A Guide for Pain Management in Developing Nations: The Diagnosis and Assessment of Pain in Cancer Patients

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Abstract: The fundamental approach to cancer patients with pain is to identify the pain sites, and describe, quantify, and categorize the pain by type at each site. There are many validated tools to serve the clinician in these efforts, particularly for pain assessment. Multimechanistic pain syndromes are common in cancer patients. Cancer patients may experience nociceptive pain. They may also experience neuropathic pain due to chemotherapy-induced or cancer-related nerve damage. Analgesic choices must be guided by the pain mechanisms, nature, and severity of the pain, comorbid conditions, and patient characteristics. Long-acting opioid analgesics or fixed-clock dosing can eliminate end-of-dose analgesic gaps. The potential for opioid abuse is an important public health challenge but one that should not undermine the appropriate treatment of moderate to severe cancer pain. Abuse-deterrent opioid formulations can be useful. Care is needed for special populations of cancer patients dealing with pain, such as geriatric, pediatric, or obese patients. While morphine has long been the "gold standard" of oral opioid products, recent clinical trials suggest that oral hydrocodone and oral oxycodone may offer advantages over oral morphine. Patient adherence is crucial for adequate analgesia and patient education can promote adherence and manage expectations.

Keywords: Cancer pain, malignant pain, opioid analgesia, opioids, undertreatment of cancer pain, assessment of cancer pain.

INTRODUCTION

In developing nations, patients often present with advanced disease at the time of diagnosis. For example, between 1995 and 1999, the incidence of all types of cancer in Colombia was 141.9 for men and 165.9 for women per 100,000 inhabitants [1]. Pain prevalence is about 64% for metastatic or terminal cancer patients, 59% for patients in anticancer therapy, and 33% for cured patients [2]. Despite high mortality for cancer, cancer patients are living longer than ever before. The prolonged survival of cancer patients today challenges the compartmentalization of "cancer pain" versus "non-cancer pain." To be sure, there are important clinical distinctions between cancer and non-cancer pain, in that cancer pain often occurs at multiple sites, normally increases in severity, may be used to assess treatment progress, and tends to exhibit predictable patterns, such as exacerbated pain associated with specific movements. Pain is often severe in cancer patients, but the functional status of cancer patients may be better than that of patients with other life-limiting diseases, such as congestive heart failure or chronic pulmonary obstructive disorder [3]. Even during the active disease, cancer pain may have far more in common with non-cancer pain than previously thought. For example, breakthrough pain—typically considered characteristic of cancer pain—may actually be more prevalent in non-cancer pain; [4] breakthrough pain has been reported in around 33% to 65% of cancer patients compared to 70% of patients with chronic non-cancer pain [5]. It has been the authors' observations that assessment tools and pharmacological treatments developed for non-cancer pain often work well in cancer patients and vice versa. Clinicians should move from "treating patients with cancer pain" toward the more clinically relevant goal of "treating pain in patients with cancer." About 80% of cancer patients experience moderate to severe pain at end of life, but only 20 nations on earth have fully integrated palliative care programs in their healthcare systems [6].

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ISSN: 1929-2260 / E-ISSN: 1929-2279/16

Although prevalent, pain in cancer patients is often undertreated and may be unwittingly trivialized by clinicians more focused on the disease than its symptoms. In some Latin American countries as well as other parts of the world, restrictions on opioids limit even appropriate access [7]. Even when opioids are on the formulary in developing nations, over-regulation may still make them virtually unavailable to practicing clinicians and their patients [8].

In a survey of 573 cancer patients, 50% of respondents said they did not believe their healthcare provider considered quality of life a priority in their overall care [9]. A retrospective claims database study from Japan, found that of 2,858 patients treated with chemotherapy, radiation, and/or surgery for cancer, only 22.9% had received a prescription for any type of analgesic in 30 days [10]. Cancer survivors may face lifelong pain syndromes; patients with a history of cancer are at greater risk for pain than patients with no such cancer history (odds ratio 1.15, 95% confidence interval, 1.03-1.28) [11].

TOOLS AND TECHNIQUES

There are safe and effective therapies to control pain in cancer patients, but pain control requires a foundation of appropriate diagnosis and assessment of the pain syndromes. In cancer patients, this relies on a foundation of localizing, qualifying, quantifying, and categorizing the pain(s) to allow for sound clinical choices. (See Figure **1**) With proper assessment and diagnosis, appropriate analgesic therapy choices can be made.

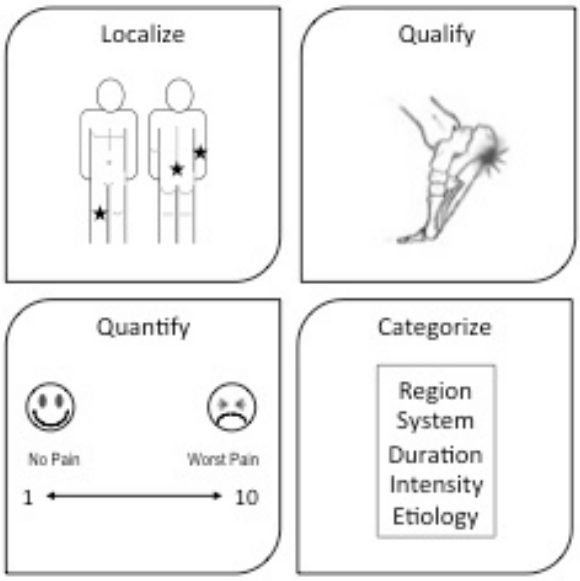

Figure 1: Cancer patients with pain should be thoroughly examined so that their pain(s) can be localized, qualified, quantified (using an assessment tool), and then categorized.

