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Managing cancer pain: Frequently asked questions

ABSTRACT

For a variety of reasons, cancer pain is often undertreated, adversely affecting the quality of life for patients and caregivers. To manage cancer pain effectively, physicians need to understand its pathogenesis, how to assess it, how to treat it, and, in particular, how to optimize opioid treatment. We discuss common questions faced by physicians in everyday practice.

KEY POINTS

Opioids can be used effectively for the management of cancer pain, provided the physician has sufficient knowledge, education, and training.

Adjuvants, if properly used, can help manage cancer pain more effectively.

Complementary and alternative therapies look promising, but too little is known about them, so caution is advised when recommending them.

Patients should be referred to a pain clinic if they have intractable pain or if they have severe side effects from opioid therapy.

Overall improvement in patient satisfaction and quality of life can be noted when pain is effectively managed.

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Some 90% of patients with cancer experience pain during their illness.[1] The pain usually worsens as the disease progresses, and patients may experience different types of pain.

Persistent pain decreases function, appetite, and sleep, induces fear, causes depression, and generally lowers the quality of life.[2] Persistent pain is demoralizing and debilitating for patients and their caregivers.[3]

Adequate pain control is important to ensure that patients can function productively, maintain social relationships, and improve their quality of life.[2] Yet 86% of practicing physicians surveyed believed that most cancer patients with pain were undermedicated,[2] and most felt that pain management is unsuccessful in more than half of patients who seek help.[3]

The critical importance of pain management has been emphasized by the World Health Organization (WHO), by international and national professional organizations, and by government agencies. All practitioners who care for cancer patients need to be well educated in managing cancer pain, a key part of which is to educate patients about the process and what to expect. This results in better pain control.[4]

Although much has been written on the management of cancer pain in a referral setting, little has been published on how to manage it in primary care. In this article, we discuss common questions faced by generalists. We emphasize the use of opioids, perhaps the most challenging aspect of cancer pain management. We also discuss when consultation with a specialist in pain management or a palliative medicine specialist is especially helpful.

TABLE 1

Common barriers to the effective use of opioids

Patient-related barriers
Reluctance to report pain
Poor communication between patients and their physicians
Lack of adherence to treatment recommendations
Concerns about analgesic use
(fear of addiction, tolerance, side effects)
Maladaptive beliefs (eg, that pain related to cancer is inevitable)
Lack of trust in the health care system
Affective barriers such as anxiety, depression, mood disorders
History of side effects from opioids
Cost

Physician-related barriers
Inadequate pain assessment
Gaps in knowledge about the principles of cancer pain management
Lack of knowledge about opioid dosing and managing side effects
Lack of sufficient training
Fear of audit by a regulatory body
Reluctance due to lack of specific guidelines

Institutional barriers
Complicated bureaucratic regulations governing supply
Regulation of the prescription and administration of opioids
Continuity of care
Time constraints
Inability to provide adequate training to physicians

WHAT ARE THE DIFFERENT TYPES OF PAIN SYNDROMES?

Pain is classified in several ways[1–6]:

Nociceptive vs neuropathic. Nociceptive pain comprises somatic and visceral components and is the result of continued tissue injury.[4] Neuropathic pain is due to injury to the peripheral and central nervous systems and occurs within an area of sensory or motor deficit.

Continuous vs intermittent. Continuous pain, even if controlled, can have breakthroughs, ie, flares of pain above the controlled baseline level. Intermittent pain is a pain flare without chronic baseline pain. Intermittent pain is further divided into incident pain (ie, on movement) and end-of-dose failure (ie, pain occurring just before the next scheduled opioid dose).[5] Pain specialists continue to debate the meaning and the use of these terms.

Malignant vs nonmalignant. Cancer pain is multifactorial,[1] being induced by the disease itself, by the treatment of cancer, and by pain unrelated to cancer or its treatment (eg, osteoarthritis or diabetic neuropathy).[2]

Familiarity with the causes and the types of pain, including pain related to cancer, is important, as this influences treatment decisions.

HOW IS PAIN ASSESSED?

The assessment of pain is vital in managing it.

Since pain is inherently subjective, the patient's self-report is the gold standard.[4] Characteristics of the pain along with a physical examination, laboratory testing, and imaging studies can define the pathophysiology of the pain and influence the decision to undertake further assessment or specific therapies.

Patients and physicians can use various scales, such as a visual analog scale, a numerical rating scale, a graphic scale, a verbal scale, a word descriptor scale, and a functional pain scale. A verbal scale can be used if the patient is alert, or a nonverbal scale if the patient has impaired cognition or speaks a different language. Intensity is the most common dimension evaluated in cancer pain, primarily via a numerical or visual analog scale. A numerical scale score of 0 to 10 has been found to be as effective as a visual analog scale (0 to 100 mm),[7,8] and the numerical rating scale is generally preferred as a measure of pain intensity.[9]

There are no clear guidelines for selecting one scale over another.[7] A clinically meaningful response (ie, meaningful to patients) is at least a two-point decrease on the 10-point numerical scale or a 13-mm decrease on the 100-mm visual analog scale. A decrease in the percentage of the pain relates to global improvement better than an absolute reduction on the numerical scale.

WHAT PROBLEMS ARE ENCOUNTERED IN MANAGING CANCER PAIN?

