Cancer Care Ontario's
Symptom Management Guides-to-Practice:
Pain

Preamble

Ontario Cancer Symptom Management Collaborative

An initiative of Cancer Care Ontario, the Ontario Cancer Symptom Management Collaborative (OCSMC) was undertaken as a joint initiative of the Palliative Care, Psychosocial Oncology and Nursing Oncology Programs. The overall goal of the OCSMC is to promote a model of care enabling earlier identification, communication and documentation of symptoms, optimal symptom management and coordinated palliative care.

The OCSMC employs common assessment and care management tools, including the Edmonton Symptom Assessment System (ESAS) screening tool to allow patients to routinely report on any symptoms they are experiencing. Symptom Management Guides-to-Practice were developed to assist health care professionals in the assessment and appropriate management of a patient's cancer-related symptoms. In addition to the symptom specific Guides-to-Practice, quick-reference Pocket Guides and Algorithms were created. Additionally, for a comprehensive management plan for patients with advanced disease, please refer to the Palliative Care Collaborative Care Plans.

Objective

The objective of this initiative was to produce Guides-to-Practice for management of patients with cancer-related symptoms. These documents are clinical tools designed to assist health care practitioners in providing appropriate patient care and are not intended to serve as standards of care.

Target Population

The target population consists of adult patients who require symptom management related to cancer. It is outside the scope of these Guides-to-Practice to address in detail the management of patients experiencing acute adverse effects secondary to systemic or radiation therapy. Please visit the Program in Evidence-Based Care for guidelines related to these topics.

Target Users

The Guides-to-Practice will be of interest to health professionals who provide care to patients with cancer-related symptom management needs at various stages of the disease pathway.

Methodology

The Guides-to-Practice were developed by the interdisciplinary Symptom Management Group (SMG) which included regional representation from across the province (refer to Post-amble for details). As an alternative to de novo development, the Guides-to-Practice were developed using the ADAPTE guideline adaptation approach that includes identifying existing guidelines, appraising their quality, selecting recommendations for inclusion and obtaining expert feedback (refer to Appendix A and B for details).

Table of Contents

Considerations

The [Scottish Intercollegiate Guidelines Network Sign 106 Control of Cancer Pain in Adults with Cancer: A National Clinical Guideline](#) (1) was used as the basis for the development of this Guide.

Key recommendations are highlighted in shaded boxes. The source documents for each recommendation are denoted according to the symbols (Table 1). For example, if a recommendation is derived verbatim from the SIGN guideline, it is indicated by the symbol SIGN 106. Recommendations that are derived from the SIGN guideline but have been modified to more accurately reflect practice and standards of care in Ontario are designated as SIGN 106 Modified.

While some references to specific articles are provided, this Guide is not intended to be a comprehensive overview of pain management; for a more in depth review the reader is encouraged to seek out the original guideline. For a quick reference tool on pain management please refer to the [Pain Pocket Guide](#) and [Algorithm](#). For a comprehensive management plan for patients with advanced disease, please refer to the [Cancer Care Ontario Collaborative Care Plans.](#)

Grades of Recommendation

The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation. For details regarding the levels of evidence please refer to the original Sign 106 guideline.

Table 1. Symbol Legend

Symbol	Definition
A.	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B.	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++or 1+
C.	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D.	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
☑	Recommended best practice based on the clinical experience.
Sign 106	Verbatim extract from the Sign 106 guideline (1) are indicated by this symbol.
Sign 106 *Modified*	Sections extracted from the Sign 106 guideline (1) but modified to better reflect the Ontario context are indicated by this symbol.
PAIN SMG	Sections written by the Pain Symptom Management Guides working group.

Introduction

Pain associated with cancer increases with progression of the disease. Approximately one third of patients with cancer report pain at the time of diagnosis, rising to three quarters in the advanced stages of cancer (2). Attempts to control pain and hence improve quality of life and reduce unnecessary suffering have been overshadowed in the past by attempts to cure the underlying disease (3). Cancer pain has many dimensions including psychological, physical, social and spiritual which must be addressed in order to improve quality of life.

In many cases an interprofessional approach is required to attain the optimum outcome for the patient. The professionals involved may include, among others: physicians, anaesthetists, surgeons, family physicians, physiotherapists, interventional radiologists, occupational therapists, oncologists, nurses, pharmacists, clinical psychologists, palliative care specialists, pain specialists and spiritual care advisors.

For the purpose of this Guide-to-Practice, pain is described as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (4). Furthermore, breakthrough pain in this Guide-to-Practice is understood as pain of moderate or severe intensity arising on a background of controlled chronic pain. Breakthrough pain may be described as spontaneous (unexpected) or incident (expected or predictable) (5).

Cancer Pain Assessment

Assessment of Pain

Research suggests that a multidimensional approach to pain assessment requires linkages between physically expressed pain, psychological state, social and spiritual issues to capture a person's reaction to his/her pain experience (6).

A comprehensive assessment of pain should consider the following domains:
- physical effects/manifestations of pain
- functional effects (interference with activities of daily living)
- spiritual aspects
- psychosocial factors (level of anxiety, mood, cultural influences, fears, effects on interpersonal relationships, factors affecting pain tolerance (7,8))

Why Assess Pain?

> ☑ **Prior to treatment an accurate assessment should be done to determine the cause(s), type(s) and severity of pain and its impact on the patient.**

Uncontrolled pain limits a person's ability to perform self care, affects his/her response to illness and reduces his/her quality of life (9). Accurate assessment and diagnosis of the etiology of the pain, type of pain, its severity, and its effect on the person are essential to plan appropriate interventions or treatments, and are an integral part of overall clinical assessment (10-15). Pain in cancer patients

cannot always be attributed to the underlying cancer. For instance, patients may have other chronic illnesses such as arthritis that may also produce pain. However the sudden appearance of new pain may signal new areas of disease or disease recurrence.

Who Should Assess Pain?

Sign 106 Modified

A. The patient should be the prime assessor of his or her pain.

Sign 106

Health professionals have been shown to underestimate the level of pain a patient is experiencing, and this discrepancy between estimations widens as the pain increases in severity (16,17). Family members may tend to overestimate pain in their relatives (18). The patient, if competent and able to communicate, is the most reliable assessor of pain and should, where possible, be the prime source of information about his or her pain (19).

Due to frailty, cognitive impairment or communication deficits not all patients are able to relate the story of their pain. Completion of pain scoring tools may not be possible. In these cases families or health professionals may act as a surrogate (16).

How should pain be assessed?

Diagnosis of the cause of pain and its functional and psychosocial impact is achieved by a full assessment (history, physical examination, investigations and standardized assessment tools). The OPQRSTUV Acronym (Table 2) suggests some assessment questions; however these may need to be tailored to each patient. Where a patient is not able to complete an assessment by self-reporting, then the health professional and/or the caregiver may act as a surrogate.

Table 2: Pain Assessment using Acronym O, P, Q, R, S, T, U and V

Onset	When did it begin? How long does it last? How often does it occur?
Provoking/Palliating	What brings it on? What makes it better? What makes it worse?
Quality	What does it feel like? Can you describe it?
Region / Radiation	Where is it? Does it spread anywhere?
Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right Now? At Best? At Worst? On Average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom?
Treatment	What medications or treatments are you currently using? How effective are these? Do you have any side effects from the medications/treatments? What medications/treatments have you used in the past?
Understanding / Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?
* Physical Assessment (focus on area of pain to determine cause and type of pain); Pertinent History (risk factors); Assess risks for addiction; Associated symptoms: e.g. nausea, vomiting, constipation, numbness, tingling, urinary retention.	

(Adapted with permission from Fraser Health. Hospice palliative care program symptom guidelines. [Internet]. Surrey, BC: Fraser Health Website; 2006. Available from: http://www.fraserhealth.ca/media/SymptomAssesment.pdf)

> **Assessment must determine the cause, effectiveness of the treatment and impact on the quality of life for the patient and their family.**

General Principles of Cancer Pain Assessment

1. Perform an adequate pain history (see section below for additional details).
2. Use tools valid for the patient's age and cognitive abilities, with additional attention to the language needs of the patient (e.g., Brief Pain Inventory (BPI), Edmonton Symptom Assessment Scale (ESAS), Palliative Performance Scale (PPS)) (see section below for additional details).
3. Record medications currently taken as well as those used in the past, including efficacy and any adverse effect.
4. Classify the pain – nociceptive, neuropathic or mixed?
5. Consider common cancer pain syndromes while conducting the history and physical examination.
6. Assess for functional impairment and the need for safety measures.
7. Incorporate a psychosocial evaluation into the assessment, including determination of the patient's/family's goals of care.
8. Use a pain diary to track the effectiveness of therapies and evaluate changes in pain.
9. Review current diagnostic tests for clues to the origin of the pain. Order a diagnostic test (e.g., MRI, CT, laboratory testing) when warranted for new pain or increasing pain, and only if it will contribute to the treatment plan.
10. Evaluate for the presence of other symptoms, as pain is highly correlated with fatigue, constipation, mood disturbances, and other symptoms.
11. Assess for risk if opioids are being considered.

Clinical history and physical examination

Sign 106

> ☑ **Detailed history taking is vital to comprehensive assessment.**

Sign 106 *Modified*

Careful history-taking (see Table 3 for details) involving effective questioning and listening to obtain information about the pain and its impact on the patient, integrating information from the disease history, review of imaging and information from other health care providers and caregivers will usually delineate the type of pain, the pain generators and lead to more effective therapy. The severity of the pain will help determine the initial management step.

Table 3. Suggested areas of focus for a detailed clinical history and physical examination

Areas of focus during history examination
• onset/duration
• site and number of pains
• intensity/severity of pains
• radiation of pain(s)
• timing of pain(s)
• qualities of pain(s)
• aggravating and relieving factors
• areas of skin with decreased or increased sensitivity
• analgesic drug history including dosage, frequency, regular or prn, adverse effects
• patient beliefs about the meaning of pain, effectiveness of its treatments and consequences of drug

Areas of focus during history examination
therapies
• presence of clinically significant psychological disorder e.g. anxiety and/or depression
• family and cultural issues including financial issues, illness issues, beliefs about pain
• history of drug or alcohol abuse to assess risk of abuse/addiction
• past and current disease treatment
• co-morbidities such as heart disease or diabetes
• other medications

PAIN SMG

Physical examination should mostly be focused on the areas of pain with general observations of the patient's overall condition. Bone tenderness should be elicited with gentle pressure and not by pounding the suspected area. If neuropathic pain is suspected then motor and sensory testing should be done.

Standardized pain assessment tools

Sign 106 *Modified*

> ☑ **Patients with cancer pain should have treatment outcomes monitored regularly using visual analogue scales, numerical rating scales or verbal rating scales and multidimensional instruments as necessary.**

Many different pain assessment tools are used but there is no universally accepted or reliable tool for the assessment of cancer pain. The 0–10 visual or verbal analog scales, or variants thereof such as a thermometer, are validated and easy to administer. Their use is common. Patient self-report is more accurate than vital signs, outward behavior, or observer estimates.

Sign 106 *Modified*

The European Association of Palliative Care has recommended the use of standardized pain assessment tools in clinical practice. These include visual analogue scales (VAS), numerical rating scales (NRS) and verbal rating scales (VRS) (20). A Distress "Thermometer" is a vertical visual analogue scale designed to look like a thermometer, with 0 meaning "no distress" and 10 (at the top of the thermometer) indicating "extreme distress." Accompanying the thermometer scale is a checklist that includes a variety of physical, psychological, practical, family support, and spiritual/religious concerns (21, 22).

Sign 106 *Modified*

Multidimensional instruments such as the Brief Pain Inventory (BPI) and the McGill Pain Questionnaire were validated in different cultures (23, 24). The BPI is a valid, clinically useful pain assessment tool that incorporates NRS and VRS is been used extensively in people with cancer. It includes a diagram to note the location of pain, questions regarding pain intensity (current, average, and worst using a 0 to 10 rating scale), and items that evaluate impairment due to pain. The BPI is translated into a large number of languages, including French, Italian, Mandarin, and Spanish.

> **C. Self assessment pain scales should be used in patients with cognitive impairment, where feasible.**
>
> **Observational pain rating scales should be used in patients who cannot complete a self assessment scale.**

Symptom assessment tools may also be helpful. Studies demonstrate a significant correlation between pain, depression, fatigue, and other symptoms commonly seen in those with cancer. These co-occurring symptoms are commonly referred to as symptom clusters. The use of multidimensional scales incorporating the most common symptoms would ensure systematic assessment. The Edmonton Symptom Assessment System (ESAS) is a validated, brief, clinically useful bedside screening tool for self-reporting symptom intensity. It was designed to enable repeated quantitative measurement of symptom intensity with minimal patient burden. It includes pain and 8 other symptoms that are rated using VAS or NRS ranging from 0 to 10 and anchored by the words "no pain" and "worst possible pain" respectively. ESAS is very useful as a screening tool and should lead to a more comprehensive assessment as outlined below.

Pain Assessment in Patients with Cognitive Impairment

The presence of cognitive impairment makes pain assessment more difficult. The level of impairment is influential. In patients suffering from dementia, a prospective study of four self assessment scales in a geriatric hospital found that only 12% could not understand any of the four self assessment scales used (the verbal rating scale (none, mild, moderate, severe), the horizontal visual, vertical visual and faces pain scales) but the ability to use the scales understandably decreased as the degree of dementia increased (25).

A systematic review of behavioural pain assessment tools for elderly people with severe dementia concluded that the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) and DOLOPLUS 2 are the most appropriate scales for this group although neither scored highly for quality and psychometric properties (26). Refer to the following websites for further information on these tools:
http://ltctoolkit.rnao.ca/resources/pain#Assessment-Tools
http://prc.coh.org/review%20of%20tools%20for%20pain%20assessment/dolophus.htm

Cancer Treatment Related Pain

Over the years, the number of "cancer survivors" has increased (27). This increase is due to an aging population as well as decreasing mortality in some tumour types due to earlier detection and more effective adjuvant therapy. A comprehensive approach to cancer treatment which may include surgery, radiation, curative, palliative and adjuvant chemotherapy may come with the price of morbidity, one of which is cancer treatment related pain. Treatment related pain may be responsible for a substantial amount of the pain in the patient living with cancer.

