,6,12,16,25)</sup> and confusion<sup>(6,16)</sup> are often less than for other opioids. Additional side effects include sedation, dizziness, pruritus, sweating, vomiting, risk of urinary retention, dry mouth, and insomnia.<sup>(2,3,12,14,22)</sup> 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.<sup>(6,22,26-28)</sup> Prolonged QT interval is associated with torsades de pointes (TdP) (a type of paroxysmal ventricular tachycardia), ventricular fibrillation and sudden cardiac death.<sup>(1,9,22,29-31)</sup> Palliative care patients are at



risk in the presence of heart disease,<sup>(22,29)</sup> abnormal liver function, low potassium and calcium, and while using selected drugs.<sup>(7,29,32,33)</sup> 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.<sup>(3,5,14,23)</sup> 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<sup>(55)</sup> or chocolate milk.<sup>(5)</sup>

Applesauce or a candy taken after a dose may alleviate the bitterness.<sup>(14)</sup> Methadone has been used intravenously<sup>(7,8)</sup> subcutaneously,<sup>(35,36)</sup> and intramuscularly,<sup>(14)</sup> although obtaining this form of the drug requires importation via Health Canada's Special Access Program.

## B. Properties

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

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### C. Indications

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

### D. Disadvantages (Challenges)

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

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## E Contraindications

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

## 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.<sup>(5)</sup>

QTc should be measured before embarking on methadone treatment and when the dose approaches 200 mg per 24 hours.<sup>(6,15,47)</sup> Risk of torsades de pointes grows as QTc increases, particularly greater than 500 milliseconds.<sup>(47)</sup> Whenever a drug increases the QTc by 30 to 60 milliseconds in an individual, this should raise a concern.<sup>(30,33,47)</sup> 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)<sup>(48)</sup>

#### “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).<sup>(49)</sup>
- 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 <sup>(1)</sup>	Conversion ratio Morphine to Methadone <sup>(1)</sup>
<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)<sup>(50)</sup>

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.<sup>(3)</sup>

- Patients 65 years and older may have a decreased clearance of methadone.<sup>(1)</sup>
- In patients with stable chronic liver disease, no dosage adjustments appear to be necessary.<sup>(21,25)</sup> Methadone's half-life may be prolonged in patients with severe cirrhosis.<sup>(51)</sup>
- Dosing frequency is normally q8h.<sup>(5,52)</sup> Intervals of 12 hours may be attempted when patients are stable at q8h dosing.<sup>(7)</sup> 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.<sup>(13)</sup>
- 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.<sup>(13)</sup>

#### 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.<sup>(52)</sup> Pulse may slow and blood pressure lower in overdoses.<sup>(5)</sup>
- Individualized patient dosing and evaluation is the best way to ensure the safe use of methadone.<sup>(5,23)</sup>

**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** <sup>(14,16,22,53)</sup>

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

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**Table B1 – Methadone Drug Interactions continued**<sup>(14,16,22,53)</sup>

Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
<b>Dextromethorphan</b>		CYP450 induction	May increase levels of Dextromethorphan
<b>DiazePAM</b>	Increase	CYP3A4	
<b>Dihydroergotamine</b>	Increase	Enzyme inhibition, CYP3A4	
<b>DiltiazEM</b>	Increase	CYP3A4	
<b>Efavirenz</b>	Decrease	CYP3A4	
<b>Erythromycin</b>	Increase	CYP3A4	
<b>Ethanol (acute use)</b>	Increase	CYP450 competition or inhibition	
<b>FentaNYL</b>	Unpredictable	Common CYP450 pathway	Possible additive effects
<b>Fluconazole</b>	Increase	CYP3A4	
<b>FLUoxetine</b>	Increase	CYP2D6 & CYP3A4	
<b>FluvoxaMINE</b>	Increase	CYP1A2 & CYP3A4	
<b>Fusidic acid</b>	Decrease	Enzyme Induction CYP3A4	
<b>Grapefruit Juice</b>	Increase	CYP3A4	
<b>Heroin</b>	Decrease	Methadone free fraction lessened	
<b>Imipramine</b>			Possible increased TCA toxicity, uncertain effect on methadone
<b>Isoniazid</b>	Increase	CYP 1A2	
<b>Itraconazole</b>	Increase	CYP3A4	
<b>Ketoconazole</b>	Increase	CYP3A4	
<b>Meclizine</b>	Unpredictable		Increased sedative effects if abused
<b>Meperidine</b>	Unpredictable		Possible opioid additive effects
<b>Methylphenidate</b>	Unpredictable	Possible CYP450 enzyme inhibition	
<b>MetroNIDAZOLE</b>	Increase	CYP3A4	Proposed in literature, but unverified
<b>Moclobemide</b>	Increase	CYP2D6, CYP1A2	
<b>Nalbuphine</b>	Decrease	Receptor displacement	Contraindicated, opioid withdrawal risk
<b>Naloxone</b>	Decrease	Enzyme Induction	
<b>Naltrexone</b>	Decrease	Receptor displacement	Contraindicated, opioid withdrawal risk
<b>Nifedipine</b>			Nifedipine increase proposed
<b>Nelfinavir</b>	Decrease	CYP3A4 Enzyme Induction	

