

A Guide for Cancer Pain Management in Latin America

Joseph V. Pergolizzi, Jr.¹, Robert B. Raffa², Emilio Esteban Gonzalez³ and Jo Ann LeQuang^{1,*}

¹*NEMA Research Group, Inc., Naples, Fla., USA*

²*Professor Emeritus, Temple University School of Pharmacy, Philadelphia, Pa. and Adjunct Professor, University of Arizona College of Pharmacy, Tucson, Ariz., USA*

³*Professor, University of Oviedo and head of Medical Oncology Department, Central University Hospital of Asturias, Oviedo, Spain*

Abstract: Cancer prevalence in Latin America (LATAM) is increasing and represents a major cause of morbidity and mortality. Managing cancer patients—who live longer than ever before—requires appropriate management of cancer pain, described by the World Health Organization (WHO) in 1988 with its now famous “pain ladder,” the rungs of which represented nonopioids, weak opioids, and strong opioids as pain relievers. Yet even today much cancer pain is undertreated. Cancer pain can be multimechanistic with a neuropathic component which may complicate pain control. Acute pain should be treated aggressively to avoid the potential transition to chronic pain, a maladaptive form of pain that can be particularly challenging to treat. Although opioids have been recognized by WHO in 1988 and since then as a safe, effective form for treating moderate to severe cancer pain, opioid consumption in LATAM nations is very low. LATAM countries make up about 9% of the world’s population but represent only about 1% of global opioid consumption. Better education about pain control in cancer and opioid therapy is needed by both healthcare providers and patients to better treat cancer pain in LATAM. But opioid-associated side effects and the risk of abuse and diversion are important risks of opioid therapy that are to be fully understood by both healthcare providers and patients before commencing therapy. Opioid risk management plans balance the need for access to opioids for appropriate patients with the mitigation of opioid-related risks of abuse and addiction. Risks as well as benefits should be clearly understood in order to consider opioid therapy. Combining education, prescription drug monitoring plans, and other risk mitigation strategies may be useful tools. Abuse-deterrent formulations, such as fixed-dose combination products of an opioid with naloxone, have been designed to resist abuse. LATAM may benefit from such new products in efforts to bring better pain control to cancer patients in a rational and responsible manner.

Keywords: Cancer pain, Latin America cancer pain, opioids, opioid therapy.

INTRODUCTION

As Latin America grows in population and global economic importance, cancer in the region has emerged as a major cause of morbidity and mortality [1]. For the purposes of this paper, we define Latin America (LATAM) as South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela) and Central America (Belize, Costa Rica, El Salvador, Honduras, Guatemala, Mexico, Nicaragua, and Panama). While LATAM cancer rates generally remain lower than those of North America and Europe, cancer is a significant public health problem and cancer rates are projected to increase markedly in the next 15 years [1]. Cancer poses significant challenges to any healthcare system in that it is associated with a disproportionately large utilization of healthcare resources, high costs, challenges for long-term management, and considerable rates of pain and disability.

Cancer is the second leading cause of mortality in Mexico, Argentina, and Brazil and the third leading cause of death in Peru [2]. Overall, prostate and breast cancers are the most common cancers in LATAM [1]. The rate of lung cancer, the most lethal cancer globally, is increasing in LATAM [3]. Infection-related cancers are prevalent in LATAM, particularly in the less-developed nations of the region, with cervical and stomach cancer being among the five most frequently occurring and deadliest cancers [1]. Indeed, stomach cancer is the most common cause of cancer-related death in Central America and in Chile and Guatemala the incidence of stomach cancer in males is 2.5 times that of U.S. males [1]. Cervical cancer rates and the associated cumulative mortality risks are 2.5% in Guyana, 2.4% in Bolivia, and 2.0% in Nicaragua, about eight times greater than the rates in the U.S. or Spain [1]. Cancer mortality rates are relatively high in LATAM as many patients initially present with advanced disease.

LATAM is subject to many of the same factors that affect cancer rates around the world. Obesity has become a worldwide public health threat and has a strong impact on LATAM [4]. An increasingly sedentary

*Address correspondence to this author at the NEMA Research Group, Inc., Naples, Fla., USA; Tel: (239) 597-3564, Fax: (239) 908-4436, E-mail: info@nemaresearch.com

lifestyle and more processed food in the diet affects patients around the world [4]. Early detection may help reduce cancer; for example prostate cancer deaths have recently decreased in Chile, Argentina, Costa Rica, and Mexico, which may reflect early detection and better treatment [1,5].

Cancer poses important challenges to all regions in the world, including those related to patient and clinician education, early detection, and the deployment of rapidly evolving treatment options. Less often discussed in this context is the important issue of management of cancer pain.

The symptomatic experience of cancer has not been thoroughly elucidated. Pain is prevalent in cancer, but prevalence varies by cancer type and can be as high as 70% [6]. In a study of 110 consecutive cancer patients admitted to intensive care, 73% had moderate to severe symptom-related distress, with pain being the most commonly reported symptom [7]. Forty percent of those 110 patients reported cancer-related pain was “the most distressing symptom” of the disease [7]. In a survey of 96 adult cancer patients, 12% said pain was the “worst aspect of their illness,” equivalent to those who feared death (12%) and more than those who feared loss of income (6%) or the breakdown of their family (3%) combined [8]. Cancer-associated pain typically worsens as the disease advances or metastasizes. Anticancer treatments may cause additional pain and distress, including postsurgical pain and chemotherapy-induced painful peripheral neuropathy [9,10]. Pain may persist after the cancer has been managed or eradicated.

Managing cancer pain—typically with opioid therapy as set forth by the World Health Organization in 1988 [11]—is possible but may be associated with unintended consequences, such as opioid-associated side effects (including respiratory depression, somnolence, and opioid-induced constipation) as well as opioid misuse and abuse. In the United States, an epidemic of prescription opioid abuse [12] has caused a backlash against opioid prescribing [13]. In reality, healthcare providers in LATAM and the United States are facing a dual pandemic. On the one hand, cancer patients are suffering needlessly from untreated or under-treated moderate to severe pain and, on the other hand, opioids prescribed to treat pain may be diverted for abuse. It is important not to try to solve one problem while exacerbating the other—in this case attempting to curtail opioid abuse at the expense of pain control, now considered a fundamental human

right [14,15]. Nevertheless, clinicians must be prudent in taking steps and to adopt opioid risk management plans aimed at reducing the risk of opioid diversion, abuse, and addiction. In LATAM, the primary issue remains access to opioids for pain patients—but in order to avoid repeating the missteps of opioid therapy in such countries as the USA, it is crucial to reinforce strategies for safe use, such as education for clinicians and patients as well as the use of new technologies, such as abuse-deterrent formulations.

Cancer Pain Control

Cancer pain is often intense and it can impede rehabilitation, exacerbate psychological distress, promote depression, interrupts sleep and markedly reduce quality of life. Despite our increasing understanding of cancer-related pain, little has been accomplished in terms of its management. In the United States in 1994, about 40% of cancer-related pain was untreated; by 2012, 33% of cancer-related pain was untreated [16,17]. This statistic may reflect a global inertia with respect to cancer pain care.

Cancer pain may be described along the continuum of the disease: many patients experience some degree of pain or discomfort prior to diagnosis. Pain is often the motivating factor which prompts patients to seek a diagnosis. Once a malignancy is detected, the patient may undergo treatment which causes additional pain, such as post surgical pain or pain following radiation or chemotherapy. Even if the cancer remits, the patient may still experience persistent pain. If the disease advances, pain typically worsens with metastases and possible bone involvement. Palliative cancer patients typically experience painful symptoms at end of life [18,19].

Pain is but one form of suffering to which cancer patients are vulnerable [19]. The diagnosis and treatment of cancer can cause considerable fear and anxiety in patients. Patients may become psychologically distressed and even despondent over their loss of function, dignity, independence, and financial resources. The patient's own belief systems as well as the broader familial and cultural context can affect how the patient responds to the many challenges of cancer. Against the backdrop of cancer-related fears and concerns, pain can be exacerbated.

It is most disturbing that even when cancer pain is present in patients under clinical supervision, pain may go untreated. In a prospective study of 3,023 cancer

patients, 41% who reported moderate to severe pain had no prescription opioid analgesics upon initial assessment, including 20% of patients who reported being in “severe pain” [16]. In this study, patients were seen again about 30 days later (ranging from 28-35 days) but treatment adequacy for pain control did not significantly improve. A total of 406 patients were undertreated for pain at the first visit, and only 31% were receiving acceptable analgesia by the follow-up visit; this erratic use of analgesia was further evidenced by the fact that 10% of the patients treated for pain at the initial visit were no longer being treated appropriately for pain by the follow-up visit [16].