These heterogeneous pains deserve attention for several reasons:
- They can be as severe as cancer pain.
- They may limit the ability to deliver chemotherapy or radiotherapy and occasionally lead to a change in or cessation of therapy.
- They may be confused with cancer as the underlying source of pain.
- They can be a source of morbidity that may limit ability to return to work as well as quality of life.
- These pains often occur in patients who are potentially cured of their disease and hence require more thought about the role of long-term, strong opioids.
- Many of the pains are neuropathic in origin and require the use of adjuvant agents that are not as familiar to the oncologist as are opioids, NSAIDs and corticosteroids.
- They require an interprofessional approach to management which can be quite complex at times.

The etiology can be broadly classified in terms of the responsible therapy i.e., surgery, systemic therapy and radiation therapy (Table 4).

Table 4. Examples of responsible therapy

Responsible Therapy	Examples
Post surgical pain	• Post breast surgery especially after axilla exploration • Post thoracotomy • Post neck dissection
Systemic therapy associated pain: Peripheral neuropathy Myalgias/arthralgias Osteonecrosis of the jaw	• Paclitaxel, docetaxel, vinorelbine, carboplatin, cisplatin, oxaliplatin, ixabepilone, vincristine, vinblastine, thalidomide, bortezomib • Aromatase inhibitor induced • Bisphosphonates
Radiation therapy associated pain	• Plexopathies/myelopathies

Management of cancer treatment related pain (CTRP)

The management of cancer treatment related pain (CTRP) follows the same process as cancer pain. One of the most important issues is the need for early recognition of cancer treatment related pain to avoid prolonged suffering. Most cancer treatment related pain is neuropathic in origin and therefore the use of neuropathic pain adjuvants is often the major approach to treatment.

How often should pain be assessed?

_{**Sign 106** *Modified*} One of the keys to successful control of cancer pain is regular review to determine the effectiveness of treatment. Unless cancer pain intensity is assessed systematically using a validated scale, or by regular communication with the patient, it is difficult to judge the benefits, or lack thereof, of any analgesic regimen, let alone to compare one regimen with another (,28,29). The frequency of the review depends upon the severity of the pain and associated distress. Pain assessment for home care patients or outpatients should be carried out regularly, at least daily when pain is not adequately controlled.

Non-Pharmacological Treatment

Radiotherapy

All patients with pain from bone metastases which is proving difficult to control by pharmacological means should be referred to a radiation oncologist for consideration of external beam radiotherapy.

Vertebroplasty

> **D. Patients with bone pain from malignant vertebral collapse proving difficult to control by pharmacological means or radiotherapy should be referred for consideration of vertebroplasty where this technique is available.**
> **D. Patients with bone pain from vertebral bone metastases proving difficult to control by pharmacological means and reduced mobility should be considered for percutaneous cementoplasty.**

Cancer patients may develop osteolytic involvement of the spine which may cause loss of vertebral height. This is associated with significant morbidity and mortality. Most of these patients will have reduced mobility and back pain that may not be responsive to drug treatment. Medical, radiotherapeutic and surgical options may be inadequate or too invasive in these cases. Percutaneous vertebroplasty involves the injection of acrylic bone cement into malignant bone cavities in order to relieve pain or stabilise the bone, or both. Percutaneous vertebroplasty involves the injection of acrylic bone cement into the vertebral body in order to relieve pain and/or stabilise the fractured vertebrae and in some cases, restore vertebral height. Balloon vertebroplasty is an extension of the vertebroplasty technique that uses an inflatable bone tamp to restore the vertebral body towards its original height while creating a cavity to be filled with bone cement (30). The procedure appears safe, but all studies report technical incidents involving cement leakage, although clinical complications are rare (31).

Although case series show benefit in patients with malignant vertebral collapse, two recent randomized, controlled trials in patients with osteoporotic vertebral collapse show that acrylic bone injection is no better than sham injection.

Case series have shown that good pain control and improved mobility can be achieved using the percutaneous injection of acrylic cement into acetabular or pelvic bones weakened by bone metastases (32-34). The procedure requires a short period of hospitalization, with few side effects. Rates of leakage of injected cement into surrounding tissues range from 6-50% however, symptomatic cases relating to cement leaks were only reported in 6-11% of cases. (32, 34).

Surgery

Various surgical procedures may relieve pain. Removal of tumours or stabilization of bones may remove localized pain. Surgical stabilization of long bones, joint replacements and vertebral stabilization techniques may reduce or eliminate pain from bone metastases.

Anaesthetic Interventions

> **B. Interventions such as coeliac plexus block and neuraxial opioids should be considered to improve pain control and quality of life in patients with difficult to control cancer pain.**
>
> ☑ **Any patient with difficult-to-control pain despite optimal management of systemic/ oral therapy should be assessed by an anaesthesiologist with expertise in pain medicine or an interventional radiologist for consideration of an appropriate intervention.**

Despite management by multidisciplinary teams according to the principles of the WHO ladder, up to 20% of cancer patients may have poorly controlled pain (35,36). It is this group of patients who is most likely to benefit from some form of anaesthetic intervention. However, there is a limited amount of high quality evidence for anaesthetic techniques to manage cancer pain. These techniques might include:

- celiac plexus block
- local anaesthetic used either via the epidural route or topically as part of pain control for breast cancer surgery and other types of surgery
- plexus or peripheral nerve blocks
- neuraxial opioids and local anaesthetics (epidural, subarachnoid and intracerebroventricular)

For additional information please refer to the Program in Evidence-based Care guideline on Intraspinal Techniques for Pain Management in Cancer Patients, available at:
http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=44121

Complementary Therapies

Complementary therapies are defined as the supportive methods used to complement the mainstream treatments for cancer pain. Although these therapies have increased in popularity, and a number of randomized trials were undertaken in this area (37-48), the evidence to support their use in the treatment of cancer pain remains weak. General themes that emerged in a literature review of these therapies were that any pain relief offered was of short duration but that patients found the experience a positive one (49). These therapies include:

- Massage
- Aromatherapy
- Music therapy
- Acupuncture
- Reflexology
- Transcutaneous electrical nerve stimulation
- Reiki
- Hypnotherapy

Pharmacological Treatment of Cancer Pain

The World Health Organization (WHO) Analgesic Ladder

The three-step ladder specifies treatment according to the intensity of pain. By referring to drug classes, rather than specific drugs, the ladder maintains a level of flexibility that allows clinicians to work within the regulations and limitations employed in their respective countries. The fundamental aim of the WHO ladder was to justify the prescribing of strong opioids for cancer pain, which had previously been problematic due to fears of addiction, tolerance and illegal use (50).
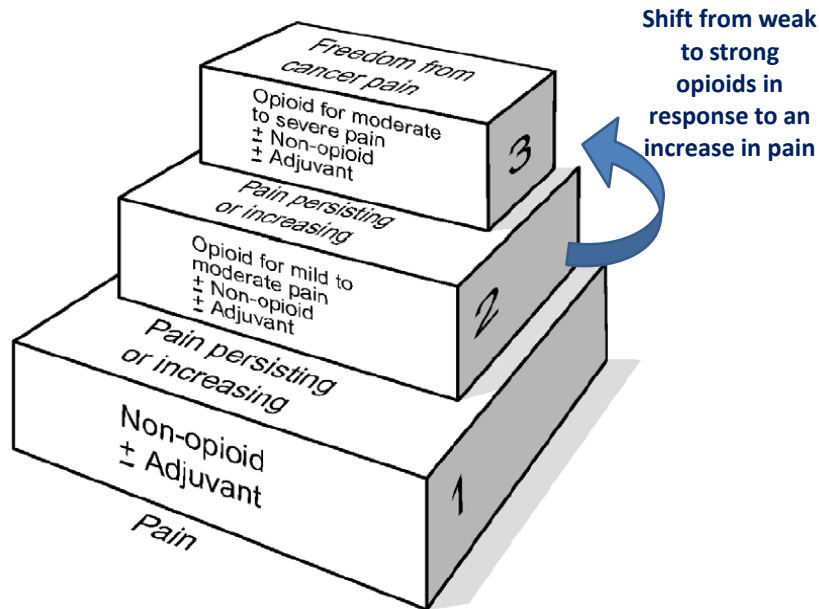

Figure 1: World Health Organization analgesic ladder (27)

The application of this analgesic regimen has been shown to achieve pain relief in the majority of patients with cancer. One retrospective report showed that using the ladder reduced pain to one third of its initial intensity in 71% of patients (36). One long term prospective study reported that "good" pain relief was achieved in 76% of 2,118 patients treated in accordance with the WHO guidelines over a ten year period (35). Despite the ladder's success in providing pain relief, its use and design has been debated (27,51,52). Most criticism of the WHO ladder questions the usefulness of weak opioids in the treatment of cancer pain (step 2). There is insufficient evidence to either support or refute the WHO recommendation that a weak opioid has superiority over an NSAID (53).

In those with rapidly advancing pain, or in need of rapid titration of analgesic therapy, the switch between steps 1 and 2 may delay optimal pain relief. In opioid-naïve patients a balance between side effects and analgesia has been demonstrated by administering a weak rather than a strong opioid (54). There is also evidence to support the successful use of strong opioids in opioid-naïve patients (55-57). Controlled trials are required to further validate these findings.

One RCT showed that moving directly from step 1 to step 3 of the WHO analgesic ladder was possible and could reduce pain scores in some cases, but attentive management of side effects was required (58). This has led to alternatives to the WHO ladder being proposed, usually replacing weak opioids at stage 2 with low doses of strong opioids. An RCT found equivalent analgesia with fewer drug and dose changes but higher incidence of nausea in patients omitting step 2 of the ladder (59).

Sign 106

The development of new formulations of opioids (eg transdermal fentanyl and buprenorphine), new routes of delivery (e.g., buccal fentanyl, intranasal fentanyl) and the more widespread availability of different opioids (e.g., oxycodone, hydromorphone and methadone) create options which were not available at the time of the development of the WHO ladder (60).

Using the World Health Organization Analgesic Ladder

> B. **A patient's treatment should start at the step of the WHO analgesic ladder appropriate for the severity of the pain.**
>
> B. **Prescribing of analgesia should always be adjusted as the pain severity alters.**
>
> ☑ **If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency.**
>
> ☑ **All patients with moderate to severe cancer pain, regardless of aetiology, should receive a trial of opioid analgesia.**
>
> ☑ **Optimum management of pain in patients with cancer requires a multidisciplinary approach.**
>
> D. **Analgesia for continuous pain should be prescribed on a regular basis, not 'as required'.**
>
> D. **Appropriate analgesia for breakthrough pain must be prescribed.**
>
> ☑ **Explain to patients with chronic cancer pain that pain control medication must be taken regularly to gain optimal results.**

Sign 106

Sign 106

Pain relief should be based on a complete patient assessment that differentiates pain distress from pain severity. The severity of pain determines the strength of analgesic required and the type and cause of the pain will influence the choice of adjuvant analgesic (any drug that has a primary indication other than for pain management, but is analgesic in some painful conditions). Type, cause and severity can only be determined from a thorough patient assessment (35,36). Effective use of the WHO ladder depends on an accurate initial pain assessment and regular follow up assessment of the patient and their pain.

Treatment should be adjusted from one step to the next according to increasing or decreasing pain severity, history of analgesic response, and side effect profile. For chronic pain, analgesia must be given regularly by the clock. Breakthrough medication must be prescribed.

The extent to which pain responds to opioid analgesics varies depending on both patient and pain characteristics. No pain is predictably unresponsive to opioids. Neuropathic pain can respond to opioids, although the response may be incomplete (61,62).

Chronic pain in patients with cancer is usually continuous and where this is so, therapeutic levels of analgesics should be maintained by giving the drug at regular intervals according to its pharmacokinetic and pharmacodynamic profile (35,36).

Treatment with Non-Opioid Drugs

Acetaminophen and NSAIDS

> **A. Acetaminophen and NSAIDS including COX-2 inhibitors should be considered, particularly for those with mild cancer pain, at the lowest effective dose and the need for ongoing or long term treatment should be reviewed periodically. If there is no significant response in one week, these drugs should be stopped. Long term use of NSAIDs should require gastric mucosa protection.**

Acetaminophen and NSAIDS are often used for management of cancer pain, though data outlining their ideal role is lacking. A systemic review (53) of NSAIDS noted that there was marked heterogeneity of study methods and outcomes, and that most studies were of short duration (< 1 week, with several being single dose only) limiting the ability to generalize the results. There were no studies of NSAIDS lasting beyond 12 weeks.

Overall, NSAIDS were more effective than placebo for cancer pain, though there was no clear evidence to support any one NSAID over another in terms of efficacy or safety. Data regarding combining NSAIDS with opioids were inconsistent, with at best, a trend towards improved pain control with the combination. Similarly, no conclusions can be drawn about the efficacy of dose escalation given the short duration of most studies.

Adverse effects of NSAIDS can be problematic with gastrointestinal, cardiac and renal toxicities being major issues. Patients at high risk of gastrointestinal adverse effects should be treated with proton pump inhibitors.

Bisphosphonates

> ☑ **There is insufficient evidence to recommend bisphosphonates for first line therapy for pain management.**

Two systematic reviews suggest that bisphosphonates may reduce cancer pain and skeletal-related events associated with bone metastases (63,64). The number needed to treat (NNT) to gain analgesic benefit is 11 (95% CI 6 to 36) at four weeks and 7 (95% CI 5 to 12) at 12 weeks. In comparison, the NNT for analgesic response to radiotherapy for bone metastases is 4.2 (65). Other evidence is heterogeneous as studies have not always used the same measurement tools for pain and sample sizes vary considerably. The evidence identified proved insufficient to evaluate:

- the comparative effectiveness of the different bisphosphonates for pain relief
- the analgesic response to bisphosphonates by individual primary disease site
- the optimum dose or route of administration
- the effectiveness of bisphosphonates compared with radiotherapy or other analgesics.

The main adverse effect of bisphosphonates is renal toxicity. The NNH is 16 (95% CI 12 to 27) for adverse events requiring discontinuation of bisphosphonates (63). Osteonecrosis of the jaw (ONJ) is a complication occurring in patients treated with bisphosphonates, especially the aminobisphosphonates.

Sign 106

Sign 106

The prevalence of ONJ in cancer patients receiving intravenous bisphosphonates is 6-10% (66). Preventive strategies include treating all dental infection prior to commencement of treatment and avoiding invasive dental treatment when receiving IV bisphosphonates. The extent of risk for osteonecrosis in patients taking oral bisphosphonates has not been determined. There are no data available to suggest that discontinuation of bisphosphonates for patients requiring invasive dental treatment reduces the risk of osteonecrosis of the jaw. The clinical judgment of the treating clinician should guide the management plan based on the individual risks/ benefits for the patient.

