Cancer Pain

Effective Date: September, 2018

The recommendations contained in this guideline are a consensus of the Alberta Provincial Palliative Care Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial Palliative Care Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Palliative Care Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

In 2017, the Canadian Cancer Society estimated that approximately 206,200 Canadians would be diagnosed with cancer, and approximately one in four Canadians is expected to die from cancer.[1] Pain is a clinically significant symptom that accompanies malignancy; according to a 2007 meta-analysis, the prevalence of pain was around 59% in cancer patients receiving anticancer treatment, and 64% in patients with metastatic or advanced stage disease.[2] Moreover, it is estimated that around one-third of cancer patients who experience pain do not receive treatment that adequately corresponds to their severity of symptoms.[3]

Pain has been formally defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[4] Experiencing uncontrolled pain has been shown to not only restrict one's capacity to self-care, but also negatively impacts response to disease and quality of life.[5] "Cancer pain" connotes pain experienced by patients with active cancer, as opposed to patients without malignancies, and is multidimensional in nature.[6] To fully assess and manage cancer pain, the physical, psychological, social and spiritual aspects of the patient's pain experience must be considered.

A multidisciplinary, interprofessional approach to pain management is necessary in order to optimize patient outcomes.[5,6] To this end, the purpose of this guideline is to provide clinical practice recommendations to members of multidisciplinary healthcare teams who screen, assess, and manage patients in their clinical practice who may experience pain associated with their cancer treatment.

GUIDELINE QUESTION

What are the recommendations for the screening, assessment and management of pain in adult patients with active cancer and cancer-related pain of any severity?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by CancerControl Alberta's Provincial Supportive Care Council and the Alberta Provincial Palliative Care Tumour Team. Evidence and recommendations were selected and reviewed by a multidisciplinary working group comprised of medical oncologists, palliative care specialists, nurse practitioners, occupational therapists, pharmacists, and a Knowledge Management Specialist from the Guideline Resource Unit. The working group then distributed the draft document via email to 103 healthcare professionals from various disciplines within the province for review and comment. The response rate was 20%. The comments from this review were incorporated into the guideline draft by the working group, and the final guideline was reviewed and endorsed in September 2018. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

SEARCH STRATEGY

The PubMed, EMBASE, and CINAHL Plus databases were searched for relevant guidelines and consensus documents published between January 2011 and January 2017. Resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASCO), British Columbia Cancer Agency (BCCA), CancerCare

Ontario (CCO), European Association for Palliative Care (EAPC), European Society for Medical Oncology (ESMO), Japanese Society of Palliative Medicine (JSPM), National Clinical Effectiveness Committee, National Comprehensive Cancer Network (NCCN), Scottish Intercollegiate Guidelines Network (SIGN), and Spanish Society of Medical Oncology (SEOM). Search terms included *cancer pain* or *oncologic pain,* and the search was limited by publication type (consensus development, systematic review, review, meta-analysis, guideline, or practice guideline) and language (English). The final search yielded 15 publications included in the review. The recommendations in the present guideline have been adapted from the evidence-based clinical guideline Scottish Intercollegiate Guideline Network (SIGN): Control of Pain in Adults With Cancer.[7] Beyond this, the working group updated the guideline by including supplementary supporting research and evidence-based recommendations from current literature.

TARGET POPULATION

The screening, assessment, and management strategies outlined in this guideline apply to adult patients with active cancer and cancer-related pain of any severity. Pain management in cancer survivors may differ from those with active cancer, and is beyond the scope of these guideline recommendations. For information on managing chronic pain in cancer survivors, the ASCO guidelines are a recommended resource. Of note, ASCO defines survivorship as "a person with a history of cancer who is beyond the acute diagnosis and treatment phase", suggesting overlap in the approach to pain between patients who have been cured of cancer, and those who have prolonged survival with cancer.[8]

RECOMMENDATIONS

1. SCREENING AND ASSESSMENT [7]

- The experience of pain is a highly complex phenomenon with physical, behavioural, cognitive, emotional, spiritual and interpersonal aspects. Prior to treatment, a comprehensive multidimensional pain assessment should be completed, taking all such factors into consideration.

- Throughout treatment, pain assessments should be performed regularly. Daily assessments are recommended for inpatients, and for outpatients with unstable pain (if feasible).

- An assessment of the patient's clinical history of pain should include:
    - The site and number of pains
    - Intensity/severity of pains
    - Radiation of pain
    - Timing of pain
    - Quality of pain
    - Aggravating and relieving factors
    - Etiology of pain: categorized as pain caused by cancer, its treatment, a cancer-related debility (e.g. decubitis ulcers) or a cause unrelated to either cancer or treatment
    - Type of pain[4]
        - *Nociceptive*: pain that arises from actual or threatened damage to non-neural tissue, and results from the activation of nociceptors
            - Subtypes: somatic, visceral
        - *Neuropathic*: pain caused by a lesion or disease of the somatosensory nervous system
    - Analgesic drug history, including adverse effects from prior or current analgesia
    - History of addiction to alcohol or drugs

  - Functional effects of pain on the patient, including malnutrition screening
  - Patient beliefs about the meaning of pain, effectiveness of treatments, consequences of drug therapies, and their personalized goals of care[5,9]
  - A personalized pain goal is the patient's goal of desired pain intensity that allows them to "achieve comfort in physical, functional and psychosocial domains."[10]
  - Wide variability exists amongst patients' personalized pain goals, and should be included as part of standard clinical practice to individualize pain management.[10]
  - Presence of clinically significant psychological disorder(s) (e.g. anxiety, depression) or cognitive impairment.