Opioids are highly effective in controlling cancer pain, yet physicians often hesitate to prescribe them for a number of reasons (TABLE 1).[10] Inadequate pain assessment has been reported as a main physician-related barrier to effective opioid use,[11] whereas patients may hesitate to take prescribed opioids because of a lack of knowledge about them and a fear of addiction and other adverse effects.[11]

WHAT ARE THE DIFFERENT WAYS TO MANAGE CANCER PAIN?

Pain should be treated promptly and aggressively, because if untreated it can lead to delays in healing, changes in the central nervous system (eg, sensitization, plasticity), chronic stress, family stress, depression, job loss, and even suicide.[12–14]

Comprehensive pain management improves outcomes and includes the rational use of opioids and adjuvant analgesics, physical rehabilitation, cognitive behavioral (nondrug) therapies, family counseling, interventional procedures (kyphoplasty, nerve blocks, local injections, spinal analgesia), and complementary therapies such as acupuncture.[12] Adjuvant analgesics include antidepressants, anticonvulsants, and local anesthetics.

HOW DO OPIOIDS RELIEVE CANCER PAIN?

Opioids bind to receptors in tissues throughout the body, including in the central and peripheral nervous systems[15] and the digestive tract. The binding of an opioid to an opioid receptor—including mu, kappa, and delta receptors and orphan receptor-like ligand-1—initiates a cascade of intracellular reactions. Due to the nature of different interactions of opioids with each of these receptors, individuals vary in their response to opioids.[15]

WHAT ARE THE CHARACTERISTICS OF COMMON OPIOIDS?

When choosing an opioid, the WHO's analgesic ladder (FIGURE 1) offers a simple, three-step approach based on pain severity:

- **Step 1**. Mild pain calls for a nonopioid analgesic with or without an adjuvant (more about adjuvants below).
- **Step 2**. Mild or moderate pain that persists or increases calls for a weak opioid such as codeine, tramadol (Ultram), or hydrocodone, with or without a nonopioid and with or without an adjuvant.
- **Step 3**. Severe pain calls for a strong opioid with or without a nonopioid, and with or without an adjuvant.

Morphine, the prototypical opioid, is well studied and versatile, as it can be given orally, parenterally, rectally, or intraspinally. It is readily available in the United States and Western Europe but not in some parts of the world, such as Asia and Africa. It is also cost-effective.

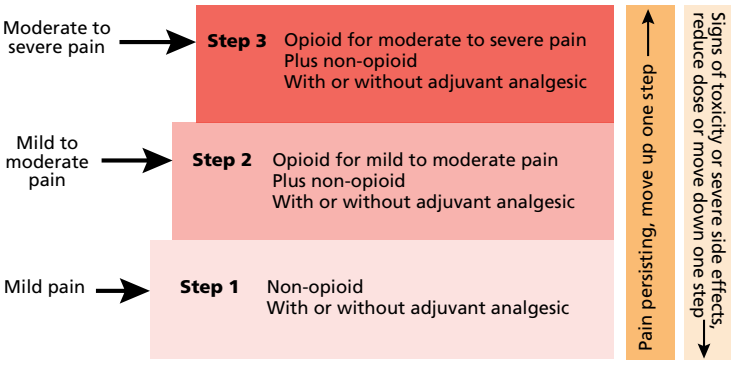

FIGURE 1. A three-step approach to pain control, based on the World Health Organization's "analgesic ladder."

Hydromorphone (Dilaudid) is similar to morphine in terms of versatility, cost, and effectiveness in pain management. An extended-release form (Exalgo) is now available in the United States.

Oxycodone is readily available in both slow-release (eg, OxyContin) and immediate-release (eg, Oxy-IR) preparations and is also cost-effective. However, there is no parenteral formulation in the United States.

Fentanyl is the only opioid available in the United States that can be given transdermally (in the form of the Duragesic patch) for patients who cannot swallow. Moderate to severe cachexia may affect its absorption. Patients can undergo magnetic resonance imaging while wearing the patch. The patch is readily available and is of moderate cost (TABLE 2). Oral and buccal preparations of fentanyl are available for control of breakthrough pain, but they are expensive; an inexpensive second opioid is usually prescribed for breakthrough pain.

Methadone is inexpensive and can be used as a long-acting or an immediate-release opioid. However, it should be used with caution in patients with a prolonged QTc interval: in general, a QTc interval of 430 to 450 msec is not a contraindication, but there is a risk of torsades de pointes when the QTc is greater than 500 msec. The physician should