Adjuvants for Neuropathic Pain (See Appendix C & Appendix D)

Cancer-related pain very frequently has a significant neuropathic component as part of a mixed nociceptive, inflammatory and neuropathic pain presentation. The approach to individuals in a palliative care setting with a relatively short prognosis by its nature requires a more aggressive and intensive multimodal approach. There are also a significant proportion of cancer survivors with chemotherapy- and radiation-related neuropathic pain requiring ongoing management (67).

Antidepressants and Anticonvulsants

Sign 106 *Modified*

> **A. The choice of antidepressant or anticonvulsant should be based on concomitant disease, drug therapy and drug adverse effects and interactions experienced. Patients with neuropathic pain should as first line co-analgesics, be given either a tricyclic antidepressant (e.g., amitriptyline, desipramine, nortriptyline or imipramine) or an anticonvulsant (e.g., gabapentin or pregabalin) with careful monitoring of adverse effects.**

Antidepressants

Sign 106 *Modified*

- Few studies evaluate tricyclics in cancer neuropathic pain. Evidence from studies in patients with non-cancer neuropathic pain was also reviewed as the same pathological mechanism of neuropathic pain is believed to be involved. There is robust evidence from a systematic review of 31 randomized trials that tricyclic antidepressants are effective in the management of neuropathic pain (68). Thirteen per cent of patients in the systematic review had to withdraw due to intolerable adverse effects.
- There is not enough evidence to support a recommendation on the use of selective serotonin reuptake inhibitors in neuropathic pain relief.
- There is some evidence that selective norepinephrine reuptake inhibitors, like venlafaxine, are effective in reducing neuropathic pain (68).
- Duloxetine is a dual action antidepressant which inhibits neuronal serotonin, norepinephrine and dopamine reuptake. It is licensed for treatment of peripheral diabetic neuropathic pain. Duloxetine is not considered as a first-line of therapy for neuropathic pain but may be considered by specialists when other treatments have failed or are unsuitable.

Anticonvulsants

Sign 106

Two systematic reviews were identified: one dealing with gabapentin in the management of pain (69) and one dealing with various different anticonvulsants (70). Only one study was carried out on patients with cancer pain though the results are considered generalizable with the same pathological mechanism of neuropathic pain involved. Both gabapentin and carbamazepine provided good pain relief in 66% of patients. There was no direct comparison between the two. The NNT for relief of

neuropathic pain in patients with diabetic neuropathy varied according to the specific anticonvulsant used as follows: carbamazepine 2.3 (95% CI 1.6 to 3.8), gabapentin 3.8 (95% CI 2.4 to 8.7), and phenytoin 2.1 (95% CI 1.5 to 3.6). The NNH was calculated by combining studies regardless of condition treated. The NNH for major harm was not statistically significant for any drug compared to placebo and for minor harm was as follows: carbamazepine 3.7 (95% CI 2.4 to 7.8), gabapentin 2.5 (95% CI 2.0 to 3.2), and phenytoin 3.2 (95% CI 2.1 to 6.3). However, it should be noted that recent studies suggest that NNH differs considerably from placebo and may include cognitive side effect and suicide (71).

Multiple randomized controlled trials indicate that pregabalin is better than placebo in relieving non-malignant neuropathic pain (72). The greater than or equal to 50% pain responder rate was higher with pregabalin than placebo in all of these studies with a combined NNT of 4.2 (73,74) One small RCT showed that pain relief was greater when gabapentin and morphine were combined. Mean daily pain (on a scale from 0 to 10, with higher numbers indicating more severe pain at a maximal tolerated dose of the study drug) was: 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin-morphine combination (p<0.05 for the combination versus placebo, gabapentin, and morphine). Smaller doses of each drug were required than if administered singly, although the incidence of dry mouth was significantly higher (p< 0.05) (75).

There is no direct evidence of comparative efficacy between anticonvulsants or between anticonvulsants and antidepressants. In malignant pain it is expected that these drugs may be effective however no randomized controlled trials have been undertaken.

Ketamine

Sign 106 *Modified*

> ☑ **The use of ketamine or methadone as an analgesic for refractory cancer pain should be supervised by a specialist in pain relief or a palliative medical specialist.**

Ketamine is used in selected patients who have persistent pain that remains uncontrolled by other means and is prescribed by specialists in cancer pain. It may be indicated in neuropathic pain, ischemic limb pain and refractory pain in cancer (76,77). Generally ketamine is administered in addition to a strong opioid and if successful will restore opioid sensitivity.

Sign 106

Topical Analgesia
There is insufficient evidence to support a recommendation for topical opioids.

Capsaicin

Sign 106 *Modified*

Capsaicin is the active component of chili peppers that results in a local burning sensation on contact with skin followed by a period of reduced sensitivity and eventual persistent desensitization in that local area. Topical formulations of capsaicin are used to treat pain from postherpetic neuralgia and diabetic neuropathy. A systematic review was carried out to establish the efficacy and safety of topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorders (78). Capsaicin was significantly better than placebo for the treatment of both neuropathic and musculoskeletal pain. This review highlights the increased risk of local adverse events (e.g. burning, stinging and erythema) and adverse-event-related withdrawals with capsaicin compared to placebo.

Cannabinoids

> ☑ **There is insufficient evidence at the moment to support first or second line therapy of cancer pain with cannabinoids but they may have a role in refractory pain, particularly refractory neuropathic pain.**

Sign 106 *Modified*

Two oral cannabinoids are available in Ontario, dronabinol (delta-9-tetrahydrocannabinol (THC)) and nabilone (synthetic analogue of THC) though neither is currently approved for cancer related pain. Recently an oral transmucosal cannabinoid spray (Sativex®) comprised of a 1:1 ratio of THC and cannabidiol (CBD) was approved for refractory cancer pain.

Limited studies are available on the effect of oral cannabinoids in pain, though there is a physiologic rationale for their use via modulation of pain through actions on endocannabinoid receptors. One systemic review (79) identified 5 RCT's of 128 patients with nociceptive cancer pain with overall mixed results, though conclusions about utility are limited, as most of the trials were single dose only. Side effects in all reported trials were common and included sedation, mental clouding, ataxia, dizziness, slurred speech, disorientation and impaired memory (79). Studies in non-malignant conditions with neuropathic pain show that cannabinoids may have a role in HIV associated neuropathic pain (80) and in central pain from multiple sclerosis (81).

Treatment with Opioid Drugs

The Role of Opioids

Opioids are the mainstay of treatment for cancer pain. They are effective, have predictable adverse effects and can be given in a variety of forms and by a variety of methods. Opioids can be classified as agonists, partial agonists, mixed agonist antagonists, depending on their actions at the receptor sites. Opioid receptors are determined genetically and individuals have differing sets of receptors, this accounts in part for individual differences in analgesic response to opioids. There is a lack of evidence, from high quality comparative trials, that one opioid has advantages in terms of either efficacy or side effects that would make it preferable to another for first line use in cancer pain. Choice of opioids remains often as a personal choice of the prescriber except in certain circumstances that will be detailed subsequently.

General Principles in Using Opioids

1) Educate the patient and/or family about the use of opioids and the expected outcomes.
2) Anticipate adverse effects like sedation and educate patients about the fact that they will quickly tolerate most adverse effects except for constipation.
3) In opioid-naïve patients and the frail elderly, start low and go slow with titration. Transdermal fentanyl is **not** recommended in opioid-naïve patients.
4) In patients already on opioids, titrate them fairly quickly to the point where they are getting adequate pain control without intolerable adverse effects.
5) Immediate release or sustained release products can both be used for titration and maintenance.
6) Give opioids regularly, around the clock for constant pain.
7) Always prescribe breakthrough doses.

General Principles in Using Opioids

8) Prevent adverse effects e.g., for constipation prescribe laxatives right from the initiation of therapy and decide on a plan for the management of constipation.

9) Monitor patients closely as you are titrating opioids. The health care team must be accessible to the patient and family. Follow any changes in function e.g. ability to sleep, carry out activities.

10) Use universal precautions where a risk for abuse is identified.

11) Specialist pain or palliative care advice should be considered for the appropriate choice, dosage and route of opioids in patients with reduced kidney function or in patients with difficult to control pain.

Patients with Renal Impairment

> **C.** **In the presence of reduced kidney function all opioids should be used with caution and at reduced doses and/or frequency.**
> ☑ **Fentanyl, methadone and oxycodone are the safest opioids of choice in patients with chronic kidney disease.**
> ☑ **Specialist palliative care advice should be considered for the appropriate choice, dosage and route of opioid in patients with reduced kidney function or in patients with difficult to control pain.**

Sign 106 *Modified* Renal impairment is commonly seen in palliative care patients due to old age, concomitant drug therapy or disease. Dehydration may result rapidly if patients are very drowsy and not encouraged to drink adequate fluids. Dehydration and renal impairment increase the potential for opioid toxicity. Early signs of opioid toxicity include nausea, sedation, subtle agitation, intermittent confusion and increased myoclonus.

Sign 106 *Modified* There are some differences between the opioids in terms of their metabolism and excretion, some metabolites may be pharmacologically active and, if excreted renally, may contribute to toxicity. There is a lack of clinical evidence to determine the relative safety of different opioids in patients with renal impairment, including those receiving dialysis.

Pharmacokinetic studies have demonstrated accumulation of renally excreted opioid metabolites. Generally toxicity is related to the activity of these metabolites or the parent drug. In patients with poor or deteriorating kidney function, the following are of considerable importance to prevent or manage toxicity:

- choice of opioid
- consideration of dose reduction and/or an increase in the dosage interval
- change from modified release to an immediate release oral formulation
- frequent clinical monitoring and review

In patients undergoing renal dialysis, opioid use is further complicated by the removal of some opioids and their active metabolites by dialysis. For these opioids, supplemental doses of immediate release analgesics may therefore be required during or after dialysis sessions to maintain pain control.

Weak Opioids for Mild (ESAS 1-3) to Moderate Pain (ESAS 4-6)

Sign 106 *Modified*

> ☑ **For mild to moderate pain, opioids such as codeine or tramadol could be given in combination with a non-opioid analgesic.**

Codeine

Sign 106 *Modified*

Codeine and acetaminophen codeine combination products are used commonly. Codeine demonstrates a ceiling dose-response curve to pain relief (82,83). Maximum analgesic effect is achieved at a dose of about 200-300 mg/day. Increasing the daily dose beyond this does not increase analgesic effect but may result in greater side effects. Approximately 7% of Caucasian people, 3% of black people and 1% of Asian people have poor or absent metabolism of codeine resulting in a reduced or absent analgesic effect (84). Toxicity from codeine is reported in patients with renal impairment, and caution in its use in such patients is required (85-87).

Tramadol

Sign 106 *Modified*

There is limited evidence from small studies to indicate that tramadol should be considered for mild to moderate pain. There is limited evidence available to make a recommendation on the use of tramadol. Unchanged tramadol and the active metabolite are both eliminated mainly by the kidneys and will accumulate in renal impairment, requiring dose reduction and an increase in the dosing interval according to the degree of impairment.

Strong Opioids for Moderate (ESAS 4-6) to Severe Pain (ESAS >7)
Morphine

Sign 106

The first choice opioid for oral use in severe cancer pain often is morphine (88). The majority of patients tolerate oral morphine well and, due to the likelihood that patients will use medication chronically, the oral route is preferable to parenteral or rectal administration. The systemic bioavailability of morphine by the oral route is poor, with wide variation between individuals, but with individual dose titration a satisfactory level of analgesia can usually be achieved. The efficacy and safety of morphine is well established in clinical practice (35,36) and the wide variety of morphine formulations available in Canada allows flexibility in dosing intervals.

Sign 106 *Modified*

Morphine is metabolized mainly in the liver and the metabolites largely excreted renally. Morphine-6-glucuronide is pharmacologically active as an analgesic. Toxicity in patients with poor renal function is well reported (89-92). Dose reduction or a decreased frequency of administration is required depending on the degree of renal impairment (90). Toxicity due to accumulation of metabolites in cerebrospinal fluid can take several days to resolve after morphine is discontinued (92). Familiarity with the use of morphine by most practitioners is an additional consideration for patient safety.

The starting dose for opioid naïve patients is usually morphine 5 mg q4h regularly with 2.5-5 mg q1h prn for breakthrough pain. For elderly or debilitated patients consider a starting dose of 2.5 mg q4h. When pain and analgesic usage is stable, this should then be converted to a bid long-acting preparation by calculating the total 24 hour intake (standing plus breakthroughs) for ease of administration. The immediate release breakthrough dose is usually 10% of the total daily dose. The frequency of breakthrough doses for oral opioids is q2h prn. After conversion to a sustained-release preparation, if pain is not well controlled, reassess the patient considering why multiple breakthrough doses are being

used and the effectiveness of the breakthrough doses. If indicated after proper assessment, the daily dose can be titrated by adding 20 to 30% of the breakthrough doses used in the preceding 24 hrs to the daily sustained-release formulation. For patients with severe uncontrolled pain consider switching back to an equivalent daily dose of immediate release morphine to allow more rapid titration of dose or switch to a sc preparation/infusion.

Hydromorphone

Sign 106 *Modified*

Hydromorphone is available as both immediate release and sustained release capsules (12 hourly), allowing titration in a similar way to morphine. The pharmacokinetic properties are similar to morphine, and there is wide inter-patient variation in bioavailability. An oral liquid is available. For patients with swallowing difficulties, the sustained release capsules can be opened and the contents sprinkled on a spoonful of cold soft food.

Sign 106 *Modified*

Hydromorphone is metabolized in the liver, principally to hydromorphone-3-glucuronide. All metabolites are excreted renally with a small amount of free hydromorphone. Evidence for the safety of hydromorphone in renal impairment is inconsistent (92). Case reports have revealed examples of hydromorphone toxicity in patients with renal failure (90,92) and evidence from a single case report of accumulation of hydromorphone-3-glucuronide in chronic renal failure (93). Further research is needed to establish the safety profile of hydromorphone in renal impairment.

The starting dose for hydromorphone in opioid naïve patients is 1 mg q4h with 1mg q1h prn, though for elderly or debilitated patients a starting dose of 0.5mg q4h is appropriate. Convert to a sustained release preparation as above as soon as possible.