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**Table B1 – Methadone Drug Interactions continued**<sup>(14,16,22,53)</sup>

Drug	Effect on Methadone Level	Mechanism of Interaction	Comments
<b>Nevirapine</b>	Decrease	CYP450 Enzyme Induction	Methadone withdrawal cases
<b>Octreotide</b>	Decrease		
<b>Omeprazole</b>	Increase	Methadone absorption	Occurred in animal studies
<b>PARoxetine</b>	Increase	CYP2D6	
<b>Pentazocine</b>	Decrease	Receptor antagonist	Can cause opioid withdrawal
<b>PENTobarbital</b>	Decrease	CYP340 enzyme induction	
<b>PHENobarbital</b>	Decrease	CYP340 enzyme induction	Can cause sharp decrease in methadone
<b>Phenytoin</b>	Decrease	Enzyme Induction, CYP3A4, CYP2B6	
<b>Primidone</b>	Decrease	Enzyme Induction	
<b>Promethazine</b>	Unpredictable		Possible increased sedation or methadone effects
<b>Propafenone</b>	Increase	CYP2D6	
<b>Propoxyphene</b>	Increase	CYP3A4	
<b>QuiNIDine</b>	Increase	CYP2D6	
<b>RifAMPin</b>	Decrease	Enzyme Induction	Cases of severe withdrawal reported
<b>RisperiDONE</b>	Decrease	Mechanism unclear	
<b>Ritonavir</b>	Decrease	CYP3A4	
<b>Sertraline</b>	Increase	CYP340 enzyme inhibition	
<b>Sodium Bicarbonate</b>	Increase	Decreased urinary excretion of methadone	
<b>Spirolactone</b>	Decrease	Enzyme Induction, CYP3A4	
<b>Stavudine</b>	Unpredictable		Decreased stavudine concentration
<b>St. John's Wort</b>	Decrease	CYP3A4	Can cause significant decrease
<b>Tramadol</b>			Potential withdrawal risk. Avoid concurrent use with methadone
<b>Trimipramine</b>	Unpredictable		Possible increased TCA toxicity, uncertain effect on methadone
<b>Verapamil</b>	Increase	CYP3A4	
<b>Zafirlukast</b>	Increase	CYP3A4	
<b>Zidovudine</b>	Unpredictable		Zidovudine concentration increase
<b>Zopiclone</b>	Unpredictable		Potential interaction, additive CNS depression

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

adenosine	domperidone	lithium	quinidine
amantadine	doxepin	losartan	risperidone
amiodarone	droperidol	maprotiline	rizatriptan
amitriptyline	enflurane	mefloquine	salbutamol
azithromycin	erythromycin	meperidine	salmeterol
butorphanol	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	olanzapine	tamoxifen
clemastine	Glyburide	ondansetron	telithromycin
clindamycin	granisetron	Paroxetine	terfenadine
clomipramine	haloperidol	pentamidine	thiopental
clozapine	halothane	Pentobarbital	thioridazine
cocaine	hydroxyzine	pimozide	tizanidine
cotrimoxazole	ibutilide	probucol	trazodone
cyproheptadine	imipramine	procainamide	triamterene
desipramine	indapamide	prochlorperazine	trifluoperazine
diltiazem	isoflurane	promethazine	vasopressin
dimenhydrinate	isoproterenol	propafenone	venlafaxine
diphenhydramine	ketamine	propofol	verapamil
disopyramide	ketoconazole	Quetiapine	voriconazole
dolasetron	levofloxacin	quinidine	zolmitriptan

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

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# APPENDIX C: 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.<sup>(4)</sup> Appears to provide neuropathic pain benefit.<sup>(1,4,9,10)</sup>
- Has a low incidence of constipation, nausea and dizziness compared to other opioids.<sup>(3)</sup> It has no major cardiovascular or blood pressure effects<sup>(3,4)</sup> and a low risk of respiratory depression.<sup>(1,5,16)</sup> 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.<sup>(3,5,7,8)</sup>
- Tramadol is used for moderate pain, and is considered a step 2 analgesic on the World Health Organization 3 step ladder,<sup>(3,8,13,16)</sup> with a ceiling effect due to increasing seizure risk when dose exceeds 400 mg daily.<sup>(4,7,8,16)</sup>
- 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.<sup>(6)</sup>

### 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.<sup>(1)</sup>
- Worldwide over 50 million patients have received tramadol, as estimated by Bamigbade and Langford in 1998.<sup>(8)</sup>

#### Market Size

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

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## Potency

- Oral potency ratio of tramadol to morphine is considered to be 10:1, <sup>(16)</sup> 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.<sup>(16)</sup>
- Tramadol 75 mg with 650 mg acetaminophen is equivalent to 400 mg ibuprofen for postoperative pain.<sup>(16)</sup>
- A single tablet of 100 mg oral tramadol is equivalent to 1000 mg acetaminophen for postoperative pain.<sup>(17)</sup>
- Sustained release morphine was shown to be more effective in severe cancer pain.<sup>(8)</sup>

