

Pain Management in the Era of the Opioid Crisis

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The vast majority of patients diagnosed with cancer will have episodes of acute or chronic pain.^{1,2} Not all those episodes require opioid management. However, opioids will be necessary in almost all patients at some point for the management of acute or chronic pain. Table 1 summarizes common pain syndromes among patients with cancer that frequently or rarely require systemic opioid treatment.

Opioids are highly effective analgesics, and all physicians involved in the treatment of cancer patients should be familiar with the most common types and dosages of opioid analgesics as well as the management of their most common side effects.³

Figure 1 summarizes the complex effects of opioids on different central nervous system regions. Systemic opioids bind to mu receptors along the nociceptive pathway and reduce neuronal activity and pain perception at the somatosensory cortex. Unfortunately, opioids also bind to mu receptors anywhere in the body where they are available. As a result, patients experience mu-related side effects such as constipation and somnolence. Mu receptors are located also along the limbic system, and they are therefore able to produce considerable reward, especially in patients with large concentrations of mu receptors in those regions. There is a slow development of tolerance and hyperalgesia along the nociceptive pathway and a much faster reduction of the reward effect centrally. This rapid loss of the reward effect is associated with the increased activity of dysphoric pathways that are not mu related. Patients who are at higher risk for the development of substance use disorders will increase opioid intake in an effort to restore the reward, followed by once again rapid loss of such effect.

Approximately 80% of patients receiving opioids for the management of cancer pain will adhere to the opioids as prescribed and will have no major difficulties with dose reduction and even discontinuation if the pain syndrome resolves.⁴ The remaining 20% are at risk for behaviors consistent with the nonmedical use of the opioid analgesic (also defined as aberrant behaviors) or will ultimately develop substance use disorders.

There are risk factors associated with the development of opioid dependence among patients with advanced cancer. Among these, the most common risk factor is a history of

alcoholism. Positive screening results for risk of alcoholism in the general population are approximately 8%, but it is considerably higher among patients with cancer.⁵⁻⁷ Parsons et al⁶ found positive results of risk screening in 100 of 598 patients with advanced cancer (17%). One possible explanation for this higher frequency of alcoholism is that alcohol is an etiologic factor for many cancers.

Other risk factors such as a history of dependence on other drugs are less frequent among patients with cancer.⁵⁻⁸ Unfortunately, the majority of patients treated with opioids for the management of cancer pain do not undergo regular screening for the risk of alcoholism or a history of drug use, therefore, there is considerable underdiagnosis of these problems. A number of studies for more than 20 years have documented that extremely simple tools such as the CAGE-AID questionnaire (Sidebar 1) can detect high risk for alcoholism much better than the regular oncology and even supportive and palliative care medical encounter. Tools such as the CAGE-AID questionnaire⁵⁻⁸ and the Screener and Opioid Assessment for Patients With Pain⁹ can be very useful in assisting in the determination of risk for nonmedical opioid use in the routine oncology setting. One challenge is the appropriate documentation of concerns of nonmedical opioid use. In a recent study 76 of 432 patients were diagnosed as using opioids nonmedically by a palliative medicine specialist (18%), but only 15 of those patients (4%) had documentation in their medical records.¹⁰ Appropriate documentation of concerns regarding nonmedical use of opioids will greatly improve the early diagnosis and early management of this complication of cancer pain management. In patients in whom screening tools have not been used, a history of smoking can be helpful. Among 300 consecutive patients with advanced cancer, the rates of CAGE-positive status among never smokers, former smokers, and current smokers were 3%, 12%, and 42%, respectively. Similarly, rates of history of street drug use were 3%, 16%, and 33%, respectively.⁸

Patients with higher risk for nonmedical opioid use are more likely to engage in behaviors such as those summarized in Sidebar 2. When these behaviors are detected, the physician should immediately suspect nonmedical opioid use and have in place a care plan for the management of this complication. Among the measures that can be implemented is the

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SIDEBAR 1. CAGE-AID Questionnaire

- Have you ever felt that you should Cut down on your drinking (or drugs)?
- Have you ever been Annoyed by people criticizing your drinking (or drugs)?
- Have you ever felt bad or Guilty about your drinking or (drugs)?
- Have you ever had a drink first thing in the morning or a drink (or drugs) to get rid of a hangover (Eye opener)?

Note: Patients scoring 2 or higher have approximately 80% risk for alcohol use or drug use disorder.

