CANCERCare
A PROGRAM OF EASTERN HEALTH

Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	The Management of Cancer Pain in Adults	**Date:**	**(O):**	May 31, 2011
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Tumor Group:	Breast Disease Site Group	**Page:**		1 of 47
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Adapted From:	Scottish Intercollegiate Guidelines Network "control of pain in adults with cancer" guideline, November 2008 (55).			

Introduction:

The prevalence of cancer-related pain has been estimated to be 30 to 50% in patients receiving chronic cancer pain treatment, and more than 70% in patients with advanced disease (1). A more recent U.S. systematic review of worldwide epidemiological surveys of cancer pain indicates that a significant number of patients with cancer, over the course of their disease, will experience pain that requires treatment (2). The literature shows that cancer pain may be relieved in 70% -90% of patients (3). Organizations, such as the WHO, international and national professional bodies, and government agencies, have been instrumental in promoting guidelines for cancer pain management in recent years. Despite that, undertreatment of cancer pain continues to be a significant problem in cancer care (4,5).

Across the province of Newfoundland and Labrador, lack of available resources prevents some patients from being able to avail of the specialized palliative care services. 'Undertreatment' of cancer-related pain can be linked to barriers to effective management, such as those created by the system, health care providers, patients and their families. A literature review revealed that health care providers, like physicians and nurses, often will exhibit misconceptions about pain medications and side effects, have insufficient knowledge or training in pain management, and lack formal assessment skills for pain (6). Patients and their caregivers/families will harbour concerns about development of tolerance, addiction, side effects, have poor communication with health care providers ('wanting to be a good patient'), and have misconceptions about the inevitability of pain.

There are certain populations of our society whom are known to be at high risk for suboptimal pain management. They include but are not limited to:

- the elderly (particularly over age of 70)
- children
- minority groups (eg. aboriginals, deaf, mentally challenged, etc...)

- women
- patients with history of previous or active substance abuse
- patients with limited financial resources, social support systems, or access to health care
- patients with cognitive, psychosocial or psychiatric impairments
- patients with metabolic abnormalities or analgesic allergies* (7).

The objectives of this pain guideline are to provide physicians and other health care professionals with the knowledge to:

- optimize pain control in cancer patients;
- minimize side effects and adverse outcomes of the therapy;
- enhance the physical, psychological and spiritual well-being of cancer patients and consequently, improve the quality of life in patients and their families;
- emphasize the need for routine pain assessment, increased proficiency in prescribing opioids, non-opioid analgesics, and adjuvant medications, and understand the potential benefits of the various treatment modalities which often require a coordinated multidisciplinary approach.

Pathophysiology of Pain

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (8). A definition widely used in nursing practice describes pain as “whatever the person says it is, and existing whenever the person says it does” (9).

Pain has been divided into two predominant mechanisms, known as **nociceptive** and **neuropathic** (4). Nociceptive pain results from injury to somatic and visceral structures. Somatic nociceptor pain is well localized and is described as ‘sharp, aching, throbbing, or pressure like’. Visceral nociceptive pain is more diffuse and is described as gnawing or cramping when caused by obstruction, and as aching, sharp, or throbbing when pain is caused by stretching of organ capsules or mesentery. Nociceptive pain responds to nonopioid and opioid analgesics.

Neuropathic pain results from injury to neural structures that create a site of aberrant somatosensory processing in the peripheral or central nervous system. Common descriptions suggestive of neuropathic pain include burning, tingling, sharp, shooting, or electrical. Neuropathic pain responds less well to opioid drugs. Both opioid and adjuvant medications are used in the treatment of neuropathic pain.

Assessment

Relieving cancer pain improves the quality of life of cancer patients and their families. Pain has been described as a complex process, which is multi-dimensional. Therefore, a comprehensive assessment of the patient is essential to the formation of an effective plan of care for pain management (3). This assessment entails:

** Adapted from the Oncology Nursing Society Position Paper on cancer pain management, 2001(6).*

- Medical evaluation: This includes a thorough medical history and physical examination, inclusive of a neurological examination, where appropriate. Diagnostic investigations are performed where indicated;
- Pain severity**:** This is crucial in determining the effect of the pain on the patient and the urgency of the treatment required. The pain assessment tools used are the NRS (numerical rating scale), the VDS (or verbal descriptor scales), the VAS (or visual analog scale), or the chromatic and FACES pain rating scale can be used for illiterate patients (*see Appendix for examples of tools*);
- Pain characteristics**:** For each pain, the pain characteristics of type, location, temporal pattern, quality, exacerbating or relieving factors, and response to prior analgesic drugs, must be evaluated;
- Barriers to pain control**:** Once these are identified, appropriate education can be initiated;
- Impact of pain**:** The effect of the pain on the patient's life and level of functioning, quality of life, mood, social support systems, and psychological state need to be evaluated.

It is important to note that patients can experience both acute and chronic pain during their cancer trajectory, whether from diagnostic procedures, treatment or from pre-existing conditions. Clinicians treating cancer patients need to be aware of common cancer pain syndromes and presentations. These are shown in Table 1 below (53). Prompt diagnosis and treatment will minimize the morbidity associated with unrelieved cancer pain.

Table 1: Most Common Cancer Pain Syndromes

Cancer Pain Syndromes	Associated Cancers or Treatments	Associated Signs/Symptoms
Bone Metastasis – can cause pain, fractures, hypercalcemia, and spinal cord compression. Most common sites are vertebrae, pelvis, femur, and skull. Plain x-rays, nuclear medicine bone scans, and occasionally magnetic resonance imaging (MRI) are the most useful tests used in diagnosis.	Breast cancer, lung cancer, multiple myeloma, prostate cancer.	• Pain is usually described as dull and aching, and localized to metastatic site. • Spine mets may impinge on nerve roots and cause pain to radiate. • Skull mets may cause headache, pain with head movement or pain in face, neck and shoulder.
Spinal Cord Compression (SCC) – failure to diagnose and treat SCC will lead to permanent neurologic deficits. Pain is usually the first symptom. MRI is the most useful diagnostic test.	Breast cancer, lung cancer, melanoma, multiple myeloma, prostate cancer, renal cancer	• Pain is usually midline and can radiate and be 'sharp' and 'shooting' if nerve roots involved • Cervical lesions can cause pain to radiate down one or both arms • Thoracic lesions often are described as a 'tight band' around the chest

		• Lumbosacral lesions can cause pain to radiate down one or both legs • Other signs of SCC include motor, sensory, and autonomic (ie. bowel and bladder) dysfunction
Plexopathies – cervical, brachial, and lumbosacral plexuses can be sources of refractory pain. Pain occurs with tumor infiltration or fibrosis after surgery or radiation therapy (RT). Pain is less prominent with RT treated plexopathies. MRI is the most useful diagnostic tool.	Cervical plexopathy – mets to cervical lymph nodes; often local extension of primary head and neck cancers	• Aching discomfort that may radiate into neck and occiput.
	Brachial plexopathy – breast cancer, lung cancer, lymphoma	• Pain usually begins in shoulder and may be associated with 'shooting or electrical' sensations in thumb and index finger or begins in shoulder and may radiate into elbow, arm, and medial forearm and into 4th and 5th digits/fingers
	Lumbar plexopathy – colorectal cancer, endometrial cancer, renal cancer, sarcoma, lymphoma	• Pain usually felt in lower abdomen, buttock, and leg. Perineal and perirectal pain may occur if sacral plexus is involved. Associated symptoms can include weakness, sensory loss, or urinary incontinence.
Peripheral Neuropathies – may involve a single major nerve (*mononeuropathy*) with most common cause being tumor compression or postoperative or postradiation fibrosis. When many nerves are involved (polyneuropathy), the cause tends to be systemic effects of chemotherapy (use of drugs such as vinca alkaloids, taxanes, platinum-based	Multiple myeloma	• Sensory motor neuropathy characterized by distal paresthesias, sensory loss, weakness, and muscle wasting.May occasionally ascend upwards like Guillain-Barre syndrome.
	Chemotherapy induced	• Dose-related peripheral neuropathies are characterized by dysesthesias in feet and hands, and hyporeflexia

compounds, thalidomide).	Post-surgical pain syndromes	• Post-radical neck dissection (tight, burning; dysesthesias and shock-like pain) Post-mastectomy pain (tight, constricting pain exacerbated by movement) • Postthoracotomy pain (aching sensation with sensory loss) • Postnephrectomy pain (numbness, fullness, heaviness associated with dysesthesias) • Post-limb amputation (pain at surgical site characterized by burning, dysesthetic sensation exacerbated by movement).
Postherpetic Neuralgia – the occurence of varicella zoster virus infection or reactivation (shingles) happens more frequently to cancer patients than the general population due to higher incidence of immunosuppression in cancer.	All types of cancer	• Characterized by burning, aching pain. Lancinating or shock-like pain sperimposed over the herpetic skin lesions. Hyperpathia may be profound.

Management:
To provide effective multi-dimensional management of cancer pain, non-pharmacological and pharmacological means in addition to treatment of the underlying cancer are employed to treat the patient's pain.