LOCALIZATION OF THE PAIN SITES

Most cancer patients with pain will experience pain in at least two sites, [12] and it is not unusual for patients with metastatic activity to have multiple pain sites. In a study of 160 consecutive patients with different types of cancer undergoing a bone scan, bone metastases were found in 32.7%, 40.6%, 38.5%, and 62.5% of patients with breast, prostate, gastrointestinal (GI), and lung cancers, respectively [13]. Patients may also identify pain sites that are associated with treatment or wholly unrelated to the cancer.

Pain localization can be performed using anterior and posterior body maps. Computerized body maps are being evaluated and found to be well accepted by patients with advanced cancer and correlated well to paper maps [14]. See Figure **2**.

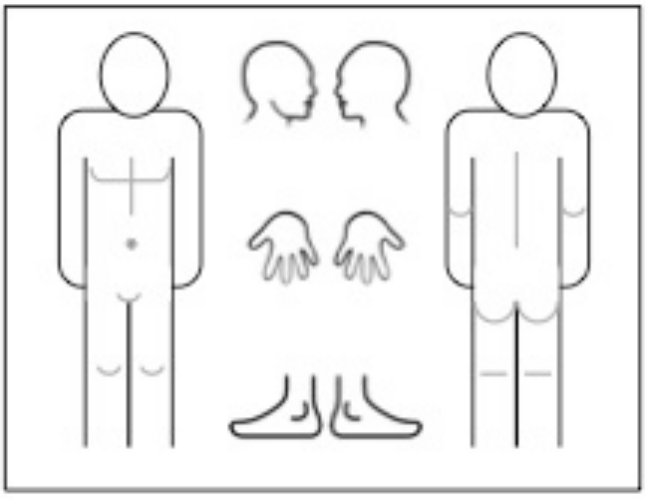

Figure 2: Anatomical maps should display anterior and posterior views but may otherwise be simple “infographics.” Although paper maps are currently common, computerized diagrams may soon be more widespread. With the clinician’s guidance, the patient is to mark the location(s) on the body where pain is experienced.

Pain sites will likely change over the course of the disease and its treatment and should be periodically revisited. The following steps of qualification and quantification of pain should be carried out individually for each pain site.

QUALIFYING PAIN IN CANCER PATIENT

Patients should be asked to describe the pain at each individual pain site. The vocabulary of pain can be a stumbling block, so the clinician may want to offer

Table 1: Important Questions to Help Qualify Pain at Each Pain Site

Question
How long have you had this pain?
Does the pain come and go or is it there all of the time?
Are there things that make this pain worse? What are they?
Are there things you can do to make this pain better? What are they?
Does this pain ever seem to "move" around?
Has this pain ever woken you up during sleep?
Does the pain get worse when you lie down?
Do you ever take any medication to help with this pain? Does it work?
How would you describe this pain? Is it like any other pain you may have experienced?
Is this pain worse at some times than others? Is there any pattern, such as, is it worse at night?
Does this pain seem to be getting worse over time?
If you had to point to the exact spot in your body where this pain is located, would the location be hard or easy to pinpoint?

suggested descriptors, such as deep, sharp, stinging, continuous, throbbing, aching, "electrical," or stabbing pain. Pain may be intermittent or continuous and may be exacerbated by certain activities. Patients should be asked if they experience the seemingly paradoxical sensation of both shooting pain and localized numbness or tingling. In addition to describing the nature of the pain at each site, the clinician should record complete details by asking a series of leading questions, listed in Table **1**. When interviewing the patient, it is important that the clinician frame the questions in ways that the patient can readily understand rather than using medical terminology. This is a time-consuming step but one that can provide insight into the patient's pain syndromes.

In general, nociceptive pain can be readily localized by the patient and may be described as sharp or dull and deep or aching. Visceral pain tends to be diffuse, difficult to localize, and is usually reported as being a continuous deep pain. Neuropathic pain may be experienced as sharp, shooting, "electrical," and may be associated with paresthesia.

QUANTIFYING PAIN

For each pain site, the patient should be asked to self-report his or her pain level. Observer reports, whether from familial caregivers or healthcare professionals, do not correlate well with self-reported pain levels [15]. A brief summary of some of the better-known pain assessment tools appears in Table **2**.

While it is important to record intensity of pain at each pain site, pain is a multidimensional experience. As a result, newer and emerging pain assessment tools attempt to quantify additional variables. Pain intensity, location of pain, and diagnosis are all important predictors of current and future pain levels, [29] yet pain outcomes may be highly variable among seemingly similar patients. Thus, adding new domains to the pain measurement tool may assist in helping predict the future pain trajectory. For example, disturbed sleep may be added to future classification systems, as it has been identified as a potentially important variable in determining pain outcomes [30]. Variations in the ESAS assessment tool are now accounting for distress levels in cancer patients, [31] another potential variable associated with pain outcomes. Two longitudinal studies found loneliness in cancer patients was a risk factor for pain, [32] but to date no pain assessment tools incorporate that metric. The PRISM tool, included in Table **2**, does not actually measure pain but rather "suffering," a broader and more complex experience [27]. Anxiety and depression, measured in some pain assessments, are often comorbid with cancer, [33, 34] and cancer patients with high levels of emotional distress report correspondingly higher levels of pain [35]. The Patient Dignity Inventory is intended for use in palliative cancer patients and measures "distress" rather than pain specifically, although distress and pain are associated conditions [28].

