Cancer Pain Management: Safe and Effective Use of Opioids

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OVERVIEW

Pain remains a serious consequence of cancer and its treatment. Although significant advances have been made in providing effective cancer pain control, barriers persist. Lack of knowledge, limited time, financial restrictions, and diminished availability of necessary medications serve as significant obstacles. Safe and effective opioid use in a patient with cancer requires skill to overcome these challenges. Understanding the mechanism of action, along with the pharmacokinetics and pharmacodynamics, of opioids will lead to appropriate selection, dosing, and titration of these agents. Rotation from one opioid or route to another is an essential proficiency for oncologists. As opioid-related adverse effects often occur, the oncology team must be expert in preventing and managing constipation, nausea, sedation, and neurotoxicities. An emerging concern is overtreatment—the excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. This can occur when opioids are used inappropriately to treat comorbid psychologic issues such as anxiety and depression. Recognizing risk factors for overuse along with key components of universal precautions will promote safe use of these medications, supporting adherence and preventing diversion, thereby protecting the patient, the prescriber, and the community. Because substance use disorders are not rare in the oncology setting, attention must be given to the balance of providing analgesia while limiting harm. Caring for patients with substance misuse requires compassionate, multidisciplinary care, with input from supportive oncology/palliative care as well as addiction specialists.

Pain is a serious consequence of cancer and its treatment. Although great strides have been made in increasing awareness of the need for effective cancer pain control, barriers persist that lead to undertreatment.[1-3] Health care professionals' lack of knowledge (despite extensive efforts to improve education), limited access to specialists, and diminished availability of necessary medications are significant obstacles. Insufficient time, resulting from increased demands to provide care for more patients during shorter visits, along with expanding requests for documentation, insurance authorizations, and other regulatory requirements, complicates delivery of comprehensive pain control.[4,5] Balancing these demands has proven challenging, and excellent pain control can suffer as a result.

Awareness of the safe and effective use of opioids in the oncology setting is essential to the provision of adequate pain relief. Understanding the mechanism of action, along with the pharmacokinetics and pharmacodynamics of opioids will lead to appropriate selection, dosing, and titration of these agents. As adverse effects often occur, the oncology team must be skilled in preventing and managing constipation, nausea, sedation, and neurotoxicities. An emerging concern is overtreatment with opioids—the excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. This can occur when opioids are used inappropriately to treat comorbid psychologic issues such as anxiety and depression. Recognizing risk factors for overuse along with key components of universal precautions will promote safe use of these medications, protecting the patient, the prescriber, and the community.

PRINCIPLES OF OPIOID USE

Opioid analgesics have been the most useful group of drugs for the management of severe pain for more than 200 years.[6] All opioid analgesics work mainly by binding the Mu opioid receptors located along the nociceptive pathway. These Mu receptors are found in multiple locations presynaptically and postsynaptically. The direct result of the opioid binding to the receptor is decreased afferent nociceptive neuronal depolarization. In recent years it has become clear that new receptors have multiple subtypes.[7] Different opioid Mu agonists will bind to slightly different subtypes of Mu receptors. This variability and the differences in pharmacokinetic and pharmacodynamic profile explain the frequently observed difference in both analgesic response and side effect to different opioid analgesics. An important pearl for clinicians is that there is considerable interpersonal variation in analgesic response to opioid agonists.

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Choice of Opioid and Initial Opioid Titration

In patients who have never been exposed to opioids before, titration is quite simple. The starting dose is well established for all major opioid analgesics and it is the equivalent to 30 mg of morphine per day orally (20 mg oxycodone, 10 mg of oxymorphone, etc.). The starting dose of an opioid is not driven by the intensity of the patient's pain expression but rather by safety considerations, and therefore, the initiation of opioids is simple and generally very safe. In patients with good renal function and good liver function and who are not receiving other drugs that might interact at the pharmacokinetic or pharmacodynamic level, all opioids are similarly safe and effective.