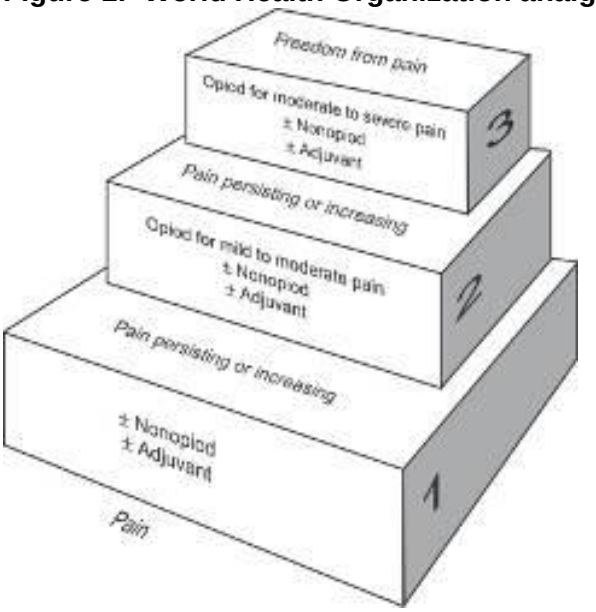
Treatment of Cancer-related Pain

Pharmacological Treatment:
Pharmacologic interventions have historically been based on the Three-Step World Health Organization's (WHO) Analgesic Ladder which specifies the strength of the primary analgesic required according to the intensity of the pain.

The WHO model has been criticized for suggesting that pain progresses sequentially through each step and does not address which adjuvant analgesics would be most appropriate for which types of cancer pain. The 'analgesic ladder' is still an effective tool, however it does not encompass all situations in pain management. Effective use of the WHO ladder depends upon a

comprehensive pain assessment, patient/family compliance, clinical judgments, and an ongoing reassessment of pain, throughout the cancer trajectory and the palliative process.

Figure 1: World Health Organization analgesic ladder



The well respected Scottish Intercollegiate Guidelines Network (55) found evidence of correlation between numerical rating scale scores and the analgesic ladder, which in turn allows quantification of pain intensity (11,12).

Table 2: Categories of Pain and Appropriate Analgesia

WHO analgesic ladder step	Score on numerical rating scale	Analgesics of choice
1. mild pain	< 3 out of 10	Non-opioids ± Ajuvant Analgesics
2. mild to moderate pain	3 to 6 out of 10	Weak opioids ± Adjuvant Analgesics ± Non-opioids
3. severe pain	> 6 out of 10	Strong opioids ± Adjuvant Analgesics ± Non-opioids

Successful pharmacological management of cancer pain can usually be accomplished with the use of opioid and non-opioid analgesics in approximately 80% of patients.

Opioids
Opioids differ pharmacologically by how they interact with three opioid receptor types (mu, delta, and kappa). Studies have confirmed that the mu receptor mediates the analgesic and adverse effects of morphine. The full spectrum of activity includes the *morphine-like agonist* drugs which bind to the mu receptor and produces analgesia to the opioid *antagonists* which binds to all 3 receptors and blocks the analgesic effect of morphine-like agonists. *Mixed agonist-antagonist* drugs can demonstrate both agonist and antagonist properties (3). The agonist drugs are the drugs of choice for treatment of cancer pain (ie. morphine, hydromorphone). They have a 'no ceiling' dose range, with the exception of codeine and tramadol.

The opioids used for mild to moderate pain, **step 2** of the WHO ladder, are referred to as *weak opioids.* They are often given in combination with a non-opioid analgesic. Examples of **step 2** opioids are codeine, oxycodone, and tramadol.

For moderate to severe pain (**step 3** of WHO ladder), *strong opioids* are indicated. The most commonly used strong opioids in the palliative setting in Newfoundland and Labrador are morphine, hydromorphone, fentanyl, sufentanil, oxycodone and methadone.

The following drugs are NOT recommended for use in cancer pain management:
- meperidine
- propoxyphene
- buprenorphine
- pentazacine
- nalbuphine
- butorphanol
- dezocine

Note: Partial agonists and mixed agonists-antagonists have limited usefulness in cancer pain management. They should **not** be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in the opioid dependent patient (57).

Non-Pharmacological Treatment:
Despite the improvements in effective pain control together with a better understanding of pain pathophysiology, availability of new pharmacological agents, various modes of administration, and the development of interdisciplinary care, 10%-20% of patients will require more intensive measures to control pain, especially in the terminal phase of their cancer. Non-pharmacological approaches to the management of cancer pain include **anesthetic procedures**, **neurosurgical techniques**, and **complementary therapies** (3,12).

Anesthetic procedures
Interventional anesthetic procedures are considered if patients with cancer pain have not achieved adequate pain relief, or are experiencing dose-limiting side effects, despite opioid rotation and a range of systemic therapies for pain and symptom management. P*eripheral neural blockades* involves the use of local anesthetics administered at multiple sites along the affected neuroaxis, and an example of which would be an intercostal block. C*entral neural*

blockade and spinal drug administration involves the use of opioid and/or adjuvant analgesics administered outside the dura, such as the delivery of epidural or intrathecal opioids (3).

Neurosurgical techniques
These invasive procedures are reserved for a select number of patients whose pain is uncontrolled by other means, or if high-dose parenteral opioids are associated with unacceptable side effects. The ablative or augmentative techniques are irreversible and have a high risk to benefit ratio (3). Examples of neurosurgical procedures include but are not limited to cordotomies and rhizotomies.

Complementary therapies
There exists a wide array of supportive interventions used to complement the mainstream treatments of cancer pain. Though there remains a lack of rigorous clinical trials, there is some evidence that as a group of interventions, they appear to be beneficial as adjuvants in the management of cancer pain (12). They are comprised of *psychosocial interventions* and *physical medicine and rehabilitative approaches.*

Psychosocial Interventions*:*
A critical review of the literature revealed an association between chronic cancer pain and psychological distress (13). Psychosocial interventions have been empirically tested and can be grouped into 4 broad categories:
- Cancer pain psychoeducation
- Cognitive behaviour treatment
- Hypnosis and imagery
- Caregiver-assisted approaches (12).

Physical Medicine and Rehabilitative Approaches*:*
- Massage
- Manuel lymphatic drainage (MLD)
- Acupuncture/acupressure
- Transcutaneous electrical nerve stimulation (TENS)
- Relaxation and imagery
- Therapeutic exercise
- Heat/cold
- Physiotherapy
- Adaptive equipment eg. wheelchairs/scooters, walkers, bathroom aids, etc... (12).

Treatment of Underlying Cancer

Surgical Interventions
Surgery may be required for diagnosis, staging, and/or palliation. Surgery encompasses a wide spectrum of procedures, with differing levels of invasiveness, requirements for anesthesia, inherent technical difficulty, and patient risks. The goal of palliative surgical interventions is to provide symptom relief and improve quality of life. Pharmaceutical management and supportive measures may still be required before, during and after a surgical intervention (12).
Some of the most common oncology surgical procedures are:

- Tumor Resection*:* This can include partial/complete resection, debulking or amputation;
- Relief of Obstruction*:* Pain and distress from mechanical obstruction of an organ or viscus is common in patients with advanced cancer. Common surgical procedures include percutaneous drainage, ablative therapy, dilation and stent placement, surgical resection or bypass;
- Drainage of Effusions*:* A malignant effusion (accumulation of fluid) may occur in the abdomen (ascites), the pleural space (pleural effusion), and/or the pericardial space (pericardial effusion);
- Repair of Bone from Metastases*:* Pain may be the most common presentation of skeletal metastases. Pain occurs in two thirds of patients with radiologically evident metastases. Radiation, systemic therapy and analgesics are first line therapies. Surgery is indicated when there is evidence of an impending pathological fracture or an unstable spine following or during radiation;
- Supportive Procedures*:* Other oncology surgical interventions that have a supportive function would include insertion of central vascular accesses, insertion of enteral feeding tubes and biopsies (12).

Radiation Therapy

The cancer symptoms most commonly relieved by external beam radiation therapy include, but are not limited to pain, bleeding and gastrointestinal obstruction, and from either locally advanced or metastatic disease. The goal of pain management with use of radiation is to help alleviate suffering, while minimizing the morbidity. Palliative radiation is generally given over a shorter time span than conventional radiation. Bone metastases are one of the most common reasons for palliative irradiation (12,53).

Radiopharmaceuticals such as Strontium 89, are used to treat numerous painful bony metastases, for which external beam radiation therapy would be impossible over such a large field. Pain relief starts with initiation of therapy, and can continue for up to 18 months. Radiopharmaceuticals can be associated with reduction of analgesia use in many patients. Thrombocytopenia and neutropenia are the most common side effects, but they are generally mild and reversible (12).

Systemic Antineoplastic Therapy

Systemic treatment includes the use of chemotherapy, anti-hormonal therapy and biological modifiers, which may decrease pain if their use can bring about significant tumor shrinkage. Time is required to determine whether this result has been achieved; therefore, appropriate pain management is still fundamentally important in the interim (53).

Question:

What are the current treatment strategies for the management of cancer pain?

Target Population:

These recommendations are aimed toward patients with cancer who are experiencing pain.