SIDEBAR 2. Behaviors Suggestive of Nonmedical (Aberrant) Opioid Use

- Frequent unscheduled clinic visits or phone calls for refills
- Self-escalation of opioid dose
- Frequent emergency room visits for opioids
- Edmonton Symptom Assessment Scale pain intensity 10/10 with all other symptoms 0/10
- Seeking opioids from multiple physicians (“doctor shopping”)
- Request for specific opioid
- Reports of stolen/lost opioids
- Family member expressing concern over the patient’s opioid use
- Obtaining opioids from nonmedical sources, stealing, selling
- Requesting opioids for insomnia or anxiety
- Abnormal urinary drug screen
- Discrepancy in pill counts

use of urinary drug screening. In a supportive and palliative care program, 61 of 1,058 patients (6%) underwent urinary drug screening because of suspected nonmedical opioid use, and 33 (54%) had abnormal results.¹¹

The majority of patients with nonmedical use of opioids obtained the drugs from family and friends. Patients with cancer have limited knowledge of the safe use, storage, and disposal

PRACTICAL APPLICATIONS

- **Recognize patients at higher risk for nonmedical opioid use.**
- **Learn about screening for chemical coping risk.**
- **Diagnose nonmedical opioid use.**
- **Manage nonmedical opioid use in the clinical oncology setting.**
- **Understand clinical criteria for referral to supportive and palliative care teams.**

TABLE 1. Pain Syndromes in Patients With Cancer

Opioids Required Frequently	Opioids Required Infrequently
• Chronic pain due to advanced cancer	• Peripheral neuropathy
• Acute pain due to a cancer complication (e.g., pathologic fracture, bowel obstruction)	• Chronic nonmalignant pain
• Postoperative pain	• Acute muscular-skeletal pain syndromes (e.g., low back pain)
• Radiation-chemotherapy-induced mucositis	• Minor dental/diagnostic procedures

of opioids.¹² Among 300 patients with advanced cancer, 26% reported unsafe use by sharing or losing opioids, and 19% stored opioids in plain sight.¹² The administration of a simple brochure with educational material resulted in considerable improvements in storage, use, and disposal behaviors.¹³

After the completion of curative radiation therapy to the head and neck, 44 of 70 patients were still receiving opioids more than 3 months later, and 23 of 70 patients (33%) were on opioids more than 6 months after the completion of treatment.¹⁴ Forty-four percent of patients who were unable to stop opioids were CAGE positive, compared with 12% of patients who were able to stop opioids ($p = .014$). The median number of days receiving opioids was 261 for CAGE-positive patients and 93 for CAGE-negative patients ($p = .008$).

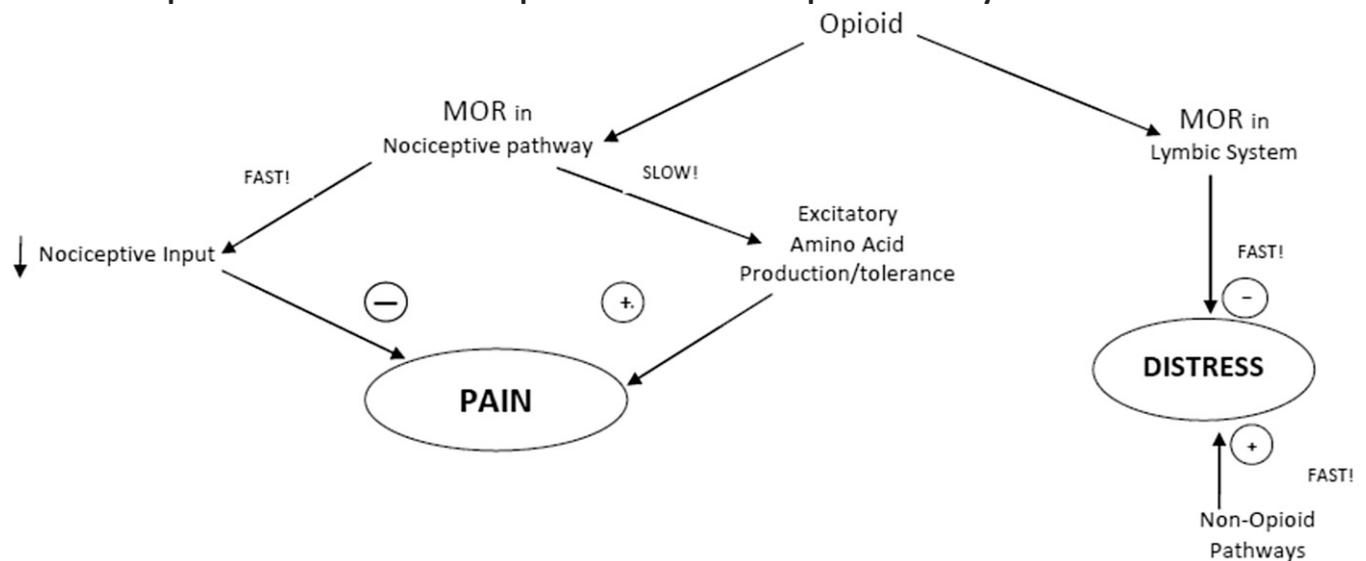
Concerns about the use of opioids have had an impact on overall opioid use for patients with cancer by their medical oncology teams. Between 2010 and 2015, the median morphine-equivalent opioid dose of patients upon the moment of referral to the Supportive Care Center at The University of Texas MD Anderson Cancer Center decreased from 78 to 40 mg/day ($p = .001$).¹⁵

