Practical Guide to Opioids and Their Complications in Managing Cancer Pain

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Approximately 60% of cancer patients experience pain, and 25% to 30% have severe pain. With some cancers, opioids will be needed before chemotherapy begins and may be more frequently prescribed than chemotherapy. Given the frequency with which pain management is necessary in cancer patients, all oncologists should be familiar with opioid prescribing principles. This article reviews the World Health Organization recommendations for analgesic therapy in this setting, as well as guidelines for opioid therapy in patients with renal failure or hepatic failure, assessment of pain, dosing strategies in both acute and chronic pain, management of opioid overdose, pain associated with dose-limiting side effects, and pain in the actively dying.

Cancer is present in 160/100,000 males and 186/100,000 females worldwide, with some variability in frequency between countries.[1] The majority of these individuals (60%) experience pain, and 25% to 30% will have severe pain.[2,3] Those with common malignancies (eg, pancreatic or lung cancer) are likely to have pain at presentation to an oncologist or with their initial diagnosis. It is also likely that with certain cancers, opioids will be needed before chemotherapy treatment is started and that opioids will be more frequently prescribed than chemotherapy.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Opioid Myths</strong></td>
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<tr>
<td>• Exaggerated pain behaviors (hostility, demanding disposition) or manipulative behaviors during poorly controlled pain is a sign of opioid dependence and abuse (addiction)</td>
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<td>• Only certain types of cancer pain respond to opioids</td>
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<td>• Patients can never drive while on opioids</td>
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<td>• Recently developed (expensive) opioid formulations provide superior pain control compared to less expensive generic ones</td>
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<td>• Titration to high-dose opioids is associated with:</td>
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<tr>
<td>Analgesic tolerance</td>
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<tr>
<td>Intolerable sedation</td>
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<td>Increased risk of dependence, abuse and opioid diversion</td>
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<td>Respiratory depression</td>
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<td>• Undertreated pain does not impair cognition</td>
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Several myths surround the use of opioids (Table 1).[4] These either hinder optimal opioid dosing or lead to miscommunication between clinician and patient. Analgesic prescribing errors are common among clinicians, despite the wide acceptance of the World Health Organization (WHO) "three-step ladder" guidelines. In our experience, > 50% of patients will have received opioid therapy with dosing errors when first referred to palliative services. Common errors are outlined in Table 2.[5]

**Table 2**

**Common Opioid Dosing Errors**

- Failure to prescribe:
  - Adjuvants and nonopioid analgesics
  - Around-the-clock opioids for continuous pain
  - Prophylactic laxatives
  - Rescue doses before activity for incident or procedure related pain
  - Rescue or as needed opioid doses for transient flares of pain
- Inadequate pain assessment and follow-up
- Inappropriate use of opioids:
  - Adding opioid doses for incident pain to around-the-clock doses when continuous pain is controlled
  - Incorrect equianalgesic dose calculation
  - Insufficient opioid titration to pain severity
  - Multiple simultaneous changes in regimen (route, dose, drug, interval)
  - Use of multiple opioids simultaneously

Analgesic Three-Step Ladder and Opioid Dosing Principles
The WHO three-step ladder approach to cancer pain management was published in its final form in 1986 (Figure 1).[6] The scheme was derived from a consensus guideline based on expert opinion produced 4 years earlier.[7-9] Since its conception, the WHO analgesic guidelines have been validated by multiple groups. The success rate of the WHO analgesic ladder when used appropriately ranges from 77% to 100%.[7-14]

More recent modifications of the WHO ladder have included the substitution of low doses of potent opioid for step 2 weak opioids, and emphasis on analgesics by mouth, analgesics around the clock (ATC), drug choices based on pain severity ("by the ladder"), dosing based on individual needs, and attention to details when prescribing analgesics.[15]
Several principles that predated the WHO step ladder were important conceptually to its development:

1. Minimal increases in opioid serum concentrations could produce dramatic pain responses (established in 1980).[16]
2. Minimal-effect concentrations of an opioid were relatively consistent in a single individual over time but highly variable between individuals.
3. Distinct pharmacodynamic differences exist between individuals, accounting for differences in opioid dose requirements seen clinically and the need to individualize therapy.[16,17]
4. Pharmacokinetic variables (volume of distribution, rates of distribution and elimination) consistently failed to correlate with individual opioid requirements and validated the recommendation that opioid dosing needs to be individualized.[18-20]
5. Morphine requirements vary 1,000-fold between individuals.[21]
6. About 90% of individuals will not require more than 300 mg of morphine daily for pain control.[22-24]
7. Over 70% of patients will have satisfactory relief with oral morphine.[22,25,26]
8. There is no ceiling effect to potent opioid dosing; it is usually side effects that limit dose titration.[27]

Both nature and nurture play a role in pain processing and opioid responsiveness. In general, pharmacogenetic factors that influence opioid receptor function are more important than factors that influence opioid pharmacokinetics.[28,29] Certain single nucleotide polymorphisms (SNPs) involving...
the mu opioid receptor (such as the A118G SNP) are associated with the need for high morphine doses for pain relief.[29,30] Other SNPs are associated with the need to switch from morphine to another opioid (involving beta-arrestin 2 and STAT6).[28] Beta-arrestin 2 is important to mu opioid receptor activity and trafficking, whereas STAT6 is important to receptor expression.

Acquired factors that portend poor pain control include incident and neuropathic pain, psychological distress, a history of addiction, and impaired cognition.[31] Other clinical characteristics associated with a need for rotation from morphine are listed in Table 3.[32-35]

### Opioid Choices

#### In Patients With Renal Failure

Certain opioids produce metabolites that induce clinical toxicity. Meperidine is metabolized to normeperidine through the cytochrome CYP3A4. Normeperidine accumulates relative to the parent drug due to a longer half-life and causes seizures.[36] Both morphine-3-glucuronide and hydromorphone-3-glucuronide are neurotoxins that produce myoclonus, allodynia, and seizures. Both metabolites activate presynaptic calcium channels, which release glutamate that subsequently activates N-methyl-D-aspartate receptors and depolarizes postsynaptic neurons.[37] Overall, hydromorphone seems clinically better tolerated than morphine in those with reduced renal function.[38] Relative to morphine or hydromorphone, however, methadone and buprenorphine kinetics are generally well preserved in patients with renal failure, and these agents may be better choices.[39-41]

Certain opioids have analgesic active metabolites that accumulate in renal failure, leading to delayed opioid toxicity. For example, oxycodone is metabolized to oxymorphone, hydrocodone to hydromorphone, hydromorphone to hydromorphone-6-glucuronide, and morphine to morphine-6-glucuronide.[22,42-44] In general, dosing intervals will need to be extended for these opioids if used in patients with renal failure. "As needed" dosing may be used in renal dysfunction until the opioid half-life can be determined by the duration of analgesia.

In general, opioids should be used cautiously in those with renal failure. The doses should be low and titration done slowly in order to avoid delayed opioid toxicity.

#### In Patients With Hepatic Failure

Opioid pharmacokinetics in hepatic failure differ from those in renal failure. Generally, glucuronidated opioids (morphine, hydromorphone, buprenorphine) are safer than opioids metabolized through cytochromes (oxycodone, fentanyl, methadone), since glucuronidation is relatively well preserved in liver failure and is significantly expressed in extrahepatic organs.[45-48] However, bioavailability of glucuronidated opioids is increased with shunting. Hence, initial doses need to be smaller than those used in normal individuals, but dosing intervals need not be increased until the onset of the hepatorenal syndrome.