Supporting Evidence:

Non-opioids
According to the WHO ladder, the analgesic of choice for step 1 or mild pain is a non-opioid, such as:

- **acetaminophen** and NSAIDS are universally accepted as effective components of cancer pain management. Acetaminophen has fewer side effects than NSAIDs and its daily dose should not exceed 4000 mg/q24h (maximum twelve 325mg tablets q24h). Mechanism of action is still unknown. One small study revealed acetaminophen improved pain and well-being in patients with persistent cancer pain despite being on a strong opioid regimen (14). Due to liver toxicities, acetaminophen should be used with caution in patients with hepatic dysfunction or a history of inappropriate alcohol use.
- **non-steroidal anti-inflammatory drugs (NSAIDs)** are known pharmacologically as cyclooxygenase (COX) inhibitors, and include common drugs like aspirin, ibuprofen, and naproxen. These have been found to be useful for the treatment of cancer pain supported by a Cochrane systematic review, but can be associated with gastrointestinal toxicities (15). Pharmacological prophylaxis for these GI toxicities could include the use of a proton pump inhibitor (ie. omeprazole, lansoprazole) or a histamine-2 receptor antagonist (ie. ranitidine, famotidine). NSAIDs are also associated with renal toxicities in susceptible patients, and can induce acute renal failure through renal ischemia or acute interstitial nephritis.

Table 3: Non-Steroidal Anti-Inflammatory Drugs*

Dosing Information for NSAIDS						
Chemical Class	**Generic Name**	**Half-Life (hours)**	**Dosing Schedule**	**Starting Dose Oral (mg)**	**Maximum Oral Dose (mg/day)**	**Comments**
Salicylates	Aspirin (ASA)	3-12	q4-6h	650	6000	May not be as well tolerated as some of the newer NSAIDs. Available for rectal administration.
	Diflunisal	8-12	q12h	500	1500	Less GI toxicity than aspirin
	Sodium salicylate	2-3	q4h	325	4000	Minimal GI toxicity. Minimal effect on platelet function
Proprionic acids	Ibuprofen	2	q6h	400	3200	200mg & 400mg tablets are available OTC (no prescription

						necessary)
	Naproxen	13	q6-8h	250	1250	
	Fenoprofen	2-3	q6-8h	200	3200	
	Ketoprofen	2-3	q6-8h	25	300	Available for rectal administration
	Flurbiprofen	5-6	q12h	100	300	
	Oxaprozin	25	q24h	600	1800	
	Tiaprofenic Acid	4	q24h	600	600	
Acetic acids	Indomethacin	4-5	q8h	25	200	Higher incidence of GI and CNS side effects than proprionic acids. Available in slow-release and rectal preparations
	Tolmetin	2-5	q8h	400	2000	
	Sulindac	16	q12h	150-200	400	Not recommended for prolonged use due to increased risk for GI toxicity
	Diclofenac	2	q8h	25	150	
	Ketorolac	4-7	q6h	10	40	Use limited to 5 days. Recommended parenteral dose ≤30mg: total daily dose ≤120mg
Oxicams	Piroxicam	50	q24h	20	20	
	Meloxicam	15-20	q24h	7.5	15	At 7.5mg, it behaves like a Cox-2 inhibitor. At greater than 7.5mg doses, it behaves like a

						traditional NSAID.
	Tenoxicam	72	q24h	10-20	20	
Fenamates	Mefenamic acid	2	q6h	250	1000	Use limited to 7 days
Selective COX 2 Inhibitors	Celecoxib	11	q12-24h	200	400	COX-2 specific NSAID. May reduce incidence of GI toxicity; lack of effect on platelets; and lack of bronchial constriction
Other	Floctafenine	8	q6-8h	200-400	1200	Not recommended for long-term use
	Nabumetone	24	q24h	1000	2000	Minimal effect on platelet aggregation

*Adapted from: Cancer Care Nova Scotia, Guidelines for the management of cancer-related pain in adults, 2005 (54).

Other non-opioid drugs that are used in the treatment of cancer-related pain are **adjuvant analgesics**. They are also known as co-analgesics (3). These are drugs that are not primary analgesics but research has shown that they have independent or synergistic analgesic properties. They are helpful for patients whose pain is partially responsive to opioids. The choice of adjuvant analgesic to use is determined by the characteristics of the pain. They include:

- Antidepressants**:** These are frequently used to treat neuropathic pain associated with surgery, radiation therapy, chemotherapy, or pain caused by malignant nerve infiltration (16,17). Typically, the doses needed for pain relief are significantly lower than the therapeutic antidepressant doses. The most common tricyclic antidepressants used are amitriptyline, imipramine, nortriptyline, and desipramine. Other examples of antidepressants used are venlafaxine, bupropion, and duloxetine.

- Anticonvulsants**:** These are also frequently used to treat neuropathic pain associated with cancer treatments (17,18). The most commonly used anticonvulsants are gabapentin, pregabalin, carbamazepine, and phenytoin.
- Corticosteroids**:** These help decrease edema around neural tissue providing pain relief (19). They have a long half-life which allows for once a day dosing. Corticosteroids can be useful in painful plexopathies, such as brachioplexopathy and sacralplexopathy. The long-term side effects, however, can be significant. Some examples of these are cushingoid effect, proximal myopathy, skin changes, and osteoporosis.
- Topical agents**:** They are applied to a painful area directly, penetrate the skin and act locally on the tissue. Topical agents have the advantage of having no systemic mechanism of action. Examples of topical agents are lidocaine (20,21), which is applied daily, capsaicin (extract from chilli peppers applied 3-4 times a day), NSAIDs, gabapentin and opioids (22).
- N-methyl-d-aspartate (NMDA) receptor blockers**:** Ketamine and methadone are used in selected patients who have uncontrolled persistent pain. They are indicated in neuropathic pain, ischemic limb pain and refractory pain in cancer (23-27).
- Bisphosphonates**:** These have been shown to help reduce cancer pain and skeletal-related events associated with bone metastases in a Cochrane systematic review (28). The most common are bisphosphonates are pamidronate and zoledronic acid. They may be used in conjunction with chemotherapy, radiation therapy, and analgesics to control pain. The main adverse effect is renal toxicity. Other noted potential complications are hypocalcemia and osteonecrosis of the jaw.
- Calcitonin**:** This is a polypeptide hormone that inhibits osteoclast-induced bone resorption and is indicated in the treatment of hypercalcemia and osteoporosis. It has been used as an option to treat bone pain from metastases after failure of other treatment modalities (29). To date a Cochrane review did not support its routine use, though it did acknowledge there was a limited amount of evidence from which to draw conclusions (30).
- Cannabinoids**:** They produce analgesia independently from opioids by modulating pain processing at multiple sites within the CNS. A systematic review found cannabinoids to be as effective as codeine, but the psychotropic side effects often limit their use (31). Cannabinoids have been proven to provide statistically significant improvement in the treatment of neuropathic pain in one randomised controlled trial (32).

Table 4: Adjuvant Analgesics*

Dosing Information for Adjuvant Analgesics						
Drug Class	**Indications**	**Preferred Drugs/ Routes**	**Usual Starting Dose (mg/day)**	**Usual Effective Dose Range (mg/day)**	**Frequency of Use**	**Dosing Schedule**
Antidepressants Tricyclics **First Generation:** **- Amitriptyline** **- Clomipramine** **- Imipramine**	Multipurpose for chronic pain; effective for both continuous and 'shooting'	Amitriptyline oral	10-25	50-150	hs	Traditionally amitriptyline was first line, but due to side effects and recent evidence of comparable analgesia, desipramine is
		Clomipramine oral	10-25	50-150	hs	
		Imipramine oral	10-25	50-150	hs	
		Doxepin oral	10-25	50-150	hs	
		Desipramine oral	10-25	50-150	hs	

- Doxepin **Second Generation:** **- Desipramine** **- Nortripyline**	neuropathic pain, but generally used as second-line agents for paroxysmal (sudden onset) pain	Nortripyline oral	10-25	50-150	hs	preferred for many patients, especially the elderly. Less hypotension with nortriptyline. Evaluate and titrate upward q3-5 days. Some patients may prefer divided doses (e.g. q8h)
Antidepressants Non-tricyclics		Fluoxetine oral	10-20	20-40	q day	Fewer side effects than tricyclics; less evidence of effectiveness
		Paroxetine oral	20	20-40	q day	
		Sertaline oral	50	150-200	q day	
Anticonvulsants	First line for paroxysmal (sudden onset) or 'shooting' neuropathic pain; second line for nonparoxysmal	Carbamazepine oral	200	600-1200	q 6-8h	Increase in increments of 100mg every 2-3 days
		Clonazepam oral	0.5	0.5-3	q8h	
		Divalproex oral	500	1500-3000	q8h	
		Phenytoin oral and iv	300 oral 500-1000 iv	300 oral ? iv	hs oral ? iv	Loading doses may be used (e.g. 500mg x 2); IV dose used for rapidly escalating neuropathic pain
		Valproate sodium oral	250	1500	hs to tid	Increase in increments of 250mg every 2-3 days
	Multipurpose for all types of neuropathic pain	Gabapentin oral	100-300	300-3600	q8h	May increase dose daily
		Pre-gabalin	50-75	300	tid	If pain not controlled after 2-4 weeks, then can increase to 300mg bid or 200mg tid
Corticosteroids	Multipurpose analgesics	Dexamethasone oral	Low-dose regimen: 2-4mg	same	q day or bid	May also improve appetite, nausea, and malaise. In patients with advanced medical disease, long-term treatment with low doses is generally well tolerated; used when pain persists after optimal opioid dosing
			High-dose regimen: 100mg then 96mg in 4 divided doses		qid	High doses used for acute episode of severe pain unresponsive to opioids. Risk of serious toxicity increases with