Oxycodone

Sign 106 *Modified*

Oxycodone is available as immediate release tablets, sustained release tablets and in combination with acetaminophen. It has more predictable bioavailability than morphine (60-87% for oxycodone versus 15-65% for morphine). The sustained release tablets have a biphasic pharmacokinetic release profile showing two peaks after oral administration. This may allow onset of analgesia within an hour of ingestion and an analgesic duration of 12 hours. Oxycodone's principal metabolites are oxymorphone and noroxycodone which are excreted renally. The contribution of the metabolites to the pharmacological activity of oxycodone is uncertain but thought to be small. Until this data is available oxycodone should be used with care in patients with renal impairment.

The lowest dose oxycodone tablets available, either in combination with acetaminophen or alone, contain 5mg of oxycodone, equivalent to ~5-10mg of morphine. As such for the opioid naïve patient, unless pain is severe, it is reasonable to start at 2.5 mg (i.e. one half of a 5 mg tablet) q4h with dose escalation to a full tablet after assessing response and side effects. As above, this can then be converted to a sustained release formulation based on 24-hour intake. A lower dose oxycodone tablet is available in the form of Percocet®Demi (oxycodone 2.5 mg and acetaminophen 325 mg) but is less commonly prescribed. Cost may be a consideration.

Transdermal Fentanyl

> ☑ **Transdermal fentanyl should not be used in opioid naïve patients.**

Sign 106 Modified

For those with stabilized severe pain who express a preference for a patch formulation or those with swallowing difficulties or intractable nausea and vomiting, fentanyl transdermal patches may be appropriate provided the pain is stable. Fentanyl is also metabolized by the cytochrome P450 system and the possibility of interaction with other drugs must be considered. Fentanyl is metabolized in the liver to compounds thought to be inactive and non-toxic. Monitoring patients with renal failure for signs of gradual accumulation of the parent drug is prudent (92).

Methadone

> ☑ **Check for significant drug interactions before prescribing ANY drug to a patient on methadone.**

Methadone may have a specific role for patients with considerable tolerance to other opioids and in patients with poorly responsive neuropathic pain. Methadone has better bioavailability than other opioids and has no active metabolites. It has a long and sometimes unpredictable half life, with considerable inter-individual variation, and should be initiated only by experienced prescribers. Methadone has a different major metabolic pathway than other opioids in that it is metabolized mostly through the cytochrome P450 system. This means it has more interaction with drugs than most opioids. Methadone requires an experienced prescriber because of its pharmacokinetics and drug interactions potential. Its metabolism can therefore be influenced by other drugs that enhance or inhibit this enzyme system. Drug interactions should be checked before adding any type of medication to a patient on methadone. Methadone for use in pain patients requires a special license or exemption (94).

Other Opioids <u>Not</u> to be Used

Meperidine and pentazocine should not be used in cancer patients with chronic pain. Meperidine is poorly absorbed orally, may be associated with a build-up of neurotoxic metabolites and has a flat dose response curve. Pentazocine is an agonist antagonist, weak opioid that is also very poorly absorbed orally. Both these drugs have little place in the treatment of cancer pain.

Opioid Formulations
Immediate release formulations

Sign 106

Immediate release opioid formulations have an onset of action of about 20 minutes and reach peak drug levels on average at 60 minutes. The rapid onset of analgesia makes these preparations more suitable for use in initiating therapy for severe pain and for treating breakthrough pain. Immediate release preparations must be given every four hours to maintain constant analgesic levels. When given every four hours these preparations will reach a steady plasma concentration, attaining full effect within 12-15 hours. Thus the full effect of any dose change can be assessed at this time. In practice, during titration, dose adjustments are usually made every 24 hours unless the pain is more severe when adjustments may be made sooner (95).

The pharmacokinetics of immediate release oral opioids are such that onset of analgesia is reached after 20-30 minutes following oral ingestion. The plasma elimination half life of morphine is 2.2 hours (96).

Sustained and controlled release formulations

> ☑ **Patients with stable pain on oral morphine, oxycodone and hydromorphone should be prescribed a twice daily sustained or controlled release preparation.**

Sign 106 *Modified*

Sign 106 *Modified*

Sustained or controlled release preparations of these drugs were developed to allow once daily (in the case of morphine) or 12 hourly dosing. There is no statistically significant difference between four hourly dosing of oral immediate release morphine, 12 hourly dosing of oral twice daily modified release morphine and 24 hourly dosing of oral once daily modified release morphine in efficacy of pain control (97,98). Sustained and controlled release opioid formulations have a slower onset and later peak effect. Many of the twice-daily preparations have an onset of action of one to two hours and reach peak drug levels at four hours. The once daily preparations have a slower onset and reach peak drug levels at 8.5 hours and are most appropriately used for maintenance or control of stable background pain. These preparations generally do not allow rapid titration for patients in severe pain, due to slow onset and the long dosing intervals (28).

Sustained and controlled release medications were shown to improve compliance and reduce sleep disturbance. The use of eight hourly dosing of these preparations intended for twice daily use is rarely indicated but is a common practice (97).

Breakthrough Pain

Sign 106

> ☑ **When using a transmucosal fentanyl formulation for breakthrough pain the effective dose should be found by upward titration independent of the regular opioid dose.**

Sign 106

Breakthrough pain is defined as a transient flare-up of pain of moderate or severe intensity arising on a background of controlled pain (5). Breakthrough pain is characteristically (99):

- rapid onset (peaks within one to three minutes)
- of moderate to severe intensity
- of short duration (median 30 minutes, range 1-240 minutes)
- associated with worse psychological outcomes
- associated with poor functional outcome
- associated with a worse response to regular opioids
- associated with negative social and economic consequences

Sign 106

Breakthrough pain can be spontaneous or incident. Spontaneous pain is sudden and unexpected. Incident pain is associated with an action such as breathing, movement or micturition and can be anticipated. This distinction is important for therapeutic management. For example, breakthrough pain medication may be taken in anticipation of an episode that is likely to precipitate incident pain, such as walking or having a wound dressing changed.

Differentiation between breakthrough pain and 'end of dose failure' of regular around the clock (ATC) analgesia is important. End of dose failure occurs at a similar time each day usually shortly before the next dose of regular analgesia and is caused by an inadequate dose of ATC analgesia. An increase in the ATC dose will address end of dose failure.
Convention established an effective means of titrating the ATC opioid by using the number of

breakthrough doses used in the preceding 24 hours and adding all or a proportion of this to the latest ATC dose. Empirically, the widely accepted ratio of the breakthrough dose to the ATC medication has been 1:6, i.e., equivalent to the four hourly opioid dose (88). In patients where the intent is to gain control of pain, traditionally there is a dual titration of the ATC and the breakthrough medication with a constant ratio maintained between the two as the doses increase.

Sign 106 *Modified*

The opioid for treating breakthrough pain should ideally have pharmacokinetics which mirror the time features of the majority of patients' specific breakthrough pain, i.e., rapid onset of action, high analgesic potency, fast offset of action and oral formulation. In Canada, a growing practice is to use the parenteral form of fentanyl or sufentanil transmucosally for rapid prevention and/or control of incident pain or other types of breakthrough pain. This requires an experienced prescriber. Newer transmucosal delivery methods such as innovative transmucosal and transnasal are under development.

Administration of Opioids
Route of Administration of Opioids

In the majority of patients taking opioids, oral delivery is preferred as it is effective and simple. Transdermal, subcutaneous or very occasionally intravenous routes are necessary when patients are unable to take the opioid orally, for example due to vomiting or swallow difficulties.

Sign 106 *Modified*

- The **oral** route should be used for administration of opioids, if practical and feasible.
- **Transdermal** opioid patches can be a useful alternative to intravenous or subcutaneous infusions for patients unable to swallow oral medication. Due to the long duration of action of each patch they are only recommended for patients whose pain is relatively stable and who do not need rapid titration.
- **Continuous subcutaneous infusion** of opioids is simpler to administer and equally as effective as continuous intravenous infusion and should be considered for patients unable to take opioids orally.

Sign 106 *Modified*

The small volume of infusate used in pain pumps means that the drugs delivered may be very concentrated. Often the patients require other drugs to be administered concomitantly via the subcutaneous route, with the potential for drug incompatibilities. Avoid administering irritant drugs subcutaneously, e.g., diazepam, chlorpromazine, prochlorperazine. Information from published or peer reviewed studies of chemical and/or physical stability should be consulted.

- **Epidural** and **intrathecal** routes are considered in specific pain syndromes when pain has been unresponsive to opioids. Consultation with palliative care or pain consultants and anesthetists are required.

Conversion Ratios Between Different Routes of Administration of Opioids

Sign 106

Current practice for converting opioid doses between different routes of administration is based on pharmacokinetic data for individual opioids, such as bioavailability after oral administration, and on expert opinion and experience. There may be wide variation from patient to patient. Conversion ratios are guidelines only and careful monitoring of patients is required when changing opioids particularly if tolerance is suspected.

Titrating Opioids

- A careful individual assessment of pain control, degree of side effects and total amount of opioid required, including breakthrough doses, in the previous 24 hours must be made daily prior to prescribing.
- Starting doses in oral morphine equivalents in opioid-naive patients are generally 5 to 10 mg four hourly in young and middle aged people and 2.5 to 5 mg four hourly in the elderly (88).
- Conventional practice is to commence an immediate release formulation of opioid which allows pain to be controlled more rapidly. This also allows earlier assessment and titration up or down if necessary.
- Once pain has been controlled the four hourly dose may be converted to a 12 hourly sustained release dose by dividing the effective total 24 hour dose by two.
- Allow 24 hours of regular and prn dosing before increasing the regular dose of immediate release opioid.

- Allow 48 hours of regular and prn dosing before increasing the regular dose of sustained release morphine, hydromormorphone and oxycodone preparations.
- Allow 72 hours before considering increasing the strength of a fentanyl patch.

Care should be taken when calculating a new regular dose for patients who are pain free at rest but have pain on movement (incident pain). If all the analgesia for this pain is incorporated into the new regular morphine dose, such patients could be rendered opioid toxic with the primary symptoms being excessive sedation, confusion and nausea. Maximizing non-opioid and adjuvant analgesics and consideration of other treatment modalities such as radiotherapy, anaesthetic nerve blocks, and stabilizing surgery is important (100,101).

Rotation between Strong Opioids

Despite dose titration and appropriate management of predictable adverse effects, a minority of patients prescribed strong opioids have inadequate pain relief, persistent unacceptable adverse effects, or a combination of the two.

Changing to a different opioid in an attempt to improve the balance between efficacy and adverse effects and thus achieve good pain control is termed opioid rotation. All opioids have the same spectrum of adverse effects but the intensity of these adverse effects can vary between individuals exposed to different opioids (102).

Evidence to support the practice of opioid switching to improve pain relief and/or drug tolerability is anecdotal or based on observational and uncontrolled studies. Despite this, for patients with inadequate pain relief and persistent intolerable opioid-related toxicity/adverse effects, a switch to an alternative opioid may be considered in an attempt to achieve a better balance between pain relief and adverse effects (56).

Conversion Ratios

> ☑ **Tables of dose conversion ratios should be used only as an initial approximate guide (See Appendix E).**

Conversion Ratios between Different Opioid Drugs (See Appendix E)

There is a need to calculate equivalent doses of opioids in two situations: 1) when patients step up from a weak opioid to a stronger opioid; 2) if the need arises to switch between strong opioids.

There is wide variation in equianalgesic dose ratios between opioids reported in published studies, Health Canada guidelines, manufacturers' literature and reference sources (103-105). An appreciation of the reasons for this is important to ensure that switching between opioids is carried out safely without overdosing, whilst as far as possible providing an acceptable level of analgesia. Dose conversion ratios between opioids are commonly derived from single dose studies, and because of the role of metabolites which take longer to reach a steady state, the applicability of these ratios to chronic opioid administration is questionable (106).

Particular attention to monitoring and dose titration up or down is needed when:
- switching between opioids at high doses where cross tolerance may need to be accounted for
- there has been a recent rapid escalation of the first opioid
- switching to methadone (in consultation with palliative care specialists or pain specialists)

When converting from one opioid to another, regular assessment and reassessment of efficacy and adverse effects is essential. Dose titration up or down according to pain control and adverse effects may be required.

Control of opioid-induced nausea and vomiting

Many opioid-naïve patients will develop nausea or vomiting when started on opioids. Tolerance in the majority of patients usually occurs within 5-10 days. Patients commencing an opioid for moderate to severe pain should have access to an antiemetic to be taken if required.

Control of Opioid-Induced Constipation

The majority of patients taking opioids for moderate to severe pain will develop constipation. Little or no tolerance develops. There remains uncertainty about the best management of constipation in this group of patients (107) although the commonest prophylactic treatment for preventing opioid-induced constipation is a combination of stimulant (senna or bisacodyl) and osmotic laxatives (lactulose or PEG 3350) (108, 109). In very resistant cases, a peripheral opioid receptor antagonist, methylnaltrexone may be effective.

Issues of Tolerance, Addiction and Risk Management

The perception that the administration of opioids for pain management frequently causes addiction is a prevalent issue that may inhibit adequate pain control. Part of this arises from confusion about the differences between addiction, tolerance, and physical dependence (Table 5).

Table 5. Definitions of addiction, tolerance and physical dependence (110)

Term	Definition
Drug addiction	Impaired control over drug use, compulsive use and craving, and continued use despite harm
Drug (Physical) dependence	Distinct from drug addiction. Drug (physical) dependence is a physiologic and neuroadaptive mechanism, whereas drug addiction is behavioral.
Pharmacologic tolerance	The reduced effectiveness of a given dose of medication over time
Pseudo- addiction	Refers to situations where a patient's behavior appears to be drug seeking but actually they are needing more medication to treat a problem that is therapeutically undertreated.
Diversion	The redirection of opioids to support other person(s) addiction or selling opioid for personal gain (trafficking).

Addiction is a chronic neurobiological disease produced by repeated exposure to an addictive drug and characterized by loss of control over drug use (111). Its hallmark is psychological dependence on drugs and a behavioral syndrome characterized by compulsive drug use and continued use, despite harm. Care must be taken to differentiate a true addiction (substance use disorder) from pseudoaddiction due to undertreatment of pain. Other drivers that are troublesome but not true addiction include: behavioral/ family/ psychological dysfunction, and drug diversion with economic or criminal intent.