The reasons for inadequate analgesia in cancer patients are likely diverse and interrelated. Cancer is a complex, progressive disease, and patients often have multiple pain sites with pain that varies in intensity and quality [20]. Not all pain reported in cancer patients can be attributed to cancer; cancer patients may have comorbid conditions or may have pain related to cancer treatments. Cancer patients may not be forthcoming about their pain, fearing that worsening pain may mean a worsening prognosis or that “bothering the doctor” about pain might distract the physician from the more important work of fighting their cancer. There can be cultural issues that inhibit patients from asking for relief from their suffering or that make them believe complaining about pain is a sign of weakness. Furthermore, cancer pain is often multimechanistic, which requires specific treatment strategies for effective control [21]. In many parts of the developing world, there are notable deficits in training for clinicians who treat cancer patients as well as a lack of political support for cancer care [22].

Multimechanistic Pain

Nociceptive pain is the pain caused by injury or noxious stimulation of the musculoskeletal, cutaneous, or visceral system. Nociceptive pain is typically associated with the inflammatory response, which may evolve into inflammatory pain. Cancer pain has a nociceptive component which may occur as the tumor puts pressure on nerves and organs. Visceral pain can be extremely challenging to treat since the viscera are so densely innervated [21,23].

Neuropathic pain is based on a fundamentally different mechanism than nociceptive pain and does not always respond to the same pain control treatments. Neuropathic pain is initiated or caused by a primary lesion or dysfunction of the central or

peripheral nervous system. Neuropathic pain may be caused by damage to the nerves, as occurs with chemotherapy-induced painful peripheral neuropathy, [10] or it may be a maladaptive aberration of the neural system, possibly owing to central sensitization [24]. Pain in cancer patients may have a neuropathic component.

Treating multimechanistic pain may require multimodal therapy, that is, specific treatments for the nociceptive and the neuropathic components. Furthermore, cancer patients may also experience treatment-related symptoms (chemotherapy-induced nausea and vomiting, dizziness), muscle spasms, and comorbidities, all of which contribute to the overall pain experience.

The Transition from Acute to Chronic Pain

Although chronic pain is typically defined in terms of duration (persistent pain that lasts three to six months), it may better be thought of as a maladaptive response caused by central sensitization. The transition from acute to chronic pain has not been thoroughly elucidated, but it appears that untreated acute pain may transition to chronic pain in a process called “chronification” or “windup” [25,26]. Chronic pain may be considered to be an abnormal amplification of pain signals owing to neural and processing dysfunctions [27]. Chronic pain can be extremely difficult to manage in that pain levels can be variable, pain locations can be diffuse and migrate, and the pain may not respond to many types of pharmacological and nonpharmacological treatments [28]. Aggressive treatment of acute painful conditions may prevent the transition from acute to chronic pain [25]. For that reason, patients should be encouraged to report their pain frankly to the clinical team so as to receive adequate analgesia.

Benefits of Cancer Pain Control

Managing cancer pain can be challenging, but unresolved pain in cancer patients is more than just a cause of suffering. Unresolved pain with cancer can lead to decreased productivity, loss of income, lower self-esteem, and loss of well-being [29]. Patients with unmanaged pain may have difficulty concentrating, may be unable to work, and may lose their ability to handle routine tasks such as driving or caring for themselves [30]. Pain is associated with insomnia and fatigue, two potentially troublesome conditions [31]. Patients dealing with persistent moderate to severe

pain may suffer breaks in their family or personal relationships and sexual dysfunction [32]. Pain is associated with exacerbation of depression and suicidal ideation [33,34]. Patients in persistent pain may be irritable, frustrated, and unable to do the things they once enjoyed [35]. Moreover, pain may cause increased utilization of healthcare resources and be associated with higher costs to both patient and healthcare systems [36]. In short, untreated cancer pain has a devastating long-term effect on the patient's quality of life and an adverse impact on the healthcare system and society at large [37].

Opioid Therapy for Cancer Pain Management

Opioid analgesics are recognized as safe and effective pain relievers when used as indicated in appropriate patients [38,39]. Nonpharmacologic approaches to pain control and nonopioid pharmacological therapy are typically not effective in managing moderate to severe cancer pain. As early as 1988, the World Health Organization (WHO) advocated the treatment of cancer pain, including the use of strong opioids such as oral morphine, for control of moderate to severe cancer pain [11]. Yet many low and moderate-income countries around the world lack adequate access to opioids, including oral morphine which is considered an affordable, indeed inexpensive, medication [40]. Using the metric of morphine equivalence (ME) which permits equianalgesic comparisons among a variety of opioid analgesic products, opioid consumption expressed in milligrams per person (mg/capita) can be compared across geographical regions [40]. Developing countries typically demonstrate the lowest levels of opioid consumption [41]. It has been estimated that for adequate pain control Chile and Colombia, for example, require opioid consumption of 210.14 and 201.14 mg/capita, respectively, but in fact in 2010 they consumed 10.81 and 6.78 mg/capita [41]. This means, in the best-case scenario, that opioid consumption has to increase 30-fold in LATAM to adequately treat pain. Yet the use of opioid analgesics remains relatively low in LATAM as well as in many other parts of the world, including Asia, the Caribbean, and eastern/southeastern Europe [42]. This low level of opioid consumption no doubt reflects inadequate pain management for many cancer patients.

There may be many reasons for the lower relative consumption of opioid analgesics in LATAM and other regions. These include lack of clinician education and training, concern about dependence and addiction,

limited ability to source the opioids, price constraints, cultural or societal taboos, international trade restrictions, political concerns, and burdensome regulations. Impediments to opioid prescribing have been significantly associated with lower clinical use of opioid analgesics (unadjusted incidence rate ratio 0.39, 95% CI, 0.29-0.52, $p < 0.0001$) [42].

Globally, the results of these disparities are unsettling. About two-thirds of the global population (66%) has virtually no consumption of opioids and no access to these medications for pain control even for the most severe forms of cancer pain [43]. Only a fraction of the world's population (7.5%) has what is considered by the WHO to be adequate opioid consumption for pain control. It should be noted that between the years 2006 and 2010, 67 countries increased opioid consumption per capita toward more adequate levels [43]. See Table 1 for LATAM consumption rates in 2010 [43].

Thus, opioid analgesics are not widely available in many nations in LATAM and may be virtually inaccessible to many patients facing moderate to severe cancer pain. Since opioids may be the only medication that can effectively treat cancer pain for some patients, this is a serious public health concern, as untreated cancer pain represents a real and urgent medical need. Since it is necessary for opioid use to increase to control cancer pain, it is likewise necessary that a rational, safe, and evidence-based approach be adopted in order to treat cancer pain patients safely while diminishing the potential risk of abuse [44,45].

Cancer Care Paradigm: The Treatment Team

Cancer patients are typically treated by an oncologist who may be viewed as the focal point of the patient's clinical team. The oncologist treats the cancer and likely interfaces with the patient's primary care or family physician. An oncologist treats the underlying disease, likely referring the patient to surgeons, radiotherapists, and others, as necessary for anticancer procedures. If the patient has severe or complex pain, the oncologist may refer the patient to a pain specialist or a neurologist (for neuropathic pain). At the point that the patient is nearing end of life, the oncologist may turn the patient over to a palliative care specialist. This cancer care team paradigm is the model in the US, Europe, and much of LATAM. However, this paradigm may neglect or not adequately address cancer pain, especially and most egregiously severe pain. Studies from around the world report

Table 1: Actual Versus Adequate Opioid Consumption in LATAM in 2010

Country	Actual ME consumption (mg/capita)	Adequate ME consumption (mg/capita)	Adequacy of Consumption
Argentina	14.87	236.17	6.30
Bolivia	0.19	152.16	0.12
Brazil	13.13	192.91	6.81
Chile	10.81	210.14	5.14
Colombia	6.78	204.13	3.32
Costa Rica	5.60	188.94	2.96
Ecuador	1.59	213.92	0.74
El Salvador	4.45	184.29	2.42
Guatemala	2.01	211.26	0.95
Guyana	4.34	206.76	2.10
Honduras	0.65	255.00	0.26
Mexico	6.47	143.32	4.51
Nicaragua	1.34	169.25	0.79
Panama	4.36	219.30	1.99
Paraguay	2.17	208.59	1.04
Peru	2.22	207.65	1.07
Suriname	1.16	199.29	0.58
Uruguay	5.91	294.51	2.01
Venezuela	3.22	162.64	1.98

similar trends: a lack of clinician education about pain control, inadequate or altogether lacking pain assessments, attitudes that pain cannot be prevented or is of minor clinical importance, limited accessibility of opioids, high regulatory barriers to adequate care, and reluctance to prescribe opioids [46].