						dose, duration of therapy, and coadministration of a NSAID
Topical agents	Neuropathic pain of any type	Mexiletine oral	150	900-1200	q8h	Mexiletine is safer than tocainide and should be tried first. Plasma concentrations should be followed to reduce the risk of toxicity
		Tocainide oral	400	1200-1600	q8h	
NMDA receptor blockers	Neuropathic pain	Ketamine sq, iv or oral	50-100mg	Build up dose slowly by increasing dose by 50 to 100mg no faster than every 24 hrs. Discontinue ketamine if no improvement at 700mg q24hrs.	q24h continuous infusion for iv	Given under medical specialist supervision only. May need to give prophylactic oral haloperidol or benzodiaxepine to cover psychomimetic side effects. Adjust opioid dose by reducing 24 hour dose by 25-50%.
		Methadone oral, rectal supp., sq or iv	Titrated		q12h or q8h for oral and sq continuous infusion for iv	Can only be administered by physicians with special authorization. Potentially useful if no longer responsive to/tolerant of morphine. Use 50-70% of oral dose for sq dosing; can be used in renal failure. Long half-life can lead to overdosing.
Bisphosphonates	Bone pain, especially breast cancer and multiple myeloma. Also used to treat hypercalcaemia	Pamidronate iv	90mg		q3-4 weeks	Give in minimum of 500ml of 0.9% nacl over 2-4hrs. Monitor calcium levels, may require Vitamin D or calcium.
		Zoledronic acid iv	4-8mg		q4-6 weeks	Given over 15 minutes. Monitor calcium levels, may require Vitamin D or calcium.
Calcitonin	Option to treat bone pain when other modalities have failed.	Calcitonin sq	8 IU/kg		q6h	Also used in hypercalcaemia. Initially start with a test dose of 1-2 IUs.
Cannabinoids	Neuropathic	Sativex buccal				

	pain and/or patient request.	spray				
		Marinol oral	2.5-10		bid	
		Cesamet oral	0.5-1		bid	
		Medical marijuana smoked or ingested				

*Adapted from: Cancer Care Nova Scotia, Guidelines for the management of cancer-related pain in adults, 2005 (54).

Opioids

Opioids are the cornerstone for the treatment of moderate to severe pain. The oral route is the preferred route, though opioids for palliative intent can be administered in various other ways such as subcutaneous, intravenous, rectally, sublingual/buccal, topical, transdermal, inhalation, and epidural/intrathecal.

The opioids most commonly used for mild to moderate pain, **step 2** of the WHO ladder, would be those referred to as *weak opioids,* and are often given in combination with a non-opioid analgesic. These include drugs such as:

- **Codeine -** has a maximum ceiling analgesic effect which is achieved at a dose of 240mg/day, beyond which produces more side effects but no additional analgesic benefit. Codeine can often be given alone, or in conjunction with acetaminophen such as Tylenol 3© or atasol 30 (33). Approximately 5% to 10% of caucasians lack the necessary enzyme (CYP2D6) which converts codeine to morphine, and therefore these patients will not obtain equivalent analgesia (34).
- **Oxycodone -** is available in both immediate-release and sustained-release preparations. Lower doses can frequently be used, when used in conjunction with nonopioids. Oxycodone can be used in the treatment of both mild to moderate (step 2) and moderate to severe (step 3) cancer pain (35).
- **Tramadol -** has a maximum dose of 400mg/24 hours. It is available in combination form with acetaminophen known as Tramacet© (36).

It is important to note that these opioids, taken in combination form with acetaminophen, may have their potential for analgesic effect limited due to restriction of the recommended daily dose of acetaminophen.

Table 5: Weak Opioids

OPIOID	ROUTE	AVAILABLE DOSAGE	FREQUENCY	COMMENTS
Codeine immediate-release (IR) sustained-release (SR)	po/sq po	15,30mg po 30,60mg sq 50,100,150,200mg	q4h q12h	metabolized by CYP2D6 – morphine in vivo; may cause constipation and GI upset; increase in toxicities when renal dysfunction is present; may be compounded with acetaminophen (ie. Tylenol 3)
Oxycodone IR SR	po/pr po	5mg po 10mg-20mg po and pr 5,10,20,40,80mg	q4-6h q8-12h	metabolized to oxymorphone in vivo; may be compounded with acetaminophen (**Percocet** – 5mg of oxycodone and 325mg of acetaminophen) or ASA (**Percodan** – 5mg of oxycodone and 325mg of ASA), used for mild pain; less toxic than equianalgesic dose of codeine; short half-life of 3-4hrs; high risk for dependence and diversion.

Tramadol IR and SR	po	100,150,200, 300,400mg	q24h	may be compounded with acetaminophen (**Tramacet** – 37.5mg of tramadol and 325mg of acetaminophen). There is some evidence that Tramadol is effective in treating neuropathic pain. Maximum dose of 400mg in a 24 hour period.

For moderate to severe pain (**step 3** of WHO ladder), the *strong opioids* are often given with non-opioids, as required to achieve pain control. The *strong opioids* most frequently prescribed in Newfoundland and Labrador are:

- **Morphine -** is the most commonly used drug for cancer pain. It is available in sustained-release form with duration of 8 to 12 hours (MS Contin©), 12 hours (M-Eslon©) or 24 hours (Kadian©) and immediate-release. There are multiple routes of administration but availability may be limited depending on region (37,38).
- **Hydromorphone** (Dilaudid©) – is used as an alternative to morphine by oral and parenteral routes. Hydromorphone is available in sustained- release formulation, and in a concentrated dosage form useful for subcutaneous or intravenous injection (39).
- **Fentanyl** - is estimated to be approx. 80-100 times as potent as morphine. The transdermal patch is most frequently used for chronic or stable pain. The patch is routinely replaced every 72 hours (40).
- **Sufentanil –** is 5 to 10 times more potent than fentanyl. It is presently only available in parenteral form (41).
- **Methadone -** has a variable half-life. It can take up to 10 days to achieve a steady state plasma level. Toxicity can occur in elderly patients and patients with liver dysfunction or impairment. It is one of the drugs of choice for patients in renal failure. It has a negative public image due to its association with withdrawal and maintenance programs for drug addicts. Only physicians with special authorization from Health Canada can prescribe it for terminally ill patients (42). An initial EKG is required, followed by subsequent EKGs where appropriate, to assess the Q-T interval.
- **Oxycodone –** is available in both immediate-release and sustained-release preparations (35).

Table 6: Strong Opioids

OPIOID	ROUTE(S)	AVAILABLE DOSAGE	FREQUENCY	COMMENTS
Morphine	sq/iv	5,10,15,25, 50mg/ml sq/iv	q1-4h	gold standard for opioids;M-6-G metabolite-increase in side effects if renal dysfunction present; should begin with lower doses in the elderly; short half-life of 2-4hrs. M-Eslon© and Kadian© are available in capsule form and the enclosed crystals can be administered via feeding tube
IR (MS-IR)	po	5,10,20,25,30,40, 50,60mg po 1,5,10,20,50mg/ml syrup po	q1-4h	
SR (MS Contin©)	po/pr	15,30,60,100, 200mg po	q12h	
SR (M-Eslon©)	po	10,15,30,60,100, 200mg po	q12h	
SR (Kadian©)	po	10,20,50,100mg po	q24h	
Hydromorphone	sq/iv/pr	2,10,20,50mg/ml sq/iv 3mg supp.	q1-4h	has a 5:1 higher potency than morphine; may have less side effects than morphine for some patients, such as renal impaired, elderly;
IR (Dilaudid©)	po	1,2,4,8mg po 1mg/ml syrup po	q1-4h	
SR (Hydromorph Contin©)	po	3,6,12,18,24,30mg	q12h	

				available in high-potency parenteral formulation useful for sq injection (10mg/ml); short half-life of 2-3hrs
Fentanyl (Duragesic)	Transdermal sq/iv sl	12,25,50,75,100ug/h patch 50ug/ml maximum 3ml	q72h continuous infusion and/or prn q30 minutes prn	25ug/hr is equivalent to 90mg oral morphine/day; **not suitable** for opioid native, acute pain; heat increases absorption; increase sweating and perspiration decreases absorption; if skin irritation occurs, use steroid spray
Sufentanil	sl	presently there is not enough evidence in the use of sufentanil for the treatment of pain in palliative patients		quick acting and very short duration; given for breakthrough/ incidental pain
Methadone	po	1,5,10,25mg po 1mg/ml susp. po	complicated dosing though usually q8h for palliative patients	long half-life can cause increase in toxicities; requires special authorization to give; often prescribing preference would be for tablet form

Oxycodone IR	po/pr	5mg po 10mg-20mg po and pr	q4-6h	metabolized to oxymorphone in vivo; may be compounded with acetaminophen (**Percocet** – 5mg of oxycodone and 325mg of acetaminophen) or ASA (**Percodan** – 5mg of oxycodone and 325mg of ASA) used for both mild to moderate and moderate to severe pain; short half-life of 3-4hrs; high risk for dependence and diversion.
SR	po	5,10,20,40,80mg	q8-12h	

Opioid Tolerance, Physical Dependence, and Addiction

Frequently, psychological opioid dependence (addiction) can be confused with opioid tolerance and physical dependence that can be seen with long-term opioid use (43). The American Pain Society (53) has defined these terms in an attempt to help health professionals understand the difference.