Pain is one of the most common reasons patients visit a physician

TABLE 2

Characteristics of opioids

DRUG	ROUTE[a]	ONSET OF ACTION	PEAK EFFECT (MINUTES)	DURATION (HOURS)	COST[b]
Morphine[c]	Intravenous (IV) or subcutaneous (SC) Oral	5–10 min 15–60 min	10–20 min 60–90 min	3–6 hours 4–6 hours 12–24 hours for sustained release	$
Codeine	Oral	30–40 min	60–90 min	3–4 hours	$
Fentanyl	Transdermal IV, SC Buccal	3–20 hours 1–1.5 min 5–10 min	23–60 hours 5–6 min 30–60 min	48–72 hours 1 hour 1–3 hours	$$
Hydromorphone	IV or SC Oral	5–15 min 20–30 min	30–60 min 90–120 min	3–4 hours 4–6 hours	$
Methadone[d]	IV or SC Oral or sublingual	15 min < 30 min	60 min 90–120 min	3–8 hours 4–5 hours	$
Buprenorphine[e]	IV Transdermal Sublingual	5–15 min 11–20 min 15–45 min	5 min 60 hours 30–120 min	6–8 hours 4 days 6–8 hours	$$$
Hydrocodone	Oral	15–30 min	60 min	4–6 hours	$
Oxycodone	Oral	20–30 min	30–60 min 3 hours for sustained release	4–6 hours 12 hours for sustained release	$
Tramadol (Ultram)	Oral	30–60 min	120 min	4–9 hours	$

[a]The intramuscular route is not mentioned here since it should be avoided as much as possible because of erratic absorption and the pain it causes on administration, when subcutaneous administration can be safely given.
[b]$=inexpensive; $$=moderate cost; $$$=expensive
[c]Morphine has different characteristics depending on whether the immediate-release or the sustained-release formulation is given.
[d]Methadone's longer duration of action is dependent on single dose or multiple doses. Experience is needed for dose titration, so referral to pain management or palliative medicine is recommended.
[e]Buprenorphine is recommended as a third-, fourth-, or fifth-tier opioid. If considering its use, referral to pain management or palliative medicine is recommended.
NOTE: Meperidine is not recommended for cancer pain management because of the risk of seizures caused by the accumulation of its toxic metabolite, normeperidine, if used for more than a few days.

Optimal use of adjuvants helps to more effectively control cancer pain

also look for drug interactions when prescribing methadone, which is metabolized in the liver via the cytochrome P450 3A4 system. Methadone use can also lead to respiratory depression, prolonged QTc interval, and sudden death.

Buprenorphine can be used as a third- or fourth-tier opioid for patients with both kidney and liver failure. It can be given sublingually or parenterally. It may not be readily available, may not be covered by insurance, and is expensive.

Selecting an opioid to try first

The following are some general considerations when selecting an opioid to try first:

- Does the patient have a history of organ failure? Has the patient had a therapeutic response to, or adverse effects from, a particular opioid in the past?

TABLE 3

Equianalgesic dosing of common opioids

DRUG	INTRAVENOUS (IV) TO ORAL[a]	DOSE EQUIANALGESIC TO 1 MG IV MORPHINE[b]	COMMENTS
Morphine	1:3	—	Route: IV, subcutaneous,[c] intramuscular, oral, rectal, intrathecal
Oxycodone	—	—	No IV form available in the United States Oxycodone:morphine 1:1 to 1:1.5
Fentanyl patch (Duragesic)	—	25 µg	Also available in buccal and oral formulations
Hydromorphone	1:2	0.2 mg	Sustained-release preparation available
Methadone	1:2	Ratio increases as daily morphine dose increases	Use only by experienced physicians is suggested
Buprenorphine (Subutex)	1:2	1:1 dose conversion with fentanyl	Available in sublingual preparation

[a]Equianalgesic dose and route conversions can vary based on the reference material. The above-mentioned amounts are used in everyday practice in Cleveland Clinic's Section of Palliative Medicine and Supportive Oncology.
[b]Opioid doses equianalgesic to morphine are based on single-dose studies.
[c]The bioavailability of the subcutaneous dose is equal to that of the IV dose.

- Which route would best fit the patient's needs? (Oral is always preferable.)
- How often will breakthrough dosing be required? (In general, the breakthrough dose is administered at the drug's half-life, but it can be administered between 1 and 4 hours.)
- How much will it cost? (Consider the cost, insurance coverage, and co-pays.)

TABLE 2 shows different characteristics of commonly used opioids, including route of administration, onset of action, peak effect, and duration of action.[16,17]

WHAT ARE THE EQUIANALGESIC DOSES OF COMMONLY USED OPIOIDS?

Equianalgesic tables are generally used to convert from one opioid to another or from one route of administration to another. There are many published equianalgesic tables, which are inconsistent, variable, and confusing.[18,19] These tables should only serve as a guide, and physicians should use their clinical judgment based on the individual patient.[18,19] All strong opioids are equally effective.

TABLE 3 lists equianalgesic doses and route conversions of commonly used opioids.[18–20]

WHAT ARE THE PRINCIPLES BEHIND OPIOID DOSING?

Successful management of cancer pain depends on using the right opioid in the right dose at the right time.[5] The starting dose depends on factors such as the type of pain, whether it is acute or chronic, the intensity, whether the patient has previously taken opioids, and whether tolerance developed. There is no evidence to suggest that one opioid is better than another, and there are no fixed formulas for opioid requirements. Appropriate doses are established by titration based on individual analgesic response and adverse effects rather than age, sex, or ethnicity.[5]

TABLE 4 shows important strategies for opioid dosing. An in-depth discussion of specific opioid dosing strategies is beyond the scope of this article.[5]

WHAT ARE THE COMMON ADVERSE EFFECTS OF OPIOIDS?