Opioid metabolism. Opioids undergo phase I oxidation or hydrolysis mainly by the cytochrome 3A4 and 2D6 enzymes, followed by phase II glucuronization that increases their hydro-solubility for renal elimination. Table 1 summarizes some of the metabolic sub-products of the main opioid agonists. It is important to note that the 3A4 cytochrome produces largely inactive metabolites. Therefore, drugs that block 3A4 will increase either the parent compound or the alternative pathway toward active metabolites. Patients undergoing this interaction will develop opioid toxicity—mainly sedation. Agents frequently involved in these interactions for patients with cancer include macrolide and fluroquinolone antibiotics, azoles, HIV antiretrovirals, irinotecan, and many of the new targeted agents. On the other hand, the 2D6 cytochrome pathway produces largely active metabolites, and the blockage of this pathway by drug interactions will result in decreased analgesic effects. This is particularly important in the case of codeine since it does not largely bind to the opioid Mu receptor but requires activation by 2D6 to morphine. The main 2D6 drugs for patients with cancer include some selective serotonin reuptake inhibitor antidepressants and neuroleptics such as haloperidol or chlorpromazine. It is important to remember that 8% to 20% of the population are genetically poor metabolizers at the 2D6 level.[8]

Table 1. Phase I Metabolism of Opioids

Drug	Cytochrome	Results
Morphine	None	
Hydromorphone	None	
Oxymorphone	None	
Fentanyl	3A4	Norfentanyl
Oxycodone	3A4	Noroxycodone
	2D6	Oxymorphone*
Hydrocodone	3A4	Norhydrocodeine
	2D6	Hydromorphone*
Codeine	2D6	Morphine*
Methadone	3A4	M1-M2
Tramadol	2D6	Desmethyltramadol*

*Active metabolite.

Some opioids have minimal or no phase I metabolism. These include morphine, hydromorphone, and oxymorphone. The likelihood of interactions at the cytochrome level from these opioids is minimal, making these three opioids ideal for patients with liver failure or potential drug interactions. Opioids with no major phase I (morphine, hydromorphone, oxymorphone) and the active metabolites of the other opioids (Table 1) undergo glucuronidation and renal elimination. Some of these glucuronides are active (e.g., morphine-6-glucuronide, glucuronide), and others are not active on the opioid receptor but neurotoxic (e.g., morphine-3-glucuronide and hydromorphine-3-glucuronide). For patients with renal failure, all these opioids should be used with frequent monitoring for neurotoxicity. Methadone is a very good alternative in renal failure since its metabolites are largely inactive and are not eliminated into the urine.

If a patient who has been on a stable dose of an opioid analgesic develops sedation it is important to ask if any new drugs have been added that might affect the pharmacokinetic profile. Also determine if the patient is now in liver or renal failure and if new drugs have been added that might increase the level of sedation of the patient from the pharmacodynamic perspective. These drugs include hypnotics, antihistamines, sedating antidepressants, and anticonvulsants frequently used for neuropathic pain.

Many extended release opioid preparations are available (Table 2). All the opioids in the table have been modified so as to delay absorption from the gut or the skin. Although methadone is not an extended release drug, it can be administered every 12 hours because of its very slow elimination after rapid oral, rectal, or subcutaneous absorption. Extended release opioids are generally not more effective or less toxic than immediate release opioids. Their main advantage is much more comfortable administration that might improve adherence

KEY POINTS

- Safe and effective control of cancer pain demands thorough knowledge of the pharmacokinetics and pharmacodynamics of opioids that guide dosing, titration, and rotation.
- Prevention and management of adverse effects of opioids requires careful assessment and knowledge regarding agents used to treat these complications.
- Overtreatment of cancer pain can occur when opioids are used to treat symptoms other than pain or dyspnea, including anxiety, depression, or sleep disorders.
- Evaluation of risk factors for opioid misuse, including current or past use of illicit substances, family history of substance use disorder, environmental exposure, along with a history of sexual or physical abuse, guides safe and effective care.
- Universal precautions, including measures to advance adherence and safe storage, will promote safe use of these medications while protecting the patient, the prescriber, and the community.

Table 2. Extended Release Opioids

Drug	Route	Frequency
Morphine	Oral	Every 12 hours
Hydromorphone	Oral	Every 24 hours
Oxycodone	Oral	Every 12 hours
Fentanyl	Transdermal	Every 72 hours
Oxymorphone	Oral	Every 12 hours
Hydrocodone	Oral	Every 12 hours

to chronic treatment for patients as compared to taking immediate release opioids such as morphine, hydrocodone, hydromorphone, or codeine every 4 hours day and night. However, extended release opioids are generally five times more expensive than immediate release opioids, and insurance payers frequently deny payment for these agents.[9] Therefore, the insurance company occasionally may request that patients change opioid analgesic or pay large amounts of money out of pocket. In these cases, chronic management with immediate release opioid is an appropriate alternative.