The currently recognized theory identifies the positive reinforcing effects through a dopaminergic mechanism in part, of drugs like opioids as the predominant role in the addiction process. Withdrawal phenomena, acting on this same reward circuitry, create negative reinforcing effects (withdrawal anhedonia) which contribute to craving and compulsive use, at least during active use and early abstinence. Physical dependence is the result of neurophysiologic changes that occur in the presence of opioids. Abrupt opioid withdrawal may result in an abstinence syndrome characterized by tachycardia, hypertension, diaphoresis, piloerection, nausea and vomiting, diarrhea, body aches, abdominal pain, psychosis, and/or hallucinations.

Physical dependence is different from addiction and is not evidence of addiction. In the face of dependence, opioids can be discontinued if the pain stimulus changes. If the pain stimulus decreases or disappears, opioid doses can usually be reduced in decrements of 50% or more every 2 to 3 days, and finally stopped. If the dose is lowered too quickly and withdrawal symptoms occur, a transient increase in the opioid dose, treatment with clonidine, or a small dose of a benzodiazepine (e.g., lorazepam) may be necessary to treat distressing symptoms.

Pharmacologic tolerance is the reduced effectiveness of a given dose of medication over time. Tolerance to side effects is observed commonly and is favorable. Tolerance to analgesia is rarely significant clinically when opioids are used routinely. Doses may remain stable for long periods if the pain stimulus remains unchanged. When increasing doses are required, generally suspect worsening

disease rather than pharmacologic tolerance. A very large dose of opioids suggests the development of tolerance and opioid rotation may be required.

To manage pain effectively, health care providers need to educate patients, families, and other professionals about the inappropriate fear of addiction. Opioids by themselves do not cause psychological dependence. Addiction is a rare outcome of pain management when there is no history of substance abuse and if universal prescribing precautions are followed (see below).

Since patients with histories of substance abuse can also develop significant pain, they deserve compassionate treatment of their pain when it occurs. Most will need to adhere to strict dosing protocols, and contracting (see Appendix F for an example) may become necessary. Physicians who are unfamiliar with these situations may need the help of specialists in pain management and/or addiction medicine.

Universal Precautions in Prescribing Opioids

The increasingly long term use of opioids in palliative care patients may expose the patient to more risk of drug abuse. Universal precautions offer a triage scheme for estimating risk that includes recommendations for management and referral. This is a thorough and respectful approach so that the stigma associated with taking opioids can be reduced, patient care improved and overall risk contained. Some people advocate universal precautions in all populations of patients on opioids. Even in patients with advanced cancer, the following universal precautions are recommended as a guide to start a discussion with patients and their caregivers (112). They are not proposed as a complete guide but rather as a good starting point for those treating chronic pain. This is an important element of risk management and patient safety.

1) **Make a Diagnosis with an Appropriate Differential Diagnosis**
   Identify the causes for pain and therapy directed to specific pain generators. In patients with advanced illnesses, the absence of specific objective findings, the symptoms can, and should be treated. Address co-morbid conditions (e.g., substance abuse or psychiatric illness).

2) **Do a Psychological Assessment Including Risk of Addictive Disorders**
   Perform a complete inquiry into past personal and family history of substance misuse. A sensitive and respectful assessment of risk should not be seen in any way as diminishing a patient's complaint of pain. Urine drug testing should be discussed routinely with high risk patients regardless of what medications they are currently taking. Those found to be using illicit or unprescribed illicit drugs should be offered further assessment for possible substance use disorders. Patients using marijuana for medical reasons may confound this issue. Those refusing such assessment should be considered unsuitable for pain management using controlled substances.

3) **Informed Consent**
   Education is part of the process of prescribing opioids for patients with advanced disease. A discussion of potential benefits of opioids, their adverse effects and the risks of addiction and tolerance should be explored at a level appropriate to the patient's understanding. Any questions the patient may have about the proposed treatment should be fully addressed.

4) **Treatment Agreement ("Contract")**
   As part of the patient education process, whether in writing or verbally agreed, expectations and obligations of both the patient and the treating practitioner need to be clearly understood. This agreement should cover keeping opioids safely at home, the process for renewal of medications, the

use of a single pharmacy for prescriptions, and the issues that would trigger review of the treatment agreement.

5) **Pre- and Post-Intervention Assessment of Pain Level**

Any treatment plan begins with a trial of therapy. A documented assessment of pre-intervention pain scores and level of function will aid in the identification of the goal of treatment. Ongoing assessment and documentation of clinical goals will support the continuation of any mode of therapy.

6) **Appropriate Trial of Opioid Therapy +/–Adjuvant Medications**

Pharmacologic regimens must be individualized based on subjective, as well as objective, clinical findings. The appropriate combination of agents, including opioids and adjuvant medications provide a stable therapeutic platform from which to base treatment changes.

7) **Reassessment of Pain Score and Level of Function**

Regular reassessment of the patient, combined with corroborative support from family and other health care providers in the team is part of good pain management and palliative care. This will help document the rationale to continue or modify the current therapeutic trial.

8) **Regular Assessment of the "Four A's" of Pain Medicine**

Routine assessment of analgesia, activity, adverse effects, and aberrant behavior will help to direct therapy and support pharmacologic options taken. It may also be useful to document a fifth "A": affect.

9) **Periodically Review Pain Diagnosis and Co-morbid Conditions, Including Addictive Disorders**

If underlying illnesses begin to evolve into possible addiction, the treatment parameters and the treatment agreement may need to be amended. If an addictive disorder predominates, aggressive treatment of an underlying pain problem will likely fail if not coordinated with treatment for the concurrent addictive disorder.

10) **Documentation**

Careful and complete recording of the continuing pain assessments and evaluation of treatment are critical for effective management and will reduce medicolegal exposure and the risk of regulatory sanction.

Patient Issues

A narrative review of the literature identified three overlapping and inter-related areas of concern to patients with cancer pain: communication, relationships and spirituality.

Communication & Relationships

Sign 106

> ☑ **Cancer services should facilitate peer support to enable patients to communicate effectively with professionals and others.**
> ☑ **Healthcare professionals should be given training to overcome the specific challenges around communication with people with cancer, their informal care givers and other professionals.**

Sign 106 *Modified*

A frequently cited issue was the importance of communication between and among the various groups involved (i.e., patients, informal care providers and healthcare professionals). For patients, good communication, planning and trust are fundamental concepts for perceived control of cancer-related pain. When appropriate, patients should be told that most pain can be relieved by medication without persistent side effects. Fears about use of medication should be addressed.

Good relationships with professionals can lead to better patient concordance with therapy and better adjustment to diagnosis (113). Informal care providers can play an active role in assessment and management of pain but informal care provider managed analgesia requires good communication with the clinician. Clinicians should be aware of the burdens realized on the informal care providers of patients with cancer pain (114). Clinicians and nursing staff should get to know the patient and family, as well as possible, to enable patients and family to voice their fears, wishes and concerns with confidence.

Points to remember:

Sign 106 *Modified*

- Good communication with patients and carers occurs when it is at their level of understanding, is non-patronizing, free of jargon and when the healthcare staff know the patient and care givers well and actively listen (113,115).
- Poor communication between patients and professionals may result in clinical assessment that is not comprehensive, and under-reporting of pain by patients (112).
- Pain, its assessment and management should be discussed at an early stage of the disease (116).
- Patients find it easier to talk about their pain when given strategies that enable them to do so: this may include diaries, and the opportunity to talk to other patients (117).

Spirituality

> ☑ **Healthcare professionals should be educated about the psychological and social dimension of the cancer experience.**
>
> ☑ **Service providers and those providing education should have a basic understanding of the range of beliefs held by patients across a multifaith and multicultural context.**
>
> ☑ **Support should be provided for professionals in dealing with the impact of their work on their own understanding of themselves and their belief systems.**

Sign 106

A series of studies explored how patients attempt to make sense of their experience of pain and how they come to terms with a life threatening illness, in the context of their belief system. There is some qualitative evidence that, in addition to conventional treatments, strengthening religious faith is important in fostering the ability of some terminally ill patients to cope (118).

Points to remember:

Sign 106 *Modified*

- Individuals need a sense of meaning to life and of making a connection with life to be able to deal with the demands of aggressive or invasive treatments (119).
- Patients experience the 'existential challenge' of cancer as a kind of pain that can be greater than physical pain (118).
- Patients value professionals who adopt a holistic approach to care and are competent in dealing with (and are able to communicate about) the spiritual, psychological, and emotional impact of pain (118).

Glossary

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Breakthrough pain: pain of moderate or severe intensity arising on a background of controlled chronic pain. Breakthrough pain may be described as spontaneous (unexpected) or incident (expected or predictable).

Opioid medications: classified as per custom into weak (e.g., codeine, dihydrocodeine and tramadol) and strong opioids (e.g., morphine, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine **and** methadone). Weak opioids generally are used for treating mild to moderate pain and strong opioids for moderate to severe pain.

Adjuvant analgesics: are drugs with other primary indications that can be effective analgesics in specific circumstances.

Abbreviations

ATC	Around the Clock
BPI	Brief Pain Inventory
COX-2	Cyclooxygenase-2
EDR	equianalgesic dose ratio
ESAS	Edmonton Symptom Assessment System
GI	gastrointestinal
HIV	human immunodeficiency virus
MDASI	M.D. Anderson Symptom Inventory
MSAS	Memorial Symptom Assessment Scale
NNT	number needed to treat
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
ONJ	osteonecrosis of the jaw
RCT	randomized controlled trial
VAS	visual analogue scale
VRS	verbal rating scale
WHO	World Health Organization

Appendices

Appendix A – Methodology

The Standards, Guidelines and Indicators Sub-group of the Re-Balance Focus Action Group, established under the Canadian Cancer Control Strategy, performed a literature review and environmental scan[i]. This review was used by the SMG as a source from which to identify existing guidelines relative to the four symptoms of interest. Additionally, SMG members reached programs in Ontario, searched the Cancer Care Ontario Program in Evidence-based Care website and their own personal sources for any relevant guidelines.

The Re-Balanced Focus Action Group used the following search criteria in their review:

Inclusion Criteria

1. Standards focused on care delivered by cancer organizations; and/or processes of care; and/or professional practice standards specific to cancer.
2. Guidelines focused on clinical practice of practitioners relevant to psychosocial, supportive or palliative care provision to cancer patient populations.
3. Guidelines that were more generic in focus but relevant to supportive care aspects of cancer populations in areas such as prevention and screening were also included.

Exclusion Criteria

1. Guidelines that did not base the development of substantive statements/recommendations on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.
2. Guidelines that were focused on providing direction to patients and families for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.

Databases Searched

Health Sciences literature databases used in this scan include HealthStar, Medline, CINHAL, Embase and PsycINFO. The internet search engine Google Scholar was utilized for the grey literature search for scientific and non-scientific sources. Databases for the following organizations were also reviewed: a) All oncology professional associations and organizations for Psychosocial Oncology and Palliative Care inclusive of Oncology Social Workers, Clinical Oncology; b) All Canadian Provincial Cancer Care Organizations within provinces; c) International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development. The literature search and environmental scan was updated in December 2008 and again in January 2009.

---

[i] Re-Balance Focus Action Group. Literature Review and Environmental Scan: Psychosocial, Supportive and Palliative Care Standards and Guidelines. Updated 2009.

Results

Based on the literature review and environmental scan described above, the Pain SMG identified eighteen pain related guidelines for inclusion in this Guide-to-Practice. Eleven guidelines (120-130) were rejected at the onset by the group because they fell outside of the scope of the Guide-to-Practice or were not methodologically sound. The remaining seven guidelines (1,131-136) were screened and assessed for quality, currency, content, consistency, and acceptability/applicability, using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (www.agreetrust.com). Taking into consideration the AGREE scores and expert consensus, the working group felt that the SIGN 106 guideline (1) was the most applicable and relevant of the seven reviewed guidelines hence it formed the basis for this Guide-to-Practice (refer to Table 6 for details).

Table 6. AGREE Scores

AGREE Scores	SIGN 106 (1)	NCCN Pain (131)	NCCN (132)	NHMRC (133)	CCNS (134)	PEBC 1-11 (135)	PEBC 13-8 (136)
Scope & Purpose	100	44.44	85.19	68.11	77.78	34	91.67
Stakeholder Involvement	66.67	27.78	41.67	75	50	26	54.17
Rigour of Development	74.60	26.98	38.10	77.38	46.03	74	79.76
Clarity & Presentation	91.67	61.11	77.78	70.83	44.44	32	68.75
Acceptability	51.85	7.4	22.22	72.22	29.63	15	33.33
Editorial Independence	83.33	50	77.78	8.33	33.33	14	91.67
Overall Quality Assessment	Recommend with Provisos. Great document in almost every respect. Current and well researched. Must be adapted to Canadian context.	Recommend with Provisos. Considered best practice not evidence based.	Recommend with Provisos. Meds used are not used in Ontario; good to see antipsychotics were used as they are often more effective; did not specify when meds should be used.	Rejected. Good for management of advanced breast cancer but not for pain.	Rejected. Inaccurate and out of date information	Good for what it stated but not very good overall for pain.	Succinct but not readable, confusion with section layout. Good methodology. More info on neuropathic drugs needed.

The ADAPTE process (http://www.adapte.org/) was then used to systematically endorse or modify applicable components of the SIGN guideline (1). The guideline development process, utilizing ADAPT, proceeds under the assumption that the original recommendations are reasonable and supported by the evidence. Confidence in this assumption is fostered from satisfactory AGREE scores. In situations were evidence was not available or not applicable to specific clinical situations, systems and contexts recommendations were modified based on the expert consensus of the working group. It is beyond the scope of the guideline development process and this document to make the connection between the recommendations and the original key evidence. For those who wish to do so, please refer to the Scottish Intercollegiate Guidelines Network Sign 106 Control of Cancer Pain in Adults with Cancer: A National Clinical Guideline (1).

Appendix B – Peer Review Summary

Expert feedback was obtained through an internal and external review:

Internal Review

The internal review consisted of an anonymous appraisal of the Guides by members from each of the working groups. The intent of this review was to ensure that the Guide development process was methodologically rigourous, the recommendations are supported by the evidence in a transparent way and that the guide was clinically relevant and applicable to practice.

A total of 39 online surveys were collected during the internal review (refer to Table 7 for details). Thirteen participants completed the pain Guide-to-Practice survey; however two respondents provided written comments only. The survey feedback was thoroughly reviewed by each of the corresponding working groups and, where appropriate, changes were made.