A lack of adequate education in treating pain appears to be a global phenomenon. U.S. oncologists surveyed (n=354) rated their own training in pain medicine in medical school and residency as 3 and 5, respectively, on a scale of 0 to 10 [47]. A survey of Chinese physicians charged with treating cancer patients (oncologists, internists, hematologists) in 11 centers from 2011 to 2013 (n=500) found that about a third (32.6%) “rarely” assessed their patients’ pain and named three main barriers to better pain care: inadequate pain assessments, patient’s reluctance to take opioid analgesics, and lack of knowledge of pain management by staff members [48]. A survey in Thailand of physicians and policy-makers involved in cancer care (n=219 physicians, 47 policy-makers) found 62.1% of physicians and 74.5% of policy-makers had inadequate knowledge of cancer pain management; 33.8% of physicians and 66.0% of

policy-makers had a negative attitude toward opioid therapy for cancer pain [49]. This study found lack of training and education was the greatest barrier to better pain control therapy for cancer patients. A survey of 1204 young physicians in Korea reported that a lack of knowledge and practical training in opioid therapy for managing cancer pain was the greatest barrier to adequate analgesia in cancer patients [50].

A survey of nurses in Sri Lanka found that their task-oriented approach toward work at the clinic rarely recognized the need for pain control among cancer patients, possibly as a consequence of a lack of education regarding cancer pain management [51]. Final-year medical students in Saudi Arabia were surveyed (n=325) about cancer pain management; 46% believed that the pain associated with cancer was not treatable, 42% considered cancer pain a “minor problem,” and 59% said that prescribing opioids to cancer pain patients was associated with a high risk for addiction [52]. When patients required increased doses of opioids to manage pain as cancer advanced, 77% of respondents believed that this reflected tolerance or drug dependence rather than worsening pain levels [52].

Clinicians are not the only ones with incomplete or inaccurate knowledge of opioid analgesia. In a survey of Taiwanese cancer patients (n=92 outpatients), 68.5% thought that opioids were “not good for a person’s body,” 62% agreed with the statement “the more opioid medicine a patient used, the greater the possibility that he/she might rely on the medicine forever,” and 61% agreed that “if a patient starts to use opioid medicine at too early a stage, the medicine will have less of an effect later” [53]. The majority of respondents in this survey (66.3%) said adult patients should not take opioids often [53]. In a multicenter survey of 1619 outpatients with advanced cancer in Japan, 28% thought that opioids were addictive and/or would shorten their life [54]. Thus, patient education is urgently needed as there may be patients who have the opportunity to receive adequate analgesia but refuse it out of misunderstanding.

In a single-center study from Zaria, Nigeria, of medical practitioners in a low-resource setting, 44% of respondents agreed “strongly” that cancer patients required pain treatment yet only 40% routinely evaluated pain among cancer patients [55]. The majority (51%) said they only treated cancer pain when the patient complained about pain. Most practitioners prescribed weak opioids for cancer pain (43%), while 32% prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) and 20% gave their patients strong opioids. The vast majority of respondents in this survey (91.5%) reported having never received any formal training in pain management [55].

Cultural barriers also come into play. In a meta-analysis of cancer pain care contrasting Western and Asian patients, Asian patients exhibited overall higher barriers to controlling their cancer pain than their Western counterparts [56]. In particular, Asian patients were more concerned about drug tolerance than Western patients; Asian cancer patients were more likely to exhibit a fatalistic approach to pain and were more likely than Western patients to view exacerbations in pain as symptoms of disease progression [56].

Yet pain can often be adequately treated using available resources, including the available healthcare personnel. In a systematic review of pain-focused interventions, it was found that 47% of the interventions evaluated—most of which were led by nurses—resulted in significant decreases in pain [57]. For palliative care cancer patients who live in rural locations, the literature describes innovative home-care

programs which rely on the support of family members under the direction of the clinical team [58].

In LATAM, cancer pain, ideally, is treated by a multidisciplinary team that consists of oncologists, general practitioners, surgeons, pain management specialists, and nursing and support staff. In a survey of 777 healthcare providers (physicians and nurses) in Argentina, Brazil, Cuba, Mexico, and Peru, the main barriers to optimal care of cancer patients included: fear of opioid diversion, restrictive prescribing regulations, international restrictions on the import of medications as well as palliative care not being a priority for healthcare policy and education [59]. Many of the international concerns that impede adequate cancer pain control affect LATAM nations.

Barriers to Adequate Cancer Pain Control

Cancer pain is inadequately controlled in most portions of the world. For the majority of the world’s population, opioid analgesics have been made all but inaccessible owing to regulations, legal requirements, costs, healthcare practices, and cultural values. Although LATAM makes up approximately 9% of the world’s population, it only accounts for about 1% of the total opioid consumption worldwide [2]. In addition to limited access to opioids, a lack of education about opioid analgesia, the benefits of pain control, and training in pain management techniques is likely a major contributor to inadequate cancer pain control. In many parts of the world, policy-makers and government entities have prohibited the use of opioids or imposed such burdensome regulations as to effectively restrict their use in cancer pain. Cost may also play a role. While oral morphine is an inexpensive drug, many other types of opioids and opioid formulations (such as transdermal systems, parenteral systems, transmucosal delivery, abuse-deterrent formulations, and so on) may be cost prohibitive for many healthcare systems, particularly those in the developing world. Among the barriers to effective cancer pain management are poor knowledge of cancer pain and how to treat it, patients who present at the clinic with an advanced tumor, inadequate understanding of how to manage opioid-associated side effects, and lack of access to opioids, particularly strong opioids [55].

Patients and their families often resist the use of opioids even for the management of moderate to severe cancer pain. Patients may be reluctant to report their pain and may reject opioid analgesia for any number of

reasons, including cost. Patients may fall prey to fear of addiction or other notions that the use of opioids is debilitating or that their use early in the disease may make them ineffective for managing severe pain at the end of the disease. Patients may believe that their pain cannot be treated or that suffering is an inevitable part of their life. Better patient education is needed to prevent needless suffering. Furthermore, opioid therapy can be thwarted by poor patient adherence which may be due to incomplete understanding of opioid therapy or the fear of uncomfortable opioid-associated side effects.

Oncology patients may harbor very specific beliefs about how their healthcare providers regard pain. In a survey of European cancer pain patients, about 50% believed that their healthcare provider did not consider their quality of life to be a primary issue and 38% believed that the healthcare team was more focused on treating the cancer than addressing pain [60]. Twelve percent of patients thought that the healthcare provider failed to recognize pain as even being a problem and 33% thought the healthcare team did not have enough time to discuss pain. Indeed, about a quarter of patients (27%) said that their healthcare provider never asked them about pain [60].

Principles of Cancer Pain Management

The principles of cancer pain management are similar across all geographical areas. Cancer patients typically have persistent round-the-clock pain and thus require 24-hour pain management strategies. Short-acting opioids provide pain control for about four to six hours and thus require dosing up to six times a day. The patient may experience analgesic gaps as serum concentrations fall at the end of each dose and before the next dose is taken. Extended-release opioids may be preferred in appropriate cancer pain patients, as they can be dosed every 12 or 24 hours [46].

Clinicians should assess pain locations (pain may be present at multiple sites) and the characteristics of the pain at each site. Patients should be asked about the location of pain, its severity, if certain things relieve or exacerbate it. Patients should be asked to describe the pain, although many individuals may find themselves struggling to find the right words. The healthcare professional may prompt the patient with descriptions of typical pain characteristics such as burning, electrical, throbbing, deep, aching, shooting, sudden, stabbing, and so on. Clinicians should be aware that pain is more than a medical symptom, it is

also an “experience” that the patient undergoes which can be modulated by psychological and other stressors. Patients should be asked about, and possibly evaluated for, cognitive impairment and mental health conditions such as depression, and asked about their level of worry and anxiety. Cancer is an inherently stressful disease: patients typically contemplate their own mortality, face an uncertain future, fear pain, worry that treatments will result in a loss of dignity as well as consider the financial devastation the disease may bring with it. Cancer patients in chemotherapy or other treatments may be struggling to cope with treatment-induced symptoms, which can be severe and distressing. All of these can contribute to a worse “pain experience” than pain experienced by a patient without a malignant condition. Pain should be measured at each session and the patient should be trained to use a validated pain scale, such as a numeric scale. It is less important which validated measure is used than that the patient becomes familiar with rating his or her pain and the same scale is used consistently. Regular pain assessments help evaluate adequate analgesia and provide a framework that allows the patient to bring up the important topic of pain at each visit.

Cancer pain may be further complicated by breakthrough pain, which can be defined as sudden-onset exacerbations of pain against an ambient background of pain [61]. Breakthrough pain may be incidental, that is, brought on by a specific incident or activity (such as rolling over in bed, standing up, moving the arm) or it may come on without warning or clear cause. Breakthrough pain is typically treated using immediate-release opioid formulations consisting of about 1/6 of the patient’s daily opioid dose [62]. Thus, a patient who is taking 30 mg of oxycodone per day for cancer pain control might be given a dose of 5 mg of oxycodone immediate-release formulation to manage breakthrough pain.