- Patients with cancer pain should have their treatment outcomes monitored regularly using validated pain assessment tools. The Edmonton Symptom Assessment System Revised (ESAS-r) is the primary pain assessment tool used by CancerControl Alberta.[11] It is a multidimensional assessment tool consisting of 10-point numerical scales with which the patient rates the severity of symptoms including pain, fatigue, and perceived well-being. The ESAS-r tool can be found in Appendix A and at https://www.albertahealthservices.ca/info/Page14546.aspx. Established cutpoints for the classification of pain are as follows:[12]
  - Mild pain: 1-3
  - Moderate pain: 4-6
  - Severe pain: 7-10

- The Edmonton Classification System for Cancer Pain (ECS-CP) is a primary classification tool for cancer pain, which is typically conducted as part of pain management (e.g. on admission to a palliative consultation service).[13] It is recommended to use the ECS-CP to guide the optimization of pain control, and subsequently reassess as the patient's condition or pain profile changes. The ECS-CP tool can be found in Appendix B and at https://www.albertahealthservices.ca/info/Page14546.aspx. The ECS-CP is comprised of five discrete features:
  - Mechanism of pain
  - Incident pain
  - Psychological distress
  - Addictive behaviour
  - Cognitive function

- Patient self-report of pain is a key part of the assessment. Self-report pain scales should still be used for patients with cognitive impairment, where feasible. If self-assessment is not possible due to factors such as frailty, cognitive impairment or communication deficits then caregivers, families or health care professionals may act as surrogates. Observational pain rating scales should be used in these situations, taking pain behaviours into consideration.[7] Examples of such behaviours include grimacing, rapid blinking, frowning, negative vocalization, tense posture, change in sleep or appetite, withdrawn/combative behaviour, or increased confusion/agitation.[14]

2. PHARMACOLOGICAL MANAGEMENT

2.1 Principles of Pain Management (WHO Analgesic Ladder)[7]

- The World Health Organization (WHO) Cancer Pain Relief Programme was developed in 1986 to establish a framework for the management of cancer pain. Key points can be summarized as follows:
    - Following clinical assessment, pain should be treated based on the degree of pain that the patient is experiencing using a step-wise approach that follows the WHO analgesic ladder (Figure 1).
    - Analgesics should be prescribed regularly for continuous pain.
    - Medication for breakthrough pain must also be prescribed.
    - Laxatives should be prescribed for the vast majority of patients on opioid analgesics.
    - Oral administration is the preferred route of administration in the setting of chronic cancer-related pain.
    - Adjuvant drugs should be considered at all steps of the analgesic ladder, with drug class chosen based on type of pain.

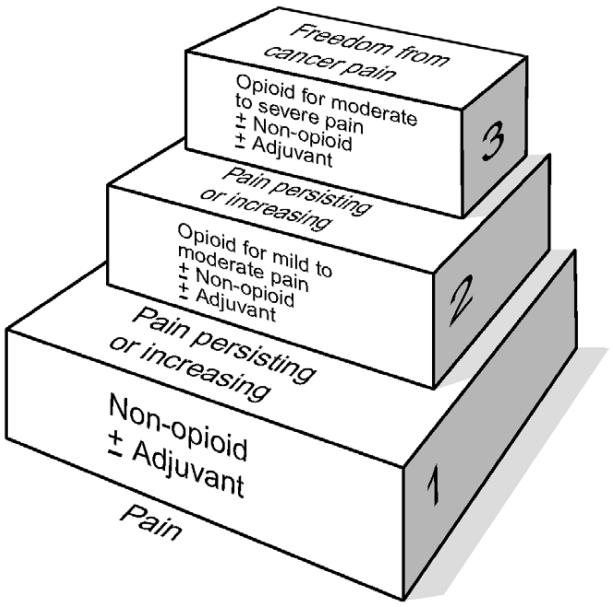

Figure 1: *WHO analgesic ladder*[7]
Acetaminophen and NSAIDs are the analgesics of choice for mild pain (Step 1, ESAS-r score 1-3). Step 2 ("weak") opioids for mild to moderate pain (ESAS-r score 4-6) include codeine, tramadol, and low dose morphine.[10] Step 3 ("strong") opioids for severe pain (ESAS-r score 7-10) include morphine, hydromorphone, and oxycodone.

- The WHO ladder has shown marked efficacy in achieving pain control in the majority of cancer patients; however, its use and design has been subject to debate.[7]
    - Criticism includes questioning the utility of Step 2 (weak) opioids in the treatment of cancer pain, as there is insufficient evidence to support or refute the WHO recommendation that Step 2 opioids (e.g., codeine) are superior to NSAIDs.[7]
    - In the setting of rapidly progressing pain, one option is to omit Step 2 opioids and start directly with low doses of Step 3 opioids instead. In support of this, a recent randomized trial by Bandieri *et al.* found that low-dose morphine reduced pain intensity significantly compared to step 2 opioids, with similar tolerability.[15]

- In patients of advanced age, modifications to pharmacotherapy may be needed due to altered cognitive or organ function. For example, opioid clearance may be decreased in this population, necessitating that these medications be administered at lower doses and titrated with caution. Patients of advanced age may also be at risk for polypharmacy and multiple drug interactions.[16]

- The affordability of medications and each patient's drug coverage should be considered when selecting a medication. To see which medications are covered under Alberta Government-sponsored drug programs, search the Interactive Drug Benefit List.

- "Opioid-naïve" patients are those who have not received chronic opioid analgesics, nor developed tolerance to opioid-derived analgesia. Fentanyl and methadone should be avoided in this patient population.[5,6]

- "Opioid tolerance" is defined as the use of ≥ 60 mg morphine daily, ≥ 30 mg PO oxycodone daily, or ≥8 mg PO hydromorphone daily (or an equianalgesic dose of another opioid) for 1 week or more.[6]

- Hospital admission and/or referral to a pain specialist may be beneficial for patients with acute, severe pain that is refractory to conventional treatment.

2.2 Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Non-opioid medications may be considered at each stage of the WHO analgesic ladder.[7]

- Acetaminophen either regularly or as needed at doses of 325 to 650 mg q4h or 1 g q6h to a daily maximum of 4 g may be trialed for cancer pain. However, if acetaminophen is used chronically, a daily maximum of 3 g should be adopted to reduce the risk of inducing hepatic toxicity. A daily maximum of 2 g is recommended for older adults with hepatic impairment or history of alcohol abuse. Combination opioid-acetaminophen products should be avoided if possible, as their dose titration is limited by the maximum allowable dose of acetaminophen per day.[6]