Pain assessments should be performed regularly and recorded. For inpatients, this may be every four to six hours or as analgesics are administered; a recent study found that cancer pain assessments could be valid for up to eight hours [36]. For outpatients, pain

Table 2: A Short Summary of Pain and Related Assessment Tools that may be Suitable for Use with Cancer Patients with Pain. This List is not Exhaustive

Pain Assessment Tool	Description	Population	Advantages	Disadvantages
Brief Pain Inventory [16]	Patients self-report using an 11-point scale with 0=no pain and 10=worst pain imaginable	Adults who can communicate and understand the principle	Widely used for cancer pain, [17] easy to administer; may be able to distinguish nociceptive and neuropathic pain [18]	Requires some degree of patient education
Edmonton Symptom Assessment Scale (ESAS) [19]	Patients self-report using a nine-item inventory including fatigue, nausea, insomnia and others on an 11-point scale	Adults who can communicate and understand the principle	Demonstrated validity in cancer populations; captures holistic information on well-being	Palliative care; some patients have difficulty with the terminology[20]
Edmonton Classification System for Cancer Pain [21]	Questionnaire on pain mechanisms, incident pain, psychological distress, addictive behaviors, and cognition	Adults who can communicate and understand the principle	Validated for use in distinguishing salient pain classification features across cultures	System is still being refined; may require some training to administer well
Numeric rating scale [22]	Patients self-report pain on an 11-point scale	Adults who can communicate and understand the principle	Simple, effective; allows for ready statistical analysis	Captures only pain intensity
Visual analog scale [22]	Patients locate their pain intensity on a continuum, usually measured in mm	Adults who can understand the principle	Can produce fine gradations, allows for ready statistical analysis	Not all patients can grasp concept; may present practical difficulties
Verbal rating scale [22]	Patients answer questions about pain that map onto a multipoint rating scale	Good communication skills	Simple, easy, patients often prefer this method	Lacks sensitivity; hard to analyze data; patients may unknowingly underreport pain (trying to be a good conversationalist or pleasant person)
Wong-Baker Faces Pain Rating Scale [23]	Six “smiley” face scales showing happy to crying faces	Suitable for children, those who do not speak the language or those who have trouble communicating	Simple, user-friendly	Limited six-point scale; does not differentiate among types of pain; cancer patients may find it difficult to rate moderate to severe pain
McGill Quality of Life Questionnaire [24]	Questionnaire about multiple aspects of life	Adults with good communication skills in palliative care	Multidimensional	Intended for palliative setting only, not specific to pain
SF-36 Bodily Pain Scale [25]	Health-related quality of life questionnaire	Adults with good communication skills	Simple, allows for ready statistical analysis	Generic rather than cancer or even disease specific
Adolescent Pediatric Pain Tool [26]	Self-report of intensity, location, and quality of pain	Adolescents	Reports on multiple dimensions of pain, may be helpful in multimodal pain therapy; has been studied in cancer patients	Challenges in interpretability, that is, what differences are clinically meaningful
Pictorial Representation of Illness and Self Measure (PRISM) [27]	Self-report of psychological variables (including coping skills)	Adults	Short test (less than 5 minutes); holistic view of experience of “suffering”	“Suffering” is a different dimension than pain; introduces complexities
Patient Dignity Inventory [28]	25-item questionnaire	Adults in palliative care	Holistic approach	Does not evaluate pain; for palliative care only

mm=millimeters.

assessments may be more sporadic, but this is suboptimal for adequate analgesia. A recent study at an oncology clinic found that pain assessments tended to be infrequent unless clinicians were given specific education about their utility and value; the rate of pain assessments increased from 22% to 75% following an educational intervention [37]. Outpatients should be assessed during each in-clinic visit. Pain levels should

be assessed and documented in the patient's chart; actions based on these findings should be documented along with any drug(s) prescribed. Patients may also be encouraged to keep a pain diary or other documentation to assess their pain on a daily or more-frequent basis. Patients are usually unfamiliar with pain rating scales, so some initial education and periodic reviews may be helpful. Healthcare professionals caring for cancer patients must remember that when it comes to pain, "If we don't ask—we don't know!"

Despite many pain measurement tools, there is no single universally acknowledged pain assessment tool for use in cancer patients. In a comparative study of 240 cancer patients with chronic pain syndromes, the numeric rating scale (NRS) had a better ability to discriminate background and peak pain intensity levels than the verbal rating scale (VRS) [38]. Furthermore, the NRS also yielded results that were more reproducible when measuring pain exacerbation than did the VRS [38]. The VRS is a familiar and easy-to-use pain assessment tool that clinicians often find practical and "natural," but even trained clinicians may define various VRS descriptors in different ways, weakening its results [39]. Quantifying breakthrough pain is more difficult, in that we know of no tools designed specially to quantify episodes of breakthrough pain [40]. For breakthrough pain, it may be sufficient to use the NRS or a visual analog scale (VAS). Clinicians should select a validated pain measurement assessment tool and apply it systematically, recognizing that there is no perfect metric.

The use of any assessment method requires training and even calibration of terminology, such as distinguishing in the ESAS tool between the categories of "tiredness" versus "drowsiness" [20]. Communications barriers, whether they be linguistic, cognitive, cultural, or age-related, can often be overcome by proper selection of the right tool, such as a visual analog scale for those who do not speak the language well or the FACES scale for pediatric and cognitively impaired patients. Encouraging and empowering patients to self-report and share information about their pain appears to improve pain assessment. In a study in South Korea, 50 consecutive cancer inpatients were evaluated at bedside for pain over the course of three days using the VRS; then for the next three days, the same patients were given a "pain board" attached to their bed with movable indicators that described their pain along an eleven-point numeric scale [41]. The pain board also allowed patients to report breakthrough pain episodes. The reliability of pain reporting improved significantly from 74% (VRS at bedside) to 96% (pain board), p=0.004. Moreover, patient satisfaction with pain control increased from 54% to 82%, p=0.002.

CATEGORIZING PAIN

In a cancer patient, pain may be related to the tumor, the treatment, or be unrelated to the cancer. Particularly in older cancer patients, who may have chronic pain conditions before the onset of cancer. For that reason, it is important to categorize pain systematically rather than assuming all pain is cancer related.