Addiction is a primary, chronic, neurobiologic 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 medication use, compulsive use, continued use despite harm, and craving.

Physical dependence is a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing level of the medication in the blood, and/or administration of an antagonist. Patients, diagnosed with cancer, occasionally require discontinuation or rapid decreases in doses of opioids when the cause of pain is effectively eliminated by other modes of treatment. Under these circumstances, the withdrawal symptoms can be avoided by slowly withdrawing the opioids. To wean a patient from opioids, clinicians can prescribe half of the previous daily dose for the first 2 days, followed

by 25% less every second day, until a total daily dose of 30mg/day of oral morphine is reached. After 2 days at the minimum dose, the analgesic may be discontinued.

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 effects over time. Usually the first indication of tolerance is a decrease in the duration of effective analgesia for a given dose.

General Principles of Opioid Treatment

Some general principles that health professionals should be aware of when caring for patients who require opioid treatment are:

- Opioids should be used when non-opioid and adjuvant analgesics are insufficient to control debilitating cancer pain;
- Most 'allergies' to morphine are not true allergies but actually side effects (eg. nausea). Patient and family education and appropriate management of side effects will help to avoid situations where patient and family assume they are 'allergic' thereby, preventing use of a potentially helpful drug;
- Opioids are equally effective at equianalgesic doses but individual response can vary between drugs;
- Medical use of opioids for pain associated with advanced illness rarely, if ever, leads to drug abuse or opioid addiction;
- There is no 'ceiling' or maximum recommended dose for strong opioids. Increasing doses may be needed to provide adequate pain relief;
- The oral route is used whenever possible, but the plan must be individualized to the patient and the setting;
- Opioid use does **not** shorten survival;
- Documentation of the use of opioids contributes to appropriate dosing and pain control, therefore strongly encourage the use of a patient pain diary;
- It is recommended to always provide the patient with primary prophylaxis for the predictable side effects (49).

Opioid Initiation

The choice of opioid drug to use should be determined by specific patient-based factors such as:

- Age – the elderly are best treated with opioids that have short half-lives and avoid those with active metabolites
- Pain intensity – eg. if the pain is severe (8 out of 10 on the VAS), a step 3 opioid on The WHO's analgesic ladder may be needed initially
- Pre-existing comorbidities - such as major organ failure like hepatic failure (slows opioid clearance and may increase side effects) or renal disease (causes an accumulation of metabolites)
- Route of administration – best suited for patient
- Patient preference – should be honoured where possible
- Patient history – past experience with opioids, side effects etc...
- Cost – though cost should not be a primary consideration in choice of opioid, it is a factor in poor compliance if the patient cannot afford the drug (49).

Opioid Maintenance

For continuous pain, the most appropriate regimen would be to provide pain medication on a regular schedule with supplemental doses for breakthrough pain. **Breakthrough pain** has been defined as a transient flare of pain of moderate or severe intensity arising on a background of controlled pain (55).

Three different types of breakthrough pain have been identified:

1. **incident pain –** related to an activity, action, or event;
2. **spontaneous pain –** no evident precipitating event;
3. **end-of-dose failure pain –** occurs just before the next anticipated dose of analgesia (3).

Opioid Titration

Opioid dose titration has traditionally been referred to as the procedure with which the dosage of an opioid should be gradually adjusted. Up titration of the opioid is indicated if the pain is not adequately controlled. Down titration may be indicated with the successful use of primary cancer treatment (eg. radiation, chemotherapy). Regular assessment is required of the patient's pain, including when and why it occurs as well as the amount of medication used in the previous 24 to 72 hour period (44,54).

Steps for Opioid Titration – Opioid Naive Patient:

1. For the opioid-naive patient, the **immediate release (IR)** formulation is often used initially until the dose required for pain control is stabilized. An appropriate starting dose would be 5 to 10mg of morphine (or 1 to 2mg of hydromorphone) q4h. In addition, breakthrough medication is required. In this particular case, 2.5 to 5mg of morphine (or 0.5 to 1mg hydromorphone) q1h as needed, would be appropriate. For elderly or renally-impaired patients, 50% of the starting dose would be appropriate.

2. The effectiveness of the analgesic can be reassessed after 24 hours as it takes five half-lives to reach a steady state. An accurate account of dose given, frequency and patient response should be kept. The total of the amount of regular and breakthrough opioid used in the last 24 hours will provide the **total daily dose (TDD)**. Divide this amount by the number of doses for the next 24 hours (eg. 6 when given q4h), and proceed to give this dose regularly q4h with 10% of the TDD given q1h prn for breakthrough pain.

3. Generally, dose adjustments should not be made more frequently than every 24 hours. However, for very severe pain, the rate of upward titration may need to be estimated more frequently. Assess for end of dose pain and the presence of incident pain, which may require further titration. Continue to use IR opioid formulations for breakthrough doses and **remember** to increase the breakthrough dose proportionally when the regular dose is increased.

4. When good pain control is achieved with a stable dose of an IR formulation, consider using a long acting **slow release (SR)** product to improve compliance. Before conversion to any SR opioid, always use IR preparations to titrate to the appropriate 24 hour dose (TDD). SR formulations should not be used to manage uncontrolled pain.

5. Steady state when using morphine SR or hydromorphone SR is achieved after 48 to 72 hours. Dosage adjustments for these drugs should be made only every 2 to 3 days. **Never** prescribe SR oral formulations more frequently than q8h.

6. When using the SR preparations, always give an IR opioid, preferably using the same drug. For mild pain, give 10% of the TDD equivalency q1h prn for breakthrough pain (ie. for morphine SR 60mg po q12h, give a breakthrough dose of morphine 10 to 15mg po q1h prn). For moderate to severe pain, give one sixth (1/6) of the TDD equivalency q1h prn for breakthrough pain (eg. for morphine SR 60mg po q12h, give a breakthrough dose of morphine 20mg po q1h prn).

7. Fentanyl transdermal patches are generally **not** an appropriate choice for patients who are opioid naive, or have unstable or poorly controlled pain (49,54,55).

Opioid Rotation

Opioid rotation is the process of switching one opioid for another. It is required for patients with inadequate pain relief and/or intolerable opioid related toxicities or adverse effects which limits dose escalation.

NOTE: Rotation from a pure agonist opioid (ie. codeine, morphine, hydromorphone, oxycodone) to a partial agonist (propoxyphene, buprenorphine) is **NOT** recommended due to the potential precipitation of withdrawal symptoms.

Table 7: Opioid Equianalgesic Dose Conversion

Opioid	Ratio of Potency of Other Oral Opioids to Oral Morphine
Morphine	1:1
Hydromorphone	1:5
Oxycodone	1.5 to 2:1
Codeine	12:1
NOTE: Decrease dose of new opioid by 25-50% due to incomplete cross tolerance If first dose ineffective, use 100% to 125% of the eqianalgesic dose	

Steps for Opioid Rotation:

1. Stop current opioid regimen,
2. Calculate the total dose of current opioid (regular and prn doses) used in the previous 24 hour period,

3. Calculate the dose of the new opioid using the Opioid Equianalgesic Dose Conversion Table above,
4. Adjust for lack of incomplete cross tolerance between opioids by decreasing the target dose from step 3 by 25-50% to obtain the new opioid dose,
5. Divide the new opioid dose (from step 4) by number of doses to be given over 24 hours and administer it as scheduled doses. Calculate breakthrough pain dose as 10-20% of calculated new opioid dose to administer prn every 1 hour,
6. Carefully titrate new opioid regimen until adequate analgesia is achieved (49,54,55).

Opioid Rotation – Fentanyl Patch

Transdermal fentanyl should generally **only** be used in patients with stable opioid requirements. Due to its long half-life of 17 hrs, the dose may be difficult to titrate if pain is not well controlled. It is especially suited to those who have poor absorption of oral opioids. It has been shown to provide 'round the clock' pain management and improves patient compliance.

Table 8: Fentanyl Transdermal Equianalgesic Conversion (49)

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

Table 9: Approximate Breakthrough Doses Recommended for Fentanyl (49)

Patch Strength (mcg per hour)	Oral Morphine Immediate Release	Oral Hydromorphone Immediate Release	Oral Oxycodone Immediate Release
12	5mg	1mg	**2.5 to 3.75mg**
25	10mg	2mg	**5 to 7.5mg**
50	20mg	4mg	**10 to 15 mg**

75	30mg	6mg	**15 to 25mg**
100	**40mg**	**8mg**	**20 to 30mg**

Steps for Opioid Rotation to Fentanyl Patch

1. Calculate the total daily dose of current opioid
2. Convert this into oral equivalent for morphine, hydromorphone or oxycodone
3. Use Fentanyl Transdermal Eqianalgesic Conversion Table to determine the equivalent dose of transdermal fentanyl
4. **Always** provide a breakthrough dose from Table 9 (Approximate Breakthrough Doses Recommended for Fentanyl). Providing breakthrough doses are important, as the conversion chart is conservative and approximate. When a patient is been treated with a Fentanyl patch, the appropriate frequency for any of the 'breakthrough' medications in Table 9, is every hour as necessary. In clinical trials, 50% of patients required a dose increase after the initial patch strength application. In this case, if adequate pain control is not achieved after the first 24 hours, then increase the dose of the initial patch strength. Consider using a 30% to 50% baseline dose increase, while using the available patch strengths.
5. Upward titration of the dose requires the immediate removal of the previous patch prior to initiating the application of a new dose.
6. Fentanyl transdermal patches require changing q72h (40,49,54,55).