The World Health Organization (WHO) recommends that cancer pain be treated using an oral or transdermal opioid formulation, as this may allow them to resume much of their old lifestyle as outpatients [11]. Opioids should be taken based on a clock-time schedule to prevent analgesic gaps. The now-famous WHO pain ladder recommends treating pain based on intensity of pain using nonopioids (step 1), weak opioids (step 2), and strong opioids (step 3), with and without adjuvant agents. Cancer pain should be treated based on the needs of the individual patient; thus, dosing should be titrated and pain regularly

evaluated to assure that the patient is being correctly treated [11].

The National Comprehensive Cancer Network (NCCN) guidelines recommend regular pain assessments, the use of adjuvant medications as needed, and opioid rotation for occasions when analgesia could be improved [63]. Opioid rotation refers to changing the patient's opioid agent from one to another in an effort to find an opioid that offers more effective pain relief and/or fewer adverse effects [64]. The methods for opioid rotation have been described in the literature and involve starting with a lower-than-equianalgesic dose of the new opioid and titrating to effective and well-tolerated pain control.

Which Opioids Are Best for Cancer Pain?

Not all opioid agents and formulations are available in all LATAM countries and there may be specific limitations attached to available agents [65]. The WHO pain ladder categorizes opioids as "weak" (e.g., codeine, tramadol, certain fixed-dose combination products such as hydrocodone plus acetaminophen) and "strong" (e.g., buprenorphine, hydromorphone, morphine, oxycodone, and others) [11]. Furthermore, the WHO analgesic paradigm describes pain relief along three steps; weak opioids treat pain at the second step (moderate intensity pain) while strong opioids treat pain at the third step (severe pain). While the terms "weak" and "strong" opioid are still in use, they may be less useful to describe opioid agents than the dose. In an open-label controlled multicenter study comparing weak opioids to low-dose strong opioid therapy, 240 opioid-naïve adult cancer pain patients were randomized to receive either a weak "step II" opioid to treat their moderate pain or a low dose of a strong "step III" opioid [66]. Patients who reported $\geq 20\%$ pain reduction on a numeric rating scale were counted as responders and the primary endpoint of the study was the group with the largest number of responder patients over the 28-day study period. The "weak opioid" group received either oral tramadol alone or combined with acetaminophen or a fixed-dose combination product of codeine plus acetaminophen. Patients were titrated on the weak opioid up to the maximum dose: 240 mg/day of tramadol or 180 mg/day of tramadol plus acetaminophen or up to 400 mg/day for codeine for patients 75 years of age and younger or 300 mg/day codeine for those > 75 years. Acetaminophen doses could not exceed 4000 mg/day. Rotation from tramadol to codeine or vice versa was permitted. The "strong opioid" group underwent a

three-day titration phase with normal-release oral morphine up to 30 mg/day. Once titrated, patients were treated with a controlled-release formulation of oral morphine. Patients were monitored weekly (days 7, 14, 21, and 28 after randomization) which included a pain assessment and inquiries about possible drug-related side effects. The primary endpoint ($\geq 20\%$ pain reduction over baseline) was achieved by 88.2% of the low-dose strong-opioid patients compared to 54.7% of the weak-opioid patients (odds ratio [OR] 6.18, 95% confidence interval [CO], 3.12 to 12.24, $p < 0.001$). The more favorable response to low-dose strong opioid therapy was evident in the first observation session (80.9% vs. 43.6%, $p < 0.001$) and persisted throughout the course of the study. Both groups reported good tolerance of their pharmacological therapy with five patients in each group dropping out because of poor tolerability or adverse effects. There were no differences observed in frequency or severity of adverse effects between groups [66]. These findings, which suggest better efficacy with no compromise in tolerability with lower doses of strong opioids than conventional weak opioid therapy for adults with moderate cancer pain, challenge many preconceived ideas about "weak" opioids being preferable to "strong" opioids for cancer pain of moderate intensity.

Furthermore, there may be other reasons to consider "strong" rather than "weak" opioids. Based in part upon cytochrome P450 polymorphisms, codeine metabolism is susceptible to heritable influences in that a subset of the population may be considered "ultra-rapid metabolizers" or "poor metabolizers" [67]. Thus, it may at times be appropriate to rotate opioids to find the optimal agent for an individual patient [64]. Low doses of "strong opioids" may be appropriate prescribing choices.

In a four-arm multicenter clinical trial of 520 patients with chronic moderate-to-severe cancer pain, patients were randomized to receive oral morphine, oral oxycodone, transdermal fentanyl, or transdermal buprenorphine [68]. Patients were observed over four weeks for pain control and adverse events. In broad strokes, the results among groups were similar in terms of pain control, tolerability, and the frequency and severity of adverse effects. The primary endpoint was defined by the group with the highest number of responders, defined as those who achieved a $\geq 30\%$ reduction in pain. The study also recognized "partial responders" as those who achieved pain relief, but $\leq 30\%$ over baseline. There was no significant difference in the percent of nonresponders to morphine (11.5%)

and buprenorphine (14.4%). Over the study period, morphine patients (32.7%) required the greatest dose increases and fentanyl patients (12.2%) the least. Compared to the other opioids in the study, more patients discontinued morphine (27%) and the fewest discontinued fentanyl (14.5%). Adverse events were similar except for effects related to the central nervous system (hallucinations, confusion, myoclonus) which were significantly more frequent with morphine (13.2%) than oxycodone and buprenorphine (6.2% each) or fentanyl (2.4%), $p=0.001$ [68].

A New Paradigm for Cancer Pain Control

The three-step “pain ladder,” first presented in 1988, an effort by the WHO to help alleviate the suffering of cancer pain patients, is now nearly 30 years old. Since its publication, many new molecules have come to market and medical research has made considerable progress in our understanding of pain mechanisms and analgesia. Furthermore, cancer care has changed drastically, so that cancer patients live longer and may survive for years with “managed disease.” The WHO advocated treating cancer pain based solely on pain intensity—severe pain was treated more aggressively than mild pain. Today, we recognize that there are different types of pain, variations in pain intensities, and multiple contributing aspects to the experience of pain. Thus, the adjuvant agents mentioned by the WHO pain ladder are today better defined. Patients dealing with cancer pain may require anticonvulsants (for neuropathic pain), antidepressants, muscle relaxants, and possibly other drugs to promote sleep or fight anxiety. Research suggests that lower doses of strong opioids may be more effective than weak opioids and without adding to the side effect burden. Thus, a new way of looking at the three-step pain ladder is to jump over step II entirely and advance from nonopioid pain relievers for mild pain (acetaminophen, NSAIDs) to strong opioids, albeit at lower doses for moderate pain. A good rule of thumb for defining pain intensity relies on the eleven-point numeric pain scale. Pain at levels of 1 to 3 can be considered mild and can be treated by a nonopioid pain reliever, while pain levels 4 to 10 can be treated by strong opioids, with doses increasing to provide adequate analgesia. This new paradigm is described in detail in the European Association for Palliative Care guidelines for treating cancer pain [69].

In a study of 54 opioid-naïve cancer pain patients (patients had multiple affected viscera or bone metastases or locally advanced disease), patients were randomized to be treated along the old three-step

WHO pain ladder paradigm (conventional therapy) or according to the new two-step paradigm (innovative therapy) [70]. Patients were followed up to 90 days and endpoints were defined as the number of days in which the patient’s worst pain was ≥ 5 or ≥ 7 on an eleven-point scale. During treatment, physicians could prescribe whatever drug they wished according to the WHO scale (weak versus strong opioids) and adjuvant agents could be added, as deemed appropriate. Upon enrollment into the study 85.7% of conventional and 86.2% of innovative treatment arm patients were currently “dissatisfied” or “very dissatisfied” with their pain control. Conventional patients were “very satisfied” (28.8%) or “fairly satisfied” (47.0%) with their pain control at the end of the study compared to 27.1% and 50.3% of the innovative group. The worst pain was ≥ 5 on 28.6% of days for conventional patients compared to 22.8% for innovative patients; the worst pain ≥ 7 was 11.2% and 8.6% for conventional and innovative patients ($p<0.001$). However, more clinically-important, distressing-to-patients, and potentially treatment-limiting side effects occurred more often in innovative patients, although the overall rate of side effects was similar in both groups [70].

Thus, the new cancer pain care model suggests that the old WHO three-step pain ladder be redefined into what is more of a “pyramid” with multiple “pathways” depending on the patient [71].