Table 7. Responses to 14 key questions on the pain internal review survey (11respondents)

Question	Strongly Agree Percent (Response count)	Agree Percent (Response count)	Disagree Percent (Response count)	Strongly Disagree Percent (Response count)
The methods for formulating the recommendations are clearly described.	37.5 % (3)	62.5% (5)	0%	0%
There is an explicit link between the supporting evidence and the recommendations.	36.5% (4)	45.5% (5)	18% (2)	0%
The recommendations are in agreement with my understanding of the evidence.	27% (3)	64% (7)	9% (1)	0%
The recommendations are specific and unambiguous.	18% (2)	82% (9)	0%	0%
The recommendations are easily identifiable.	36.5% (4)	45.5% (5)	18% (2)	0%
The recommendations are achievable.	27% (3)	73% (8)	0%	0%
The health benefits, side effects, and risks have been considered in formulating the recommendations.	36% (4)	64% (7)	0%	0%
When applied, the Guide-to-Practice will produce more benefits for patients than harm.	55% (6)	45% (5)	0%	0%
The different options for management of the condition are clearly presented.	36% (4)	55% (6)	9% (1)	0%
The Guide-to-Practice is supported with tools for application.	36% (4)	64% (7)	0%	0%
The Guide-to-Practice is user friendly.	18% (2)	64% (7)	18% (2)	0%
The Guide-to-Practice presents a series of options that can be implemented.	36% (4)	64% (7)	0%	0%
Question	**Yes, Strongly Agree** Percent (Response count)		**No, Strongly Disagree** Percent (Response count)	
Do you perceive any barriers or challenges in using this Guide-to-Practice?	55% (5)		45% (6)	
Would you be able to apply these recommendations to the clinical care decisions for which you are professionally responsible?	100% (11)		0%	

External Review

The external review process consisted of: I) a Targeted Peer Review, intended to obtain direct feedback on the draft guides from a small number of specified content experts and II) a Professional Consultation, that intended to disseminate the draft guide as widely as possible to its intended readership, provide a forum for recipients to explain any disagreement with the recommendations, and to further ensure the quality and relevance of the document.

I)   Targeted Review

Seven reviewers were invited to participate in the external target review and five provided responses (refer to Table 8 and 9 for details).

Table 8. Overview of the Pain Targeted Peer Reviewers

Guide	Sample	Results
Pain	**7 Reviewers:** 1 Palliative care physician 1 Neurologist 1 Pain specialist 1 Nurse practitioner 1 Pharmacist 2 Methodology experts	**5 Responses:** 1Neurologist 1 Pain specialist 1 Pharmacist 2 Methodology experts

Table 9. Responses to key questions on the pain target peer review survey (5 respondents)

Question	1 Lowest Quality % (Response count)	2 % (Response count)	3 % (Response count)	4 % (Response count)	5 Highest Quality % (Response count)
Rate the Guide-to-Practice development methods.	0%	0%	0%	100% (5)	0 %
Rate the Guide-to-Practice presentation.	0%	0%	20% (1)	60% (3)	20%(1)
Rate the Guide-to-Practice recommendations.	0%	0%	20% (1)	60% (3)	20% (1)
Rate the completeness of the reporting.	0%	20% (1)	20% (1)	60% (3)	0%
Does this document provide sufficient information to inform your decisions?	0%	0%	20% (1)	60% (3)	20% (1)
Rate the overall quality of the Guide-to-Practice.	0%	0%	20% (1)	80% (4)	0%
Question	1 Strongly Disagree % (Response count)	2 % (Response count)	3 % (Response count)	4 % (Response count)	5 Strongly Agree % (Response count)
I would make use of this Guide-to-Practice in my professional decisions.	0%	20%(1)	20%(1)	20% (1)	40%(2)
I would recommend this Guide-to-Practice for use in practice.	0%	0%	0%	60% (3)	40% (2)

II) Professional Consultation

The Professional Consultation consisted of a sample of approximately 290 health care practitioners. Participants were contacted by email and asked to read the guides and complete a brief corresponding electronic survey.   Forty-nine responses were received (refer to Table 10 and 11 for details). Eleven respondents reviewed the Pain guide.

Table 10. Overview of the Professional Consultation sample

Profession	Sample	Results
All Guides		
Palliative Care Physicians	49	18
Nurses	32	15
Pharmacists	20	1
Family Physicians	6	4
Medical Oncologists	14	4
Radiation Oncologists	17	1
Surgical Oncologists	11	0
Provincial Palliative Care Committee	9	0
PEBC Supporting Care Group / Researchers/Academics	9	3
Dietitians	75	2
Psychiatrists	6	1
Neurologists	16	0
Respirologists	26	0
TOTAL:	**290**	**49 (Response rate 17%)**

* Participant were encouraged to forward the electronic survey to interested colleagues, hence the total sample size is only an estimate.

Table 11. Responses to key questions on the Professional Consultation survey (49 respondents)

Question *	1 Strongly Disagree Percent (Response count)	2 Percent (Response count)	3 Percent (Response count)	4 Percent (Response count)	5 Strongly Agree Percent (Response count)
I would make use of this Guide-to-Practice in my professional decisions.*	2.1% (1)	2.1%(1)	14.6 (7)	31.2% (15)	50% (24)
I would recommend this Guide-to-Practice for use in practice	2.1 % (1)	2.1% (1)	10.3% (5)	29.2% (14)	56.3% (27)
Question	**1 Lowest Quality** Percent (Response count)	**2** Percent (Response count)	**3** Percent (Response count)	**4** Percent (Response count)	**5 Highest Quality** Percent (Response count)
Rate the overall quality of the Guide-to-Practice.	0	2.1% (1)	14.6% (7)	35.4% (17)	47.9% (23)

* Some participants answered 'Other' and provided written comments or skipped questions

Appendix C- Characteristics of Nociceptive and Neuropathic Pain

Table 1. Examples and Characteristics of Nociceptive Pain

	Superficial Somatic Pain	Deep Somatic Pain	Visceral Pain
Nociceptor location	Skin, subcutaneous tissue, and mucous membranes	Muscles, tendons, joints, fasciae, and bones	Visceral organs[a]
Potential stimuli	External mechanical, chemical, or thermal events Dermatologic disorders	Overuse strain, mechanical injury, cramping, ischemia, inflammation	Organ distension, muscle spasm, traction, ischemia, inflammation
Localization	Well localized	Localized or diffuse and radiating	Well or poorly localized
Quality	Sharp, pricking, or burning sensation	Usually dull or aching, cramping	Deep aching or sharp stabbing pain, which is often referred to cutaneous sites
Associated symptoms and signs	Cutaneous tenderness, hyperalgesia hyperesthesia, allodynia	Tenderness, reflex muscle spasm, and sympathetic hyperactivity[b]	Malaise, nausea, vomiting, sweating, tenderness, reflex muscle spasm
Clinical examples	Sunburn, chemical or thermal burns, cuts and contusions of the skin	Arthritis pain, tendonitis, myofascial pain	Colic, appendicitis, pancreatitis, peptic ulcer disease, bladder distension

Sources: References 22-24 and 88-89.

[a]Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys, and bladder.

[b]Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating; pallor; dilated pupils; nausea; vomiting; dry mouth; and increased muscle tension.

Table 2. Examples and Characteristics of Neuropathic Pain

	Painful Mononeuropathies and Polyneuropathies	Deafferentation Pain	Sympathetically Maintained Pain[a]	Central Pain
Definition	Pain along the distribution of one or multiple peripheral nerve(s) caused by damage to the affected nerve(s)	Pain that is due to a loss of afferent input	Pain that is maintained by sympathetic nervous system activity	Pain caused by a primary lesion or dysfunction of the CNS
Pain characteristics and associated symptoms	Three main types: • Continuous, deep, burning, aching or bruised pain • Paroxysmal lancinating (shock-like) pain • Abnormal skin sensitivity	• Quality: burning, cramping, crushing, aching, stabbing, or shooting • Hyperalgesia • Hyperpathia • Dysesthesia • Other abnormal sensations	• Quality: burning, throbbing, pressing, or shooting • Allodynia • Hyperalgesia • Associated ANS dysregulation and trophic changes[b]	• Quality: burning, numbing, tingling, shooting • Spontaneous and steady or evoked • +/- sensory loss • Allodynia • Hyperalgesia
Sources	• Metabolic disorders (e.g., diabetes) • Toxins (e.g., alcohol chemotherapy agents) • Infection (e.g., HIV, herpes zoster) • Trauma • Compressive (nerve entrapment) • Autoimmune and hereditary diseases	• Damage to a peripheral nerve, ganglion, or plexus • CNS disease or injury (occasional)	• Peripheral nerve damage (e.g., CRPS II) • Sympathetic efferent (motor) innervation • Stimulation of nerves by circulating catecholamines	• Ischemia (e.g., stroke) • Tumors • Trauma (e.g., spinal cord injury) • Syrinx • Demyelination
Clinical examples	• Diabetic neuropathy • Alcoholic neuropathy • Postherpetic neuralgia • Carpal tunnel syndrome	• Phantom limb pain • Post-mastectomy pain	• CRPS • Phantom limb pain • Postherpetic neuralgia • Some metabolic neuropathies	• Post-stroke pain • Some cancer pain • Pain associated with multiple sclerosis

Sources: References 22-23, 87, and 97a-97d.

[a]Sympathetically maintained pain is a pain mechanism, not a diagnosis. It is associated with several types of pain, but it also may exist as a single entity.[97c]

[b]Focal autonomic dysregulation can manifest with signs and symptoms such as swelling, pallor, erythema (redness), sweating, and temperature changes. Trophic changes include thinning of the skin, abnormal hair or nail growth, and bone changes.

ANS: autonomic nervous system; CNS: central nervous system; CRPS: complex regional pain syndrome types I and II; CRPS II: complex regional pain syndrome type II; HIV: human immunodeficiency virus.

Appendix D – Pharmaceutical Adjuvants for Neuropathic Pain

Drug Class	Specific Drugs	Dosages	Important Side Effects	Other Issues
Tricyclic Antidepressants	Desipramine Nortriptyline Imipramine Trimipramine Amitriptyline	For all begin with 25mg HS and increase gradually to 75-150mg HS. In frail elderly, may want to begin with 10mg Titrate q3-7 days	Dry mouth, sedation, urinary retention, constipation, dry mouth especially with amitriptyline	• Generally avoid amitriptyline especially in elderly because more adverse effects • Do not use if : 2° or 3° heart block on ECG, arrhythmias, ↑QT interval, or history of arrhythmias • NNT 2-3 • Do not use with SSRI drugs • All covered by ODB
SNRI	Venlafaxine	37.5-300mg daily	Nausea, dizziness, sedation	• Dosage adjustments in renal failure required • Some response in trials on post-mastectomy pain but inconsistent results in other NP except painful diabetic polyneuropathy • Do not use with SSRIs • Covered by ODB
Anticonvulsant	Carbamazepine	200-600mg daily	Sedation, nausea	• Do not use if bone marrow suppression, liver dysfunction • Monitor CBCs & LFTs • Not particularly effective • Covered by ODB
Anticonvulsant	Gabapentin Pregabalin	300-3600mg daily Titrate q7-14 days starting at 100-300mg OD to TID 50-600 mg max dose daily Titrate q7-14 days Starting dose 25-50mg BID	Sedation, cognitive dysfunction, peripheral edema, ataxia at higher doses Risk of depression and suicide	• Dosage adjustments in renal failure • Do not discontinue suddenly-usually over at least 1 to 2 weeks • Not covered by ODB except under EAP which generally requires a failed trial of TCA's, intolerance or contraindication to TCA's • Available under Palliative Care Facilitated Access for patients with prognosis <6 months by MD calling 416 327 8109.
Anticonvulsant	Phenytoin	300-600mg daily	Gingival hypertrophy, ataxia	• Monitor levels • Poor safety profile-very interactive with other drugs. Limited efficacy • Covered by ODB

Drug Class	Specific Drugs	Dosages	Important Side Effects	Other Issues
Anticonvulsant	Valproic acid & Derivatives	Depends on specific drug	Sedation, nausea, vomiting, tremor	• Poor efficacy-not recommended • Monitor CBC & LFTs • Covered by ODB
	Lamotrigine	50-600mg daily		• Neither of these drugs is recommended-NNT high & should be reserved for patients unresponsive to other drugs
	Topiramate	25-400mg daily		• Neither of these drugs is covered by ODB for neuropathic pain
Cannabinoids	Nabilone (Cesamet®) delta-9-THC (Marinol®)	0.5-6.0mg daily 5-20mg daily	Sedation, dizziness Cognitive impairment rare	• Medical marijuana available through special license –not generally recommended • Nabilone is covered by ODB • THC is covered only with LU code, for refractory chemotherapy associated emesis; not specifically covered for neuropathic pain • cannabidiol spray is not covered by ODB
	THC/cannabidiol spray (Sativex®)	Start at 1 spray q4h and titrate		
	Medical marijuana			
NMDA Antagonists	Ketamine	Variable-can be given orally,sc or IV	Cognitive impairment, sedation	• To be used by experienced providers
	Amantadine	100-400mg daily	Agitation, anxiety, confusion, ataxia, sedation, skin mottling	• Not very effective & significant side-effects
Corticosteroids	Prednisone	20-50mg daily	Cushingoid effects, GI bleeding, edema, depression, proximal myopathy, agitation, hyperexcitability	• Limited and short term use only • Have been used to limit pain in first week post-taxane therapy
	Dexamethasone	4-16mg daily		

EAP= Exceptional Access Program; ODB=Ontario Drug Benefits

Appendix E – Dose Conversion Tables

(Table from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/fentanyl_hpc-cps-eng.pdf)

It should be noted that these conversion ratios, based on available evidence, are conservative in the direction specified; if converting in the reverse direction, a reduction in dose of one third should be used following conversion, or specialist advice sought.

Drug	Approximate Equivalent Dose [a]	
	Parenteral	**Oral**
Codeine	120	200
Fentanyl	0.1-0.2	n/a [b]
Morphine	10	20-30 [c]
Hydromorphone	2	4-6
Oxycodone	n/a	30
Sufentanil	0.01-0.04	n/a [b]
Tramadol	[d]	[d]
Methadone	[e]	[e]

a. From single dose studies using immediate-release dosage forms. These approximate analgesic equivalences should be used only as a guide for estimating equivalent doses when switching from one opioid to another. Additional references should be consulted to verify appropriate dosing of individual agents.
b. Route of administration not applicable.
c. With repeated dosing.
d. Tramadol's precise analgesic potency relative to morphine is not established. Consult the product monograph for dosing recommendations.
e. For methadone, see text.