All patients with chronic cancer pain should be started on regular opioids, ideally using an extended release formulation (Sidebar 1). In addition, patients with cancer pain require access to immediate release opioids for episodes of break-through pain. Each dose should be approximately 10% (ranging between 5% and 20%) of the daily regular opioid dose. Close to 100% of the patients need to be prescribed a regular laxative every day since constipation is a universal and frequently under diagnosed problem. In addition, patients should be prescribed antiemetics since approximately half of the patients started on an opioid agonist will develop nausea for the first 3 days. Metoclopramide is an excellent option because of its combination of central and pro-kinetic effects. After the first 3 to 4 days, nausea is either minimal or absent.

Opioid titration. Even after ideal management, only approximately 50% of the patients will reach their personalized pain goal (3/10) after one visit.[10] Therefore, it is important to either follow up or phone the patient less than 1 week after the initial management to further titrate the opioid dose and to consider adjuvant drugs or drugs for the management of side effects. The minimal clinically important increase or decrease in dose will be approximately 30% of the daily dose. Opioid titration is always conducted as a percentage rather than an absolute number because of the large dose range. For example, a patient coming for follow-up in poor pain control receiving 100 mg of equivalent morphine daily dose will require an increase of at least 30 mg per day. A patient coming with a similar degree of poor pain control but receiving a dose of 300 mg of equivalent morphine per day will require an increase of approximately 100 mg per day.

When calculating the daily morphine equivalent dose, ask the patient how many extra opioid doses they received per day. For example, a patient started on 15 mg of extended release morphine every 12 hours and 7.5 mg of immediate release morphine orally every 4 hours as needed. One week later the patient complains of pain 8/10. The patient is receiving four immediate release doses per day. Total morphine equivalent dose for this patient is regular daily dose 30 plus breakthrough pain 30, making a total daily dose of 60 mg. An appropriate increase for this patient would be approximately 30% to 50% of the daily dose (20–30 mg). Therefore, the new regular opioid dose should be approximately 90 mg/day (either 30 mg every 8 hours or 45 mg every 12 hours). The new extra dose will need to be approximately 9 to 10 mg every 4 hours as needed since the ideal extra dose is approximately 10% of the daily dose.

Opioid rotation. Approximately 80% of patients with cancer will need at least one change in the type of opioid. The main reasons for opioid rotation are the development of opioid induced neurotoxicity or lack of appropriate pain control after appropriate dose titration. Sidebar 2 summarizes the main clinical features of patients who develop opioid-induced neurotoxicity. Whenever patients develop clinical findings—including a combination of sedation, myoclonus, hyperalgesia either localized at the area of the existing pain or generalized cutaneous hyperalgesia, or elements of delirium (confusion, inattention, disorientation, hallucinations, psychomotor agitation)—an opioid rotation should be conducted. Opioid rotation works by eliminating the offending drug, and it is more important to make the diagnosis of opioid-induced neuro-

Sidebar 1. Ideal Initial Management of Chronic Pain Due to Cancer

- Extended opioid regularly (oral or transdermal)
- Immediate release opioid for breakthrough pain, orally (10% of the daily dose)
- Laxative regularly and titrate to normal frequency before cancer (e.g., senna, polyethylene glycol)
- Antiemetic available for all patients upon initiation or dose increase (metoclopramide)
- Consider adjuvant drugs
- Follow up by telephone or in person in approximately 1 week

Sidebar 2. Clinical Findings in Patients with Opioid-Induced Neurotoxicity

- Sedation
- Myoclonus
- Hyperalgesia (localized or generalized)
- Hallucinations
- Psychomotor agitation
- Confusion

toxicity and proceed to change the type of opioid than which new opioid the patient is rotated to.

The total morphine equivalent daily dose of the current opioid is determined by adding the regular and all breakthrough pain doses for the past 24 hours. This dose can then be translated into the dose of the new opioid using dose ratio tables. For example, for a patient receiving a total daily dose of morphine of 300 mg per day, the equivalent daily dose of oxymorphone could be approximately 100 mg per day, for oxycodone 200 mg per day, etc.