TABLE 5 lists the most common adverse effects of opioids, their mechanisms, and their management.[21–23]

Complementary and alternative therapies look promising, but we still know too little about potential adverse effects; recommend with caution

TABLE 4

Important opioid dosing strategies

The opioid regimen should be simple and convenient. The oral route is preferred, as it improves compliance.

Around-the-clock dosing controls continuous pain, and rescue doses are used for intermittent pain. Sustained-release preparations are preferred for around-the-clock dosing. Immediate-release preparations are preferred for intermittent dosing.

In patients who have not previously taken opioids, the choice of initial opioid for around-the-clock dosing is empirical. Starting doses should be low and adjusted to the desired effect.

Analgesia and adverse effects should be evaluated 12 to 24 hours after the start of opioid therapy.

Alternative routes allow continued drug delivery when oral dosing becomes impractical. It is appropriate to use a patient-controlled analgesia pump for rapid dose-titration during a pain crisis. Small doses of opioids, eg, morphine 1 mg per minute, may be initiated for pain relief before an analgesia pump is used.[5]

An important strategy in managing incident pain is to avoid increasing around-the-clock dosing.

Adjuvants should be given if the pain does not respond to opioids, despite titration.

Avoid sustained-release preparations or patches as initial dosing for acute pain. Once the appropriate dose of pain medication is determined with the use of immediate-release opioids, then pain medications can be converted to sustained-release preparations or patches.

Adverse effects are among the most common reasons for failure of opioids to relieve pain. If these effects are not anticipated and treated prophylactically, patients may avoid taking their opioid drugs or may complain that they are "allergic" to them. In reality, true allergy to any of the opioids is rare. Patients comply better if they are taught to expect that most adverse effects are either preventable or manageable.[21] A simple strategy includes reducing the opioid dose by 25% to 50%, using different opioids ("rotation"), changing the route of administration, and directly treating adverse effects.[21,22]

WHAT IS OPIOID ROTATION AND HOW IS IT DONE?

Opioid rotation involves changing to a different drug using the same administration route, with the aim of improving the analgesic response or reducing adverse effects.[16] It may be useful in widening the therapeutic window, ie, establishing a more advantageous relationship between analgesia and toxicity.[16] This strategy applies, for example, to patients who have an adverse reaction to morphine, and who may need rotation to fentanyl or methadone.

The major indication for switching opioids is poorly controlled pain with unacceptable adverse effects due to opioid toxicity, the rapid development of tolerance, refractory pain, or difficult pain syndromes.[24] A recent prospective study showed that 42% of patients underwent opioid rotation, and the two most common reasons were inadequate analgesia and severe adverse effects.[25] Opioid rotation resulted in relief of confusion (72%), nausea and vomiting (68%), and drowsiness (53%).[25]

Before trying opioid rotation, review the patient's pain syndromes and the use of an adjuvant analgesic, and assess for evidence of opioid toxicity or contributing abnormal biochemical factors such as hydration status.[24,26] Most opioids are mu-receptor agonists and may exhibit cross-tolerance, a phenomenon in which the alternative drug does not have the expected effects because of similar pharmacologic action of the first drug. Because the degree of cross-tolerance may change as opioid doses are escalated, it is advisable to proceed with caution when switching from one opioid to another in patients who are receiving very high doses. Opioid rotation generally would be ineffective if there is complete analgesic cross-tolerance between opioids.

The common equivalency conversion tables are based either on studies in patients who received low doses of opioids or on single-dose studies.[16,24] By substituting opioids and using lower doses than expected according to the equivalency conversion tables (generally a 25% to 30% decrease), it is possible in most cases to reduce or relieve the symptoms of opioid toxicity and to manage patients highly tolerant to previous opioids while improving analgesia.[24]

Alternatives to opioid rotation are route conversion (oral to parenteral or spinal), addition of an adjuvant analgesic, and opioid dose reduction.

TABLE 5

Side effects of opioids

SIDE EFFECT	FEATURES	MANAGEMENT
Constipation	Most annoying side effect Multifactorial, but opioids most likely cause	Best treated prophylactically at the start of opioid therapy General measures: adequate fluid intake, exercise, bulk-containing foods (eg, bran), natural stool softeners like prune juice An aggressive bowel regimen should be implemented: stool softeners (eg, docusate [Colace]), laxatives (eg, magnesium hydroxide), or enemas can be tried alone or in combination; the oral route is preferable for stool softeners and laxatives A newer option is methylnaltrexone (Relistor), approved by the US Food and Drug Administration for opioid-induced constipation in patients with advanced illness when laxatives are not effective; 8-12 mg in two subcutaneous doses, every other day; cost is about $38 per dose
Nausea	With or without vomiting The patient eventually tolerates the nausea	Rule out other causes of nausea such as gastroparesis, bowel obstruction, and opioid-induced constipation Use a multimodal approach, even a combination of drugs if needed—eg, benzodiazepines, dopamine antagonists, serotonin-receptor antagonists, antihistamines, anticholinergics, corticosteroids
Sedation	The patient eventually usually tolerates the sedation Additive effects with other sedative drugs	Opioid switch Route conversion to epidural opioid Methylphenidate (Ritalin) Dextroamphetamines Modafinil (Provigil) and donepezil (Aricept)
Respiratory depression	More likely at the start of opioid treatment, at dose titration, or after opioid switching	Naloxone (Narcan) Dose reduction
Myoclonus	Most common manifestation of opioid neurotoxicity Due to dopaminergic up-regulation and presynaptic release of glutamate	Opioid dose reduction or rotation Clonazepam (Klonopin), diazepam (Valium), baclofen (Lioresal), valproic acid (Depakene), or dantrolene (Dantrium) can be used
Delirium	Strong association with opioids Due to inhibition of cholinergic neurotransmitters	Opioid dose reduction, route conversion, rotation The neuroleptic haloperidol (Haldol) or an atypical neuroleptic—eg, quetiapine (Seroquel), olanzapine (Zyprexa), aripiprizole (Abilify) can be used to treat delirium Add benzodiazepine to neuroleptic if delirium persists
Sexual dysfunction	Due to hypogonadism	Check testosterone levels Hormone replacement therapy may be useful
Hyperalgesia	More common than known Multiple mechanisms responsible	Opioid dose reduction with or without an adjuvant analgesic Opioid rotation An *N*-methyl-*D*-aspartate receptor antagonist (methadone, ketamine [Ketalar]) may help