- NSAIDs should be used with caution in cancer patients due to risk of renal, GI and cardiac toxicities, as well as thrombocytopenia and bleeding disorders.[6] No evidence exists to support superior efficacy or safety between NSAIDs; instead, each patient's cardiovascular and GI risk factors should be considered.[7]
    - To limit the risk of adverse effects, daily maximum doses should not exceed 3200 mg for ibuprofen and 1500 mg for naproxen.[6]
    - Patients at high risk of GI complications should receive prophylaxis with double doses of H2 receptor antagonists, standard doses of proton pump inhibitors (PPIs), or misoprostol.[14,17] Cyclooxygenase-2 (COX-2) inhibitors may also be considered, with or without PPI use.[14,17]
    - "High risk" patients are considered to be those with a history of previous complicated ulcers or three or more risk factors (age ≥ 65 years, high-dose NSAID use, previous uncomplicated ulcer, concurrent ASA use).[18]
    - Adverse effects associated with long-term PPI use include hypomagnesemia, impaired vitamin B12 absorption, *Clostridium difficile* infections, and hip fractures. Therefore, PPI use should only be initiated when necessary, and de-prescribed once no longer indicated.[18]
    - NSAID use should be re-evaluated if the patient's renal function deteriorates or if hypertension develops/worsens.[6]
        - Risk factors for renal toxicities include age ≥60 years, compromised fluid status, diabetes, interstitial nephritis, papillary necrosis, multiple myeloma and concurrent use of other nephrotoxic drugs, or renally excreted chemotherapy.[6]
    - NSAIDs should be discontinued if an ulcer or hemorrhage occurs. Concomitant administration of NSAIDs with aspirin and/or prophylactic or therapeutic anticoagulation should also be avoided.[6] NSAIDs should be avoided in patients with moderate to severe hepatic impairment or active liver disease.
    - Ibuprofen is associated with a lower risk of GI side effects relative to other NSAIDs. COX-2 inhibitors also produce significantly fewer GI symptoms, though these agents demonstrate an increased risk of thrombotic cardiovascular adverse reactions and are contraindicated in

ischemic heart disease, peripheral arterial disease or cerebrovascular disease. Naproxen (in doses ≤1000 mg/day) and ibuprofen (in doses ≤1200 mg/day) appear to be associated with less cardiovascular risk.[14]

2.3 Adjuvant Analgesics

Corticosteroids:

- There is weak evidence supporting the use of corticosteroids in cancer pain. As described in a 2015 Cochrane review, some studies have shown significant but short-lived pain relief with corticosteroids, making them potentially useful especially in patients with short life expectancies.[19]

- Dexamethasone is often the steroid of choice as it has less mineralocorticoid activity than other alternatives.[6]

- A phase 3 randomized, placebo-controlled trial showed that use of dexamethasone 8 mg PO taken one hour before the start of palliative radiotherapy for bone metastases, and then daily for 4 subsequent days after radiotherapy, significantly reduced the incidence of pain flare as compared to placebo.[20]

Bone modifying agents:[7]

- Although the role of bone-modifying agents such as bisphosphonates and denosumab (a RANK-ligand inhibitor) is primarily the prevention of skeletal related events (e.g. fracture, spinal cord compression, need for radiation to bone), clinical trials have established that these agents can also have an analgesic effect with long-term use in patients with metastatic bone pain from a variety of tumours.[6,14]

- Due to differences in patient populations and methods for assessing bone pain, direct comparison of bisphosphonates across studies to determine their relative effectiveness for bone pain is difficult.[6]

Antidepressants and anticonvulsants:[7]

- Most studies regarding antidepressant and anticonvulsant use have been done in non-cancer settings. Specific antidepressants (e.g. duloxetine, venlafaxine, tricyclic antidepressants) and anticonvulsants (e.g. gabapentin, pregabalin) could be considered in patients who have neuropathic pain, with careful monitoring of side effects.

- Pain relief with these agents takes significantly longer when compared to opioids (4-8 days on average); however, analgesia still occurs much earlier than effect on mood.[14]

- Duloxetine and venlafaxine are now accepted as first-line options for neuropathic pain.[21] Specifically, duloxetine has shown evidence in the setting of chemotherapy-induced peripheral neuropathy.[22]
    - An initial dose of duloxetine 30 mg PO daily may be used, and titrated up to 60-120 mg PO daily; venlafaxine may be started at 37.5 mg PO daily and increased to 75-225 mg PO daily.[6] Overall dosing ranges recommended in the literature are 60-120 mg daily for duloxetine, and 150-225 mg daily for venlafaxine extended release.[21]
    - Tricyclic antidepressants (TCAs) are also considered first-line alternatives for neuropathic pain, however their potential adverse effects should be carefully considered when prescribing. Low doses should be used initially, and increased every 3-5 days if tolerated.[6] Adverse effects

associated with TCAs include dry mouth, confusion, sedation, urinary retention and constipation.[5]
    - Tertiary amines (e.g. amitriptyline, imipramine) are more efficacious for pain, however secondary amines (e.g. nortriptyline, desipramine) are better tolerated and have less anticholinergic adverse effects.[6]

- Gabapentin and pregabalin are now accepted as the first-line anticonvulsants used for neuropathic pain.[21]
    - Recommended dosing for gabapentin starts at 100-300 mg at bedtime, and may be increased up to 900-3600 mg daily in divided doses, 2-3 times per day.[6] Of note, gabapentin's bioavailability is inversely proportional to dose due to saturable absorption. Pregabalin is absorbed more efficiently and should be started at 150 mg daily, in divided doses, and increased as necessary to a maximum of 600 mg in divided doses, 2-3 times per day.[6]
    - Adverse effects of these agents include sedation, cognitive disturbances, peripheral edema, ataxia, and depression. When discontinued, their doses should be tapered over 1-2 weeks.[5]

- Carbamazepine, valproic acid and phenytoin are no longer recommended as first line for the treatment of neuropathic pain.[21]

Ketamine:[7]

- Ketamine is a controversial agent that could be considered in select patients when traditional agents have failed to provide adequate relief. In one randomized, placebo-controlled study, subcutaneous ketamine demonstrated no clinical benefit as an adjuvant to opioids and standard analgesics in cancer pain. Other studies have suggested ketamine can improve pain control in those poorly responsive to opioid therapy.[23-25] Adverse effects associated with its use include sedation, sensory illusions, dissociative feelings, and the possible induction of mood disorders; neurotoxicity via intrathecal administration has been seen as well. The use of ketamine as an analgesic should be supervised by a specialist in pain relief or palliative medicine.

Topical analgesia:[7]

- A small evidence base suggests that topical opioids may be an effective local analgesic when applied to inflamed tissues, especially oral mucositis and decubitus ulcers. However, there is insufficient evidence to provide a recommendation regarding the use of topical opioids in cancer pain.