There is considerable interpersonal variation in the opioid dose ratio, and therefore, frequent follow-up after conducting an opioid rotation is important. Opioid rotation is safe for most opioid agonists since most patients develop a significant level of cross-tolerance. Since cross-tolerance to sedation and respiratory depression is not complete, in most cases, the opioid rotation is conducted by reducing the dose of the new opioid by 30% to 50%.

One of the most remarkable exceptions to this rule of cross-tolerance is methadone.[11] Methadone is one of the most exciting opioid analgesics because of its ability to control pain that has been refractory to multiple other opioids, its lack of active toxic metabolites, its long half-life that allows for administration once or twice a day, and its very low cost that makes it affordable for low-income patients or those who are uninsured. However, methadone also has significant 3A4 cytochrome interactions and can be dangerous for opioid rotation because of its lack of cross-tolerance with all other Mu opioid agonists. For this reason, only experienced clinicians should conduct opioid rotations to methadone.

Opioid Side Effects

Adverse effects to opioids are common and should be assessed regularly (Table 3). The vast majority of patients will need regular laxatives. The most commonly used include senna and polyethylene glycol. These laxatives should be given daily, and patients should be instructed to self-titrate the dose of laxative until they have bowel movements of the same frequency and volume as they had before the diagnosis of cancer. Patients will quite commonly underestimate their level of constipation since their intake is less, they are less physically active, and they may assume constipation as "normal." The addition of an opioid can lead these patients to severe cases of obstipation, emesis, abdominal pain, anorexia, and even bowel perforation. Universal precautions regarding education and management of constipation are required whenever an opioid analgesic is prescribed.

Nausea is a frequent side effect during the initiation of opioids but is much less frequent during titration or opioid rotation. Preventative antiemetics including metoclopramide can be very useful.

Sedation is also a frequent side effect of opioid initial titration or opioid rotation. In patients who develop persistent opioid sedation, methylphenidate has been shown to reduce this side effect and allow patients to function better.[12] Methylphenidate can be used intermittently for the first few days after each dose change, and it can also be used as needed so patients can self-titrate during daytime.

Respiratory depression is rare but life threatening. It may result from excessive dose, patient chemical coping, drug or active metabolite accumulation from renal or liver failure, pharmacokinetic changes from drug interaction, or pharmacodynamic effects when combined with alcohol, benzodiazepines, and other sedatives.

As previously noted, neurotoxicity is the most dramatic side effect of opioid analgesics. Delirium occurs in more than 85% of patients with cancer at some point before death, and opioids might be a contributor in these patients, so it is important to conduct early opioid rotation. There are also multiple other causes for delirium in patients with advanced cancer, and delirium will ultimately occur in the vast majority of patients with cancer before death, even when they are not receiving any opioid analgesics.

Table 3. Opioid Side Effects

Common
Sedation
Constipation
Nausea
Less Common
Opioid-induced neurotoxicity (Sidebar 2)
Sweating
Urinary retention
Pruritus
Adult respiratory distress syndrome
Addiction
Respiratory depression
Hypogonadism

SCREENING AND MANAGING OPIOID OVERTREATMENT, MISUSE, AND ABUSE

An emerging challenge to safe and effective cancer pain control is overtreatment with excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. Many of the same barriers that have contributed to undertreatment, such as lack of knowledge, time, and reimbursement, have advanced opioid overuse. As a result of these obstacles, comprehensive pain assessments are not conducted, and referrals for mental health counseling or physical therapy are not provided because these treatments are frequently not compensated by third-party payers. Seemingly, the provider may believe the only option is to prescribe an opioid.