## In Combination

- Maybe safely combined with NSAIDs.<sup>(8)</sup> Tramadol has no effect on prostaglandin synthesis and hence no ability to induce GI bleeding or reduced platelet activity.<sup>(13)</sup>
- 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.<sup>(16)</sup>

## Metabolism and Excretion and Absorption

- Mainly excreted by the kidneys (90%).<sup>(4,8,16)</sup>
- Following multiple oral administration of tramadol 100 mg four times daily, C<sub>max</sub> is 16% higher and AUC 36% higher than after a single 100 mg dose, indicating that oral bioavailability increases to approximately 90-100% on multiple administration, possibly due to saturated first-pass hepatic administration.<sup>(4)</sup>
- Has a total of 23 metabolites, all metabolites are almost completely excreted via the kidneys.<sup>(4)</sup>
- 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.<sup>(5)</sup> It was suggested that tramadol may have some efficacy in patients in which codeine is not effective and are CYP2D6 deficient,<sup>(13)</sup> although this has not been studied and is unknown. Africans (Nigerian's studied) with the CYP2D6 #17 gene or

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Oriental with the CYP2D6 #10 gene may have altered tramadol metabolism, and reduce its ability to act as an analgesic.<sup>(16)</sup>

- Tramadol has not been well studied in renal and hepatic impairment, although some dosing suggestions appear.<sup>(16)</sup> It is contraindicated in severe hepatic failure and or severe renal failure (creatinine clearance less than 30 mL per minute).<sup>(7,14)</sup>
- High fat breakfast results in a 17% higher Cmax and 10% higher AUC.<sup>(4)</sup>
- 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.<sup>(16)</sup>

### Adverse Effects

- 15% of patients have side effects. Dizziness 5%, nausea 5%, dry mouth 3%, sedation 2%, vomiting 1%.<sup>(16)</sup> Start with low doses to improve tolerance to side effects.<sup>(16)</sup>
- Nausea and vomiting respond to metoclopramide, phenothiazines and dexamethasone.<sup>(16)</sup> Anaphylactic reactions estimated incidence is 1 in 700,000<sup>(8)</sup> with an estimated fatality of one in 3.5 million.<sup>(8)</sup>
- Does not cause histamine release, so has a lower risk of pruritus.<sup>(13,16)</sup>
- Provides more acceptable side effects than tricyclic antidepressants or antiepileptics.<sup>(10)</sup>
- Dependency has occurred (range of 1 in 6000 to 1 in 100,000).<sup>(13)</sup> Most tramadol abuse is associated with polysubstance use and only 4.3% of the abuse is due to tramadol as a single agent.<sup>(16)</sup> 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.<sup>(11)</sup>
- Low abuse potential has been suggested<sup>(1,8)</sup> and is reflected in the drug scheduling worldwide and not subject to the same prescribing formalities as morphine.<sup>(8)</sup> Tramadol 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.<sup>(13)</sup> Tramadol can cause additive CNS depression and respiratory depression when used with other agents that are CNS depressants e.g., alcohol, other opioids.<sup>(14)</sup>

- Tramadol may affect other drugs, causing increased digoxin and warfarin levels, or reduced carbamazepine levels.<sup>(14)</sup>

### Seizure Risk

- Higher incidence of serotonin syndrome and convulsions when tramadol combined with interacting drugs. These include SSRI's, TCA'S, MAO inhibitors, reversible inhibitors of monoamine oxidase, other opioids, buspirone, LSD, cocaine, ecstasy, amphetamines, cyclobenzaprine, St. John's wort, olanzapine, risperidone.<sup>(13,14,16)</sup>
- Activity of tramadol only partially reversed with naloxone (about 30%).<sup>(3)</sup> In tramadol overdose, naloxone administration may increase the risk of seizure.<sup>(7,14)</sup>
- Treatment of seizure in Zytram XL product monograph suggests the use of diazepam.<sup>(7)</sup> 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.<sup>(15)</sup>
- Seizure risk is much higher than other opioids. Occurs in one of 7000 patients,<sup>(16)</sup> median onset of 2 days.<sup>(13)</sup>
- Deaths – 12 in the USA associated with convulsions and tramadol use. In two, tramadol was used solely.<sup>(13)</sup>

### Additional Dosing Information

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



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# APPENDIX D: INCIDENT PAIN - GENERAL