The most frequently observed somatic nociceptive pain in cancer patients is bone pain, often caused by bone metastases and occurring in over 40% of cancer pain cases [42]. The second-most observed pain in cancer patients is visceral pain, occurring in about 28% of cases [42]. Chemotherapy-induced peripheral neuropathic pain syndromes are increasingly recognized as a common cancer-related pain [43] but they are associated with the treatment rather than the disease. However, neuropathic pain may also occur as the result of nerve damage associated with the cancer. In a study of 951 adult cancer outpatients, 32.6% reported neuropathic pain [44]. A multicenter study of 1,051 terminal cancer patients found 113 of them (10.8%) had neuropathic pain which reduced their physical, cognitive, and social function [45]. Nociceptive pain, such as inflammatory pain, may be somatic or visceral. Visceral pain may be challenging to treat because the organs involved often possess extensive nerve networks [46].

Acute pain syndromes, such as postsurgical pain, must be differentiated from chronic pain, which is more than just pain of long duration. Chronic pain may be associated with central nervous system sensitization, altering the patient's pain thresholds and essentially "amplifying" pain signals [47]. Chronic pain can be difficult to localize and despite its name may be intermittent; it often has a neuropathic component.

Pain in cancer patients will change with the patient's disease progression and course of treatment. For example, many forms of chemotherapy-induced peripheral neuropathy will resolve without treatment over weeks or months after chemotherapy is stopped [43]. Tumor growth may exacerbate cancer pain. Thus, treating pain in cancer patients requires ongoing evaluation and assessment.

THE WHO PAIN LADDER REVISITED

In 1986, the World Health Organization (WHO) released a cancer pain treatment paradigm in the form of a simple but elegant "pain ladder" [48]. Acknowledging that much cancer pain was under-treated or even untreated around the world—a situation that continues to prevail in most parts of Latin America—WHO advocated strongly for the use of oral morphine and other opioids in the palliative care of cancer patients facing moderate to severe pain at end of life. The WHO Model List of Essential Medicine also lists oxycodone and hydrocodone in this connection. The WHO pain ladder is a scheme in which patients advance, one step at a time, up a three-rung ladder from nonopioid analgesics (at the start) to so-called "strong" opioids as pain persists or worsens (at the top). See Figure **3**.

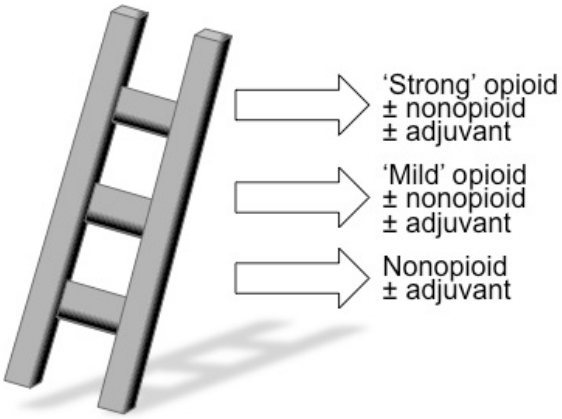

Figure 3: An artist's rendition of the WHO pain ladder. Patients start on the first rung and advance up the ladder, step by step, as pain intensity increases [48].

There is much laudable about the WHO pain ladder; there has probably never been such an influential public health intervention in the field of cancer pain treatment. It is practical, intuitively understandable, and has contributed much to cancer pain relief around the world. On the other hand, the understanding of pain has advanced since 1986 and many new analgesics have come to market since then. One serious drawback to the WHO pain ladder is that it treats pain in one dimension only: intensity. While pain intensity is a very important consideration in analgesia, the understanding of multimechanistic pain syndromes might lead a clinician today to think of pain in terms of mechanisms rather than intensity. Moreover, modern recognition of the biopsychosocial experience of pain forces the view that pain is a multidimensional experience with concomitant factors such as emotional distress or clinical depression playing a role in pain outcomes. Furthermore, while the WHO pain ladder allows for combination therapies it does not emphasize them or explain how such prescribing choices would be made (see Table **3**). A third critique of the WHO pain ladder is that it offers no specific provision for transient breakthrough pain, a common characteristic of cancer pain [49]. It also does not incorporate important prescribing choices available to clinicians today, namely fast-acting versus long-acting analgesic products and products with novel routes of administration, such as transmucosal or transdermal. These products were not available when the WHO pain ladder was first introduced.

PAIN GUIDELINES

There are numerous guidelines for the treatment of adult pain, but not all are specific to pain in cancer patients. According to the National Comprehensive Cancer Network (NCCN) of the United States, it is important to distinguish pain owing to an oncologic emergency (such as bone fracture, epidural metastases, infection, and so on) from non-emergency pain and to recognize that, when prescribing opioids, it is crucial to know if the patient is opioid tolerant [50]. The 2013 NCCN guidelines recommend that an opioid and rescue medication be established for treating moderate to severe cancer pain in adults and that these agents be administered regularly to treat persistent pain along with a bowel regimen to address possible side effects, very often overlooked in outpatient management. Cancer patients with moderate to severe pain should be considered for a referral to a pain specialist; those in severe pain should be re-evaluated for opioid titration [50]. NCCN guidelines for breakthrough pain recommend that such episodes should be treated with rapid-acting opioids with pharmacodynamics similar to that of the onset and duration of the breakthrough pain [49].

The American Pain Society/American Academy of Pain Medicine guidelines for chronic opioid therapy in non-cancer pain offers guidance that can be useful in the setting of cancer, namely that opioid therapy should only be considered if its potential therapeutic benefits outweigh or are likely to outweigh its potential harms—and even if a strong case can be made for selecting opioid analgesics, a trial period should be considered to evaluate the drug [51]. Prior to commencing opioid therapy, a detailed patient history and physical examination are recommended. If opioid analgesics are considered, the patient should be informed about the potential risks and benefits; this includes informing the

Table 3: An Overview of Adjuvant Medications that may be Appropriate in Treating Pain in Cancer Patients

Pain Syndrome	Type of Pain	Prescribing Categories	Examples
Nociceptive	Visceral	Opioids with NSAIDs	Fixed-dose combination product of acetaminophen plus hydrocodone
	Soft tissue		
	Muscle spasms	Muscle relaxants	Diazepam, carisoprodol, cyclobenzaprine
Neuropathic	Neural compression	Opioids with corticosteroids	Loose dose combinations
	Neural injury	Opioids, tricyclic antidepressants, anticonvulsants, neuroleptics	Opioids plus imipramine, desipramine, pregabalin, others

patients that long-term opioid therapy may be associated with mild to severe side effects and possibly preclude their driving or operating machinery. If side effects are intolerable or a particular opioid agent is not effective at clinically appropriate doses, dose increases or opioid rotation may be considered [51].