- There is weak evidence to support the use of lidocaine and/or capsaicin as second-line treatment for neuropathic pain.[21]

Cannabinoids:

- Sativex®, a nabiximol oral mucosal spray containing 2.7 mg of tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) per actuation, is the only cannabinoid currently indicated in the setting of opioid-refractory cancer pain. Its use has yielded mixed results in recent studies.[26-28]

- Cannabinoids should be used with caution in patients taking CYP 3A4 inducers and inhibitors, as these agents have been shown to affect the metabolism of THC and CBD.[29] CYP 2C9 and 2C19 have also been implicated in the metabolism of THC and CBD respectively, and both THC and CBD have been shown to inhibit CYP 3A4, amongst other CYP enzymes.[30-32] Adverse effects associated with

THC use include mental clouding, ataxia, dizziness, disorientation, impaired memory, xerostomia, and blurred vision.

- Cannabinoids should only be considered as a last-line option for patients with cancer pain that is refractory to opioids, non-opioids and adjuvant analgesics.[7]

2.4 Opioid Drugs

Mild to moderate pain:[7]

- For mild to moderate pain, a step 2 opioid may be given with or without a non-opioid analgesic.

- **Codeine** is considered to be a step 2 opioid, with a maximum analgesic effect achieved at 240 mg/day.[7] However, its utility is limited, as it is metabolized by CYP 2D6 into morphine in order to produce analgesia. CYP 2D6 exhibits genetic polymorphisms between individuals and ethnic groups; thus, patients with altered cytochrome functioning could receive suboptimal pain relief, or experience toxicity with its use.[7,16]

- Limited evidence from several small studies indicates that **tramadol** could be considered as a step 2 analgesic. It is a weak mu-opioid agonist with some serotonin and norepinephrine reuptake inhibition.[6] The maximum dose of tramadol should not exceed 400 mg PO per day in order to minimize potential seizure risk. Dose reduction is recommended in the elderly and those with hepatic and/or renal dysfunction.[6]

- Low-dose **morphine** is another option in this setting, as it has been shown to reduce pain intensity significantly compared to step 2 opioids, with similar tolerability.[15]

Moderate to severe pain:[7]

- For moderate to severe pain, **oral morphine, hydromorphone or oxycodone** are recommended as first-line options for therapy.

- Oral **morphine** is preferred over parenteral or rectal administration due to the likelihood that patients will use this medication chronically. Although oral morphine has wide interpatient variability in its bioavailability, pain control can usually be achieved with individualized dose titration.[7]
    - Immediate-release formulations have an approximate onset and duration of action of 20 minutes and 4 hours respectively. Steady plasma concentration of this drug is reached within 12-15 hours, at which time the effect of dose changes may be assessed. In practice, dose adjustments are usually made every 24 hours unless the pain is more severe, in which case earlier adjustments may be made.[7]
    - Modified-release formulations have a slower onset and later peak effect; thus, they are harder to titrate in acute situations and best reserved for situations where stable background pain control has been achieved.[7]

- Similar to morphine, **hydromorphone** has wide interpatient variability in its bioavailability.[7] It is available as immediate- and sustained-release oral formulations, oral liquid, suppositories and SC/IM/IV injectables.[33]

- **Oxycodone** has more predictable bioavailability than morphine and is available as immediate- and controlled-release oral formulations.[33] Controlled-release formulations have a biphasic pharmacokinetic release profile, allowing both an onset of analgesia within 1 hour and a duration of analgesic effect which persists for 12 hours.[7] Injectable forms of oxycodone can be compounded, but it should be noted that few pharmacies are equipped to do so.

- **Transdermal buprenorphine** is a partial mu-agonist with limited evidence in cancer-related pain.[34] It may exhibit a ceiling effect in terms of analgesic efficacy, although this has not been demonstrated in clinical studies. Initial dose should be based on manufacturer recommendations and increased to effect and tolerability. Patches are changed weekly and doses should not exceed 20 mcg/hour due to risk of QT prolongation. Because of its partial agonist activity, buprenorphine may precipitate withdrawal symptoms if it displaces pure agonists from their receptor sites. As such, patients must be tapered to no more than 30 mg oral morphine equivalents per day before initiation.[6,14]

- **Tapentadol** is a mu-opioid agonist with norepinephrine reuptake inhibition. Studies have shown it to be no more or less effective than oxycodone or morphine in cancer pain, and to have a similar side-effect profile apart from possibly better GI tolerability.[14]

- Transdermal **fentanyl** patches may be a convenient option in patients with severe but stable pain, especially for those with swallowing difficulties, intractable nausea and vomiting or poor compliance. It also appears to produce less constipation than other opioids.[6,14] Patches are changed every 72 hours. As patches can vary in their appearance, and to avoid the risk of patient confusion, patients should not be changed from one formulation or make to another without adequate patient counseling.[7] Fentanyl should not be started in opioid-naïve patients, and specialist/pharmacist consultations may be required to assist with management of this medication.

- **Methadone** has a long and unpredictable half-life, and should only be initiated within specialist settings with careful monitoring.[7] Specific information on using methadone for cancer pain is beyond the scope of this guideline.

Administration of opioids:[7]

- The oral route should be used for administration of opioids, if practical and feasible.

- Transdermal, subcutaneous or intravenous routes may be necessary if patients are unable to take opioids orally. Subcutaneous administration of opioids is simpler and equally effective as continuous intravenous infusion, and should be considered for patients unable to take opioids orally.[35]

- Transdermal opioid systems are an alternative for patients with stable pain.

Scheduling of opioid administration:[7]

- Immediate-release opioids are normally administered every 4 hours around-the-clock. A double dose may occasionally be given at bedtime in an effort to allow the patient to sleep uninterrupted through the night (overnight dose(s) would be omitted).[36]

- Longer-acting opioid formulations should be considered for patients with stable daily opioid requirements.

- Breakthrough opioids may be given as often as every 1 hour.

- Dosing intervals may be extended in patients with compromised organ function (e.g. q6h around-the-clock and q2h breakthrough dosing). Long-acting formulations should also be avoided in this population, due to unpredictable pharmacokinetics and the potential for drug to accumulate.

- In terms of pain control, studies have shown no significant difference between four hourly dosing of oral immediate-release preparations and once daily dosing (in the case of morphine) or 12 hourly dosing of modified-release formulations.