Although limited data exist in the oncology setting, strong support for opioid overutilization comes from the treatment of pain in chronic nonmalignant pain settings. Higher doses of opioids in this population are often associated with mental

Table 4. Factors that Place Individuals at Risk for Overtreatment with Opioids

Long-Term Survival
Comorbid Mental Health Conditions
Anxiety
Depression
Sleep disorders
"Chemical copers" or those with limited coping skills
Limited or No Financial Resources
Pre-Existing Substance Use Disorders

Table 5. Potential Reasons for Aberrant Drug-Taking Behavior

Pseudo-addiction (Inadequate Analgesia)
Amount of drug ordered (e.g., dose, number of tablets) too low
Insurance limits prevent adequate supply
Pharmacy shortages diminish availability
Psychiatric Conditions
Mood disorders (e.g., anxiety, depression)
Encephalopathy or cognitive disorders
Inability to Follow Treatment Plan
Low literacy
Misunderstanding regarding "prn"
Substance Use Disorder
Criminal Intent

health conditions such as anxiety or depression, along with substance use disorders.[13] Emerging data suggest that prolonged use of opioids leads to hypogonadism, fractures, and cognitive blunting.[14] Provocative data from the laboratory suggest opioids may accelerate tumor growth.[15] Finally, in some patients, opioid use is not leading to improved function or quality of life— essential goals for those with chronic nonmalignant pain and long-term cancer survivors.

Risk Factors for Overtreatment

Providing effective pain control should include consideration of factors associated with risk for overtreatment (Table 4). The cancer and/or its treatment may have resulted in persistent pain, the uncertainty of recurrence can be associated with significant anxiety or depression, and limited coping strategies along with reduced financial resources (sometimes a consequence of cancer treatment and/or losing one's job) all contribute to a state of great distress.[16] Coupled with a history of substance use disorder, the patient may conclude that opioids may be the most appropriate, or only, solution.

To avoid labeling, when apparent aberrant behavior occurs, the oncology team must carefully reflect on alternate explanations (Table 5). Is the patient calling frequently for refills because he or she is not getting an adequate supply of medications, because either our orders are insufficient or the insurance company has a ceiling on the dispensed amount of tablets at a number too low to meet the need? Or is the patient overwhelmed with trying to understand when to take a drug "prn" or "as needed," and they default to every 3 hours, regardless of their pain intensity? Or is the patient selling the medication to purchase other powerful illicit agents or to feed their children?

Universal Precautions

To provide safe and effective pain care, experts suggest implementing universal precautions. These measures are considered universal because we cannot predict who has a substance use disorder. These precautions employ screening, agreements, and adherence monitoring strategies.[17] Comprehensive assessment of the current and past use of legal (e.g., tobacco, alcohol) and illicit substances (e.g., prescription drugs obtained from family or purchased illegally) is warranted. Cannabis use should be specifically evaluated, as many do not consider it to be illicit, particularly as more states are legalizing its recreational or medical use. Screening tools, such as the CAGE questionnaire, can be used to complement this assessment by determining the extent of harmful behaviors. Substance use disorders are not rare in the oncology setting.[18,19]

Agreements, formerly called contracts, detail both the patient's and provider's responsibilities in managing pain.[20] Key components generally include the requirement to use one prescriber and one pharmacy along with the condition that any changes in the plan must first be discussed. These agreements also clarify how the patient can contact the provider or their team and the expected frequency of clinic visits. Safe storage and handling of medications may be included to prevent diversion and community exposure to controlled substances. There are limited data regarding the efficacy of these agreements in the oncology setting.

Adherence monitoring strategies include the use of pill counts, prescription monitoring programs, and urine toxicology screening. Pill counts can be performed in the clinic to determine appropriate use of an opioid or other medication by comparing the number of pills remaining with what might be expected. Complementing this information is the regular use of prescription monitoring program records. Forty-nine states currently provide databases that inform prescribers about the dispensing of controlled substances. Although the information provided among states varies, using a patient's name and date of birth, the prescriber can determine the drug, date it was dispensed, dose, number of tablets, name of prescriber and pharmacy, and payment method (i.e., self-pay versus third-party payer). This informs safe prescribing but also assists when seeing new patients with low health literacy who do not know the name or dose of their medication.

Random toxicology screening can tell the prescriber whether the drug ordered is present and if nonprescribed substances have been ingested.[21] Most screening is conducted using urine, as it is less invasive and more cost-

effective. Basic screens use immunoassay to ascertain the presence of certain classes of substances (or their metabolites), with most including opioids, amphetamines, benzodiazepines, barbiturates, cocaine, phencyclidine, and tetrahydrocannabinol. If findings are abnormal, more elaborate and expensive testing can be performed to determine the presence of specific agents (e.g., oxycodone or morphine) using gas chromatography-mass spectroscopy. Caution is warranted when interpreting findings as false negatives and positives can occur. For example, screens may be negative for opioids when patients are appropriately using fentanyl patches, as fentanyl is often missed by immunoassays. Additionally, patients who are supposed to be taking hydrocodone might have a urinary drug screen positive for hydrocodone, hydromorphone, and morphine since the liver metabolizes hydrocodone into these substances.