## PRINCIPLES SUFentanil SUBLINGUAL

### GUIDELINES

#### Background

- Sublingual **SUFentanil** has been utilized for the treatment of incident pain in the palliative care population for many years.<sup>1-10</sup>
- Use of sublingual **SUFentanil** is recommended for patients with incident pain not relieved by usual breakthrough opioids, or when the usual breakthrough opioids result in unacceptable adverse effects.
- Examples of incident pain includes pain precipitated by:
  - planned turns, transfers or ambulation
  - bathing/changing clothes
  - dressing changes or wound management
  - disimpaction/catheterization
  - diagnostic imaging (CT/MRI)
  - treatment (radiotherapy)
- **SUFentanil** is a highly lipid-soluble, short-acting, potent synthetic opioid agonist that is rapidly absorbed sublingually and has a very short half-life.
- **SUFentanil** is available in 50 mcg/mL amps (1 mL).
- Administration by the sublingual route provides for rapid absorption and avoids first pass metabolism of the oral route, resulting in rapid development of serum levels sufficient for relief of severe pain.
- The onset of analgesic action is evident at 3-5 minutes<sup>11</sup> but the most predictable window of analgesia is 15 to 30 minutes.
- **SUFentanil** is approximately 7.5 to 10 times more potent than fentaNYL<sup>12, 13</sup>, and 750 to 1000 times more potent than morphine.<sup>14</sup> Proper labeling is crucial to prevent any confusion between these agents, especially in hospital.
- As there is incomplete and variable opioid cross-tolerance along with significant individual variation, there is no known consistent equianalgesic conversion factor to utilize when initiating **SUFentanil**.
- Due to its unique properties, prescribing **SUFentanil** safely and effectively requires careful monitoring during dose initiation and dose titration.
- Sublingual **SUFentanil** should be considered following a thorough assessment of the cause(s) of incident pain, seeking and addressing reversible cause(s), and adequate trials of oral or subcutaneous breakthrough opioids.<sup>29</sup>
- The management of incident pain can be difficult due to its rapid onset, intensity

and transient nature.

- Oral analgesics often do not have a rapid enough onset to be effective.
- **Morphine** or **HYDRMorphine** oral formulation would be an appropriate first choice, given 1 hour pre-incident. If not successful, try subcutaneous for rapid effect (15-20 minutes) and ensure all other adjuvants have been tried.
- Breakthrough (BT) opioids, typically 10% of total daily dose (TDD), can be maximized to 20% of TDD if tolerated.<sup>30, 31</sup> This approach should be assessed for effectiveness and acceptability prior to considering the use of sublingual **SUFentanil**.
- **SUFentanil** should NOT be used in opioid naïve patients.
- If **SUFentanil** is initiated in the home, initial doses should be given under a monitored situation, i.e. RN in the home.

## Definitions

- **Breakthrough pain** is a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.<sup>15</sup>
- **Incident pain** is a type of breakthrough pain precipitated by a movement or a voluntary action, and is predictable or expected.<sup>16, 17</sup>
- **Opioid naïve** is a patient who has not received a minimum of 60mg oral morphine equivalent daily for at least seven continuous days.<sup>19-22</sup>
- **Opioid tolerant** is taking a minimum of 60mg oral morphine equivalents daily for at least seven continuous days.
- **Opioid Titration** is the incremental adjustment of the dosage of an opioid to better control pain and reduce adverse effects.<sup>23</sup>
- **Established dose** is the dose of **SUFentanil** determined effective for management of incident pain established after a process of careful titration and monitoring of sedation level, respiratory rate and pain relief.<sup>2</sup>
- **Pasero Opioid-induced Sedation Scale** <sup>24, 25</sup>

S = sleep, easy to arouse

1 = awake and alert

2 = slightly drowsy, easily aroused

3 = frequently drowsy, arousable, drifts off to sleep during conversation

4 = somnolent, minimal or no response to stimuli

- **Stacking** is rapid opioid titration using one or more drugs repeatedly at short intervals, more frequently than the opioid half-life, to result in a rapid rise in serum concentration.<sup>23</sup>

- **Titration of sublingual SUFentanil** is the process of administering increasing doses while monitoring sedation, respiratory rate and pain intensity to determine the dose of **SUFentanil** that provides effective incident pain control.
- **Gradual sublingual SUFentanil titration** is the stepwise incremental dosing spaced at least 2 hours apart.
- **Rapid sublingual SUFentanil titration** uses the stacking principle and is incremental **SUFentanil** dosing until adequate analgesia is evidenced, up to three doses. Palliative Care Physician **must be** contacted prior to initiating a rapid titration.

## Cautions

- As with any opioid therapy, patients receiving concomitant Central Nervous System depressants are at increased risk of opioid-induced sedation and potential for respiratory depression.
- Excessively frequent use of sublingual **SUFentanil** can be an indication of poor pain management or of substance use issues and requires consultation.

## SUFentanil

- **SUFentanil** requires careful incremental titration to obtain the right dose that achieves relief of the incident pain.
- **SUFentanil** titration is implemented according to one of two procedures for administration of sublingual **SUFentanil**: gradual dose titration or rapid dose titration. Gradual dose titration is covered here, and for rapid dose titration please consult a Palliative Care Physician.
- Once the established effective dose has been identified through titration, a physician must be contacted to discontinue the titration order and obtain a new order for the established **SUFentanil** sublingual dose.
- For each **SUFentanil** dose increment monitor sedation level using the opioid induced sedation scale, respiratory rate and pain intensity (or relief): a) at baseline before pain provoking activity, b) after beginning pain provoking activity (ideally at 10 min post dose) c) post activity (25-30 minutes post dose). Monitor pain intensity DURING activity.
- Each dose should be administered under the tongue approximately 10 minutes prior to the activity. The patient should be instructed to hold the liquid medication under the tongue for two minutes without speaking or swallowing.
- If a given dose is sufficient, the patient may appear drowsy for 10-15 minutes.
- Once dosage determined for each patient, repeat same dose for each incident (i.e. no need for incremental titration each time).