Management of breakthrough pain:[7]

- Breakthrough pain is defined as a transient flare of pain of moderate or severe intensity, arising on a background of controlled pain. Patients with moderate or severe breakthrough pain should receive breakthrough analgesia.

- Breakthrough analgesics should be dosed as approximately 10% of the total daily dose and given as often as every one hour if needed. For ease of calculation, half of the q4h dose may be used (i.e. 1/12 of the daily dose). If more than four doses of breakthrough analgesic are used per day on a consistent basis, the patient's baseline pain management should be reassessed. *Note:* breakthrough doses may also be taken preventatively ~30 minutes prior to activities which are known to produce patient discomfort (e.g. bathing, car rides, imaging studies).

- Breakthrough pain is distinct from pain due to "end of dose failure" of the regular, around-the-clock analgesia. End of dose failure occurs at a similar time each day, usually before the next dose of regular analgesia, and an increase in the around-the-clock dose should manage this issue.

Opioid risk mitigation:

- Recognizing that two thirds of cancer patients are surviving ≥ 5 years after diagnosis, clinicians should assess the potential risks and benefits of long-term use of opioids. Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction. A universal precautions approach is recommended to minimize abuse, addiction, and adverse consequences of opioid use such as opioid-related deaths. Patients and family members should be educated regarding the risks and benefits of long-term opioid therapy and the safe storage, use, and disposal of controlled substances. If opioids are no longer warranted, clinicians should taper the dose to avoid abstinence syndrome.[8]

- A recent study observed that patients who initiated therapy with extended-release opioids were at higher risk for unintentional overdose than those who initiated therapy with immediate-release opioids for chronic pain.[37,38] Furthermore, the Centers for Disease Control and Prevention suggests that patients who receive ≥90 morphine milligram equivalents (MMEs) per day are at a higher risk of overdose.[37]

- Strategies to mitigate opioid-associated risks include regularly assessing each patients' risk factors for misuse, and their therapeutic responses to therapy. Patients should also be educated on the safe use, storage, and disposal of opioids when therapy is initiated.[6]

- Factors associated with opioid misuse/abuse in non-cancer patients include male gender, age <65 years, history of opioid misuse, depression, family history of substance abuse, smoking, history of

incarceration, and post-traumatic stress disorder. Screening tools, such as the CAGE questionnaire (Appendix C) may be used to assess patient risk of opioid misuse.[39]

- If patients with moderate to high risk of misuse are prescribed opioids, adherence monitoring should continue for the duration of treatment.

- Adherence monitoring measures may include pill counts, education, use of a controlled substance agreement, shorter dispensing intervals, and review of prescription data from the Pharmaceutical Information Network or other prescription drug monitoring programs.

Titrating opioids:[7]

- Prior to dose titration, an individual assessment of pain control, opioid-induced adverse effects, and current opioid usage (including breakthrough doses) in the previous 24 hours must be made. Immediate release formulations allow for more rapid pain control and dose titration.

- For patients with incident pain (i.e. clinically significant flares of pain on a background of no or well-controlled pain, often precipitated by movement), background analgesia and pre-emptive analgesia for movement-related pain, and non-opioid and adjuvant analgesics, should all be maximized. Other modalities such as radiotherapy or anesthetic nerve blocks may be considered.
    - In general, note that if all analgesia for incident pain is incorporated into the new regular opioid dose, these patients could be rendered opioid toxic.

General principles of opioid conversion:[7]

Conversion between strong opioids (opioid rotation)

- Opioid rotation is the practice of changing from one opioid to another, in an attempt to improve the balance between efficacy and side effects. Although all opioids have the same spectrum of side effects, their intensities can vary between individuals.
- Patients prescribed step 3 opioids who have inadequate pain control and/or persistent intolerable side effects should receive a thorough, holistic reassessment of pain and pain management. For patients in whom pain is not controlled despite optimization of dose, or where opioid-related side effects preclude further upward titration, opioid rotation should be considered.

Conversion ratios

- Different references provide different conversion ratios, however, the information in Table 1 represents the conversion ratios most often used by our practitioners.
- Dose conversion ratios between opioids are commonly derived from single dose studies and rarely take into account active metabolites; thus, tables of dose conversion ratios should be used only as an initial approximate guide. Since variability does exist, patients should be monitored closely and doses tailored to the individual based on efficacy and adverse effects/toxicity.

Table 1: Opioid equianalgesic dose conversion (equivalence to 10mg of morphine PO)

Drug	PO dose	PO:SC ratio	SC dose
Morphine	10 mg	2:1	5 mg
Codeine	100 mg	2:1	50 mg
Tramadol	100mg	-	-
Oxycodone	5-7.5 mg	2:1[7]	-
Hydromorphone	2 mg	2:1	1 mg
Methadone	1 mg	-	-
Fentanyl CSC infusion	-	-	0.05 mg
Fentanyl patch	Use chart supplied by manufacturer		

Adapted from Table 5-4 in the Pallium Palliative Pocketbook, 2016 [16]

Conversion between oral and parenteral routes

- Current practice for converting opioid doses between different routes of administration is based on pharmacokinetic data for individual opioids, and on expert opinion and experience.
- In practice, a PO:IV conversion ratio of 2:1 for morphine and hydromorphone is used. A PO:SC conversion ratio of 2:1 is used for morphine, codeine, oxycodone and hydromorphone, as above (Table 1).

Process of opioid conversion (as per the National Comprehensive Cancer Network)[6]