Updated cancer pain treatment guidelines from Japan recommend that sustained-release or immediate-release opioids be used for patients with mild to moderate *stable* forms of pain, but that immediate-release or parenteral opioids be used in patients with *unstable* and/or severe pain [52]. Adjunctive treatments may be warranted for pain with specific etiologies, for example, bisphosphonate may be administered in patients with pain from bone metastasis whereas celiac plexus block or other forms of nerve blocks may be considered in patient with pain due to pancreatic cancer or other cancers [52].

ANALGESIC CHOICES

The selection of an appropriate analgesic for a cancer patient in pain depends on multiple factors of varying degrees of importance to specific patients. Thus, the decision-making process for finding the right analgesic should be individualized for each patient. Of course, safety and effectiveness are foundational considerations for all patients. The prescriber should understand as much as possible about the nature of the pain and prescribe an agent suitable for the intensity level and pain mechanism(s) involved. Combination therapy is typical for cancer patients, who often have mixed pain syndromes (nociceptive, neuropathic, and visceral pain are all common in cancer patients and are not mutually exclusive). Combination therapy may include non-pharmacological treatments, such as physical therapy, massage, or complementary and alternative medicine. Patients should be instructed about likely or possible side effects and be informed that some side effects, such as constipation, can be managed; opioid-related side effects can be treatment limiting.

When selecting analgesic product(s), the onset of action may play an important role, particularly in patients dealing with highly variable pain levels. When prescribing opioids, the abuse liability of the drug must be taken into account; this may play only a very minor role when prescribing an opioid for an elderly palliative patient, but would emerge as a primary consideration when selecting the right analgesic for a middle-aged cancer patient with a recent history of substance abuse. Abuse-deterrent formulations are currently on the market and in development and are being introduced globally. In today's healthcare environment, cost must be considered, but healthcare costs can be tricky to measure in that they often include far more than the price of the pill. To promote adherence and patient satisfaction, the analgesic should also be convenient and acceptable to the patient. Personal preferences, familial beliefs about pain, and cultural attitudes should also be taken into account; for example, some patients fear taking opioids more than they fear pain [53]. Education is a key and underutilized element in pain therapy—patients should be told about pain control options, their risks and benefits, and also the risks of untreated pain, for example, loss of function, depression, suffering, and social isolation. For a summary of the multiple objectives of analgesic therapy for cancer patients, see Table **4**.

When selecting appropriate analgesics, there are three further points that deserve consideration: comorbidities, special populations, and concerns related to dose titration.

Comorbidities

Comorbid conditions are associated with poorer prognoses in some forms of cancer, such as colorectal cancer [54]. While it is unclear if comorbidities elevate a cancer patient's risk for cancer pain, comorbidities

Table 4: Goals Related to Analgesic Selection for Treating Pain in Cancer Patients

Goals	Prescribing Considerations
Promote adherence and patient satisfaction	Choose a product that the patient accepts and has a familiarity (oral products, for example); alternately, select a product that minimizes the need for adherence, such as a transdermal patch
Relieve pain	Choose an effective product and titrate to the right dose for the individual patient
Consider comorbidities	Make sure analgesic does not interact with other drugs or adversely affect the patient's comorbidities
Assess pain	Evaluate pain levels regularly and prescribe combination therapy for multimechanistic pain syndromes; adjust doses or rotate opioids if analgesia becomes inadequate
Reduce analgesic gaps	Choose long-acting products, educate the patient and caregivers on fixed-clock dosing schedules, select transdermal patches if appropriate
Mitigate side effects	Choose drugs with greatest effectiveness and best tolerability, address side effects prophylactically (such as starting a bowel regimen with opioid prescription). Patients should be encouraged to report side effects.
Manage expectations	Educate patient with a realistic sense of pain control, that is, that pain may not be totally eliminated but can be substantially reduced. Alternately, make sure that patients know that uncontrolled pain may reduce their functional status and have other adverse effects.
Monitor closely	Watch for tolerance, opioid-induced hyperalgesia, worsening side effects, and changes in the patient's underlying disease—any of which can warrant prescribing changes
Reduce abuse	Understand and observe for aberrant drug behaviors, address concerns proactively, consider prescribing abuse-resistant products

can be associated with pain in and of themselves, such as diabetic neuropathy or low back pain from osteoarthritis. In a study of 114 chemotherapy outpatients, patients with comorbidities were more likely to have more pain than those without comorbid conditions [55]. The contribution of comorbid conditions to the cancer patient's pain burden may be underestimated. In a study of 3,792 cancer survivors, health-related quality of life scores varied more by comorbidity than by physical or emotional function, pain, or fatigue [56].

In cancers with low survival rates, comorbid conditions may play a minor role in outcomes, [57] but in terms of pain control, clinicians must be mindful that comorbid conditions often indicate polypharmacy, which, in turn, may limit prescribing choices or increase the chances of potentially dangerous pharmacokinetic drug-drug interactions [58, 59]. Moreover, care must be taken with comorbid cancer patients that specific analgesics are not contraindicated, for example, in patients with compromised renal function or pulmonary dysfunction.

Special Populations

Sadly, cancer occurs in all populations, including such vulnerable populations as the very young, the elderly, and the frail. Opioids can be used in these patients but oncologists may not be aware of the full range of opioid options [60]. Detailed information on diagnosing and assessing pain in pediatric oncology patients exceeds the scope of our article, but is a topic of great importance.