WHAT DO ALL THESE FINDINGS MEAN TO YOUR ONCOLOGY PRACTICE?

Approximately 20% of patients with cancer who need opioids for the management of cancer-related pain are at risk for the development of nonmedical opioid use or a substance abuse disorder. The routine clinical encounter misses approximately 80% of patients who are at this increased risk. Extremely simple and free bedside validated tools allow for effective, universal screening for those patients who may be at a higher risk of nonmedical opioid use. Figure 2 proposes an algorithm for the screening and follow-up of these patients.

THE TREATMENT OF PATIENTS WITH CANCER-RELATED PAIN AND NONMEDICAL OPIOID USE

Patients who are identified as having histories of addiction or being at risk for nonmedical opioid use may be challenging for clinicians, especially those patients on high opioid doses or complex regimens or those exhibiting nonmedical opioid-related behavior. These patients would benefit from referral to palliative care or pain-specialist teams for structured treatment that includes documentation of treatment agreements, intermittent urine drug screening, frequent

FIGURE 1. Opioid Effects on the Nociceptive and Non-Nociceptive Pathways

Abbreviation: MOR, mu opioid receptor.

visits with shorter intervals, and restricted quantities of “breakthrough” opioids. These specialist teams encounter high-risk patients more frequently and have more resources and experience in managing complex clinical issues using an interdisciplinary approach.¹⁶ The concurrent strategies that may be used by these teams are outlined in the following discussion.