## Criteria

- Patient must meet the following criteria to consider **SUFentanil**:
  - Select adult palliative patients (19 years and older) experiencing incident pain
  - Cognitively and physically able to hold medication sublingually for 2 minutes
  - Opioid tolerant – taking a minimum of 60mg oral morphine equivalents daily for at least seven continuous days. (Initiation of **SUFentanil** is not recommended for the opioid naïve patient)
  - Do not use with patients with known hypersensitivity to **fentaNYL**, **alfentanil**, **remifentanil** and **meperidine**.<sup>28</sup>
- Registered Nurses/ Registered Psychiatric Nurses/ Licensed Practice Nurses (RN/RPN/LPN) administering an order for sublingual **SUFentanil** must ensure they are well informed about the medication and meet all of the requirements for administering it.<sup>26</sup> RN/RPN may perform **SUFentanil** gradual dose titration.
- Licensed Practice Nurses (LPNs) can administer established doses of **SUFentanil**. Initiation of sublingual **SUFentanil** and titration are out of scope for LPN practice.<sup>27</sup>

## Titration

### **Gradual Dose Titration** (suggested starting dose 12.5 mcg)

Gradual dose titration is recommended when:

- Patient has more stable management of background pain and a stable opioid dose.
- Patient has fatigue and is less able to tolerate rapid titration.
- Patient with history of medication or opioid sensitivity.
- A more cautious approach with a starting dose of 12.5 mcg is desired.

Stepwise incremental sublingual **SUFentanil** dosing is given over a period of time during a nursing shift or over several days. If the patient tolerates the initial dose of 12.5 mcg and has not experienced sufficient incident pain relief or side effects, subsequent stepwise doses of sublingual **SUFentanil** can be given spaced by at least 2 hours, until adequate analgesia is evidenced, adverse effects or a total of 100 mcg has been given.

Input from a physician experienced and skilled in the use of sublingual **SUFentanil** should be sought for patients requiring doses greater than 100 mcg.

Once a dose is reached that manages the patient's incident pain, the RN/RPN must contact the physician for an ongoing order for the established doses of sublingual **SUFentanil** q2h PRN.

In the gradual dose titration procedure there is less concern regarding over-medication, and usual opioid administration and monitoring practices are sufficient.

Gradual Dose Titration: SUFentanil Sublingual Dosing	
<b>Step One</b>	<b>SUFentanil 12.5 mcg</b> sublingual. Place and hold the liquid medication under the tongue for 2 minutes without speaking or swallowing. Attempt pain provoking activity 8 minutes later.
<b>Step Two</b>	If insufficient for pain relief and dose tolerated, after waiting at least two hours, repeat the above procedure using a dose of <b>SUFentanil 25 mcg</b> .
<b>Step Three</b>	If insufficient for pain relief and dose tolerated, after waiting at least two hours, repeat the above procedure using a dose of <b>SUFentanil 50 mcg</b> .
<b>Step Four</b>	If insufficient for pain relief and dose tolerated, after waiting at least two hours, repeat the above procedure using a dose of <b>SUFentanil 75 mcg</b> .
<b>Step Five</b>	If insufficient for pain relief and dose tolerated, after waiting at least two hours, repeat the above procedure using a dose of <b>SUFentanil 100 mcg</b> .

## Monitoring

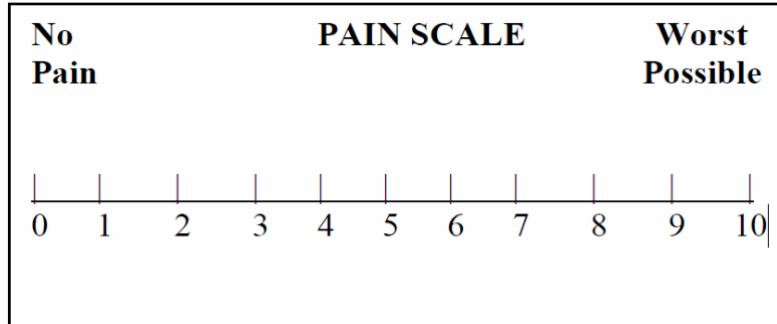
- With dose initiation and any dose increase, monitor sedation level, RR and pain level.
- For each **SUFentanil** dose increment, monitor pain intensity, RR, and sedation using the Pasero Opioid-induced Sedation Scale: a) prior to giving **SUFentanil** (baseline), b) before starting activity a minimum of 10 minutes after sublingual **SUFentanil** administration and c) after pain provoking activity. Monitor pain intensity DURING activity.
- Stop titration if RR is equal to/less than 10 breaths per minute, or sedation scale is 3 or 4.
- Stop titration after any dose is given, when pain is relieved.
- Contact physician to discontinue **SUFentanil** titration order and to obtain a new order once a satisfactory sublingual **SUFentanil** dose is established. (i.e. 12.5, 25, 50, 75, 100 mcg q2h PRN). Contact physician if pain unrelieved.