Geriatric patients can benefit from opioid analgesics when prescribed carefully and monitored closely [61, 62]. In fact, the American Geriatric Society specifically recommends opioid pain relievers for many elderly pain conditions, even preferring them to non-opioids [63].

Although rarely discussed in this context, an emerging special population is the obese and morbidly obese cancer patient, whose weight can modify the pharmacokinetics and pharmacodynamics of opioid analgesics [64]. Indeed, some genetic polymorphisms have been associated with adiposity, reduced pain thresholds, and an increased requirement for morphine to achieve analgesia [65]. But there is a paucity of evidence in the literature related to prescribing opioid analgesics to obese cancer patients; more research is warranted.

Another "special population" is the cancer patient at high risk for opioid misuse or abuse. There are numerous risk factors for opioid abuse, which may change over time [66]. Clinicians can face a prescribing conundrum when treating cancer patients with a history of recent substance abuse or an active addiction [67]. It is beyond the scope of our article to discuss how to prescribe to such patients, other than to offer broad guidance that such patients do experience "legitimate"

pain and should be accorded analgesic relief, albeit with considerable caution and close supervision [68]. The recent development of opioid formulations designed to resist or deter abuse may be helpful in this context.

Titration and Product Characteristics

Appropriate titration occurs when the patient is administered a starting dose of an analgesic product and upon regular consistent pain assessments has the dose increased in small steps until adequate pain relief is achieved. Titration of an oral analgesic is facilitated when the drug is available in many dose sizes and when the patient, upon titration, has a relatively low pill burden. While patients tend to accept oral analgesics as familiar types of medicine, oral agents can be a problem for patients with dysphagia [69]. Oral opioid analgesics with relatively short half-lives can be readily titrated. In a study of 40 cancer patients whose pain was not well controlled on codeine or dextropropoxyphene therapy, titration of oral morphine could be performed successfully and rapidly [70]. Alternate routes of administration may be appropriate for some outpatients, such as transdermal patches.

STARTING OPIOID THERAPY

The initiation of opioid therapy occurs at an important juncture in the care of cancer patients in that opioids are typically introduced when pain is moderate to severe and many patients—quite correctly—associate worsening pain with disease progression. Catastrophizing may elevate their own distress and anxiety and, in turn, exacerbate their pain [71]. Thus, the onset of opioid therapy occurs at what is often a particularly stressful time for the patient.

Rapid control of paroxysmal pain may be effectively achieved with immediate-release formulations of opioids, but controlled-released products may be more appropriate for long-term use. Since adherence decreases as the pill burden increases, having a patient take fewer controlled-release tablets in a day results in improved patient compliance [72]. This may owe in part to the patients' erronenous notion that taking several pills will result in undesired "overmedication" or other risks. Intravenous opioids have a more rapid onset of action than similar doses of oral opioids, but when appropriately titrated, oral opioids can offer safe and effective analgesia for cancer patients with pain [73]. Moreover, oral opioids are practical for outpatients.

Oral morphine is recommended by WHO as a first-line drug for the control of pain in cancer patients, [48] partly because oral morphine is widely available, inexpensive, and its short half-life permits rapid titration. Despite the fact that oral morphine was and remains the "gold standard" for pain control in cancer patients, a recent meta-analysis of oral morphine for control of pain in cancer patients found a surprising paucity of high-quality evidence favoring that agent and relatively few comparative studies to support the idea that oral morphine is superior to other strong oral opioids [74]. The European Association for Palliative Care (EAPC) guideline for the use of opioid pain relievers to control cancer pain found, "no important differences between morphine, oxycodone, and hydromorphone" when administered orally and any of these three agents may be used as a first-choice analgesic agent on the third step of the WHO pain ladder [75]. A meta-analysis of randomized clinical trials of oxycodone for the treatment of moderate to severe cancer pain (7 studies, n=613) found oxycodone was statistically superior to other strong opioids based on reduction of pain intensity scores and had statistically significantly lower rates of such side effects as nausea and constipation, but similar rates of dizziness, vomiting, pruritus, sleepiness, anorexia, and dysuria [76]. A systematic review of oxycodone versus morphine and hydromorphone in the treatment of cancer pain found no significant differences among agents in terms of effectiveness or side effects [77]. A meta-analysis of oral morphine for treating cancer pain found it to be effective but noted that 6% of patients discontinued oral morphine because of intolerable side effects [78]. A systematic review of oral hydromorphone in the treatment of cancer pain (n=1,208) found it offered equivalent analgesia compared to oral morphine or oral oxycodone but could not draw conclusions about side effects as they were reported differently across studies [79]. See Table **5** for a short overview of selected individual studies comparing oral morphine to hydrocodone and/or oxycodone.

OPIOID-NAÏVE VERSUS OPIOID-EXPERIENCED PATIENTS

An important consideration in initiation of opioid therapy is whether the patient has developed a tolerance to opioid agents. Opioid-experienced patients are not always easy to identify; they may have had previous opioid analgesia associated with their cancer, may have taken opioids for other types of pain syndromes, or may be using prescription pain relievers

Table 5: An Overview of Effectiveness and Tolerability in Clinical Trials Comparing Oral Morphine to Either Oral Hydrocodone or Oral Oxycodone or both. Because there are Few such Comparative Studies, Studies Involving Non-Cancer Patients are also Included