The chronic or long-term use of opioid analgesics has been controversial, particularly for patients with nonmalignant pain. As cancer patients live longer and longer with pain, chronic opioid therapy may now be required for cancer patients as well. In a systematic review and meta-analysis of studies related to long-term use of opioids, ($n=26$ studies, 27 treatment groups, 4893 patients), moderate pain reductions over baseline pain scores could be provided by such opioid therapy, offering durable and clinically meaningful pain control [72]. In this meta-analysis, the treatment-limiting effect of certain opioids was evident, in that 22.9%, 12.1%, and 8.9% of patients taking oral, transdermal, or intrathecal opioids, respectively, discontinued treatment because of adverse events and 10.3%, 7.5%, and 5.8% discontinued because of ineffective pain control [72].

Opioid Dosing

There can be great variation in the opioid dose required by an individual patient. Particularly in cancer treatment, doses may need to be increased over time

in order to provide adequate analgesia for a given patient owing to opioid tolerance as well as disease progression. Arriving at the appropriate dose requires titration (dose finding) to ascertain the optimal dose, which can be defined as the amount of the drug that provides maximal pain control with minimal side effects. This can be a balancing act, and patients should be advised that complete pain control may not be possible. Complete avoidance of all side effects may also be an impossibility.

Opioid-related side effects can be distressing, even treatment limiting, and patients should be advised about them and report them. Some opioid-associated adverse events, such as nausea and dizziness, may resolve over a short period of time, while others, such as opioid-induced constipation, are more persistent. Constipation can be a very common and particularly bothersome side effect for patients [73-75]. Many side effects can be managed and patients should be encouraged to express their concerns about adverse events so that these effects can be addressed.

During opioid dose titration, pain should be regularly assessed using a validated instrument, such as the eleven-point pain scale. However, adequate analgesia ultimately is a subjective finding.

The U.S. Experience with Opioids

The United States consumed 481.99 mg/capita in morphine equivalent (ME) doses during 2010, far in excess of the actual requirement of 209.88 mg/capita [43]. Over prescribing opioids has occurred in the United States for a variety of reasons, including a growing awareness of pain control as a fundamental human right [76], marketing efforts on the parts of pharmaceutical companies [12], increased patient awareness and demand for pain control [12] and even the patient-centric Affordable Care Act (ACA) [77] which ties a degree of reimbursement for healthcare services to patient surveys that ask about adequate pain control [78]. The United States is currently experiencing an opioid abuse epidemic which has been widely reported in the news and medical literature [79]. Efforts are underway to mitigate this widespread abuse, including the development of abuse-deterrent opioid formulations [80], prescription drug monitoring programs [81,82], greater clinician education, the use of opioid agreements and patient education [83,84], and identification of risk factors for opioid misuse and abuse as well as universal precautions [85,86].

Universal precautions recommend that patients be assessed on an individual basis for their potential risk of opioid abuse [85]. If the patient has an appropriate pain indication and opioid therapy is being considered, the patient should be informed about risks and benefits of opioid treatment and be asked to sign a treatment agreement that sets forth in writing treatment goals, appropriate use, and consequences for inappropriate use. A number of risk factors for opioid misuse and abuse have been described in the literature, such as active substance abuse (even alcohol abuse) or a recent history of such substance abuse [87]. Screening tools may be used to better quantify risk [88,89]. Clinicians should be aware that risk factors can change with time, so patients should be periodically re-assessed [86].

Opioid Risk Management

The concept of opioid risk management refers to the efforts undertaken in order to minimize the harms associated with opioid therapy while, at the same time, providing appropriate pain patients adequate access to opioid analgesic products. Although opioid abuse is a serious public health threat, the risk of opioid addiction in patients administered opioid for chronic pain in a clinically supervised setting appears to be low; in a meta-analysis of 26 studies (n=4893 patients), the rate of overt opioid addiction among patients was 0.27%; limitations of this finding are that not all studies reported this outcome and some patients may have concealed their abuse [72]. Nevertheless, the reported rate of opioid addiction was far less than the number of patients who discontinued opioids for adverse effects, which was as high as 22.9% for those taking oral opioids long term [72]. Of course, clinical vigilance with respect to safe use and proper opioid disposal is warranted. While it is difficult to say with certainty what percentage of cancer pain patients might become addicted to opioids administered to them for cancer pain control, this number represents but a subset of the patients prescribed opioids.

When opioid therapy is considered for a cancer patient, the physician should discuss the benefits of opioid analgesia as well as the associated risks and side effects. Patients and their healthcare team should formulate clear goals, which may be described in writing in a patient agreement. While clinicians tend to think of these goals in terms of pain reduction (such as a 20% reduction in pain), functional goals may be more meaningful to patients such as being able to sleep well through the night or walk up a flight of stairs. Many

patients are fearful about using opioid medications because of the well-known risk of dependence and addiction. Clinicians would do well to educate patients and their families about the difference between physical dependence and addiction. Dependence means that the drug cannot be stopped abruptly without causing withdrawal symptoms and is an expected and normal result of long-term opioid use. Physical dependence can be managed by tapering off the opioid in a supervised clinical program. Addiction, on the other hand, is a biopsychosocial phenomenon in which a user feels powerless to control the use of opioids and craves them [90]. All addicted persons are physically dependent, but not all dependent people are addicted.

An important tool for preventing opioid abuse is the use of so-called “abuse-deterrent formulations” (ADF) opioids. In the United States, the Food and Drug Administration (FDA) has announced that it intends to approve only ADF opioids in the future [91-93]. There are many different and technologically innovative approaches to ADF products which may be used individually or in combination. Abuse-deterrent packaging offers tamper-proof bottles or products with a chip embedded for easier tracking (to limit diversion). Physical changes to the product have resulted in oral opioids that are extremely difficult to crush and dissolve, making it difficult for the drug abuser to extract the active agent. Some ADF products use an aversive agent, such as capsaicin or ipecac, which causes an unpleasant experience for anyone attempting to tamper with the product. Perhaps the most innovative and sophisticated approach to ADF opioids are those with pharmacologic barriers, including sequestered antagonists and prodrug formulations [94-98].

Finding the Right Opioid in the Arsenal

In determining appropriate opioid therapy for a given patient, clinicians have a wide array of products and formulations to choose from. Indeed, there are important reasons that the opioid arsenal contains a wide range of products in order to meet specific individual requirements. However, based on current understanding of pain management and opioid therapy, the ideal opioid agent would be a “strong” (step III) opioid agent available in formulations that permit dosing versatility, so that patients may start therapy on low doses. Oral formulations are probably the most versatile in that they can be readily used by outpatients and are usually well accepted by patients. Since cancer pain is a round-the-clock phenomenon, prolonged-

release formulations may be appropriate and can significantly minimize the pill burden. The product should address both nociceptive and neuropathic pain (since both are common in cancer pain), and should be associated with a reasonable rate and severity of side effects. Finally, to resist or deter abuse, the product should be available in an ADF version.

As just one example of an innovative approach to mitigating adverse effects, a new prolonged-release oxycodone/naloxone formulation has been introduced to market which may present an important and valuable new analgesic option for cancer patients (Targin®) [99]. See Figure 1. It may be particularly well suited for cancer pain patients in LATAM. This product is an ADF opioid that helps minimize the risk of opioid-induced constipation (OIC), one of the most troubling and distressing side effects associated with long-term opioid therapy [100]. The opioid antagonist (naloxone) is subject to extensive first-pass metabolism (98%) which allows the antagonist to work locally only in the gut. The oxycodone is also released in the gut but it

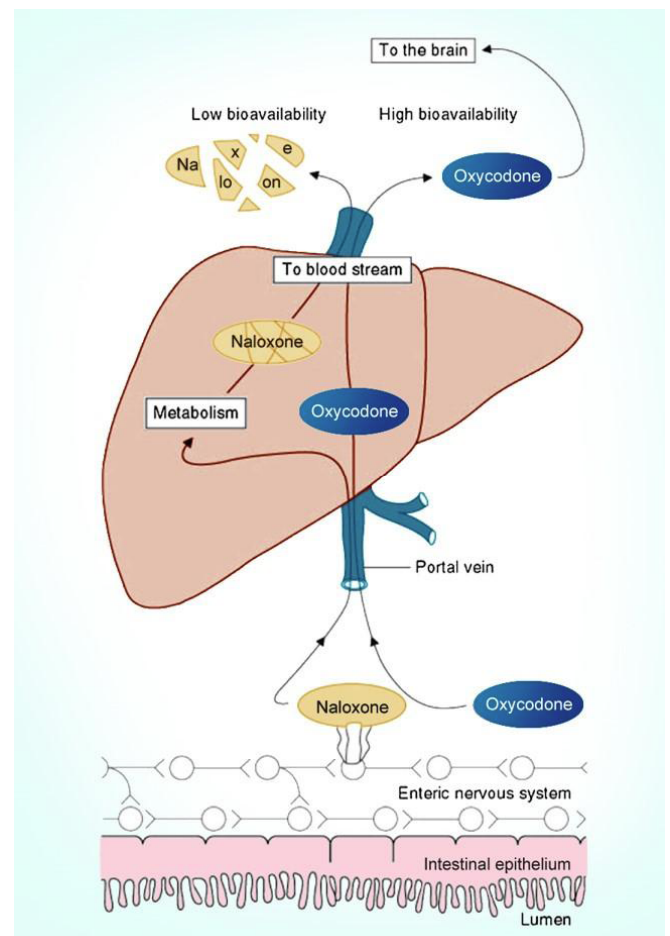


Figure 1: A summary illustration of the mechanism of action of oxycodone/naloxone.

must compete with naloxone for opioid receptors in the bowel, resulting in minimal opioid-associated effects on peripheral opioid receptors in the gut. This helps to defeat opioid-induced constipation. The 2:1 ratio of oxycodone to naloxone assures that much of the oxycodone enters systemic circulation to provide analgesic benefits [99]. Thus, this strong opioid (oxycodone) formulation can provide effective pain relief while minimizing the risk of opioid-induced constipation [101]. As such, it can facilitate pain control for cancer patients and, as an ADF product, it is designed to resist and deter abuse. These are global concerns and would certainly be applicable to LATAM.