- First, determine the amount of current opioid(s) that was taken in the last 24 hours.
- Then, calculate the equianalgesic dose of the new opioid, using the appropriate dose conversion ratios (see Table 1).
    - If the patient's pain was effectively controlled, reduce the dose by 25-50% to account for incomplete cross-tolerance between opioids. Then, titrate to effect during the first 24 hours of using the new opioid or as soon as is feasible.
    - If the patient's pain was not controlled, they may start with 100% or 125% of the dose.
    - *Example - conversion of PO morphine to SC hydromorphone:*
        - If a patient were taking morphine 20 mg PO every 4 hours, he or she would have used 120 mg of morphine PO over 24 hours. As per Table 1, 10 mg of PO morphine is equivalent to 2 mg PO hydromorphone. Thus, 120 mg/day of PO morphine is equivalent to 24 mg/day of PO hydromorphone, or 4 mg PO hydromorphone every 4 hours. Using our conversion ratio of 2:1 for PO:SC/IV, this is equivalent to hydromorphone 2 mg SC q4h.
        - If the patient's pain is adequately controlled, reduce his/her dose by 25-50% to get a new dose of 1-1.5 mg hydromorphone SC q4h. If their pain control is inadequate, start with 100% to 125% of the new dose: hydromorphone 2-2.5 mg SC q4h.
- **Methadone:** In studies, conversions to methadone were carried out within specialist palliative care inpatient units with careful monitoring. Methadone initiation in other settings without specialist advice is not recommended.
- **Transdermal fentanyl:** Each transdermal fentanyl patch is applied for 72 hours. Due to the formation of a subcutaneous depot of drug beneath the skin, there is a lag time of approximately 12 hours between application of patch and full effect. As such, the previous around the clock opioid should be continued for approximately 12 hours after the fentanyl patch is initiated. Likewise, depletion of the subcutaneous depot takes around 12 hours and new opioids should not be initiated until 12 hours after removal of the final fentanyl patch. In this scenario, pain should be managed with breakthrough doses in the interim. Due to the long time to steady-state drug levels with these products, it is recommended that at least 3 days should be allowed between dose titrations.

Opioid-induced adverse effects:

- With the exception of constipation, most opioid-induced adverse effects are transient and improve over time. Non-pharmacologic and non-opioid pain interventions should be maximized to allow for reduced dosing of opioids, and opioid rotation may be considered if these adverse effects persist.[6]

- Many opioid-naïve patients will develop **nausea and/or vomiting** when started on opioids. Tolerance in most patients usually occurs within 5-10 days. Patients starting an opioid for moderate to severe pain should have access to a prophylactic antiemetic to be taken if needed.[7]
    - Anti-dopaminergic antiemetics are preferred in practice. Metoclopramide, haloperidol and prochlorperazine may be considered as both prophylactic agents and treatment. Other anti-nausea options include serotonin antagonists (ondansetron, granisetron) or olanzapine; however, there is no direct evidence to support their use in opioid-induced nausea.[6] Consultation with the Palliative Care program is recommended to discuss the use of any non-evidenced options for the management of opioid-induced nausea.
    - If nausea persists over one week, the etiology should be reassessed and opioid rotation considered.[6]

- **Constipation** is a persistent adverse effect of opioids as little or no tolerance develops over time. The optimal laxative in this setting is unknown. Stimulant laxatives (e.g. senna, typically at an initial dose of 2 tablets at bedtime to a maximum of eight tablets (34.4 mg) per day) and osmotic laxatives (e.g. polyethylene glycol 3350, 17 grams once or twice daily) have been suggested as prophylactic measures, in addition to exercise and maintenance of fluids and dietary fiber intake. Conversely, supplemental medicinal fiber (e.g. psyllium) may worsen constipation.[6]
    - Methylnaltrexone is the only agent that has been shown to reverse opioid-induced constipation in palliative care patients. Its use should be reserved for patients who are resistant to other laxatives.[14]
    - Naloxegol is another peripherally acting opioid antagonist indicated for the reversal of opioid-induced constipation, however it has not yet been studied in cancer patients.[6] Studies of naloxone combined with sustained-release oxycodone suggest reduction in constipation without adverse effect on analgesia.[40]
    - Docusate has been shown to confer no additional benefit over placebo with regards to stool frequency or softening, nor improvement of constipation symptoms.[41]

- Opioid-induced **pruritus** may be transient or persistent. Treatment options for persistent pruritus include ondansetron and first-generation antihistamines. Nalbuphine and naloxone have also been suggested, but their feasibility is limited by their non-oral formulation and the risk of reversing analgesia. If symptomatic management fails, assess for other causes; if rash/hives are seen, consider true allergy.[6]

- **Neurotoxic** adverse effects of opioids include delirium, hallucinations, vivid dreams, myoclonus, sedation and hyperalgesia.[6,14] Reducing opioid doses, trialing an opioid rotation, increasing hydration, and/or using non-opioid analgesics to allow for reduced opioid dosing should be considered.
    - Delirium: Other potential causes, including infection, electrolyte disturbances and disease progression, should be investigated if symptoms of delirium arise. Neuroleptic drugs, including haloperidol, olanzapine or risperidone, may be considered to manage symptoms of delirium.[6]
    - One randomized trial from 2016 demonstrated that patients who received risperidone or haloperidol had higher delirium symptom scores and incidences of extrapyramidal effects as compared to placebo. The authors of this study concluded that supportive strategies and

reversing delirium precipitants were superior options than antipsychotic agents for managing symptoms of delirium.[42]
    - Sedation: If sedation persists for ≥2-3 days, other causes should be assessed (e.g. CNS pathology, dehydration, infection, hypercalcemia).[6] Limited evidence suggests that methylphenidate may counteract opioid-induced sedation.[43]
    - No recommendations are available to manage myoclonus or hyperalgesia at this time, beyond opioid dose reduction and/or rotation.[14]
- **Respiratory depression**: Hypercarbia precedes hypoxia, and patients with limited cardiopulmonary reserve are more susceptible to this effect. Management involves careful patient monitoring and withholding opioids until resolution of symptoms so long as oxygen saturation and respiratory rate are adequate. In more acute situations, cautious use of naloxone may be considered.[6]

- **Endocrinopathies** (hypogonadism/hyperprolactinemia) and sleep-disordered breathing are two other possible adverse effects of long-term opioid use.[39]

2.5 Management of Cancer Pain in Patients with Renal Impairment

- Dehydration and renal impairment increase the potential for opioid toxicity. In this setting, the renal clearance of codeine, morphine and oxycodone and their metabolites is reduced, while evidence for the safety of hydromorphone is inconsistent. Caution and dose reductions are required with each medication's use.[5,7,14] As per the manufacturer, the maximum daily dose of tramadol in severe renal impairment (CrCl <30 mL/min) is 200 mg per day, and extended-release formulations are not recommended.[44] Tapentadol use in severe renal impairment (CrCl <30 mL/min) is not recommended.[45] Early signs of opioid toxicity include subtle agitation, vivid dreams, pseudo-hallucinations (usually at the periphery of the visual field) and myoclonus.[7]

- In patients with poor or deteriorating kidney function, the following are of considerable importance to prevent or manage toxicity:[7]
    - Choice of opioid
    - Consideration of dose reduction and/or increase in dosage interval
    - Change from modified release to an immediate-release oral formulation
    - Frequent clinical monitoring and review

- Buprenorphine and fentanyl are considered safe in the setting of chronic kidney disease stages 4 or 5 (eGFR <30 mL/min/1.73 m^2). Methadone has also been shown to be relatively safe in renal failure; however, only physicians with proper experience can initiate this treatment. Specialist palliative care advice should be sought for the appropriate choice, dosage and route of opioid in patients with reduced kidney function.[5,7]

- In patients undergoing renal dialysis, opioid use is further complicated by the removal of some opioids and their active metabolites; supplemental doses of short acting analgesics may be required during/after dialysis sessions to maintain pain control.[7]

3. NON-PHARMACOLOGICAL MANAGEMENT

Radiotherapy:

- For information on radiotherapy to relieve pain in patients with bone metastases, please refer to the AHS Palliative Radiotherapy guideline.