Study	Agents	Cancer Patients?	Effectiveness	Side Effects	Comments
Pedersen 2013 [80] 44 adults R, DB	Oral morphine vs. oral oxycodone following nephrolithotomy	No	Similar at 4 hours	Significantly less nausea with morphine (p=0.03)	
Ericson 2013 [81] Retro, 50,223 cases	Patients initiated on controlled-release oral morphine or oxycodone	No	Rate of opioid rotation was 19% greater in morphine than oxycodone patients (p<0.001)	Not reported	
Mercadante 2010 [82] 60 adults R, C	Pancreatic cancer patients with visceral pain comparing oral sustained-release morphine vs. oxycodone	Yes	No significant differences in pain between groups at 4 weeks	No significant differences in side effects between groups at 4 weeks	Doses escalated over course of study with disease progression
Berger 2004 [83] 3,048 adults Retro	Patients initiating pain therapy with controlled-release oral oxycodone, controlled-release oral morphine, or transdermal fentanyl	Cancer and non-cancer patients	Cancer patients switched drugs more frequently than non-cancer patients (23.8% of oxycodone, 24.6% of fentanyl, and 29.8% of morphine patients)	Not reported	Switch rates for non-cancer patients were 10.6% for oxycodone, 19.0% for fentanyl, and 26.0% for morphine
Mucci-LoRusso 1998 [84] 100 patients R, DB, PG	Paients taking oral controlled-release oxycodone or morphine every 12 h for 12 d	Yes	Similarly effective in controlling pain	Similar side effects but oxycodone was associated with less pruritus ($p \leq 0.004$) and no hallucinations (2 patients in morphine group had hallucinations)	

C=controlled; d=day; DB=double blind; h=hour; PG=parallel group; R=randomized; Retro=retrospective.

inappropriately. A careful patient interview should be conducted to gauge the patient's tolerance of opioids.

The opioid-naïve patient is more likely to experience adverse events, particularly at the onset of treatment, and requires education about the risks, benefits, and potential side effects of opioid therapy. The NCCN guidelines recommend that opioid-naïve patients with pain $\geq$4 on an 11-point NRS be started on short-acting opioids along with a concurrent bowel regimen [49]. According to a systematic review by Klepstad and colleagues, opioid naïve patients may be started with 30 mg or oral morphine per day [73].

According to the NCCN guidleines, opioid-experienced patients with pain $\geq$ 4 can be treated with 10% to 20% more of the total opioid they took in the previous 24 hours; with the new dose, an assessment of effectiveness and adverse events should be taken 60 minutes after administration. If pain persists or worsens, the dose may be increased by 50% or 100% with effectiveness and adverse events documented 60 minutes after dosing. This cycle can be repeated until the pain level falls in the range of 0 to 3, at which point the current dose can be maintained [49]. Pain assessments should be performed regularly thereafter to assure adequate analgesia. It is not unusual for pain levels to stabilize for a time but then increase, which may be the result of opioid tolerance (larger doses required to maintain same level of analgesia) or disease progression or a combination. Opioid-induced hyperalgesia may also occur, in which pain signals become aberrantly amplified such that the opioid exacerbates rather than relieves pain [85]. For these reasons, pain assessments should be regularly taken and analgesia therapy adjusted as needed.

COMMON OPIOID CONVERSIONS

Over the course of therapy, opioid conversion may be necessary. This may be in the form of opioid rotation (to improve response) or to change to a

Table 6: Relative Analgesic Ratios of Selected Opioid Analgesic Products (Converting One Drug to Another) from the EAPC Guideline [75, 86]. This Table is not Exahustive and is Intended for Illustrative Purposes

Drug > Drug	Relative Analgesic Ratio	Strength of Recommendation
Morphine PO > oxycodone PO	1:1.5	Strong
Oxyocodone PO > hydromorphone PO	1:4	Strong
Morphine PO > hydromorphone PO	1:5	Weak
Morphine PO > transdermal buprenorphine	75:1	Weak
Morphine PO > transdermal fentanyl	100:1	Strong

PO=per oral or by mouth.

product that is more convenient or may improve adherence. An example is the patient who discontinues an oral opioid in favor of a transdermal patch [86]. Conversion ratios may be used to transition from one opioid to another or one formulation of an opioid to another formulation of that same opioid. Conversion ratios are not well established in evidence-based literature, but those appearing in Table **6** are frequently used conversions and their commonly accepted conversion ratios [86]. Moreover, it has been suggested that once a dose conversion has been calculated, it should be reduced slightly, but there is no evidence to support this fairly well-accepted clinical practice [86].

According to the guidelines, in converting intravenous (IV) morphine to oral morphine, the ratio is 3, that is,10 mg of IV morphine is equivalent to 30 mg of oral morphine. Ratios are 2 for levorphanol (2 mg of IV levorphanol equals 4 mg of oral levorphanol) and 10 for oxymorphone (1 mg of IV oxymorphone equals 10 mg of oral oxymorphone) [49]. Opioid conversions involving methadone are complex and should be left to pain specialists, if done at all. Conversions to or from tapentadol have been studied and are estimated in oral morphine equivalents at a ratio of 1 to 3.3 in both directions, particularly in the setting of equianalgesia [87].

COMBINATION THERAPIES

Advocated in the original 1986 WHO pain ladder and present in today's updated and revised guidelines, combination or multimodal therapy has long been recognized for treating pain in cancer patients. (See Table **3**) For example, cancer pain often involves a neuropathic component and its treatment can be challenging. Although evidence-based guidelines for benign neuropathic pain support the use of antidepressants and anticonvulsants with further evidence for other treatment choices, such as the lidocaine patch 5%, there is a paucity of evidence evaluating such treatments for cancer pain [88]. Dosing regimens may also play an important but less appreciated role in the treatment of multimechanistic cancer pain. In a multicenter randomized trial of 75 cancer patients with neuropathic pain, patients were grouped to receive a fixed dose of oxycodone and escalating doses of pregabalin (Group A) or a fixed dose of pregabalin with escalating oxycodone doses (Group B) [89]. Using the NRS, pain diaries, and other evaluations at 3, 7, 10, and 14 days after starting the regimen, it was found that both groups experienced effective neuropathic pain control but Group A had a greater reduction in pain with fewer side effects. Corticosteroids are known to reduce swelling and inflammatory pain and are important adjuvant agents that may help alleviate neuropathic pain and bone pain. The anti-inflammatory action of glucocorticosteroids relates to their collagenase inhibition which appears to reduce pro-inflammatory cytokines [90].