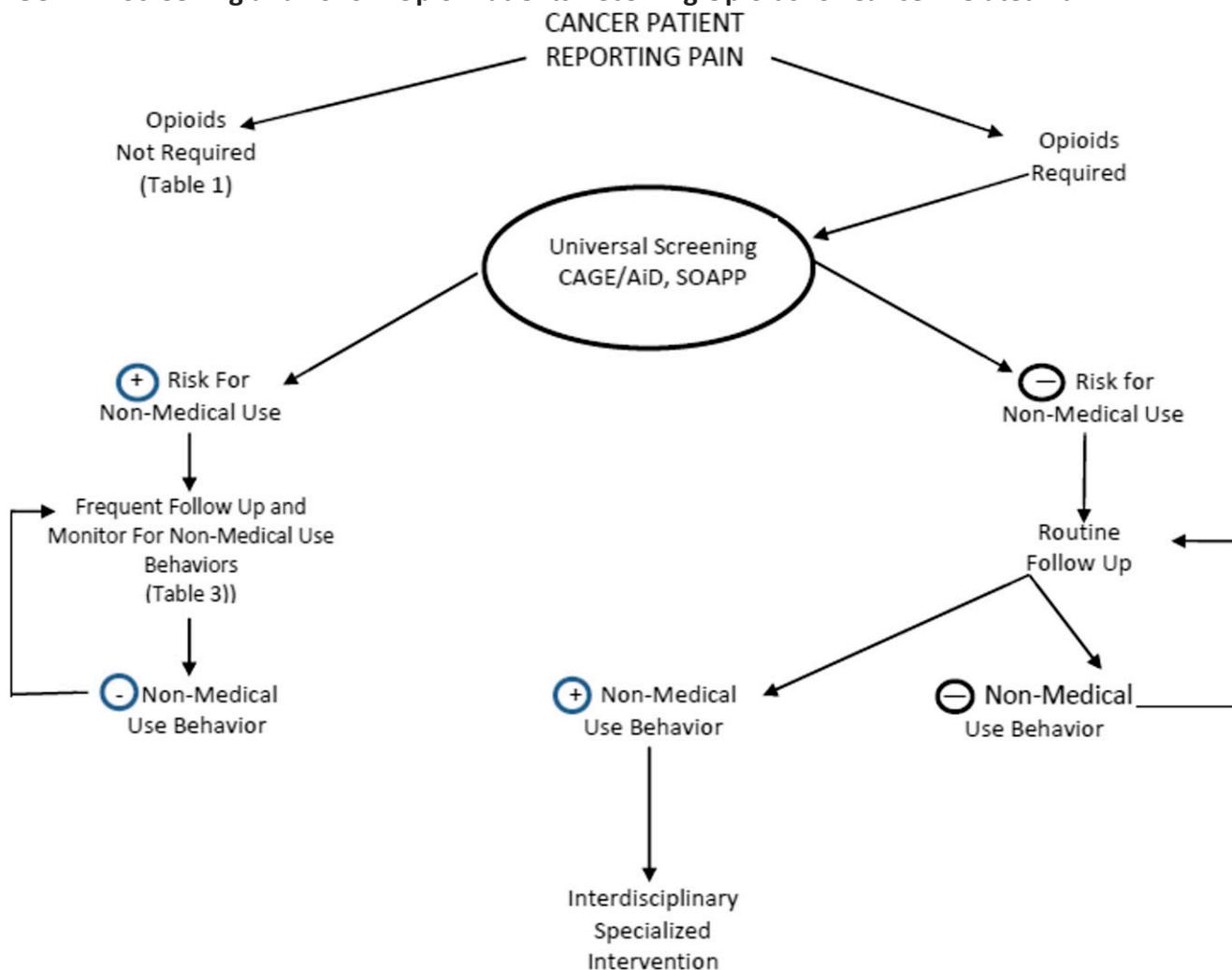
Interdisciplinary Approach

Because patients with aberrant opioid-related behavior may have multiple underlying biomedical, psychosocial, financial, and legal issues, the expertise of multiple providers working in concert is likely the most effective approach. Depending on resources, specialized interdisciplinary teams may consist of a variable combination that includes physician, nurse, psychologist, social worker, and pharmacist. An innovative program within the supportive care clinic at MD Anderson implemented a compassionate high-alert team to address nonmedical opioid-related behavior in patients with cancer. The team has a full complement of multidisciplinary members, plus patient advocacy and risk management or security representatives if legal or safety concerns seem imminent. The team rather than any individual provider prepares a plan before patient arrival and then collectively meets with the patient, providing support in a nonjudgmental manner with an emphasis on the need for patient and family safety. This specialized team intervention decreased the median number of nonmedical use behaviors from 3 to 0.4 per month ($p < .001$) and the morphine-equivalent daily dose (MEDD) from 165 to 112 mg/day ($p = .018$), without increasing pain severity compared with a control group.¹⁷ Another National Cancer Institute cancer center with an interdisciplinary palliative care team found ambulatory patients who have no evidence of disease are less likely to respond with reductions in pain scores compared with those with active cancer.¹⁸

Past studies revealed that patients with aberrant behavior and chemical coping are more likely to receive a higher MEDD for pain control and are more likely to experience opioid side effects.^{19,20} Besides chemical coping and diversion, clinicians should be aware of other factors that increase pain perception or expression, including somatization, delirium, hyperalgesia or allodynia, opioid tolerance, drug interactions, and neuropathic pain. Most studies related to aberrant behavior or chemical coping are from the outpatient setting, and a very different approach may be required for inpatients. Pain perception and expression may be altered for a number of reasons: patients may be more ill in the hospital, they may be more likely to experience cognitive impairment and delirium, and they may be on intravenous patient-controlled analgesia. Few studies have reported outcomes on inpatients at risk for chemical coping or with a history of aberrant behavior delivering their own breakthrough doses by patient-controlled analgesia. A couple of case reports have noted the potential for harm²¹ occurring in patients with advanced cancer on patient-controlled analgesia, including unnecessary dose escalation and opioid induced neurotoxic side effects such as delirium.²² Palliative care units with robust interdisciplinary teams²³ may be especially well placed to manage patients with histories of aberrant behavior or chemical coping on intravenous opioids, but more research is needed in this regard.

Patient and Family Education Regarding Opioid Management

From the outset, patients and their families should understand that opioids are not the sole focus of therapy and will be combined with other pharmacological agents as well as nonpharmacological modalities.²⁴ Standardized documentation should be provided, including pain treatment agreements along with informed consent detailing information about the potential risks and benefits associated with opioid

FIGURE 2. Screening and Follow-Up of Patients Receiving Opioids for Cancer-Related Pain

Abbreviation: MOR, mu opioid receptor.

therapy, possible adverse effects, and education on opioid safety and disposal strategies.^{12,13}

Comorbid Psychiatric Conditions and Psychological Interventions

Patients should be evaluated and treated for any underlying comorbid psychiatric conditions, and comanagement with psychiatry should be considered. A study of patients with co-occurring opioid use disorder and chronic noncancer pain reported a lifetime prevalence of more than 90% for having comorbid psychiatric conditions, such as anxiety and mood disorders. Similarly, there is a risk that some oncology patients could use opioids in a maladaptive manner to cope with the stress of advanced cancer and mental health conditions that may emerge during their disease.