Appendix E – Dose Conversion Tables Continued

Conversion doses from oral morphine to transdermal fentanyl

Oral 24-hour morphine (mg/day)	Transdermal Fentanyl (mcg/h)
60-90	25
90 – 134	37 (if available, otherwise 25) *
135 – 189	50
190 – 224	62 (if available, otherwise 25) *
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

*12mcg/h fentanyl patch may not being covered by ODB, therefore if the patient has a private drug plan, combinations involving the 12mcg/h patch may be considered

Appendix F – Table of Opioids

Drug	Availability	
Codeine	acetaminophen 300mg/codeine 8, 15, 30, 60 codeine single entity codeine IR 15, 30, 60mg tabs codeine IR elixir 5mg/ml SR codeine 50 mg, 100 mg, 150 mg, 200 mg	Maximum recommended daily dose of acetaminophen is 4000mg in most patients and less if liver or renal dysfunction
Morphine	IR tabs: 5,10, 20, 25, 30, 40, 50 and 60mg IR Elixir: 1, 5, 10, 20, 50 mg/ml SR tablets (q12h), do not crush: 15, 30, 60, 100, 200mg SR capsules (q12h): 10, 15, 30, 60, 100, 200mg SR capsules (q24h): 10, 20, 50, 100mg	Dosage adjustment or avoid if renal function decreased morphine injection 2mg/mL and 10mg/mL require palliative facilitated access. 200mg SR tablet is scored and can be split in half do not chew. Do not split other strengths of SR tablets. SR capsules (q12h and q24h formulations can be opened and mixed with soft food. Do not crush beads inside capsule.
Hydromorphone	Immediate release tabs 1, 2, 4 & 8mg SR capsules 3, 6, 12, 18, 24, 30mg (q12h) Oral liquid: 1mg/mL Suppositories 3mg	Dosage adjustment or avoid if renal function decreased SCR capsules can be opened and mixed with soft food. Do not crush beads inside capsule
Oxycodone	acetaminophen 325mg/oxycodone 5mg 1-2 tabs q4h (max 10/day) Single entity IR tabs 5, 10, 20 mg CR tabs 10, 20, 40, 80 mg (q12h)	Caution re: total daily dose of acetaminophen No clinically significant active metabolites for oxycodone but may see toxicity in renal failure
Fentanyl	Transdermal 12, 25, 50, 75 & 100µg/h	Not for opioid naïve patients No active metabolites Application to skin must be correct-requires patient education about this
***Methadone**	Tabs 1, 5, 10, 25 mg Elixir: 1 & 10 mg/ml	For use by experienced prescribers only Drug interactions may occur
***Tramadol/ acetaminophen**	acetaminophen 325mg/tramadol 37.5mg 1-2 tabs q4-6h (max 8/day)	Drug interactions need to be checked Contraindicated with MAOIs Caution in patient with seizures Reduce dose in renal impairment Indication is moderate to moderately severe pain in adults and has not been evaluated beyond 12 weeks in clinical trials.
***Tramadol CR**	tramadol extended release: 100 mg, 200 mg, 300 mg (max 300mg) tramadol controlled release: 150 mg, 200 mg, 300 mg, 400 mg (max 400mg)	Begin with low dose Drug interactions need to be checked Contraindicated with MAOIs Caution in patient with seizures Reduce dose in renal impairment Titrate slowly for best tolerability

Note: Drug coverage may change over time. Please consult the Ontario Drug Benefit (ODB) e-formulary for current information on coverage and limited use codes., or contact a pharmacist. For information regarding Facilitated Access to Palliative Care Drugs, see the ODB Exceptional Access Program document. For Frequently Asked Questions, see the Facilitated Access to Palliative Care Drugs.

References

1) Scottish Intercollegiate Guidelines Network SIGN 106, 'Control of Cancer Pain in Adults with Cancer: A National Clinical Guideline; 2008 Nov.

2) Portenoy R. Cancer pain, epidemiology and symptoms. Cancer 1989;63(11 Suppl):2298-307.

3) Stjernsward J, Colleau S, Ventafridda V. The World Health Organization Cancer Pain and Palliative Care Program. Past, Present, and Future. J Pain Symptom Manage 1996;12(2):65-72.

4) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain 1986(Suppl 3):S1-226.

5) Portenoy R, Hagen N. Breakthrough pain: definition, prevalence and characteristics. Pain 1990;41(3):273-81.

6) Sela RA, Bruera E, Conner-Spady B, Cumming C, Walker C. Sensory and affective dimensions of advanced cancer pain. Psychooncology 2002;11(1):23-34.

7) O'Boyle CA, Moriarty MJ, Hillard N. Clinical and psychological aspects of cancer-related pain. Irish J Psychol Med 1988;5(2):89- 92.

8) Cleeland CS, Nakamura Y, Mendoza TR, Edwards KR. Dimensions of the impact of cancer pain in a four country sample: New information from multidimensional scaling. Pain 1996;67(2-3):267-73.

9) Tittle MB, McMillan SC, Hagan S. Validating the Brief Pain Inventory for use with surgical patients with cancer. Oncol Nurs Forum 2003;30(2 part 1):325-30.

10) Cherny N, Coyle N, Foley K. Suffering in the advanced cancer patient: a definition and taxonomy. J Palliat Care 1994;10(2):57-70.

11) Clinical states: cancer pain. In: McMahon S, Koltzenburg M, Editors. Wall and Melzacks' textbook of pain. 5th ed. New york: Churchill Livingstone; 2006. p.1089-131.

12) Payne R. Cancer pain. Anatomy, physiology and pharmacology. Cancer Pain 1989;63:2266-74.

13) Boureau F, Doubrere J, Lu M. Study of verbal description in neuropathic pain. Pain 1990;42(2):145-52.

14) Tearnan B, Cleeland C. Unaided use of pain descriptors by patients with cancer pain. Pain 1990;5(4):228-32.

15) Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann K. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. Pain 1996;64(1):107-14.

16) Grossman S, Sheidler V, Swedeen K, Mucenski J, Piantadosi S. Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage 1991;6(2):53-7.

17) Field L. Are nurses still underestimating patients' pain postoperatively? Br J Nurs 1996;5(13):778-84.

18) Elliott B, Elliott T, Murray D, Braun B, Johnson K. Patients and family members: the role of knowledge and attitudes in cancer pain. J Pain Symptom Manage 1996;12(4):209-20.

19) Cleeland C, Gonin R, Hatfield A, Edmonson J, Blum R, Stewart J, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330(9):592-6.

20) Caraceni A, Cherny N, Fainsinger R, Kaasa S, Poulain P, Radbruch L, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an expert working group of the European Association of Palliative Care. J Pain Symptom Manage 2002;23(3):239-55.

21) Hølen JC, Saltvedt I, Fayers PM, Hjermstad MJ, Loge JH, Kaasa S. Doloplus-2, a valid tool for behavioural pain assessment? BMC Geriatrics 2007;7(29):1-9.

22) City of Hope Pain and Palliative Care Resource Center. Doloplus 2 brief [Internet]. 2004 Apr [updated 2006 Jun; cited 2010 Jul 30]. Available from: http://prc.coh.org/PainNOA/Dol%202_B.pdf

23) Mystakidou K, Parpa E, Tsilika E, Kalaidopoulou O, Georgaki S, Galanos A, et al. Greek McGill pain questionnaire: validation and utility in cancer patients. J Pain Symptom Manage 2002;24(4):379-87.

24) Caraceni A, Mendoza T, Mencaglia E, Baratella C, Edwards K, Forjaz M, et al. A validation study of an Italian version of the Brief Pain Inventory. Pain 1996;65(1):87-92.

25) Pautex S, Herrmann F, Le Lous P, Fabjan M, Michel J, Gold G. Feasibility and reliability of four pain self-assessment scales and correlation with an observational rating scale in hospitalized elderly demented patients. J Gerontol Ser A: Biol Sci Med Sci 2005;60(4):524-9.

26) Zwakhalen SM, Hamers JP, Abu-Saad HH, Berger MP. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. BMC Geriatr 2006;6:3.

27) Anonymous. Report: number of cancer survivors increasing. FDA Consumer. 38(5):8, 2004 Sep-Oct

28) Jadad A, Browman G. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA 1995;274(23):1870-3.

29) Mcquay H, Moore A. Bibliography and systematic reviews in cancer pain. A report to the NHS national cancer research and development programme London: Department of Health; 1997.

30) Lieberman I, Reinhardt MK. Vertebroplasty and Kyphoplasty for Osteolytic Vertebral Collapse. Clin Orthopaed Rel Res 2003;415(Suppl):S176-86.

31) Barragan-Campos HM, Vallee JN, Lo D, Cormier E, Jean B, Rose M, et al. Percutaneous vertebroplasty for spinal metastases: complications. Radiology 2006;238(1):354-62.

32) Weill A, Kobaiter H, Chiras J. Acetabulum malignancies: technique and impact on pain of percutaneous injection of acrylic surgical cement. Eur Radiol 1998;8(1):123-9.

33) Kelekis A, Lovblad K, Mehdizade A, Somon T, Yilmaz H, Wetzel S, et al. Pelvic osteoplasty in osteolytic metastases: technical approach under fluoroscopic guidance and early clinical results. J Vasc Interven Radiol 2005;16(1):81-8.

34) Marcy P, Palussière J, Descamps B, Magné N, Bondiau P, Ciais C, et al. Percutaneous cementoplasty for pelvic bone metastasis. Support Care Cancer 2000;8(6):500-3.

35) Zech D, Grond S, Lynch J, Hertel D, Lehmann K. Validation of World Health Organization guidelines for cancer pain relief: a10-year prospective study. Pain 1995;63(1):65-76.

36) Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer 1987;59(4):850-6.

37) Fellowes D, Barnes K, Wilkinson S. Aromatherapy and massage for symptom relief in patients with cancer. (Cochrane Review). In The Cochrane Library Issue 4, 2004. Chichester; John Wiley.

38) Post-White J, Kinney M, Savik K, Gau J, Wilcox C, I. L. Therapeutic massage and healing touch improve symptoms in cancer. Integr Cancer Ther 2003;2(4):332-44.

39) Cepeda MS, Carr DB, Lau J, Alvarez H. Music for pain relief (Cochrane Review). In The Cochrane Library Issue 4, 2006. Chichester; John Wiley.

40) Siedliecki S, Good M. Effect of music on power, pain, depression and disability. J Adv Nurs 2006;54(5):553-62.

41) Lee H, Schmidt K, Ernst E. Acupuncture for the relief of cancer- related pain-A systematic review. Eur J Pain 2005;9(4):437-44.

42) Alimi D, Rubino C, Pichard-Leandri E, Fermand-Brule S, Dubreuil-Lemaire M, Hill C. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. J Clin Oncol 2003;21(22):4120-6.

43) Robb KA, Newham DJ, Williams JE. Transcutaneous electrical nerve stimulation vs. transcutaneous spinal electroanalgesia for chronic pain associated with breast cancer treatments. J Pain Symptom Manage 2007;33(4):410-9.

44) Stephenson NLN, Swanson M, Dalton J, Keefe FJ, Engelke M. Partner-delivered reflexology: Effects on cancer pain and anxiety. Oncol Nurs Forum 2007;34(1):127-32.

45) Olsen K, Hanson j, Michaud M. A phase II trial of reiki for the management of pain in advanced cancer. J Pain Symptom Manage 2003;26(5):990-7.

46) Syrjala K, Cummings C, Donaldson G. Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. Pain 1992;48(2):137-46.

47) Rajasekaran M, edmonds P, Higginson I. Systematic Review of Hypnotherapy for treating symptoms in terminally ill Adult Cancer Patients Palliat Med 2005;19(5):418-26.

48) Liossi C. Hypnosis in Cancer Care. Contemp Hypnosis 2006;23(1):47-57.

49) Soden K, Vincent K, Craske S, Lucas C, Ashley S. A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 2004;18(2):87-92.

50) Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. Ann Oncol 2005;16(Suppl 4):iv132-5.

51) Ventafridda V, Stjernsward J. Pain control and the World Health Organization analgesic ladder. JAMA 1996;275(11):835-6.

52) Twycross R, Lickiss N. Pain control and the World Health Organization analgesic ladder. JAMA 1996;275(11):835.

53) McNicol E, Strassels S, Goudas L, Lau J, Carr D. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain (Cochrane Review). In The Cochrane Library Issue 1, 2006.

54) Grond S, Radbruch L, Meuser T, Loick G, Sabatowski R, Lehmann KA. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. J Pain Symptom Manage 1999;18(3):174-9.

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

56) Mercadante S, Bruera E. Opioid switching: a systematic and critical review. Cancer Treat Rev 2006;32(4):304-15.

57) Vielvoye-Kerkmeer A, Mattern C, Uitendaal M. Transdermal fentanyl in opioid-naive cancer pain patients: an open trial using transdermal fentanyl for the treatment of chronic cancer pain in opioid-naive patients and a group using codeine. J Pain Symptom Manage 2000;19(3):185-92.

58) Maltoni M, Scarpi E, Modonesi C, Passardi A, Calpona S, Turriziani A, et al. A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. Support Care Cancer 2005;13(11):888-94.

59) Marinangeli F, Ciccozzi A, Leonardis M, Aloisio L, Mazzei A, Paladini A, et al. Use of strong opioids in advanced cancer pain: a randomized trial. J Pain Symptom Manage 2004;27(5):409-16.

60) Davis MP. Management of cancer pain: Focus on new opiod formulatins. Am J Cancer 2006;5(3):171.

61) Dellemijn P, Vanneste J. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 1997;349(9054):753-8.

62) Cherny N, Thaler H, Friedlander-Klar H, Lapin J, Foley K, Houde R, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. Neurology 1994;44(5):857-61.

63) Wong J, Wiffen P. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley.

64) Carr DB, Goudas LC, Balk eM, Bloch R, Ioannidis JP, Lau J. Evidence report on the treatment of pain in cancer patients. J Natl Cancer Inst Monogr 2004;32:23-31.

65) Mcquay Hj, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases (Cochrane Review). In The Cochrane Library Issue 2, 2000. Chichester; John Wiley.

66) Bamias A, Kastritis e, Bamia C, Moulopoulos L, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005;23(34):8580-7.