An essential component of universal precautions is education about safe storage and disposal of controlled substances.[22] Unfortunately, the majority of patients are unaware of the importance of these measures.[23] One of the most common sources of prescription opioids for abuse is family members and acquaintances. Unfortunately, in the case of patients receiving high doses or opioids, one single tablet taken by an opioid-naive relative or acquaintance can result in death. Since these drugs are frequently called "painkillers," relatives or acquaintances with a minor pain who are opioid naive may ask the patient to share a tablet, and patients should be warned about the danger of this practice.

Substance Use Disorder: Addiction and Chemical Coping

Addiction and chemical coping can occur in patients receiving opioids for cancer pain. By binding to the receptors in the limbic system, opioids not only have an analgesic effect but also produce reward. Patients at risk for opioid misuse will become dysphoric if they do not receive escalating doses. Patients' use of opioid in an effort to manage emotional distress rather than purely physical pain has been defined as chemical coping. This syndrome is more common among young, male patients with a history of alcoholism, drug abuse, and smoking.[24] Patients who rapidly escalate the opioid dose, frequently complain of pain with intensity of 10/10, or are at risk for chemical coping should be referred to a supportive care/palliative care team for interdisciplinary management of this complex problem. Collaboration with addiction specialists may be useful.

One might consider the phenomenon of opioid misuse as a continuum with chemical coping being an early stage of substance use disorders. In our clinical experience, when patients use opioids to treat anxiety, depression, or sleep disorders, these actions can often be countered with compassionate use of motivational interviewing to assist them in gaining insight into their behaviors and to appropriately treat their emotional distress. Early identification is necessary.

Patients with ongoing, untreated substance use disorders, such as regular use of heroin or other illicit substances, require more complex care than can usually be provided in an oncology setting without significant interdisciplinary support.[25] The goal may be the provision of pain control while employing "harm reduction"—preventing diversion of substances to the community while providing safe and effective care. A week's supply of opioid may be prescribed, rather than 1 month, and frequent urine screening may be employed. Interdisciplinary care is warranted.

People with a past history of substance use disorder and those who are in recovery may present a unique challenge. Fears of relapse when presented with an opioid for the treatment of cancer pain may lead the patient to refuse these medications. Thoughtful discussions about using these opioids, trying non-opioid analgesics, employing interventional therapies, and incorporating the patient's sponsor or case manager can be helpful to provide effective relief while limiting the risk of relapse.

A number of new opioid preparations are currently aimed at reducing the risk of illegal use.[26] The idea behind their formulation is that many abusers tamper with tablets to facilitate intranasal or intravenous administration since these routes result in a more rapid peak serum level and a feeling of euphoria. All these preparations consist of an extended release opioid agonist (morphine, oxymorphone, oxycodone, or buprenorphine) modified in one of three different ways: (1) introducing barriers to crushing, chewing, or dissolving; (2) adding an aversive substance that will cause irritation if inhaled, injected, or chewed; and (3) adding an opioid agonist, such as naloxone or naltrexone, that will not be absorbed if the tablet is taken orally as prescribed but will reduce the opioid effect or result in withdrawal if inhaled, injected, or chewed.

These preparations are now in different levels of approval in the United States and other countries. Although they may help reduce the intravenous injection of extended release opioids and perhaps reduce overdose mortality, these preparations will not be able to avoid the two most common sources of chemical coping: taking more than the prescribed dose of intact tablets, and using the immediate release rescue opioid aberrantly. These preparations are also likely to dramatically increase financial toxicity for patients who already face difficulties paying for opioids.