DISCUSSION

LATAM is a large, culturally diverse and densely populated region of the world that historically has under-treated pain. Cancer pain presents a particularly serious challenge to the healthcare systems of LATAM for a variety of reasons: the prevalence of certain cancers is increasing in LATAM and new cancer therapies allow cancer patients to live longer than ever before in history—but often they live with moderate to severe levels of pain. When WHO issued its now famous “pain ladder” for adult cancer patients a quarter century ago, cancer pain was typically only managed short term in a palliative setting. Things have changed drastically, and the healthcare systems of LATAM have the opportunity to bring many of the innovations and advancements in treatment and new drug molecules and formulations to use in the care of their cancer patients.

LATAM, like other regions of the world, is in urgent need of greater and more evidence-based training in cancer pain care, including the appropriate role of opioids for analgesia. This education is needed for physicians, clinicians, nurses, pharmacists, patients, and the caregivers and families of patients. There are many prejudices against the use of opioid analgesics along with historical notions that pain is an unavoidable part of cancer. However, today it is possible for many cancer patients to live fulfilling and productive lives years after a cancer diagnosis, providing they have access to adequate analgesia.

By the same token, LATAM healthcare providers can benefit by seeking to understand the experience in the United States with opioid misuse and abuse and to learn from these experiences. As stated by the Spanish-American philosopher George Santayana, “those who cannot learn from history are doomed to

repeat it.” Many tools exist to manage the risk of opioid abuse and these should be used freely, as it appears that it is the interplay of multiple strategies that is most effective. These tools are risk assessment metrics, pain evaluations, the use of ADF products, patient-provider treatment agreements, patient education, and clinical supervision. Other tools, not discussed in this paper, include prescription drug monitoring programs and drug testing such as urine assays.

CONCLUSION

The nations of LATAM are confronting the terrible problem of cancer and its associated pain. LATAM represents a highly populated region of the world that underutilizes the benefits of opioid analgesics. The clinicians of LATAM can become advocates for pain control and educate themselves and their patients about the appropriate role of opioid analgesics in the management of cancer pain. Opioids are associated with the risk of addiction and abuse, which can be mitigated with strategies such as ADF products. Opioids are also associated with a number of side effects, such as opioid-induced constipation, which can be addressed using innovative new products such as oxycodone/naloxone combinations.

REFERENCES

- [1] Bray F, Pineros M. Cancer patterns, trends and projections in Latin America and the Caribbean: a global context. *Salud publica de Mexico* 2016; 58(2): 104-117. <https://doi.org/10.21149/spm.v58i2.7779>
- [2] Pan American Health Organization. *Health in the Americas*. Washington, DC: World Health Organization; 2002.
- [3] Raez LE, Santos ES, Rolfo C, *et al.* Challenges in Facing the Lung Cancer Epidemic and Treating Advanced Disease in Latin America. *Clinical lung cancer* 2016.
- [4] Goss PE, Lee BL, Badovinac-Crnjevic T, *et al.* Planning cancer control in Latin America and the Caribbean. *The lancet oncology* 2013; 14(5): 391-436. [https://doi.org/10.1016/S1470-2045\(13\)70048-2](https://doi.org/10.1016/S1470-2045(13)70048-2)
- [5] Pow-Sang M, Destefano V, Astigueta JC, *et al.* Prostate cancer in Latin America. *Actas urologicas espanolas* 2009; 33(10): 1057-1061. [https://doi.org/10.1016/S0210-4806\(09\)73181-X](https://doi.org/10.1016/S0210-4806(09)73181-X)
- [6] van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO* 2007; 18(9): 1437-1449. <https://doi.org/10.1093/annonc/mdm056>
- [7] Gupta M, Sahi MS, Bhargava AK, Talwar V. A Prospective Evaluation of Symptom Prevalence and Overall Symptom Burden Among Cohort of Critically Ill Cancer Patients. *Indian journal of palliative care* 2016; 22(2): 118-124. <https://doi.org/10.4103/0973-1075.179601>
- [8] Alifrangis C, Koizia L, Rozario A, *et al.* The experiences of cancer patients. *QJM: monthly journal of the Association of Physicians* 2011; 104(12): 1075-1081. <https://doi.org/10.1093/qjmed/hcr129>