TABLE 6

Management of opioid overdose

Give naloxone (Narcan) intravenously or subcutaneously

Dilute an ampule of naloxone 400 µg/mL to 10 mL in normal saline

Give 0. 5 mL (40 µg) every 3 minutes

Discontinue once the patient is arousable or the respiratory rate is > 10 breaths/minute

If the overdose is from a long-acting opioid or methadone, naloxone infusion may be required

Naloxone is given in small increments until toxicity is reversed without inducing withdrawal or pain exacerbation

WHAT IS OPIOID TOXICITY AND HOW IS IT MANAGED?

Opioid overdose is commonly the result of an error in pain assessment, opioid prescribing, or dose administration. Opioid overdose classically presents as sedation or respiratory depression. The combination of coma, reduced respiratory rate, and pinpoint pupils is highly suggestive of opioid toxicity, and treatment should be initiated promptly.

For intractable pain or severe effects from opioid use, referral to a pain clinic is advised

This scenario, however, is the extreme example of opioid overdose, and it is rare when a patient is given the correct opioid dose titrated gradually over a period of time. The more common scenario is when a patient's pain has finally been managed and the patient is resting comfortably with slow respirations. This would not warrant naloxone (Narcan) administration but rather close observation and monitoring of vital signs.

Naloxone has antagonist activity at all of the receptor sites.[27] It is important to be alert for acute opioid withdrawal in patients taking high-dose opioids for a long time.[27] There are no guidelines as to the route of administration and the dosing of naloxone. TABLE 6 summarizes the management of opioid overdose using naloxone.[5]

WHAT IS THE ROLE OF ADJUVANTS?

An adjuvant analgesic is any drug with a primary indication other than pain, but with analgesic properties in some painful conditions. Adjuvants are best used when a patient cannot obtain satisfactory pain relief from an opioid.[28] Antidepressants, anticonvulsants, neuroleptics, antiarrhythmics, antihistamines, *N*-methyl-D-aspartate (NMDA) receptor antagonists, steroids, muscle relaxants, bisphosphonates, and radiopharmaceuticals can be adjuvant agents.[29]

Adjuvants are generally used to complement the analgesic effects of opioids to achieve optimal pain control with a minimum of adverse effects.[28] The following scenarios should prompt the use of adjuvants in clinical practice[28]:

- The toxic limit of a primary pain medication has been reached.
- The therapeutic benefit of the primary pain medication has reached a plateau.
- The primary analgesic could not be used because of substance-abuse behavior, multiple organ failure, allergy, etc.
- The patient has multiple pain syndromes.
- The patient has additional symptoms unrelated to pain, eg, insomnia or depression.

Delta-9 tetrahydrocannabinol (THC) alone has not been found to be effective in controlling acute pain, but the combination of THC and cannabidiol was more effective in relieving cancer pain than THC alone.[30]

TABLE 7 lists adjuvants with specific indications and points to remember when prescribing them.[28,29]

WHAT IS THE ROLE OF NSAIDs FOR CANCER PAIN?

Nonsteroidal anti-inflammatory drugs (NSAIDs) have a well-established role in treating cancer-related pain, either on their own for mild pain or in combination with opioids for moderate to severe pain, leading to additive analgesia. Using NSAIDs as adjuvants is common practice in certain cancer pain syndromes, such as malignant bone pain, although there is considerable variation in response.[31]

NSAIDs have long been known to inhibit peripheral prostaglandin synthesis, but recently they have also been suggested to have a central action. The central effect is related to NMDA receptor-induced activation of the nitric oxide system.[31]

NSAIDs have ceiling effects, and there is no therapeutic advantage to increasing the