Several nonpharmacologic interventions have been shown to be effective in managing noncancer-related pain and may be useful in decreasing opioid use. These include multidisciplinary biopsychosocial rehabilitation,²⁵ cognitive behavioral therapy, mindfulness-based therapy,²⁶ relaxation techniques, biofeedback, and distraction techniques.²⁷

Patients should receive brief motivational interviewing with an objective, nonjudgmental, and empathic style that includes personalized feedback, particularly about markers of risk or harm. Although studies are not universally positive, and research in patients with cancer is lacking,²⁸ brief motivational interviewing has been successful in managing patients with alcohol misuse.²⁹

Nonopioid and Adjuvant Analgesics

In patients at risk for opioid misuse and mild pain, nonopioid and adjuvant analgesics should be considered. Some pain syndromes such as chemotherapy-induced peripheral neuropathy are known to be particularly resistant to opioids. Pain due to chemotherapy-induced peripheral neuropathy warrants duloxetine as a first-line therapy and consideration of other nonopioids, such as gabapentin and nortriptyline, rather than opioids. Similarly, providing there are no contraindications, nonsteroidal anti-inflammatory drugs³⁰ and acetaminophen should be considered as options for bone pain or their opioid-sparing potential. Opioids should be considered only in patients with moderate to severe pain that is

unresponsive to nonopioid therapies, because this population derived benefit from opioids in randomized trials.³¹

Opioid Type and Formulation

On the basis of studies using administrative data and healthy volunteers, immediate-release oral opioids³² or rapidly administered intravenous opioids³³ may increase the risk for opioid misuse.³⁴ A large Veterans Affairs study of 750 overdose deaths found that patients with cancer-related pain were less likely to overdose than those with noncancer conditions, but among those patients with cancer, the use of only as-needed immediate-release opioids increased the risk for overdose death compared with those taking extended-release or scheduled immediate-release opioids.³⁵ Reassuringly, preliminary evidence from this study suggested that patients with cancer receiving palliative care were less likely to overdose. Given the potential risk with rapid-onset opioids, extended-release formulations or long-acting opioid analgesics such as buprenorphine or methadone should be considered in those patients with established chronic cancer-related pain and aberrant behavior. Methadone and buprenorphine are approved for treating opioid addiction and coupled with psychosocial support are the current standard of care for reducing illicit opioid use, relapse risk, and overdoses, while improving social function.³⁶ It is unclear whether they have similar benefits for patients with cancer by mitigating or preventing opioid misuse, although both medications are known to be effective for cancer pain.^{37,38} The goal to manufacture tamper-proof oral formulations that cannot be injected or inhaled has merit because these routes are often associated with misuse because of their rewarding effects. However, these formulations can still be misused orally¹⁶ and are expensive, and their overall clinical impact on decreasing opioid misuse has not yet been determined. The future holds promise for development of nonaddictive opioids, targeting nonopioid pain pathways, or using

medications such as kappa antagonists that counteract the aversive effects of opioid withdrawal.³⁹

Selective Use of Naloxone

A nonrandomized observational study of patients with chronic pain reported that coprescribing naloxone, a short-acting opioid antagonist, reduced emergency department visits without causing an increase in prescribed opioid doses.³⁹ Despite the potential for benefit, there are still many unanswered issues, including demonstration of improved outcomes and decreased health care use. Current recommendations regarding MEDD and the need for concomitant naloxone prescription vary (e.g., Virginia recommends consideration of naloxone for patients with MEDD \geq 120 per day, while the Centers for Disease Control and Prevention recommend considering offering naloxone for patients with MEDD \geq 50 per day). Most regulations are consistent in excluding cancer-related pain, but for chronic noncancer pain, there is agreement that a history of drug overdose, a history of substance use disorder, or concurrent use of benzodiazepines³⁴ warrants a naloxone prescription. Most states also allow pharmacists to dispense or distribute naloxone without a patient-specific prescription from another health professional. Although excluded from regulations, patients with cancer and histories of overdose or addiction should be considered for prescribed intranasal naloxone with instructions for administration by relatives and caregivers.

CONCLUSIONS

The vast majority of patients with cancer need opioids for the management of pain. Oncologists can safely and effectively manage the majority of these patients. Universal screening for risk factors and careful monitoring for the emergence of nonmedical opioid use behaviors help decide on the need to refer patients for specialized care.

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