Changing Opioid Routes

The oral route, for opioid administration, should always be considered first since it is considered to be relatively safe, inexpensive and convenient. Though, often patients in the last days and weeks of life often require more than one route of administration for their opioid treatment (3,44,45,49,53).

- **The oral route is the preferred route** in most palliative care settings. Maximal analgesia is reached at 1.5 to 2 hours for IR preparations, and 3 to 4 hours for SR preparations. The main problem with the oral route is the biotransformation of opioids in the liver. Once the opioid is absorbed in the gut and transported to the liver, it undergoes "first-pass metabolism" before entering the systemic circulation, which decreases the bioavailability of the total administered dose. Hence the reason why oral opioid doses are much higher than IV or SQ.
- The **rectal route** has more rapid absorption, within about 10 minutes, and a similar pattern of duration when compared to the oral route. It may not be reliable secondary to the amount and consistency of stool in the rectum. The rectal route should be avoided in patients with rectal or anal lesions or who are neutropenic or thrombocytopenic. Opioids can be placed in colostomies if the flow of effluent is slow enough to allow absorption.
- **Subcutaneous (SQ)** has an absorption rate of 10 to 15 minutes. **Intravenous injection (IV)** provides an early immediate peak serum level. SQ starts to lose potency at 45 to 90 minutes and IV medications by 20 minutes. Indications for parenteral use include inability to swallow, nausea and/or vomiting, GI obstruction or impaired absorption, and uncontrolled pain where rapid titration is necessary. The IV route can be very effective when rapid delivery of analgesia is needed. Intramuscular administration of opioids should be **avoided** in palliative care patients. SQ route is a popular alternative route which does not require a venous access.

- **The transdermal route** is a non-invasive alternative to oral medications. Transdermal patches may not be appropriate for patients with fever, diaphoresis, cachexia, morbid obesity, or ascites. These conditions may have a significant effect on the absorption, blood levels, and clinical effects of the drug. It is **not** recommended to cut patches in order to manipulate dosing.
- **The buccal route** has a quick absorption rate of approximately 10 minutes. Use of concentrated forms of opioids (ie. morphine 20-50mg/ml, or hydromorphone 10-50mg/ml) is recommended. The volume of drug dose must be kept at or below 0.5ml to avoid swallowing or prevent choking. The 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.
- **Epidural** and **intrathecal** administration are used in difficult or refractory pain situations, and are always under the supervision of anaesthesiology. Both these routes require the use of *preservative free-formulations*. Intrathecal injection delivers the drug directly into the cerebral spinal fluid (46).
- **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.

Table 10: Opioid Conversion According to Route*

Opioid	Oral (PO)	Parenteral (SQ, IV)
Morphine	10mg	**5mg**
Codeine	100mg	**65mg**
Hydromorphone	2mg	**1mg**
Oxycodone	5.0-7.5mg	**---**
Common ratio in chronic dosing PO:SQ is 2:1, but for some patients may be 3:1		

***Adapted from: Medical Care of the Dying 4th ed, pp. 195, 201. © Victoria Hospice Society 2006 (47)

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Opioid Adverse Effects

The management of opioid-induced side effects or toxicities remains a major clinical challenge, and can be highly distressing to patients and their families. The lack of quality clinical trials comparing the various therapeutic approaches for management contributes to this challenge. The next best option then is to provide a consensus of expert opinion on how best to manage these side effects. The following therapeutic management regimens were adapted from the Hospice Palliative Care Program, Symptom guidelines at Fraser Health in British Columbia (49), with the Eastern Health Pain and Symptom Team, Cancer Care Program.

- **Constipation** is a common adverse effect and is much easier to prevent than it is to treat. Therefore, a bowel regimen **must** be initiated at the commencement of opioid treatment.

For prevention, Sennosides 8.6mg or 12mg, can be given po once or twice daily and titrated to effect, up to a maximum of eight [8] tablets in a 24 hour period. If constipation remains a problem, Lactulose may be added at a dose of 30 ml po q8h, until the patient has a good result. The patient should continue the prescribed bowel regimen as long as the opioid treatment is being administered.

For constipation management (no bowel movement for 3 days or more), a thorough assessment of the abdomen should be carried out by a qualified health professional. Abnormal bowel sounds, including high pitched 'tinkling' sounds noted with a hyperactive bowel, or the absence of bowel sounds all together could indicate the presence of a bowel obstruction, and warrants medical intervention.

In the absence of a bowel obstruction, constipation management would include the use of the medications listed above plus:

1. **if soft stool in rectum -** rectal laxative, such as Biscodyl suppository 10mg pr, if not effective within 1 hour, give Fleet enema pr.
2. **if hard or impacted stool in rectum –** use oil retention or soap suds enema pr, if not effective within 1 hour, disempact if indicated.
3. **if no stool in rectum –** give Golytely one glass per hour po until result obtained.

Note: Avoid using bulk forming agents (ie.fiber) in patients with poor oral fluid intake, since patient must be able to tolerate 1.5 to 2 litres of fluid per day. Therefore, these agents are a poor choice for cancer patients. Metoclopramine inhibits dopamine centrally and peripherally, therefore increasing peristalsis in the digestive tract, which results in its dual function of treating constipation, in addition to the management of nausea and vomiting (ex. Metoclopramide 10 to 20mg po q6h).

- **Nausea/vomiting** is usually mild and rarely persistent, tolerance develops rapidly. Antiemetics can generally be discontinued in a few days when tolerance develops. Metoclopramide is the usual first choice as it targets common causes of nausea in advanced diseases. If nausea is not controlled with a specific antiemetic, add a second antiemetic from another group if nausea continues for 48 hours, but **do not** stop the initial agent. Monitor for overlapping toxicities. Give antiemetics prophylactically to prevent nausea with high dose opioids.

Table 11: Established Agents for the Treatment of Nausea*

Agents	Examples	Action
Dopamine antagonists – central action	metoclopramide, butyrophenes (e.g. haloperidol), phenothiazines (e.g. chlorpromazine)	blocks dopamine receptors at chemoreceptor trigger zone.
Dopamine antagonists – peripheral action	metoclopramide, domperidone	promotility effects on gastrointestinal tract.

Antihistamines	dimenhydrinate	effects on vomiting center and vestibular apparatus.
Corticosteroids	dexamethasone	reduces raised intracranial pressure; other antiemetic effects not well understood; improves sensation of well-being and appetite.
5-HT3 (serotonin) antagonists	ondansetron, granisetron	blocks 5-HT3 receptors in the gut predominantly; useful in chemotherapy-induced and postoperative vomiting; metoclopramide at high doses has weak 5-HT3 antagonistic activity.
Progestational agents	megestrol acetate	unknown; improves appetite, caloric intake, and nutritional variables in cancer cachexia.
Thalidomide		centrally acting antiemetic effect; other effects on improving appetite and sensation of well-being.
Cannabinoids	dronabinol	central effects.
Neurokinin-1 antagonists	aprepitant	central effects; antagonize substance P.
Octreotide		reduced gastrointestinal secretions in patients with inoperable bowel obstruction.
Anticholinergic agents	hyoscine butylbromide, scopolamine	reduced gastrointestinal secretions in patients with inoperable bowel obstruction.

***Adapted from Principles and Practice of Palliative Care & Supportive Oncology 2007© (43).*

- **Sedation** is often transient, especially when opioid initiated or increasing doses, and will generally be relieved in 2 to 4 days. The use of psychostimulants may be beneficial (ex. Ritalin, with a starting dose of 2.5mg po bid AM and noon, up to a maximum of 60mg in 24 hour period).

- **Delirium/restlessness** may be seen both upon initiation of opioids (frequently in the elderly) and during ongoing opioid therapy when metabolite accumulation occurs. Where possible, identify the underlying cause and treat as appropriate. Common medications used:
  1. **for mild restlessness -** Haloperidol 0.5 to 1.5mg po tid and/or Lorazepam 1 to 2mg sl or po prn.

  2. **for delirium and agitation in terminal illness**
     - ***hypoactive delirium*** (restless and confused but cooperative) - Haloperidol 1.5 to 5mg po/sq q4-8h and/or Methotrimeprazine 10 to 15mg for mild and up to 50mg for severe delirium q4-6h or Quetapine (Seroquel®) 12.5 to 25mg po bid and 12.5 to 25mg po bid prn.

- ***hyperactive delirium*** (with paranoia, confusion and/or aggression) **–** start Haloperidol 1 -2 mg sq q60 minutes x 3 doses. If no relief noted, then consider other alternatives. For example, Methotrimeprazine 12.5 to 25mg sq q6h prn **OR** Quetapine (Seroquel®) 12.5 to 25mg po bid and 12.5 to 25mg po bid prn **OR** Chlorpromazine 50 to 100mg po q6h prn.

- **Pruritus** may occur secondary to the histamine release in drugs like morphine. Patients may require opioid rotation.
- **Xerostomia** (dry mouth) is a common effect of morphine. Good mouthcare and frequent sips are effective for most patients.