TABLE 7

Adjuvant analgesic drugs and their indications

GROUP	DRUGS	INDICATIONS	COMMENTS
Nonsteroidal anti-inflammatory drugs	Ibuprofen (Motrin) Naproxen (Aleve) Etodolac (Lodine) Ketorolac (Toradol)	All kinds of pain, particularly malignant bone pain	Most commonly used Caution in renal failure and at-risk patients Risk of gastrointestinal bleeding especially with concomitant use of steroids
Corticosteroids	Prednisone, dexamethasone	Nerve compression, raised intracranial pressure, spinal cord compression, bone pain, pain due to bowel obstruction	Give dexamethasone twice a day in the morning and at noon for simplicity; can also help with associated conditions such as fatigue, anorexia Side effects include insomnia, mood swings, weight gain, diabetes-induced hyperglycemia, proximal myopathy
Antidepressants	Amitriptyline (Elavil) Trazodone (Desyrel) Fluvoxamine (Luvox) Fluoxetine (Prozac) Paroxetine (Paxil) Venlafaxine (Effexor) Bupropion (Wellbutrin) Citalopram (Celexa) Olanzapine (Zyprexa) Clonidine (Catapres)	Neuropathic pain, pain syndromes associated with depression, insomnia, anxiety, and fatigue	Tricyclic antidepressants should be used cautiously in cardiac patients; atypical antidepressants are favored for their lower side effect profile, but evidence is far less than for tricyclics
Anticonvulsants	Gabapentin (Neurontin) Lamotrigine (Lamictal) Carbamazepine (Tegretol) Pregabalin (Lyrica) Valproic acid (Depakene) Phenytoin (Dilantin)	Neuropathic pain of any type; pain associated with history of seizures	Drugs like gabapentin and pregabalin are relatively safe, with fewer drug-drug interactions
Bisphosphonates	Pamidronate (Aredia) Alendronate (Fosamax) Ibandronate (Boniva) Zoledronic acid (Zometa)	Bone pain (especially with prostate cancer, breast cancer, multiple myeloma)	Pamidronate has been extensively studied in patients with bone metastases
***N*-methyl-*D*-aspartate receptor antagonists**	Ketamine (Ketalar) Memantine (Namenda) Amantadine (Symmetrel)	Neuropathic pain, hyperalgesia	Recommend referral to pain management or palliative medicine, specifically ketamine for its side effect profile; oral administration of ketamine is effective, but experience is limited; data on memantine and amantadine are very limited
Anticholinergics	Hyoscine butylbromide (scopolamine) Glycopyrrolate (Robinul)	Bowel obstruction	These drugs may also ameliorate symptoms other than pain, eg, secretions and cramping
Muscle relaxants	Tizanidine (Zanaflex) Baclofen (Lioresal)	Neuropathic pain, muscular contractions	Baclofen has wide dose range
Local anesthetics and topical agents	Lidocaine patch, capsaicin cream, EMLA (prilocaine with lidocaine), mexiletine (oral)	Neuropathic pain, hyperalgesia	Topical agents have proven to be very effective agents
Benzodiazepines	Diazepam (Valium) Lorazepam (Ativan) Clonazepam (Klonopin)	Muscular contractions, pain associated with anxiety, insomnia	Evidence is limited and conflicting and provides little support
Others	Octreotide (Sandostatin)	Bowel obstruction	Good safety profile

TABLE 8

Opioid metabolism and use in patients with organ failure

DRUG	METABOLISM AND EXCRETION	LIVER FAILURE	RENAL FAILURE	COMMENTS
Morphine	Metabolized by glucuronidation and renally cleared	Start at lower doses Avoid sustained-release formulations in cirrhosis patients	Metabolites are accumulated in renal failure Dose reduction	As-needed schedule as initial dosing strategy Metabolites are removed by hemodialysis but not peritoneal dialysis
Fentanyl	Lipophilic Metabolized by CYP3A4	Reduced clearance Do not use patch in advanced liver disease	Reduced clearance as uremia inhibits CYP3A4 Do not start with a transdermal patch	Watch for delayed toxicity Not removed by dialysis
Hydromorphone	Metabolized by glucuronidation and renally cleared	Minor influence on pharmacokinetics	Accumulation of metabolites and potential for neurotoxicity	Better tolerated than morphine in renal disease Start with lower doses
Oxycodone	Metabolized by CYP2D6 and CYP3A4 Cleared renally	Avoid sustained-release formulations	Increases half-life of oxycodone and central nervous system toxicity at normal doses	Use as-needed doses to find optimal individual dosing interval
Methadone	Metabolized by multiple cytochromes and forms inactive metabolites Excreted in feces	Safe in liver failure	Excreted in feces, so it is safe in renal failure	Appears to be the safest opioid in liver and renal failure
Buprenorphine	Metabolized by CYP3A4 and excreted in feces	Relatively safe	Safe	Not many studies on the safety
Tramadol (Ultram)	Metabolized by CYP2D6; metabolites excreted renally	Dose reduction	Dose reduction	One of the metabolites has a higher affinity for mu-receptors than tramadol itself
Nonsteroidal anti-inflammatory drugs	Glucuronidation	May lead to acute on chronic liver failure Usually reversible	Can precipitate renal toxicity	Usually avoided in preexisting renal disease

dose beyond that which is recommended.