Pasero Opioid-induced Sedation Scale	
<b>S</b>	Sleeping: easy to arouse, NORMAL SLEEP
<b>1</b>	Awake and alert
<b>2</b>	Slightly drowsy, easily aroused
<b>3</b>	Frequently drowsy, arousable, drifts off to sleep during conversation
<b>4</b>	Somnolent, minimal or no response to verbal and physical stimuli

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## Established Dose

- Once Titration is completed, a physician order must be obtained to discontinue titration and to obtain a new order for the established dose.
- Dosing interval for the established doses of sublingual **SUFentanyl** is recommended as Q2H PRN. The two hour window is required to avoid undue “stacking” given the significant carry-over of serum drug levels past the first 60 minutes.<sup>34</sup>
- An established sublingual **SUFentanyl** dose can be administered by the RN/RPN/LPN using usual opioid administration and monitoring processes and does not require additional monitoring and documentation of sedation and RR rate that is required during titration. Continue to monitor and document activity related pain relief.
- When requiring administration of doses of sublingual **SUFentanyl** (available in a 50 mcg per 1 mL strength) in volumes greater than 1 mL, this will require sequential dosing of a maximum of one mL volumes per time in order to avoid the patient swallowing the medication. Repeated volumes of a maximum one mL are given two minutes apart, providing sufficient time for sublingual absorption in between doses.

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## Appendix D References

Information was compiled using the CINAHL, Medline (2000 to December 2010) and Cochrane DSR, ACP Journal Club, DARE and CCTR databases, limiting to reviews / systematic reviews, clinical trials, case studies and guidelines / protocols using 'incident pain' and SUFentanil 'fentaNYL' or 'sublingual opioids' search terms. References were updated between 2011 and March 2015. Articles not written in English were excluded.

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Information was added to the Northern Health Palliative Care Program Symptom Guidelines 4<sup>th</sup> Edition (Oct, 2019) from an adaption of the Fraser Health Clinical Protocol (Apr, 2015): SUFentanil – Sublingual for Management of Incident Pain in Patients in Hospice Residence and Tertiary Hospice Palliative Care Units.

**Approved by: Northern Health Hospice Palliative Care Consult Team,  
October 2019**

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# SPINAL CORD COMPRESSION

## Rationale

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

## Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) with advanced life threatening illness and experiencing the symptom of spinal cord compression. This guideline does not address disease specific approaches in the management of spinal cord compression.

The vertebral column is the most common site of skeletal metastasis.<sup>(1)</sup> Seventy percent of patients dying from cancer have spinal metastases at autopsy.<sup>(1)</sup> Cord compression occurs in 5% to 10% of all patients with malignancy <sup>(1-8)</sup> but account for 25% of all central nervous system tumours.<sup>(3)</sup>

## Definition of Terms

**Spinal Cord Compression** develops when the spinal cord is compressed by a tumour, abscess or other lesion. It is regarded as a medical emergency independent of its cause, and requires swift diagnosis and treatment to prevent long-term disability due to irreversible spinal cord injury.<sup>(9, 10)</sup>

## Standard of Care

1. Assessment
2. Diagnosis
3. Prognosis
4. Education
5. Treatment: Non-pharmacological
6. Treatment: Pharmacological

## RECOMMENDATION 1 - ASSESSMENT OF SPINAL CORD COMPRESSION

On-going comprehensive assessment is the foundation of effective management of spinal cord compression, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics (*see Table 1*). Assessment must

determine the cause, effectiveness and impact on quality of life for the patient and their family.

**Table 1: Spinal Cord Compression Assessment using Acronym O, P, Q, R, S, T, U and V\***

<b>O</b> Onset	When did it begin? How long have you had the pain, constipation, weakness? Have you had this before?
<b>P</b> Provoking/ Palliating	What brings the pain on? What makes it better? Does cough, sneeze or pressure make it worse?
<b>Q</b> Quality	What does it feel like? Can you describe it? Is it a band-like pain?
<b>R</b> Region/ Radiation	Where is it? Does it spread anywhere?
<b>S</b> Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right now? At best? At worst? On average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom?
<b>T</b> Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
<b>U</b> Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
<b>V</b> Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

\* also include a Physical Assessment (as appropriate for symptom)

### Symptoms:

- **Pain** is the presenting symptom in 90 to 95% of patients<sup>(1, 11)</sup> Two types of pain:<sup>(1)</sup>
- **Local back pain** (midline/paravertebral) nearly always present.<sup>(1)</sup>
  - Usually constant, close to site of lesion.<sup>(1)</sup>
  - Relieved by sitting or standing up (as opposed to disc disease which is relieved by laying down). <sup>(1, 8)</sup>