SUMMARY

Safe and effective opioid use in patients with cancer requires balance and skill. These skills include comprehensive assessment, understanding the pharmacokinetics and dynamics of these agents, and knowledge of dosing, titration, and rotation. Balance speaks to the awareness that opioids might be misused, either inadvertently by patients who note they fall asleep or feel less anxious when using these drugs, or purposefully by those with substance use disorders or criminal intent. Universal precautions can support adherence and prevent diversion. Caring for patients with misuse requires interdiscplinary care, with input from supportive oncology/palliative care and addiction specialists.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References

1. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol.* 2014;34:4149-4154.
2. Breuer B, Chang VT, Von Roenn JH, et al. How well do medical oncologists manage chronic cancer pain? A national survey. *Oncologist.* 2015; 20:202-209.
3. 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. *J Clin Oncol.* 2012;30:1980-1988.
4. Kwon JH. Overcoming barriers in cancer pain management. *J Clin Oncol.* 2014;32:1727-1733.
5. Paice JA, Ferrell B. The management of cancer pain. *CA Cancer J Clin.* 2011;61:157-182.
6. Kurita GP, Kaasa S, Sjøgren P. Opioid Analgesics. In Bruera E, Higginson, I, von Gunten C (Eds).*Textbook of Palliative Medicine and Supportive Care 2nd Edition.* Boca Raton, FL: CRC Press Taylor and Francis Group, 2015;395-408.
7. Pasternak GW, Pan YX. Mu opioids and their receptors: evolution of a concept. *Pharmacol Rev.* 2013;65:1257-1317.
8. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014;95(4):376-382.
9. Dalal S, Tanco KC, Bruera E. State of art of managing pain in patients with cancer. *Cancer J.* 2013;19:379-389.
10. Dalal S, Hui D, Nguyen L, et al. Achievement of personalized pain goal in cancer patients referred to a supportive care clinic at a comprehensive cancer center. *Cancer.* 2012;118:3829-3877.
11. Parsons HA, de la Cruz M, El Osta B, et al. Methadone initiation and rotation in the outpatient setting for patients with cancer pain. *Cancer.* 2010;116:520-528.
12. Reissig JE, Rybarczyk AM. Pharmacologic treatment of opioid-induced sedation in chronic pain. *Ann Pharmacother.* 2015;39:727-731.
13. Merrill JO, Von Korff M, Banta-Green CJ, et al. Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. *Gen Hosp Psychiatry.* 2012;34:581-587.
14. Sullivan MD, Von Korff M, Banta-Green C, et al. Problems and concerns of patients receiving chronic opioid therapy for chronic noncancer pain. *Pain.* 2010;149:345-9353.
15. Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth and metastasis. *Cancer Metastasis Rev.* 2011;30:225-238.
16. Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. *J Clin Oncol.* 2014;32:1739-1747.
17. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA.* 2011;305:1346-1347.
18. Dev R, Parsons HA, Palla S, et al. Undocumented alcoholism and its correlation with tobacco and illegal drug use in advanced cancer patients. *Cancer.* 2011;117:4551-4556.
19. Blackhall LJ, Alfson ED, Barclay JS. Screening for substance abuse and diversion in Virginia hospices. *J Palliat Med.* 2013;16:237-242.
20. Starrels JL, Becker WC, Alford DP, et al. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med.* 2010;152:712-720.
21. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med.* 2012;13:886-896.
22. Francoeur RB. Ensuring safe access to medication for palliative care while preventing prescription drug abuse: innovations for American inner cities, rural areas, and communities overwhelmed by addiction. *Risk Manag Healthc Policy.* 2011;4:97-105.
23. Reddy A, de la Cruz M, Rodriguez EM, et al. Patterns of storage, use, and disposal of opioids among cancer outpatients. *Oncologist.* 2014;19:780-785.
24. Nguyen LM, Rhondali W, de la Cruz M, et al. Frequency and predictors of patient deviation from prescribed opioids and barriers to opioid pain management in patients with advanced cancer. *J Pain Symptom Manage.* 2013;45:505-516.
25. Kircher S, Zacny J, Apfelbaum SM, et al. Understanding and treating opioid addiction in a patient with cancer pain. *J Pain.* 2011;12:1025-1031.
26. Santos SP, Bruckenthal P, Barkin RL. Strategies to reduce the tampering and subsequent abuse of long-acting opioid potential risks and benefits of formulations with physical or pharmacologic deterrents to tampering. *Mayo Clin Proc.* 2012;87:683-694.