- **Syncope** (dizziness) occurs secondary to orthostatic hypotension caused by venous pooling following by histamine release. Patients prone to this effect should be instructed to change position slowly when moving from lying to sitting or standing.

Opioid Toxicities

- **Myoclonus** (spontaneous jerking movements) can occur with any dose and route of opioids. Myoclonus may precede the onset of opioid-induced neurotoxicity. If the dose cannot be reduced due to persistent pain, consider opioid rotation or symptomatic treatment with benzodiazepines, such as Lorazepam and/or Clonazepam. Midazolam can be used as well for terminal restlessness and myoclonus, especially when due to opioid toxicity. Hydration may also be considered to promote renal clearance of the metabolites, thereby helping to reduce the myoclonus.

- **Respiratory depression** occurs rarely in patients receiving opioids regularly as tolerance to the respiratory depressant effects develop rapidly. The risk of respiratory depression is greater in patients with respiratory impairment (ie. pneumonia, those with CO2 retention, or chronic obstructive pulmonary disease) and when opioids are used in opioid-naive patients, or are too rapidly titrated.

Difficult Pain Problems

Pain Crisis

Cancer is occasionally associated with sustained episodes of excruciating pain known as a *pain crisis* or *pain emergency* that require rapid titration of powerful analgesic strategies, such as that developed at the Tom Baker Cancer Centre in Calgary, Alberta (48). Hagen et al found this technique provided all patients with relief from their excruciating pain after a mean of 89 minutes, with a range from 4 to 215 minutes, without any evidence of significant toxicity. The Hagen Protocol, as it became known, was adapted by our pain team and has been successfully implemented within our healthcare facility. If patients are experiencing severe pain, new onset pain, or exacerbation of previously stabilized pain, accompanied by significant distress, they are encouraged to visit their nearest emergency department for evaluation and treatment.

The definition of a *pain crisis* or *emergency* in the Hagen Protocol is defined as a verbal pain intensity score of 8 or greater that was further sustained for at least 6 hours, and escalated over

a course of several hours to days. This protocol should be restricted to use for only those patients who meet the criteria outlined in this definition.

There are some general contraindications for use of morphine sulphate in non-terminally ill patients, including:

- hypersensitivity to morphine sulphate or any component of the formulation (some preparations contain sodium metabisulfite);
- increased intracranial pressure;
- severe CNS depression;
- severe respiratory insufficiency or depression;
- acute or severe asthma;
- heart failure secondary to chronic lung disease;
- cardiac arrhythmias;
- head injuries;
- brain tumor;
- acute alcoholism;
- delirium tremens;
- convulsive disorders;
- post biliary tract surgery;
- suspected surgical abdomen;
- surgical anastomosis;
- concomitantly with MAO inhibitors or 14 days of such treatment.

Caution should also be exercised when using morphine in patients with:

- impaired respiratory function;
- with severe hepatic dysfunction;
- in renal impairment;
- in CNS depression;
- in elderly and/or debilitated patients with acute abdominal conditions.

However, in terminally ill patients, the use of morphine sulphate will depend on the decision of the attending physician as per his/her experience and knowledge or familiarity with the patient.

Management of a pain crisis using the Hagen Protocol (adapted)

Pain emergency? (Pain ≥ 8/10 on a visual analogue scale)

Initial pain assessment
Vital signs

IV infusion of Morphine Sulphate 10-20mgs in 50 mls of normal saline (or an equianalgesic dose of alternative opioid) infused over 15 minutes

Evaluate 30 minutes after infusion complete (total 45 minutes from start of infusion)

Reassess patient (vitals, verbal pain score, adverse effects)

Pain > 5/10

Double previous bolus size dose as needed
i.e. Morphine Sulphate 20mgs iv (infuse over 15 minutes)

Evaluate 30 minutes after infusion complete (total 45 minutes)

Reassess patient as before and continue an upward dose titration in the manner described until an effective analgesic dose is identified (then repeat as needed q1h prn) or toxicity develops.

Pain ≤ 5/10

Repeat effective dose q1h prn x 24h

Calculate the previous total 24h dose. Increase baseline opioid dosage as needed after 12-24 h of stable analgesia.

In either case, after 24 hrs of effective pain control, calculate the total dose administered in that time period, divide this number by 6 to get the q4h dose OR divide the number by 24 to get the amount delivered per hour by continuous infusion iv or sq. Give 1/10 – 1/6 the total 24 hour dose q1h prn as the breakthrough dose.

Recommendations:

All patients experiencing pain, related to cancer or its management, in Newfoundland and Labrador should have access to timely, effective and appropriate treatment.

Search Strategy:

Literature searches, for this guideline, were conducted in Pubmed, CINAHL, and the Cochrane Library using the keywords “patient care management” AND “pain” AND “neoplasm” and “guidelines”. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 1990, up to May 2011. The inclusion/exclusion process consisted of selecting guidelines from reputable international cancer organizations, with preference given to those from Canadian sources. Nine source guidelines were identified but only five were chosen to be reviewed due to due to currency, appropriate content and/or were Canadian in origin (49-57).

The five identified source guidelines (53-57) were put through the ADAPTE process (58), including an AGREE II assessment (59), and the Scottish Intercollegiate Guidelines Network “control of pain in adults with cancer” (55) guideline was chosen to be adapted for use in our guideline. The SIGN guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ for guideline development in Canada. Presently, Canadian experts in the field are involved in in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Fiona OShea MD, Dr. H. Bliss Murphy Cancer Center, St. John’s, NL; Telephone 709-777-7436. For more information on any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

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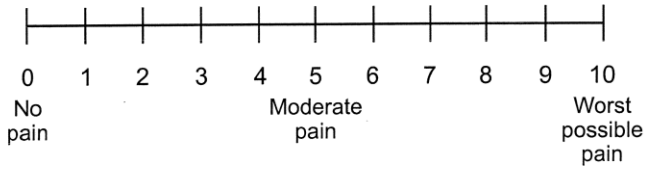
Patient Name: _____ Date: _____

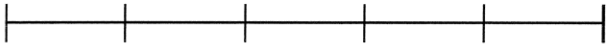
0-10 Numeric Pain Intensity Scale*



*If used as a graphic rating scale, a 10-cm baseline is recommended.
From: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research & Quality, Rockville, MD; pages 116-117.

Patient Name: _____ Date: _____

Simple Descriptive Pain Intensity Scale*

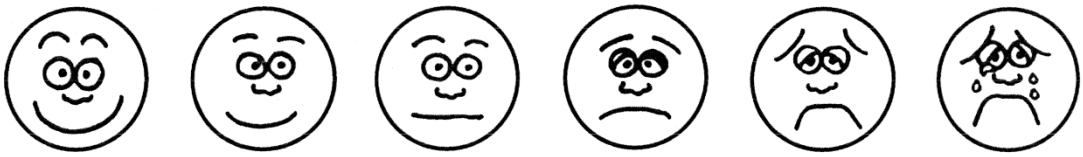


No pain | Mild pain | Moderate pain | Severe pain | Very severe pain | Worst possible pain

*If used as a graphic rating scale, a 10-cm baseline is recommended.
From: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research & Quality, Rockville, MD; pages 116-117.

Patient Name: _____ Date: _____

Wong-Baker FACES Pain Rating Scale



0 = VERY HAPPY, NO HURT
1 = HURTS JUST A LITTLE BIT
2 = HURTS A LITTLE MORE
3 = HURTS EVEN MORE
4 = HURTS A WHOLE LOT
5 = HURTS AS MUCH AS YOU CAN IMAGINE
(Don't have to be crying to feel this much pain)

Explain to the person that each face is for a person who feels happy because he has no pain (no hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.

Rating scale is recommended for persons age 3 years and older.

Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

From: Hockenberry MJ, Wilson D: *Wong's Essentials of Pediatric Nursing*, 8th Edition. St. Louis: 2009; Mosby.

Brief Pain Inventory (Short Form)

Study ID# _____ Hospital# _____

Do not write above this line

Date: _____ Time: _____

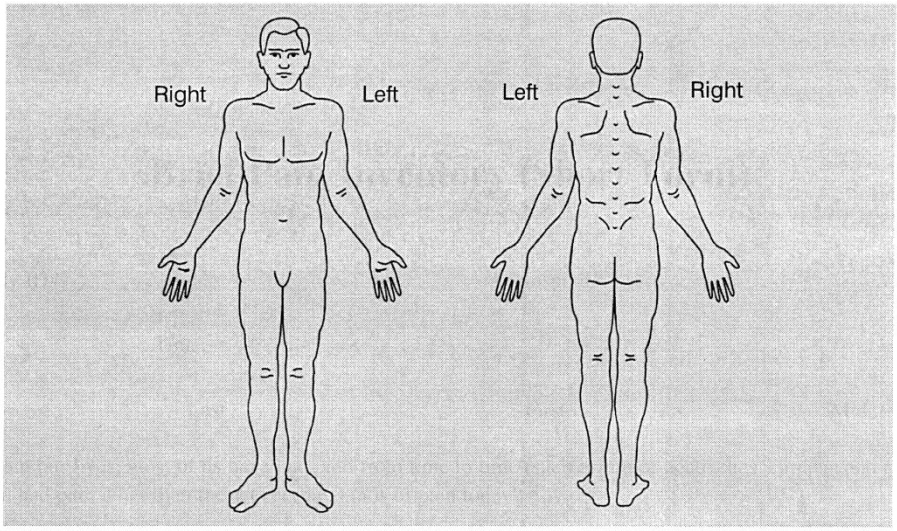
Name: _____

Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

8) In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much RELIEF you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No relief										Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and housework):

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Capital Health CARITAS HEALTH GROUP

Guidelines for using the Edmonton Symptom Assessment System (ESAS)

Regional Palliative Care Program

Purpose of the ESAS

This tool is designed to assist in the assessment of nine symptoms common in cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath, (there is also a line labelled "Other Problem"). The severity ***at the time of assessment*** of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that the symptom is absent and 10 that it is of the worst possible severity. The patient and family should be taught how to complete the scales. It is the patient's opinion of the severity of the symptoms that is the "gold standard" for symptom assessment.