Complementary and alternative medicine may also be useful in treating cancer when combined with pharmacological therapy. For example, the National Comprehensive Cancer Network guidelines recommend acupuncture for the treatment of certain cancer pain and also for the relief of drug-related side effects, such as nausea, vomiting, and constipation [91].

PATIENT EDUCATION

Cancer patients dealing with moderate to severe pain can feel overwhelmed and thus be less than responsive to educational efforts by the clinical team. However, patient education may help equip cancer patients to better understand their pain and, in so doing, give them skills and confidence to better manage their pain. A study of 150 patients with various types of cancer (mean age 65.4 ± 7.72 years) using the Patient Pain Questionnaire (PPQ), the BPI, the

American Pain Society's Patient Outcome Questionnaire (APS-POQ), and the Chronic Pain Self-Efficacy Scale (PCAS) found that trust in the clinical team is a significant predictor of pain knowledge [92]. The clinical team should make it a priority to inform and educate cancer patients about pain. A European study based on eight in-depth interviews with breast cancer surgery patients reported that none remembered having ever been given information about pain associated with breast cancer surgery and while most expected postsurgical pain, none expected persistent pain [93]. Patient education may thus also improve adherence to analgesic therapy.

ADHERENCE

Adherence remains a major clinical challenge, even in pain control. A cross-sectional study of 92 oncology outpatients in Taiwan found that the patients' personal opinions about opioid therapy and pain correlated significantly with their adherence and the more negative those beliefs were, the less adherent the patients were to around-the-clock dosing regimens [94]. Adherence rates in these 92 patients were low: 63.6% for around-the-clock dosing and 30.9% for as-needed dosing, with women less adherent than men [95]. In a study of lung cancer patients on long-acting opioid therapy, the self-reported adherence rate was 85.4%, with lower adherence positively associated with advanced age (p=0.04) [96]. It is not unusual for patients to take less opioid than prescribed. In a study of 630 patients taking hydrocodone for a variety of non-cancer pain syndromes, 27.6% of patients took less than the prescribed amount [97].

The motivations behind non-adherence can be complex. The Morisky Medication Adherence Scale (MMAS) differentiates between intentional and unintentional non-adherence; the former includes outright refusal of the drug, while the latter includes forgetting a dose or being careless with medications in general [98]. In a pilot study of cancer patients treated with analgesics, 85.5% took the drug during the index period, but 51% reported taking less than prescribed [99]. In that study, the most frequently observed form of non-adherence was intentional and involved discontinuing the drug because the patient felt better (74%).

While some cancer patients are not prescribed adequate analgesia, many have prescriptions but do not take them. In a study of 1,107 cancer patients, 67% reported pain; of this group, 25% did not take any analgesics. Among those in pain, men were less likely to use pain relievers than women (44% vs. 52%, p=0.023), minorities used less than whites (42% vs. 53%, p=0.001), and patients with lower educational levels used less than those with more education 45% vs. 53%, p=0.013) [100]. When patients in pain but not taking analgesics in this study were asked their motivations, 85% said their physician did not recommend them, 80% were concerned about addiction or physical dependence (patients could give more than one answer), and 76% said they could not pay for the drugs. This lack of adherence does not mean these patients did not want pain relief; 94% of them reported trying alternative therapies to control their pain [100]. This study did not address the seemingly paradoxical finding that patients who found prescriptions cost prohibitive nevertheless purchased other remedies.

Most clinicians have observed that some patients simply do not like prescription medications. A study of 40 geriatric patients (≥ 75 years) found that this population generally disliked taking prescription drugs, but most took them anyway [101].

For cancer patients, already taking many drugs and often subjected to multiple major medical interventions, pain medication may be perceived as one more burden. Cancer patients, like other patients, may be wary about opioid therapy for fear of addiction, tolerance, or because they dislike the way the drugs make them feel. For those reasons, the clinical team should make special efforts to educate patients about the benefits of pain therapy, the nature of side effects, and how side effects can be managed. Pain should be assessed regularly, at which time educational efforts can be presented or reviewed, such as helping to control side effects or adjusting the dose or medications to provide more optimal pain control. In a study of 96 patients with non-cancer pain syndromes, patient educational interventions were associated with improved analgesic adherence [102].

CONCLUSION

People with cancer are living longer, which means the majority of them will require long-term pain control therapy. Cancer patients are complex pain patients: their pain may relate to their underlying disease, their treatments, or be independent of them. Diagnosis and assessment should be based on localization, qualification, quantification, and categorization. Quantification (pain assessments) should be performed

at baseline and then at regular intervals (such as dosing intervals) using validated pain scales, such as the numeric rating scale (NRS). Multiple pain mechanisms are often involved in pain syndromes in cancer patients and combination therapy may be most efficacious in addressing multimechanistic pain syndromes. Cancer patients often have a combination of nociceptive (inflammatory) pain, visceral pain, bone pain, or neuropathic pain, the latter often associated with chemotherapy. The WHO pain ladder recommends oral morphine for treating moderate to severe cancer pain, but the literature suggests that oral morphine, oxycodone, and hydromorphone are equivalent agents, with some evidence to suggest that oral oxycodone is better tolerated than oral morphine. Adherence may be suboptimal for analgesics in cancer patients, but may be improved with better patient education and open communication between clinician and patient.

ACKNOWLEDGMENTS

This manuscript was prepared with editorial and medical writing services from Jo Ann LeQuang of LeQ Medical, Angleton, Texas. Mundipharma paid for her services.

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Received on 20-11-2015 Accepted on 18-01-2016 Published on 29-01-2016

DOI: http://dx.doi.org/10.6000/1929-2279.2016.05.01.6