Vertebroplasty and kyphoplasty:

- Cancer accompanied by osteolytic involvement of the spine may cause vertebral height loss, and is associated with significant mobility loss, morbidity and mortality. Vertebroplasty and kyphoplasty may provide sustained pain relief in patients with metastatic bone pain. Kyphoplasty has also been shown to improve cancer pain in randomized controlled trials.[46]
    - Percutaneous cementoplasty involves the injection of acrylic bone cement into malignant bone cavities in order to relieve pain, stabilize bone, or both.[7]
    - Percutaneous vertebroplasty involves injecting acrylic bone cement into the vertebral body to relieve pain, stabilize fractured vertebrae, and/or restore vertebral height.[7]
    - Balloon kyphoplasty involves the use of an inflatable bone tamp to restore the vertebral body to its original height, and create a cavity to be filled with bone cement.[7]

- Patients with bone pain from malignant vertebral collapse proving difficult to control by pharmacological means should be referred for consideration of vertebroplasty where this technique is available.

Anaesthetic interventions:[7]

- Interventions such as celiac plexus block and neuraxial opioids should be considered to improve pain control and quality of life in patients with difficult to control cancer pain.

- Patients with difficult-to-control pain despite optimal management of systemic/oral therapy may benefit from assessment by an anesthetist with expertise in pain medicine, for consideration of an appropriate intervention. Patients most likely to benefit include those with significant locally advanced disease, neuropathic pain or marked movement-related pain.

Surgical interventions:

- Surgical procedures including prophylactic vertebral stabilization or stabilization of weight-bearing long bones may attenuate pain due to bone metastases and improve clinical outcomes.[5,47,48] Consultation with an orthopedic specialist may be warranted for patients with impending pathologic fractures to determine optimal strategies for surgical pain management.

Complementary therapies:[7]

- Complementary therapies, including massage, aromatherapy, music therapy, acupuncture, reflexology, reiki, hypnotherapy, and transcutaneous electrical nerve stimulation (TENS) are increasing in popularity but lack supporting evidence in reducing long-term cancer pain.

4. SUPPORTIVE CARE

4.1 Multidisciplinary Approaches to Pain Management[6,7]

- Effective multidisciplinary teamwork is required to achieve adequate cancer pain management. Qualitative literature has identified three main issues of concern to patients with cancer pain: communication (between patients/carers and healthcare professionals, amongst healthcare professionals, and amongst patients/carers), spirituality and coming to terms with illness, and the impact of cancer pain on relationships.

- Patients value professionals who adopt a holistic approach to care, encompassing the spiritual, psychological and emotional impact of pain.

- Physical modalities of care to consider include: walking supports, patient's bed and bath arrangements, nutritional interventions related to appetite (e.g. ability to prepare meals independently, ability to chew/swallow related to pain), therapeutic/conditioning exercises, activity pacing, and determining the necessity for immobilization or support to painful areas (e.g. splint, sling, back brace, cushioning).

- Cognitive modalities to consider include mindfulness-based stress reduction, distraction training, relaxation training, active coping training, graded task assignments, patient's abilities with medication management and understanding of treatment schedule/dosing, caregiver support and education needs, and the patient's ability to report their status and participate in assessment of pain.

4.2 Psychosocial Care[7]

- Psychological factors can have a profound influence on the perception of pain and the patient's behavioural and emotional response.

- Patient beliefs concerning pain (e.g. perceived lack of control, concerns over addiction/disease progression) should be assessed and discussed as part of comprehensive, biopsychosocial cancer pain assessment.

- Comprehensive cancer pain assessment should include routine screening for psychological distress, and screening for psychological distress should be carried out using a validated tool.

- Cognitive behaviour therapy should be considered as part of a comprehensive treatment program for those with cancer-related pain, and resulting distress and disability.

- Patients should receive education about the range of pain control interventions available to them.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
AE	Adverse effect
ASA	Acetylsalicylic acid
ASCO	American Society of Clinical Oncology
BID	Twice a day
CBD	Cannabidiol
CNS	Central nervous system
COX	Cyclooxygenase-2
ECS-CP	Edmonton Classification System for Cancer Pain
ESAS-r	Edmonton Symptom Assessment Scale Revised
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
MME	Morphine milligram equivalents
NSAID	Non-steroidal anti-inflammatory drug
PO	By mouth
PPI	Proton pump inhibitor
PRN	As needed
SC	Subcutaneous
TCA	Tricyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
THC	Tetrahydrocannabinol
WHO	World Health Organization

DISSEMINATION

- Present the guideline at relevant local and provincial Tumour Team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Palliative Care Provincial Meeting in 2020. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

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APPENDIX A: Edmonton Symptom Assessment System Revised

The ESAS-r and accompanying materials are available at: http://palliative.org/tools.html