- [9] Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-oncology* 2012; 14 Suppl 4: iv45-54.
- [10] LeQuang J, Pergolizzi J. *Chemotherapy-induced peripheral neuropathy: review of clinical studies*. Boca Raton, Florida: CRC Press; 2012.
- [11] World Health Organization. WHO's pain ladder for adults 1988; <http://www.who.int/cancer/palliative/painladder/en/>. Accessed 7 May, 2013.
- [12] Maxwell JC. The prescription drug epidemic in the United States: a perfect storm. *Drug and alcohol review* 2011; 30(3): 264-270. <https://doi.org/10.1111/j.1465-3362.2011.00291.x>
- [13] Dowell D, Haegerich T, R C. CDC Guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep* 2016; 65(1): 1-49. <https://doi.org/10.15585/mmwr.r6501e1>
- [14] Daher M. Pain relief is a human right. *Asian Pacific journal of cancer prevention: APJCP* 2010; 11 Suppl 1: 97-101.
- [15] Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesthesia and analgesia* 2007; 105(1): 205-221. <https://doi.org/10.1213/01.ane.0000268145.52345.55>
- [16] Fisch MJ, Lee JW, Weiss M, *et al*. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2012; 30(16): 1980-1988. <https://doi.org/10.1200/JCO.2011.39.2381>
- [17] Cleland CS, Gonin R, Hatfield AK, *et al*. Pain and its treatment in outpatients with metastatic cancer. *The New England journal of medicine* 1994; 330(9): 592-596. <https://doi.org/10.1056/NEJM199403033300902>
- [18] Pergolizzi JV, Gharibo C, Ho KY. Treatment Considerations for Cancer Pain: A Global Perspective. *Pain practice: the official journal of World Institute of Pain* 2014.
- [19] Ferris FD, Bruera E, Cherny N, *et al*. Palliative cancer care a decade later: accomplishments, the need, next steps -- from the American Society of Clinical Oncology. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2009; 27(18): 3052-3058. <https://doi.org/10.1200/JCO.2008.20.1558>
- [20] Twycross R. [Pain treatment in cancer patients.]. *Schmerz (Berlin, Germany)* 1990; 4(2): 65-74. <https://doi.org/10.1007/BF02527837>
- [21] Pergolizzi J. Chronic pain--moving from symptom control to mechanism-based treatment. *Current medical research and opinion* 2011; 27(10): 2079-2080. <https://doi.org/10.1185/03007995.2011.619446>
- [22] Leon MX, De Lima L, Florez S, *et al*. Improving availability of and access to opioids in Colombia: description and preliminary results of an action plan for the country. *Journal of pain and symptom management* 2009; 38(5): 758-766. <https://doi.org/10.1016/j.jpainsymman.2009.03.007>
- [23] Montgomery K, Hurley R. *Nerve destruction for the alleviation of visceral pain*. Vol 4. Philadelphia: Elsevier Saunders; 2013.
- [24] Rocha AP, Kraychete DC, Lemonica L, *et al*. Pain: current aspects on peripheral and central sensitization. *Revista brasileira de anesthesiologia* 2007; 57(1): 94-105. <https://doi.org/10.1590/S0034-70942007000100011>
- [25] Pergolizzi JV, Jr., Raffa RB, Taylor R, Jr. Treating acute pain in light of the chronification of pain. *Pain management nursing: official journal of the American Society of Pain Management Nurses* 2014; 15(1): 380-390. <https://doi.org/10.1016/j.pmn.2012.07.004>
- [26] Apkarian AV, Baliki MN, Farmer MA. Predicting transition to chronic pain. *Current opinion in neurology* 2013; 26(4): 360-367. <https://doi.org/10.1097/WCO.0b013e32836336ad>
- [27] Deumens R, Steyaert A, Forget P, *et al*. Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. *Progress in neurobiology* 2013; 104: 1-37. <https://doi.org/10.1016/j.pneurobio.2013.01.002>
- [28] Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life sciences* 2004; 74(21): 2605-2610. <https://doi.org/10.1016/j.lfs.2004.01.003>
- [29] Bulkley J, McMullen CK, Hornbrook MC, *et al*. Spiritual well-being in long-term colorectal cancer survivors with ostomies. *Psycho-oncology* 2013; 22(11): 2513-2521. <https://doi.org/10.1002/pon.3318>
- [30] Lacasse A, Bourgault P, Choiniere M. Fibromyalgia-related costs and loss of productivity: a substantial societal burden. *BMC musculoskeletal disorders* 2016; 17: 168. <https://doi.org/10.1186/s12891-016-1027-6>
- [31] Alsaadi SM, McAuley JH, Hush JM, Maher CG. Prevalence of sleep disturbance in patients with low back pain. *European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2011; 20(5): 737-743. <https://doi.org/10.1007/s00586-010-1661-x>
- [32] Sun V, Grant M, Wendel CS, *et al*. Sexual Function and Health-Related Quality of Life in Long-Term Rectal Cancer Survivors. *The journal of sexual medicine* 2016; 13(7): 1071-1079. <https://doi.org/10.1016/j.jsxm.2016.05.005>
- [33] Verrocchio MC, Carrozzino D, Marchetti D, Andreasson K, Fulcheri M, Bech P. Mental Pain and Suicide: A Systematic Review of the Literature. *Frontiers in psychiatry* 2016; 7: 108. <https://doi.org/10.3389/fpsy.2016.00108>
- [34] Fassberg MM, Cheung G, Canetto SS, *et al*. A systematic review of physical illness, functional disability, and suicidal behaviour among older adults. *Aging & mental health* 2016; 20(2): 166-194. <https://doi.org/10.1080/13607863.2015.1083945>
- [35] Mohler MJ, Coons SJ, Hornbrook MC, *et al*. The health-related quality of life in long-term colorectal cancer survivors study: objectives, methods and patient sample. *Current medical research and opinion* 2008; 24(7): 2059-2070. <https://doi.org/10.1185/03007990802118360>
- [36] Liedgens H, Obradovic M, De Courcy J, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *ClinicoEconomics and outcomes research: CEOR* 2016; 8: 113-126.
- [37] Chopra I, Kamal KM. A systematic review of quality of life instruments in long-term breast cancer survivors. *Health and quality of life outcomes* 2012; 10: 14. <https://doi.org/10.1186/1477-7525-10-14>
- [38] NCCN. Adult Cancer Pain. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) 2014; Version 2.2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf. Accessed 4 July, 2014.
- [39] Trescot AM. Review of the role of opioids in cancer pain. *Journal of the National Comprehensive Cancer Network: JNCCN* 2010; 8(9): 1087-1094. <https://doi.org/10.6004/jnccn.2010.0077>
- [40] Hastie BA, Gilson AM, Maurer MA, Cleary JF. An examination of global and regional opioid consumption trends 1980-2011. *Journal of pain & palliative care pharmacotherapy* 2014; 28(3): 259-275. <https://doi.org/10.3109/15360288.2014.941132>

- [41] Gilson AM, Maurer MA, Ryan KM, Rathouz PJ, Cleary JF. Using a morphine equivalence metric to quantify opioid consumption: examining the capacity to provide effective treatment of debilitating pain at the global, regional, and country levels. *Journal of pain and symptom management* 2013; 45(4): 681-700. <https://doi.org/10.1016/j.jpainsymman.2012.03.011>
- [42] Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* 2016; 387(10028): 1644-1656. [https://doi.org/10.1016/S0140-6736\(16\)00161-6](https://doi.org/10.1016/S0140-6736(16)00161-6)
- [43] Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *Journal of pain and symptom management* 2014; 47(2): 283-297. <https://doi.org/10.1016/j.jpainsymman.2013.03.015>
- [44] Moyano JR, Figueras A. The medical consumption of opioids in Colombia, 1997-2007. *Journal of pain & palliative care pharmacotherapy* 2010; 24(4): 367-373. <https://doi.org/10.3109/15360288.2010.523067>
- [45] Florez-Rojas S, Delgado M. [Availability and barriers to opioid access in Colombia: the experience of an academic institution]. *Universitas Medica* 2011; 52(2): 140-148.
- [46] Dalal S, Bruera E. Access to opioid analgesics and pain relief for patients with cancer. *Nat Rev Clin Oncol* 2013; 10(2): 108-116. <https://doi.org/10.1038/nrclinonc.2012.237>
- [47] Breuer B, Fleishman SB, Cruciani RA, Portenoy RK. Medical oncologists' attitudes and practice in cancer pain management: a national survey. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2011; 29(36): 4769-4775. <https://doi.org/10.1200/JCO.2011.35.0561>
- [48] Zhang Q, Yu C, Feng S, et al. Physicians' Practice, Attitudes Toward, and Knowledge of Cancer Pain Management in China. *Pain medicine (Malden, Mass)* 2015; 16(11): 2195-2203. <https://doi.org/10.1111/pme.12819>
- [49] Srisawang P, Harun-Or-Rashid M, Hirose T, Sakamoto J. Knowledge, attitudes and barriers of physicians, policy makers/regulators regarding use of opioids for cancer pain management in Thailand. *Nagoya journal of medical science* 2013; 75(3-4): 201-212.
- [50] Kim MH, Park H, Park EC, Park K. Attitude and knowledge of physicians about cancer pain management: young doctors of South Korea in their early career. *Japanese journal of clinical oncology* 2011; 41(6): 783-791. <https://doi.org/10.1093/jjco/hyr043>
- [51] De Silva BS, Rolls C. Attitudes, beliefs, and practices of Sri Lankan nurses toward cancer pain management: an ethnographic study. *Nursing & health sciences* 2011; 13(4): 419-424. <https://doi.org/10.1111/j.1442-2018.2011.00635.x>
- [52] Kaki AM. Medical students' knowledge and attitude toward cancer pain management in Saudi Arabia. *Saudi medical journal* 2011; 32(6): 628-632.
- [53] Liang SY, Tung HH, Wu SF, et al. Concerns about pain and prescribed opioids in Taiwanese oncology outpatients. *Pain management nursing: official journal of the American Society of Pain Management Nurses* 2013; 14(4): 336-342. <https://doi.org/10.1016/j.pmn.2011.08.004>
- [54] Akiyama M, Takebayashi T, Morita T, et al. Knowledge, beliefs, and concerns about opioids, palliative care, and homecare of advanced cancer patients: a nationwide survey in Japan. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer* 2012; 20(5): 923-931. <https://doi.org/10.1007/s00520-011-1161-5>
- [55] Ogboli-Nwasor E, Makama J, Yusufu L. Evaluation of knowledge of cancer pain management among medical practitioners in a low-resource setting. *Journal of pain research* 2013; 6: 71-77. <https://doi.org/10.2147/JPR.S38588>
- [56] Chen CH, Tang ST, Chen CH. Meta-analysis of cultural differences in Western and Asian patient-perceived barriers to managing cancer pain. *Palliative medicine* 2012; 26(3): 206-221. <https://doi.org/10.1177/0269216311402711>
- [57] Martinez KA, Aslakson RA, Wilson RF, et al. A systematic review of health care interventions for pain in patients with advanced cancer. *The American journal of hospice & palliative care* 2014; 31(1): 79-86. <https://doi.org/10.1177/1049909113476129>
- [58] Tateno Y, Ishikawa S. Clinical pathways can improve the quality of pain management in home palliative care in remote locations: retrospective study on Kozu Island, Japan. *Rural and remote health* 2012; 12: 1992.
- [59] Torres Vigil I, Aday LA, De Lima L, Cleeland CS. What predicts the quality of advanced cancer care in Latin America? A look at five countries: Argentina, Brazil, Cuba, Mexico, and Peru. *Journal of pain and symptom management* 2007; 34(3): 315-327. <https://doi.org/10.1016/j.jpainsymman.2006.11.015>
- [60] Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO* 2009; 20(8): 1420-1433. <https://doi.org/10.1093/annonc/mdp001>
- [61] Caraceni A, Martini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliative medicine* 2004; 18(3): 177-183. <https://doi.org/10.1191/0269216304pm890oa>
- [62] Davies A, Buchanan A, Zeppetella G, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *Journal of pain and symptom management* 2013; 46(5): 619-628. <https://doi.org/10.1016/j.jpainsymman.2012.12.009>
- [63] Swarm RA, Abernethy AP, Angheliescu DL, et al. Adult cancer pain. *Journal of the National Comprehensive Cancer Network: JNCCN* 2013; 11(8): 992-1022. <https://doi.org/10.6004/jnccn.2013.0119>
- [64] Nalamachu SR. Opioid rotation in clinical practice. *Advances in therapy* 2012; 29(10): 849-863. <https://doi.org/10.1007/s12325-012-0051-7>
- [65] Cleary J, De Lima L, Eisenclaus J, Radbruch L, Torode J, Cherny NI. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Latin America and the Caribbean: a report from the Global Opioid Policy Initiative (GOPI). *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO* 2013; 24 Suppl 11: xi41-50.
- [66] Bandieri E, Romero M, Ripamonti CI, et al. Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2016; 34(5): 436-442. <https://doi.org/10.1200/JCO.2015.61.0733>
- [67] Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *The New England journal of medicine* 2009; 361(8): 827-828. <https://doi.org/10.1056/NEJMc0904266>
- [68] Corli O, Floriani I, Roberto A, et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the