Ketorolac (Toradol), indomethacin (Indocin), and diclofenac (Voltaren) have potent analgesic activity, whereas the "oxicam" NSAIDs show predominantly anti-inflammatory effects.[30]

No NSAID is clearly superior for a particular type of pain. Certain NSAIDs block the NMDA receptor and inhibit cyclo-oxygenase-1 and cyclo-oxygenase-2. There is a poor correlation between the analgesic effects of NSAIDs and cyclo-oxygenase inhibition. There is no evidence to support the use of selective cyclo-oxygenase-2 inhibitors for cancer pain, and these agents have no advantage over nonselective NSAIDs on the basis of limited gastrointestinal toxicity.[32]

In cancer pain, NSAIDs may delay the development of tolerance and allow lower doses of opioids to be used, with fewer central ner-

vous system side effects.[31,32] Despite the extensive use of NSAIDs, relatively few randomized studies have documented their efficacy in cancer pain compared with other chronic pain syndromes. Data on safe and effective doses from studies of nonmalignant pain may not apply to cancer pain, since cancer patients often have several serious conditions and are on multiple medications. In addition, the potential for adverse effects of NSAIDs (gastrointestinal bleeding, renal failure, thrombosis) may be greater in patients with advanced cancer.

In conclusion, NSAIDs may help if used judiciously in somatic pain and visceral pain, and perhaps even in neuropathic pain.[31]

HOW IS CANCER PAIN MANAGED IN PATIENTS WITH ORGAN FAILURE?

Given the prevalence of chronic illnesses such as diabetes, hypertension, and heart failure, cancer patients are likely to have some degree of hepatic or renal dysfunction. As most pain medicines are metabolized or excreted hepatically or renally, knowledge about how pain drugs affect these organ systems or vice-versa has become more important in the prevention of drug toxicity. TABLE 8 lists the dosage adjustments needed for various pain drugs used for chronic pain.[32–34]

- Opioids that can be used in liver failure or cirrhosis: morphine, hydromorphone, methadone, levorphanol, buprenorphine.
- Opioids that can be used in renal failure: methadone, fentanyl, and buprenorphine are safest; oxycodone and hydromorphone are moderately safe; morphine is the least safe.[35,36]
- Opioids that can be used in both kidney and liver failure: methadone, buprenorphine.

To avoid substance abuse problems, set a dosing structure, control refills, and monitor the patient

HOW CAN PROBLEMS RELATED TO SUBSTANCE ABUSE BE AVOIDED?

Substance abuse is less a problem in managing cancer pain than in chronic nonmalignant pain. Prescribing opioids safely is challenging, and very little has been published on substance abuse and the management of cancer pain. However, in the absence of practice guidelines, the best approach is to establish a dosing structure, control prescription refills, and monitor the patient.

Abuse is the misuse of an opioid via self-titration or altering the dosing schedule or route of administration. Patients who misuse opioids—ie, take them differently than prescribed—are not necessarily addicted.

Addiction is the abuse of a drug associated with psychological dependence, despite harm.

Diversion can occur without addiction and is done for financial gain, and this is the worst offense as it may harm others.

Pseudoaddiction is abnormal, demanding, often hostile behavior resulting from uncontrolled pain; once the pain is controlled, the behavior resolves.

Behaviors such as forging prescriptions, stealing or borrowing drugs, frequently "losing" prescriptions, and resisting changes to medication despite adverse effects are more predictive of addiction than are behaviors such as aggressive complaining about the need for more drugs, drug-hoarding, and unsanctioned dose escalations or other forms of noncompliance, as the latter three are more likely to indicate poorly controlled pain.[37]

Predictors of opioid abuse include a family history or a personal history of alcohol or drug abuse (including prescription drugs); a history of psychiatric illness (including anxiety disorder); male sex; nonwhite race; a history of driving under the influence of alcohol or drugs; a record of drug-related convictions; lost or stolen prescriptions; and using supplemental sources to obtain opioids.[38] Socioeconomic status and disability level were not found to be significant predictors.[38]

Different scales are available to predict the risk of aberrant drug behavior in patients on chronic opioid therapy. Of the many available, the Screener and Opioid Assessment for Patients With Pain and the Current Opioid Misuse Measure assess all the key factors.[38]

After an assessment, the next step is monitoring. Unfortunately, no specific method has been validated. In one study, urine toxicology testing was more effective at identifying problems than monitoring patient behavior alone, and monitoring behavior alone would have resulted in missing about half of the patients with a problem.[39] The same study showed that

even in the absence of aberrant drug-related behavior based on predictors, a significant number of urine toxicology screens were positive.[39]

A negative urine screen for the patient's opioid suggests diversion. The clinician should order a screen for the prescribed opioid because a general screen may not detect nonmorphine opioids. A general screen may detect polysubstance abuse, which is common in individuals with addiction.

The effective management of patients with pain who engage in aberrant drug-taking behavior necessitates a comprehensive approach to manage risk, treat pain effectively, and assure patient safety.[40] "Pain contracts" are important as they set the stage for expected behaviors and urinary screens. Frequent visits and established limits such as a single prescriber, one pharmacy, no early refills, and urine drug screens help to minimize abuse.

TABLE 9 summarizes a strategy to manage opioid therapy in patients with history of substance abuse.[40]

TABLE 9

Strategies to manage opioid therapy in patients with a history of substance abuse

Multidisciplinary team approach
Appropriate screening and risk-management strategies
One physician / short prescriptions / longer-acting drugs
"Pain contract"—expectations of the patient, role of physician, risks and benefits, rationale of your policies, consent for treatment and testing
Urine toxicology screening and monitoring
Readdress pain and symptom control frequently
Involve family members and friends for social support
Refer to specialized pain clinic when difficult to manage

WHAT IS THE ROLE OF COMPLEMENTARY AND ALTERNATIVE THERAPIES?