- Exacerbated by any increase in intrathoracic pressure (sneeze, cough, Valsalva maneuver, straining at stool).(1, 4)
- Above historic points may be only clue to impending spinal cord compression.(1)
- **Radicular pain** from spinal root compression occurs in 66% of patients.(1)
  - More common with lumbosacral (90%) and cervical (79%) metastases than with thoracic metastases (55% of cases).(1)
  - Patients complain of a band or girdle of pain/tightness radiating from back to front; in extremities, radicular pain usually unilateral.(1)
  - Exacerbated by recumbency, movement, cough, sneeze, Valsalva maneuver.(1, 3, 12)
  - Worse at night.(1, 3, 8, 12)
  - Improved by sitting or standing.(1, 8)
  - Radiates in a dermatomal pattern.(1)
  - May produce numbness and tingling (cervical, thoracic or lumbar root).(1) When progresses numbness usually precedes weakness.
  - May resemble pain from intervertebral disc disease, pleurisy, cholecystitis or pancreatitis.(1)
  - Distinguish from brachial or lumbosacral plexus involvement.(1)
  - Localizes the lesion within one or two vertebral segments.(1)
- **Weakness** in legs is the next symptom if left untreated (76% of patients).(1)
  - Experienced as stiffness, dragging of a limb or unsteadiness.(1, 12)
- **Sensory disturbances** may accompany or be preceded by (in 51% of patients).(1)
  - Numbness usually begins in the toes, gradually ascends to level of cord compression (usually without paresthesias).(1, 12)
  - Sensation of coldness.(1, 12)
  - Upper limit of sensory level often one to two vertebral bodies below site of compression.(1)
  - Sensory loss progresses to ataxia (3% of patients).(1)
- **Autonomic dysfunction** (57% of patients).(1)
  - Early signs: loss of bladder control, hesitancy, urgency.
  - Late signs: urinary retention, overflow incontinence.(1, 12)
  - Constipation.(1)
  - Loss of perspiration below level of the lesion.(1)

- Sexual difficulties.<sup>(12)</sup>
- Signs and symptoms probably not due solely to compression of cord; ischemia secondary to vascular involvement may also be a factor (especially when cord compression develops suddenly over a few hours).<sup>(1, 8)</sup>

**Distribution:**<sup>(1, 3, 5, 12)</sup>

- Thoracic spine – 70% <sup>(8,13)</sup> which has a smaller ratio of spinal canal to cord diameter than the other two spinal segments.<sup>(8)</sup>
- Multiple contiguous levels – 10% to 38%.<sup>(7)</sup>
- Lumbosacral spine – 20%.
- Cervical spine – 10%.

**Incidence In Malignancy:**<sup>(1)</sup>

- Lung – 16%
- Breast – 12%
- Unknown primary – 11%
- Lymphoma – 11%
- Myeloma – 9%

## RECOMMENDATION 2 - 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 spinal cord compression is identifying underlying cause(s) and treating as appropriate. While underlying cause(s) may be evident, treatment may not be indicated, depending on the stage of the disease.

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

Identifying the underlying etiology of the spinal cord compression is essential in determining the interventions required.

The importance of early diagnosis cannot be over-emphasized; symptoms are usually present for some weeks before neurological emergency occurs.<sup>(3, 4)</sup> In rural communities where treatment may require travel the importance of early diagnosis is even more crucial.

- Extent of diagnostic workup indicated in any given case depends on overall condition of patient. In patients expected to live more than 1 to 2

months and who are not already paraplegic the following tests are indicated:<sup>(1)</sup>

- Evidence of epidural metastases may be seen on plain x-rays in approximately 85% of patients<sup>(1)</sup> but only predicts the level of compression in 19%.<sup>(3)</sup>
- Urgent referral for **CT scans and MRI** improves early detection. MRI scans are more sensitive than CT Scans and are the standard for diagnosis.<sup>(3, 6, 7)</sup> Whole spine MRI is more sensitive in detecting small CNS metastases that can be missed with other imaging methods. <sup>(6,11)</sup> Myelography has a place where CT scan and MRI are not available.<sup>(4)</sup>

### RECOMMENDATION 3 - PROGNOSIS

- The degree of neurologic function at diagnosis and the start of treatment is the most significant factor in determining the recovery of function.<sup>(1, 14)</sup>
- Rapid onset (less than 48 hours) and progression of symptoms are poor prognostic indicators.<sup>(2)</sup> Patients who are not mobile at presentation do not generally regain the ability to walk.<sup>(6)</sup> Of patients who are paraplegic pre-treatment, only 10% will regain ambulation after treatment.<sup>(13)</sup>
- If the patient has been paralyzed for more than 48 hours, the chance of neurological recovery is very poor.<sup>(3)</sup> “Emergency” treatment at this point may not be indicated but palliative radiation for pain management may be beneficial (per British Columbia Cancer Agency).<sup>(15)</sup>