- variability of response to opioids. *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO* 2016; 27(6): 1107-1115.
<https://doi.org/10.1093/annonc/mdw097>
- [69] Caraceni A, Hanks G, Kaasa S, *et al.* Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *The lancet oncology* 2012; 13(2): e58-68.
[https://doi.org/10.1016/S1470-2045\(12\)70040-2](https://doi.org/10.1016/S1470-2045(12)70040-2)
- [70] Maltoni M, Scarpi E, Modonesi C, *et al.* A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer* 2005; 13(11): 888-894.
<https://doi.org/10.1007/s00520-005-0807-6>
- [71] Raffa RB, Pergolizzi JV, Jr. A modern analgesics pain 'pyramid'. *Journal of clinical pharmacy and therapeutics* 2014; 39(1): 4-6.
<https://doi.org/10.1111/jcpt.12110>
- [72] Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane database of systematic reviews (Online)* 2010(1): CD006605.
- [73] Abramowitz L, Beziaud N, Labreze L, *et al.* Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. *Journal of medical economics* 2013; 16(12): 1423-1433.
<https://doi.org/10.3111/13696998.2013.851082>
- [74] Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *The American journal of gastroenterology* 2011; 106(5): 835-842; quiz 843.
<https://doi.org/10.1038/ajg.2011.30>
- [75] Leppert W. Emerging therapies for patients with symptoms of opioid-induced bowel dysfunction. *Drug design, development and therapy* 2015; 9: 2215-2231.
<https://doi.org/10.2147/DDDT.S32684>
- [76] International Pain Summit Of The International Association For The Study Of P. Declaration of Montreal: declaration that access to pain management is a fundamental human right. *Journal of pain & palliative care pharmacotherapy* 2011; 25(1): 29-31.
<https://doi.org/10.3109/15360288.2010.547560>
- [77] U.S. Congress. One hundred eleventh Congress of the United States of America at the Second Session. An Act Entitled the Patient Protection and Affordable Care Act 2010; H.R. 3590: <https://www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf>. Accessed 31 March, 2016.
- [78] Aston G. Smart pain management makes good business sense. *Hospitals & health networks / AHA* 2012; 86(6): 38-40, 49-50, 31.
- [79] Manchikanti L, Helm S, 2nd, Fellows B, *et al.* Opioid epidemic in the United States. *Pain physician* 2012; 15(3 Suppl): ES9-38.
- [80] Cicero TJ, Ellis MS. Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin. *JAMA psychiatry* 2015; 72(5): 424-430.
<https://doi.org/10.1001/jamapsychiatry.2014.3043>
- [81] Benak LD, Eccher D, McKinney RE, Smith CM. Prescription drug monitoring through the Maine Office of Substance Abuse. *Journal of forensic nursing* 2007; 3(3-4): 141-145.
<https://doi.org/10.1111/j.1939-3938.2007.tb00102.x>
- [82] CDC. Prescription Drug Monitoring Programs (PDMPs). *Injury Prevention & Control: Prescription Drug Overdose* 2015; <http://www.cdc.gov/drugoverdose/pdmp/>. Accessed 11 January, 2016.
- [83] Buchman DZ, Ho A. What's trust got to do with it? Revisiting opioid contracts. *Journal of medical ethics* 2014; 40(10): 673-677.
<https://doi.org/10.1136/medethics-2013-101320>
- [84] McGee S, Silverman RD. Treatment agreements, informed consent, and the role of state medical boards in opioid prescribing. *Pain medicine (Malden, Mass)* 2015; 16(1): 25-29.
<https://doi.org/10.1111/pme.12580>
- [85] Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain medicine (Malden, Mass)* 2005; 6(2): 107-112.
<https://doi.org/10.1111/j.1526-4637.2005.05031.x>
- [86] Pergolizzi JV, Jr., Gharibo C, Passik S, *et al.* Dynamic risk factors in the misuse of opioid analgesics. *Journal of psychosomatic research* 2012; 72(6): 443-451.
<https://doi.org/10.1016/j.jpsychores.2012.02.009>
- [87] Angheliescu DL, Ehrentraut JH, Faughnan LG. Opioid misuse and abuse: risk assessment and management in patients with cancer pain. *Journal of the National Comprehensive Cancer Network: JNCCN* 2013; 11(8): 1023-1031.
<https://doi.org/10.6004/jnccn.2013.0120>
- [88] Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *Journal of pain and symptom management* 2006; 32(3): 287-293.
<https://doi.org/10.1016/j.jpainsymman.2006.03.010>
- [89] Butler SF, Budman SH, Fernandez KC, Fanciullo GJ, Jamison RN. Cross-Validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *Journal of addiction medicine* 2009; 3(2): 66-73.
<https://doi.org/10.1097/ADM.0b013e31818e41da>
- [90] Barry DT, Irwin KS, Jones ES, *et al.* Opioids, chronic pain, and addiction in primary care. *The journal of pain: official journal of the American Pain Society* 2010; 11(12): 1442-1450.
<https://doi.org/10.1016/j.jpain.2010.04.002>
- [91] Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology and drug safety* 2013; 22(12): 1274-1282.
<https://doi.org/10.1002/pds.3522>
- [92] Alexander L, Mannion RO, Weingarten B, Fanelli RJ, Stiles GL. Development and impact of prescription opioid abuse deterrent formulation technologies. *Drug and alcohol dependence* 2014; 138: 1-6.
<https://doi.org/10.1016/j.drugalcdep.2014.02.006>
- [93] FDA. Guidance for Industry: abuse-deterrent opioids, evaluation and labeling 2013; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>. Accessed 25 April, 2013.
- [94] Pergolizzi JV, Jr., LeQuang JA. Abuse-deterrent formulations of opioid analgesics. *Pain practice: the official journal of World Institute of Pain* 2014; 14(3): 204-206.
<https://doi.org/10.1111/papr.12093>
- [95] Pergolizzi JV, Jr., Zampogna G, Taylor R, Jr., Raffa RB. Long-term efficacy, safety and tolerability of Remoxy for the management of chronic pain. *Expert review of neurotherapeutics* 2015; 15(3): 231-238.
<https://doi.org/10.1586/14737175.2015.1015418>
- [96] Raffa RB, Pergolizzi JV, Jr. Opioid formulations designed to resist/deter abuse. *Drugs* 2010; 70(13): 1657-1675.
<https://doi.org/10.2165/11537940-000000000-00000>

- [97] Raffa RB, Pergolizzi JV, Jr., Muniz E, Taylor R, Jr., Pergolizzi J. Designing opioids that deter abuse. *Pain research and treatment* 2012; 2012: 282981.
<https://doi.org/10.1155/2012/282981>
- [98] Raffa RB, Taylor R, Jr., Pergolizzi JV, Jr. Sequestered naltrexone in sustained release morphine or oxycodone - a way to inhibit illicit use? *Expert opinion on drug safety* 2014; 13(2): 181-190.
<https://doi.org/10.1517/14740338.2013.841136>
- [99] Mercadante S, Giarratano A. Combined oral prolonged-release oxycodone and naloxone in chronic pain management. *Expert opinion on investigational drugs* 2013; 22(1): 161-166.
<https://doi.org/10.1517/13543784.2013.752460>
- [100] Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *Journal of opioid management* 2009; 5(3): 137-144.
- [101] Burness CB, Keating GM. Oxycodone/Naloxone prolonged-release: a review of its use in the management of chronic pain while counteracting opioid-induced constipation. *Drugs* 2014; 74(3): 353-375.
<https://doi.org/10.1007/s40265-014-0177-9>

Received on 29-09-2017

Accepted on 07-11-2017

Published on 29-12-2017

DOI: <http://dx.doi.org/10.6000/1929-2279.2017.06.04.3>