Complementary and alternative medicine therapies are commonly used by cancer patients, with an average prevalence rate of 31%.[41–43] As the names suggest, they have been used both as an alternative to and as a complement to conventional medicine. Practitioners of complementary and alternative medicine emphasize its holistic, individualistic, empowering, and educational nature.

Patients do not routinely ask their physicians about these therapies,[44] and physicians often have only a limited knowledge of them.[45] Surveys of North American physicians showed that they view certain of these therapies as legitimate and effective.[46,47]

The role of complementary and alternative medicine in cancer pain has been the subject of debate, as relatively little is known about adverse effects and drug interactions. Nevertheless, the American Cancer Society and the National Comprehensive Cancer Network guidelines on cancer pain recommend nonpharmacologic treatment be added for patients who report a pain score of 4 or greater on a 10-point scale after analgesic adjustment.[48,49]

Most studies of complementary and alternative therapies for cancer pain are of poor quality, with significant shortcomings in methodology and study design and with no clear definition of outcomes.[50]

Acupuncture is probably the most studied of these therapies, but clinical trials so far have not shown it to be an effective adjunct analgesic for cancer pain.[51] A placebo-controlled, blinded randomized trial using auricular acupuncture showed a pain score decrease of 36% from baseline at 2 months compared with controls.[52]

Studies involving cognitive therapy, supportive psychotherapy, and hypnosis showed modest benefit.[53,54] Two trials involving relaxation and imagery reduced cancer pain compared with controls.[55,56]

Studies of massage therapy have shown mixed results; two studies reported a significant reduction in pain immediately after intervention, and no study found pain relief after 4 weeks.[57–60] Studies involving Reiki and touch therapy were inconclusive.[60,61]

Music therapy has been used to treat patients physically, psychologically, socially, emotionally, and spiritually, with evidence still equivocal. A large prospective observational study involving 200 patients conducted by Gallagher et al[62] showed pain was reduced by 30% after music therapy intervention. The

same study showed a reduction in depression and anxiety.[62] Music therapy could be used as a component of a multimodal approach to pain.

Herbal preparations are often used to treat cancer and symptoms by patients and naturalists. Some herbal medicines are known to cause toxicity in cancer patients. Examples are PC-SPES, mistletoe, and saw palmetto.[63]

At this juncture, there is *some* evidence that some complementary and alternative therapies can relieve cancer pain, and the most promising therapy seems to be related to mind-body medicine (eg, biofeedback, relaxation techniques). But before we can legitimately integrate these therapies into the management of cancer pain, we need large randomized controlled trials to determine if they are effective in patients on chronic high-dose opioids and if they decrease the need for opioids.

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Dabigatran

(OCTOBER 2011)

TO THE EDITOR: The article "Dabigatran: Will it change clinical practice"[1] has a dangerous error. In its Key Points, it says "dabigatran is a potent, reversible direct thrombin inhibitor." In fact, it is *not* reversible.[2]

Shamefully poor editing.

VAN SMITH, MD, FACP

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IN REPLY: This is not an error. When we[1] and others[2] said that dabigatran is a reversible direct thrombin inhibitor, we were referring to its effect at the molecular level, the appropriate description of its mechanism of action. However, we suspect that Dr. Smith means that there is no antidote to give in cases of bleeding or overdose. We share his concern and we discussed this in our article.

Unlike heparin, direct thrombin inhibitors act independently of antithrombin and inhibit thrombin bound to fibrin or fibrin degradation products. There are two types of direct thrombin inhibitors: bivalent (eg, hirudin) and univalent (eg, argatroban, ximelagatran, and dabigatran). The bivalent ones block thrombin at its active site and at an exosite and form an irreversible complex with it. The univalent ones interact with only the active site and *reversibly* inhibit thrombin, eventually dissociating from it and leaving a small amount of free, enzymatically active thrombin available for hemostatic interactions. Therefore, in contrast to the hirudins, they produce relatively transient thrombin inhibition.[2–4]

As we pointed out in our article, the lack of an antidote for dabigatran and the lack of experience in treating bleeding complications are major concerns. Fortunately, the drug has a short half-life (12–14 hours) so that the treatment is to withhold the next dose while maintaining adequate diuresis and giving transfusions as indicated. Activated charcoal, given orally to reduce absorption, is under evaluation but must be given within 1 or 2 hours after the dabigatran dose.[1] Dabigatran can be removed by dialysis (in part because it is a reversible inhibitor), a measure that may be necessary in life-threatening cases. Recombinant activated factor VII or prothrombin complex concentrates may be additional treatment options.[1,4] With time will come experience and, we hope, evidence-based guidelines.

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CORRECTION

An error appeared in the article, "Managing cancer pain: Frequently asked questions," in the July 2011 issue (Induru RR, Lagman RL. Managing cancer pain: Frequently asked questions. Cleve Clin J Med 2011; 78:449-464). On page 456, the fourth line of the right-hand column, "*N*-methyl-D-acetate" is incorrect. It should read "*N*-methyl-D-aspartate." The error has been corrected in the online version of the article.

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