Start I.V. corticosteroids to reduce edema and improve neurological function while completing diagnostic workup when history and physical examination suggest spinal cord compression.<sup>(1, 3, 16)</sup>

- Spinal cord compression is an emergency necessitating immediate assessment and treatment<sup>(2, 3, 6, 14)</sup> requiring urgent consultation of the radiation oncologist and neurosurgeon at the closest available site.<sup>(10)</sup> A Radiation Oncologist will treat with radiotherapy on weekends.<sup>(13)</sup>

### RECOMMENDATION 4 - EDUCATION

- Patients at risk should be identified and taught the signs and symptoms of spinal cord compression and the urgency of reporting promptly.<sup>(1)</sup>
- Explain procedures and details of ongoing investigations with patients and family.<sup>(6)</sup>

### RECOMMENDATION 5 - TREATMENT: NON-PHARMACOLOGICAL

- Malignant spinal cord compression should be individualized and should take into consideration pretreatment ambulatory status, previous treatment, co-morbidities, technical surgical factors, the presence of bony

compression and spinal instability, potential surgical complication, potential radiotherapy reactions and patient preferences.<sup>(17)</sup>

- Management requires a combined effort from the family physician, radiation oncologist and spinal surgeon.<sup>(14)</sup>
- **Radiation therapy** should be started immediately after diagnosis.<sup>(1, 6, 13)</sup>
  - Radiation therapy provides definitive treatment in most patients.<sup>(2, 3, 5, 8, 14, 16)</sup> Indications for radiation therapy include known radiosensitive tumour and no spinal instability<sup>(1, 5, 7, 11, 17)</sup> and for palliative therapy in patients who present with paraplegia.<sup>(7)</sup>
  - Radiation therapy alone gives equivalent results to laminectomy plus adjuvant radiation therapy<sup>(1, 4)</sup> and is effective in over 85% of cases of spinal cord compression.<sup>(6)</sup>
  - Patients who are ambulatory at the time of the diagnosis have a higher probability of obtaining good response to treatment and a longer survival.<sup>(3)</sup>
  - Patients who experience progressive neurological deficits despite receiving radiotherapy should be considered candidates for urgent surgical decompression and/or stabilization.<sup>(7)</sup>
- **Surgery** may be considered if the patient is ambulatory and otherwise stable with good performance status.<sup>(1-3)</sup>
  - Surgery is the first choice where the site of the primary tumour is unknown, where there is relapse after radiation treatment, and in cases of spinal instability or vertebral displacement.<sup>(8, 11)</sup> It should also be considered when neurological symptoms progress during radiotherapy, in plegia of rapid onset, or where tumours are not radiosensitive. <sup>(4, 12, 14)</sup>
- **Rehabilitation** must commence on diagnosis and must encompass the skills of various professionals. Ensure that goals are short term and attainable so as to achieve the best possible quality of life.<sup>(6, 8)</sup>
  - If patient immobile, treat as if they have an unstable spine during repositioning.<sup>(6)</sup>
  - Apply anti-embolic stockings if patient has impaired mobility.<sup>(6)</sup>
  - Ensure emotional and psychosocial support for patient and family.<sup>(6)</sup>

## RECOMMENDATION 6 - TREATMENT: PHARMACOLOGICAL

**Dexamethasone** 10 to 100 mg I.V. STAT<sup>(3, 4, 11)</sup> then 16 to 96 mg PO daily, then taper over 10 to 14 days after improvement or irreversibility.<sup>(1, 5, 11)</sup>

- Shown to improve neurologic function and relieve pain, reduce edema and have a direct oncolytic effect.<sup>(1)</sup> Dexamethasone may also temporarily prevent the onset of cord ischemia.<sup>(2)</sup>



- In patients with short prognosis or poor performance status, corticosteroids may be the only treatment feasible.<sup>(1, 2)</sup>
- Consider the use of prophylactic heparin if the patient has impaired mobility.<sup>(6)</sup>

Severe pain will usually require rapid titration of an opioid drug to achieve analgesia.<sup>(1)</sup>

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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 spinal cord compression 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.

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**Approved by: Northern Health Hospice Palliative Care Consult Team,  
October 2008**

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# SUPERIOR VENA CAVA OBSTRUCTION

**\*\*\*This section is currently under development\*\*\***

## Causes

- Compression or invasion by a mediastinal tumour

## Clinical features

- General
  - Dyspnea, cyanosis, neck vein distension, edema of the face, neck and upper extremities
- A mediastinal tumour may cause cough, dysphagia, hoarseness or chest pain.
- Neurologic symptoms include blurred vision, dizziness, syncope and headache.

## Diagnosis

- Clinical presentation, CXR, CT scan

## Treatment

- General – Fluid and salt restriction with diuretic (furosemide), oxygen, elevation of the head of the bed.
- Dexamethasone 16-24mg PO/SC/IV daily
- Treatment of tumour
  - radiotherapy or chemotherapy for sensitive tumours
  - Further treatment will depend on stage of disease and prognosis

The above information provided from the first edition of the NH Palliative Care Guidelines and Protocols, December 2004.

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