67) Evidence-based Recommendations for the Pharmacological Management of Neuropathic Pain Position Statement, June 2008 Australian Pain Society.

68) Saarto T, Wiffen P. Antidepressants for neuropathic pain (Cochrane Review). In The Cochrane Library Issue 3, 2007.

69) Wiffen P, Moore R Derry S, Mcquay H J. Gabapentin for acute and chronic pain (Cochrane Review). In The Cochrane Library Issue 1, 2010. Chichester; John Wiley.

70) Wiffen P, Collins S, Mcquay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain (Cochrane Review). In The Cochrane Library Issue 2, 2006. Chichester; John Wiley.

71) Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss s. Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide, or Violent Death. JAMA. 2010;303(14):1401-1409.

72) Moore A, Straube S, Wiffen P, Derryl S, Mcquay H. Pregabalin for acute and chronic pain in adults (Cochrane Review). In The Cochrane Library Issue 1, 2010 The Cochrane Collaboration; John Wiley

73) Finnerup NB et al. An evidence-based algorithm for the treatment of neuropathic pain. Med Gen Med. 2007; 9(2):36.

74) Werhagen L, Hultling C, Molander C. The prevalence of neuropathic pain after non-traumatic spinal cord lesion. Spinal Cord 2007;45:609-615.

75) Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352(13):1324-34.

76) Twycross R, Wilcock A. Paliative care formulary. 3rd Ed. London: Palliativedrugs.com; 2007.

77) Bell, Eccleston, Kalso. Ketamine as an adjuvant to opioids for cancer pain (Cochrane Review). In The Cochrane Library Issue 1, 2006. Chichester; John Wiley.

78) Mason L, Moore R, Derry S, Edwards J, Mcquay H. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004;328(7446):991.

79) Campbell FA, Tramer MR, Carroll D, Reynolds DJM, Moore RA,Mcquay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001;323(7303):13-6.

80) Abrams D, Jay C, Shade S, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68(7):515-21.

81) Rog D, Nurmikko T, Friede T, Young C. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65(6):812-9.

82) Quiding H, Persson G, Ahlström U, Bångens S, Hellem S, Johansson G, et al. Paracetamol plus supplementary doses of codeine. An analgesic study of repeated doses. Eur J Clin Pharmacol 1982;23(4):31-9.

83) Chary S, Goughnour B, Moulin D, Thorpe W, Harsanyi Z, Darke A. The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. [Abstract]. J Pain Symptom Manage 1994;9(6):363-71.

84) Lurcott G. The effects of the genetic absence and inhibition of CyP2D6 on the metabolism of codeine and its derivatives, hydrocodone and oxycodone. Anesthesia Progress 1998;45(4):154–6.

85) Mercadante S, Arcuri E. Opioids and renal function. J Pain 2004;5(1):2-19.

86) Launay-vacher V, Karie S, Fau JB, Izzedine H, Deray G. Treatment of pain in patients with renal insufficiency: The World Health Organization three-step ladder adapted. J Pain 2005;6(3):137-48.

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

88) Hanks G, Conno F, Cherny N, Hanna M, Kalso E, Mcquay H,et al. Expert Working Group of the Research Network of the european Association for Palliative Care. Morphine and alternative opioids in cancer pain: The EAPC recommendations. Br J Canc 2001;84(5):587-93.

89) Broadbent A, Khor K, Heaney A. Palliation and chronic renal failure: Opioid and other palliative medications - Dosage guidelines. Progr Palliat Care 2003;11(4):183-90.

90) Mercadante S, Arcuri e. Opioids and renal function. j Pain 2004;5(1):2-19.

91) Launay-vacher v, Karie S, Fau jB, Izzedine H, Deray G. Treatment of pain in patients with renal insufficiency: The World Health Organization three-step ladder adapted. j Pain 2005;6(3):137-48.

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

93) Babul N, Darke A, Hagen N. Hydromorphone metabolite accumulation in renal failure. J Pain Symptom Manage 1995;10(3):184-6.

94) Health Canada. Methadone Exemption Application. Available from: http://www.hc-sc.gc.ca/hc-ps/pubs/precurs/meth_on-eng.php

95) Morphine in cancer pain: modes of administration. Expert Working Group of the European Association for Palliative Care. BMJ 1996;312(7034):823-6.

96) Säwe J, Dahlström B, Rane A. Steady-state kinetics and analgesic effect of oral morphine in cancer patients. Eur J Clin Pharmacol 1983;24(4):537-42.

97) Warfield CA. Controlled-release morphine tablets in patients with chronic cancer pain: a narrative review of controlled clinical trials. Cancer 1998;82(12):2299-306.

98) O'Brien T, Mortimer P, McDonald C, Miller A. A randomized crossover study comparing the efficacy and tolerability of a novel once-daily morphine preparation (MxL capsules) with MST Continus tablets in cancer patients with severe pain. Palliat Med 1997;11(6):475-82.

99) Portenoy R. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 1999;79(2-3):303-12.

100) Fallon M, O'Neill W. Spinal surgery in the treatment of metastatic back pain: three case reports. Palliat Med 1993;7(3):235-8.

101) Mercadante S. Opioid titration in cancer pain: a critical review. European Journal of Pain 2007;11(8):823-30.

102) Goudas L, Carr D, Bloch R, Balk E, Ioannidis J, Terrin N, et al. Management of Cancer Pain. Rockville, MD: Agency for Healthcare Research and quality; 2001. AHRQ Publication No. 02-e002.

103) Lee M, Leng M, Tiernan E. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. Palliat Med 2001;15(1):26-34.

104) Mercadante S, Ferrera P, Villari P, Casuccio A. Rapid switching between transdermal fentanyl and methadone in cancer patients. J Clin Oncol 2005;23(22):5229-34.

105) Pereira J, Lawlor P, Vigrano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids: A critical review and proposals for long-term dosing. J Pain Symptom Manage 2001;22(2):672-87.

106) Anderson R, Saiers J, Abram S, Schlicht C. Accuracy in equianalgesic dosing. conversion dilemmas. j Pain Symptom Manage 2001;21(5):397-406.

107) Miles C, Fellowes D, Goodman M, S. W, Fellowes D, Goodman M, et al. Laxatives for the management of constipation in palliative care patients (Cochrane Review). In The Cochrane Library Issue 4, 2006. Chichester; John Wiley.

108) Sykes N. A volunteer model for the comparison of laxatives in opioid-related constipation. J Pain Symptom Manage 1996;11:363-9.

109) Fallon M, Hanks G. Morphine constipation and performance status in advanced cancer patients Palliat Med 1999;13(2):159-60.

110) Savage S, Covington EC, Heit HA, Hunt J, Joranson D, Schnoll SH. Definitions related to the use of opioids for the treatment of pain. A Consensus Document From the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine; 2001.

111) JBallantyne JC, K. Steven LaForge KS.Opioid dependence and addiction during opioid treatment of chronic pain. Pain 2007;129:235–255.

112) Douglas L. Gourlay, Howard A. Heit, Abdulaziz Almahrezi, Universal Precautions in Pain Medicine: A Rational Approach to the Treatment of Chronic Pain. Pain Medicine 2005 6(2):107-112.

113) McLoughlin PA. Community specialist palliative care: experiences of patients and carers. Int J Palliat Nurs 2002;8(7):344-53

114) Vates P, Aranda S, Edwards H, Nash R, Skerman H, McCarthy A. Family caregivers' experiences and involvement with cancer pain management. J Palliat Care 2004;20(4):287-96.

115) Kimberlin C, Brushwood D, Allen W, Radson E, Wilson D. Cancer patient and caregiver experiences: communication and pain management issues. J Pain Symptom Manage 2004;28(6):566-78.

116) Bostrom B, Sandh M, Lundberg D, Fridlund B. Cancer-related pain in palliative care: patients' perceptions of pain management. J Adv Nurs 2004;45(4):410-9.

117) Schumacher KL, Koresawa S, West C, Dodd M, Paul SM, Tripathy D, et al. The usefulness of a daily pain management diary for outpatients with cancer-related pain. Oncol Nurs Forum 2002;29(9):1304.

118) Duggleby W. Enduring suffering: a grounded theory analysis of the pain experience of elderly hospice patients with cancer. Oncol Nurs Forum 2000;27(5):825-3125.

119) McGrath P. Creating a language for 'spiritual pain' through research: A beginning. Support Care Cancer 2002;10(8):637-46.

120) Scottish Intercollegiate Guidelines Network SIGN 44. Control of cancer pain in cancer patients: A National Clinical Guideline; 2000 Nov.

121) Ellis P, Davies AM, Evans WK, Haynes AE, Lloyd NS, the Lung Cancer Disease Site Group. The Use of chemotherapy in patients with advanced malignant pleural mesothelioma: A Clinical practice guideline. Program in Evidence Based Care Series #7-14-1, Cancer Care Ontario; 2005.

122) Cancer-related Pain Management Working Panel. Cancer-related pain management: A report of evidence-based recommendations to guide practice. Program in Evidence Based Care Series 16-2, Cancer Care Ontario; 2008.

123) Berry S, Waldron T, Winquist E, Lukka H, and the Members of the Genitourinary Cancer Disease Site Group, The Use of bisphosphonates in men with hormone-refractory prostate cancer: Practice guideline. Program in Evidence Based Care Series 3-14, Cancer Care Ontario; 2005.

124) Imrie K, Stevens A, Makarski J, Esmail R, Meharchand J, Meyer R, the Hematology Disease Site Group. The Role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma: A clinical practice guideline. Program in Evidence Based Care Series 6-4, Cancer Care Ontario; 2007.

125) Singapore Ministry of Health. Cancer pain. Singapore: Singapore Ministry of Health; 2003.

126) iSource National Breast Cancer Centre. Clinical Practice Guidelines: Management of Women with Epitelial Ovarian Cancer. Commonwealth of Australia, National Health and Medical Research Council; 2004.

127) National Institute for Clinical Excellence. Guidance on Cancer Services: Improving Outcomes in Breast Cancer. National Institute for Clinical Excellence; 2002.

128) Registered Nurses Association of Ontario. Assessment and Management of Pain.' Nursing best practice guideline; 2007.

129) Mid Trent Cancer Network. Symptom control guidelines. Network Palliative Care Group; 2006.

130) Nursing Professional Advisory Committee. Telephone Nursing Practice and Symptom Management Guidelines. Cancer Care Ontario; 2004.

131) National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Adult cancer pain. National Comprehensive Cancer Network Website; 2008.

132) National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Palliative care. National Comprehensive Cancer Network Website; 2008.

133) iSource National Breast Cancer Centre. Clinical practice guidelines: Management of advanced breast cancer . Commonwealth of Australia, National Health and Medical Research Council; 2001.

134) Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J. Guidelines for the management of cancer-related pain in adults. Supportive Care Cancer Site Team, Cancer Care Nova Scotia; 2005.

135) Warr D, Johnston M, the Breast Cancer Disease Site Group. Use of Bisphosphonates in women with breast cancer practice guideline. Program in Evidence Based Care Series 1-11, Cancer Care Ontario; 2004.

136) Librach L, Lloyd N, Jarvis N, Warr D, Jadad AR, Wilson J, the Supportive Care Guidelines Group. The Use of gabapentin and tricyclic antidepressants in the treatment of neuropathic pain in cancer patients: A Clinical practice guideline. Program in Evidence Based Care Series 1-11, Cancer Care Ontario; 2006.

Post-amble

Working Group

A wide variety of health professionals were invited to participate in the development of this Guide-to-Practice, as well as in the external review. Every effort was made to ensure as broad a professional and regional representation as possible.

Geoff Davis MD (Pain Group Lead)
Regional Lead Palliative Care Program
Medical Director Palliative Care
Thunder Bay Regional Health Sciences Centre and St.
Joseph's Care Group
980 Oliver Road
Thunder Bay, Ontario P7B 6V4

Kate Bak
Policy Research Analyst
Oncology Nursing, Psychosocial and Palliative Care
Cancer Care Ontario
620 University Avenue
Toronto, Ontario M5G 2L7

S. Lawrence Librach
W. Gifford-Jones Professor, Pain Control & Palliative
Care, University of Toronto
Director, Temmy Latner Centre for Palliative Care
Mount Sinai Hospital
Joseph & Wolf Lebovic Building
60 Murray Street, 4th Floor, Box 13
Toronto, Ontario, Canada, M5T 3L9

Michelle Quirion
Nurse Manager
Sudbury Regional Cancer Centre
Hopital Regional de Sudbury Regional Hospital
41 Ramsey Lake Road
Sudbury, Ontario   P3E 5J1

Suzanne Rowland
Nurse Practitioner
Palliative Care/Chronic Pain
Southlake Regional Cancer Centre
596 Davis Drive
Newmarket, Ontario, L3Y 2P9

**Edward Fitzgibbon MD, MSc(Epi), CCFP
(Pain Group Lead)**
Medical Director
Palliative Care Program
The Ottawa Hospital
Room 5235, 501 Smyth Road
Ottawa, Ontario K1H 8L6

Catherine Bond Mills
Pharmacist
London Regional Cancer Program
790 Commissioners Rd E
London, Ontario
N6A 4L6

Prabhjot Minhas
Project Coordinator
Oncology Nursing, Psychosocial and Palliative Care
Cancer Care Ontario
620 University Avenue
Toronto, Ontario M5G 2L7

Ashley Ross
Pharmacist
Radiation Oncology and Palliative Care
Kingston General Hospital
76 Stuart Street
Kingston, Ontario, K7L 2V7

Debbie Selby
Physician, Palliative Care Consultant
Odette Regional Cancer Centre
2075 Bayview Ave H336
Toronto ON M4N 3M5

Acknowledgements

The members of the working group would like to thank the following contributors for their guidance throughout the development of this Guide, Deborah Dudgeon MD FRCPC, Esther Green RN MSc (T), Sheila McNair PhD, Doris Howell PhD, Raquel Shaw-Moxam MSc, and Tricia Staples MBA.

Conflict of Interest

All authors completed conflict of interest declarations. One author, G.D., indicated that he had a prioir affiliation with Purdue Pharma, Jonathan Ortho and Pfizer with regards to research on products mentioned in the Guide-to-Practice.

Funding

This Guide-to-Practice was supported by Cancer Care Ontario.

Copyright

This Guide-to-Practice is copyrighted by Cancer Care Ontario.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the Guide-to-Practice is expected to use independent medical judgment in the context of **individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontari**o makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

August 2010