The ESAS provides a clinical profile of symptom severity over time. It provides a context within which symptoms can begin to be understood. However, it is not a complete symptom assessment in itself. For good symptom management to be attained the ESAS must be used as just one part of a holistic clinical assessment.

How to do the ESAS

The patient circles the most appropriate number to indicate where the symptom is between the two extremes.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

The circled number is then transcribed onto the symptom assessment graph (see "ESAS Graph" below).

Synonyms for words that may be difficult for some patients to comprehend include the following:

Depression	-	blue or sad
Anxiety	-	nervousness or restlessness
Tiredness	-	decreased energy level (but not necessarily sleepy)
Drowsiness	-	sleepiness
Wellbeing	-	overall comfort, both physical and otherwise; truthfully answering the question, "How are you?"

When to do the ESAS

a) In palliative home care, it is a good practice to complete and graph the ESAS during each telephone or personal contact. If symptoms are in good control, and there are no predominant psychosocial issues, the ESAS can be completed weekly for patients in the home. In hospice and tertiary palliative care units the ESAS should be completed daily. In other settings the palliative consultants will utilize this tool in their assessment on each visit.

b) If the patient's symptoms are not in good control, daily assessments need to be done in person by the attending health professionals until the symptoms are well-controlled (see "d" below).

c) If symptom management is not attained, or consultation about possible care options is needed, patient assessments by Palliative Care Consultants are available (**attending physician must agree**). Consultative discussions not requiring in-person patient assessments are available from Palliative Care Consultants upon request.

d) If, after all therapeutic options have been exhausted and consensus is reached that a symptom cannot be further improved, visits and assessments can return to their normal pattern for that patient.

(OVER)

CH-0373 Mar 2001

Who should do the ESAS

Ideally, patients fill out their own ESAS. However, if the patient is cognitively impaired or for other reasons cannot independently do the ESAS, then it is completed with the assistance of a caregiver (a family member, friend, or health professional closely involved in the patient's care). If the patient cannot participate in the symptom assessment, or refuses to do so, the ESAS is completed by the caregiver alone.

Note: when the ESAS is completed by the caregiver alone the subjective symptom scales are not done (i.e. tiredness, depression, anxiety, and wellbeing are left blank) and the caregiver assesses the remaining symptoms as objectively as possible, i.e. pain is assessed on the basis of a knowledge of pain behaviors, appetite is interpreted as the absence or presence of eating, nausea as the absence or presence of retching or vomiting, and shortness of breath as laboured or accelerated respirations that appears to be causing distress for *the patient*.

When a patient is irreversibly cognitively impaired and cannot participate in doing the ESAS, the caregiver continues to complete the ESAS as outlined above and the Edmonton Comfort Assessment Form (ECAF) may also be used (see ECAF guidelines).

The method in which the ESAS was completed must be indicated in the space provided at the bottom of the ESAS Numerical Scale and the ESAS Graph as follows:

Bottom of ESAS Numerical Scale

Completed by *(check one)*

Patient ☐
Caregiver ☐
Caregiver -assisted ☐

Bottom of ESAS Graph

Completed by ☐☐☐☐☐☐☐ ←insert appropriate letter from key in date column (date indicated at the top of form)

Key:
P = Patient ☐
C = Caregiver ☐
A = Caregiver -assisted ☐

Where to document the ESAS

The ESAS is always done on the ESAS Numerical Scale and the results *later transferred* to the ESAS Graph. Graphing symptom severity directly onto the ESAS Graph without the use of the numerical scale is not a valid use of the ESAS nor a reliable method of symptom assessment (attention to the graphed historical trend may affect the current scores and so undermine one of the main purposes of the ESAS, i.e. to assess the current symptom profile as accurately as possible).

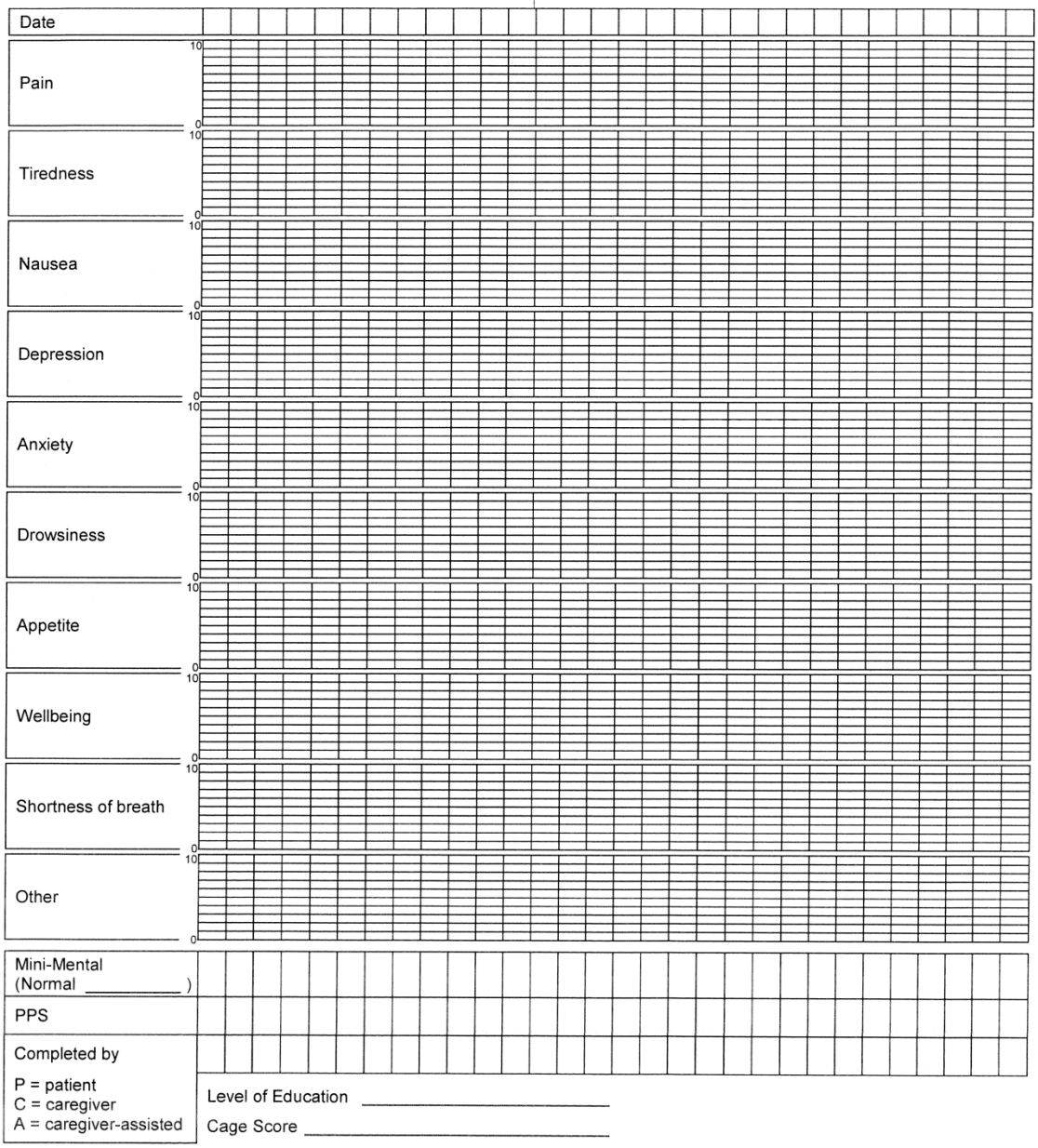
Other Information About the ESAS

The ESAS Graph also contains space to add the patient's Mini-Mental Status Exam score. The "normal" box refers to the normal range for the patient, based on age and education level (see Instructions for MMSE). As well, a space for the Palliative Performance Scale (PPS) is included. The ESAS is available in other languages and also in faces for those patients who do not read.

Capital Health

CARITAS HEALTH GROUP

Edmonton Symptom Assessment System Graph
(ESAS)



CH-0208 May 2001

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CARITAS HEALTH GROUP

Edmonton Symptom Assessment System: Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Patient's Name _____

Date _____ Time _____

Complete by *(check one)*
- ☐ Patient
- ☐ Caregiver
- ☐ Caregiver assisted

BODY DIAGRAM ON REVERSE SIDE

CH-0202 May 2001

Please mark on these pictures where it is you hurt.