Alberta Health Services Covenant Health

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Patient's Name _____

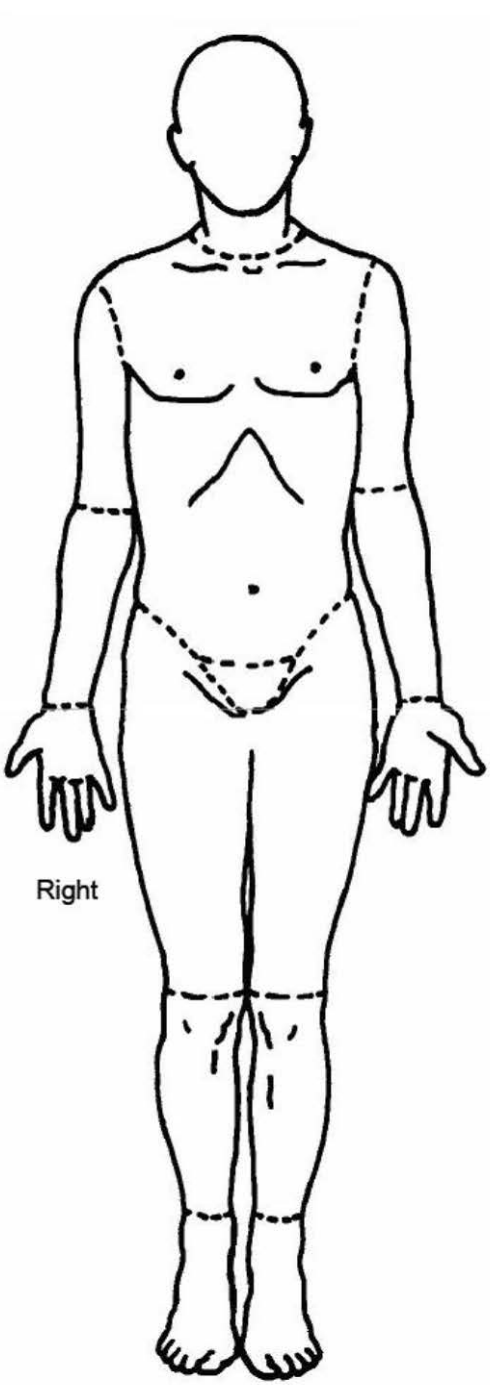
Date _____ Time _____

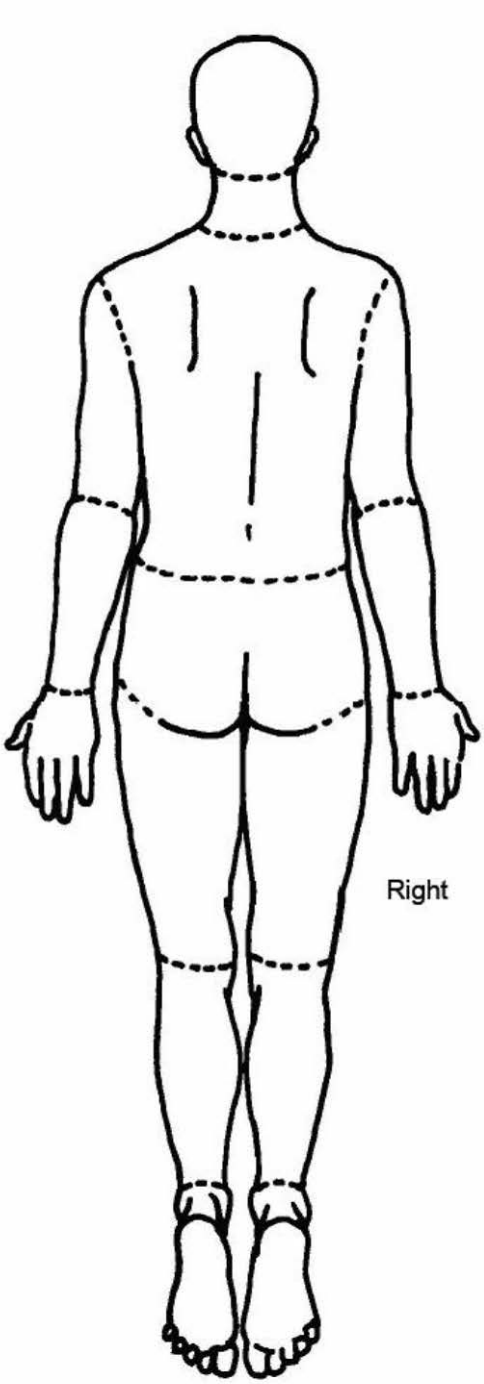
Completed by (check one):
- ☐ Patient
- ☐ Family caregiver
- ☐ Health care professional caregiver
- ☐ Caregiver-assisted

BODY DIAGRAM ON REVERSE SIDE

ESAS-r
Revised: November 2010

Please mark on these pictures where it is that you hurt:





APPENDIX B: Edmonton Classification System for Cancer Pain (ECS-CP)

The ECS-CP and accompanying materials are available at: http://palliative.org/tools.html

Edmonton Classification System for Cancer Pain

Patient Name: _____

Patient ID No: _____

For each of the following features, circle the response that is most appropriate, based on your clinical assessment of the patient.

1. Mechanism of Pain

No No pain syndrome
Nc Any nociceptive combination of visceral and/or bone or soft tissue pain
Ne Neuropathic pain syndrome with or without any combination of nociceptive pain
Nx Insufficient information to classify

2. Incident Pain

Io No incident pain
Ii Incident pain present
Ix Insufficient information to classify

3. **Psychological Distress**

Po No psychological distress
Pp Psychological distress present
Px Insufficient information to classify

4. **Addictive Behavior**

Ao No addictive behavior
Aa Addictive behavior present
Ax Insufficient information to classify

5. Cognitive Function

Co No impairment. Patient able to provide accurate present and past pain history unimpaired
Ci Partial impairment. Sufficient impairment to affect patient's ability to provide accurate present and/or past pain history
Cu Total impairment. Patient unresponsive, delirious or demented to the stage of being unable to provide any present and past pain history
Cx Insufficient information to classify.

ECS-CP profile: N__ I__ P__ A__ C__ ***(combination of the five responses, one for each category)***

Assessed by: _____ **Date:** _____

APPENDIX C: CAGE Questionnaire

The CAGE Questionnaire accompanying materials are available at: http://palliative.org/tools.html

The CAGE Questionnaire

CAGE Assessment:

1.	Have you ever felt you should cut down on your drinking?	Yes	No
2.	Have people annoyed you by criticizing your drinking?	Yes	No
3.	Have you ever felt bad or guilty about your drinking?	Yes	No
4.	Have you ever had a drink first thing in the morning or a drink to get rid of a hangover (eye-opener)?	Yes	No

Please specify: -

_____

_____

_____

_____

Two or more "yes" responses indicate a positive CAGE

(2/4 = a positive CAGE) _____ **/ 4 (+ or -)**
(circle one)

Initial: _____