**Fentanyl**

Parenteral fentanyl has a rapid onset and short duration of action (lasting only 30 minutes).[49,50] The analgesic half-life of the parenteral formulation makes it unsuitable for treating chronic pain.[51]

Fentanyl patches deliver drug over the course of 3 days. Matrix patches can be cut for dose
adjustments and do not "dose dump," as reservoir patches do. Fentanyl transdermal patches can be used for stable continuous cancer pain, but should not be used to treat acute postoperative pain.[52,53] Patient satisfaction and acceptability are important benefits to the use of transdermal fentanyl.[22,54,55]

However, there are some drawbacks to the use of transdermal fentanyl compared with morphine. It is not superior in efficacy, lacks flexibility to changing pain severity, and is more costly than generic morphine. Additionally, the drug absorption through the skin is highly variable from patient to patient.[22,53,55,56]

There is an increasing tendency to use transdermal fentanyl as the first opioid, to use the patches during the titration phase of pain management in those with unstable pain, and to use them in the absence of dysphagia or nausea and vomiting (which would preclude the use of oral morphine). Moreover, half of opioid rotations to fentanyl transdermal patches in the acute care setting are inappropriate, according to guidelines from WHO and the European Association of Palliative Care (EAPC).[57] Rotating from transdermal fentanyl to oral morphine or oral hydromorphone results in doses that significantly differ from those anticipated by equianalgesic conversion tables derived from morphine or hydromorphone rotations to fentanyl.[58]

Methadone

Methadone has unique pharmacokinetic and pharmacodynamic characteristics that set it apart from other potent opioids. Oral bioavailability is 80% and half-life is highly variable between individuals (ranging from 17 to 100 hours).[59-63] Methadone accumulates with repeated dosing, and its potency relative to morphine is dose-dependent.[64] Methadone is metabolized through multiple cytochromes (CYP2D6, CYP2B6, and CYP3A4) and, as a result, is subject to multiple drug-drug interactions. Interindividual variability in cytochrome expression accounts in part for the 17-fold difference in blood concentrations between patients.[65,66] As a result, methadone should be prescribed only by those who have an extensive experience with its use and are knowledgeable about its pharmacology.

Analgesic non-cross tolerance between potent opioids is the reason why opioid rotations work in the majority of circumstances. Potential mechanisms for non-cross tolerance are listed in Table 4.[28,29]

<table>
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<tr>
<td><strong>Mechanisms of Opioid Non–Cross Tolerance</strong></td>
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<tr>
<td>• Differential binding to major opioid receptors (mu, kappa, delta) and receptor splice variants</td>
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<tr>
<td>• Individual pharmacogenetics involving opioid metabolism, opioid receptor expression, and intracellular regulation of “downstream” responses</td>
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<tr>
<td>• Opioid ligand–specific G protein interactions due to unique receptor conformational changes</td>
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Assessment of Pain

Assessment and continuity are integral to good pain management. The timing of assessment depends on the nature of the pain (acute, crescendo, chronic, stable), the care setting, and goals of care. In those who are being treated at a distance, pain management may be facilitated by telephone triage and computer-based support systems.[67-69] Between visits, pain diaries improve compliance and reduce pain intensity.[70,71]

The Joint Commission for Accreditation of Hospitals and the American Medical Association have collaborated to establish performance measures for cancer pain outcomes, for the purpose of quality-assurance monitoring. These performance measures are: (1) screening and comprehensive assessment of cancer pain, (2) the use of opioids for cancer pain management, and (3) prevention of opioid-induced constipation.[72] Standardized assessment should define who assesses, how assessment is performed, and when assessment is to be repeated once treatment is started.[73-75] Assessment of pain intensity alone—without taking into account function, pain interference, and opioid side effects—is unsafe. Comprehensive assessment includes pain location, quality, radiation, aggravating and alleviating factors, previous treatment, and responses. Realistic goals do not include the elimination of pain, but rather, a 33% to 50% reduction in pain intensity, maintained or improved physical function, reduced pain interference, and minimal opioid side effects.[76] Clinically
significant pain relief occurs when there is a 2-point decrease in the numerical rating of pain (0 = no pain, 10 = severe pain).[76-78]

Opioid Dosing Strategies

Seven principles should guide opioid prescribing practices (Table 5). Factors influencing effective pain management involve drug, dose, and timing. The right opioid given either in the wrong dose or at the wrong interval will not be efficacious. The use of sustained-release morphine every 12 to 24 hours (depending on the preparation) is more efficient than immediate-release morphine given every 4 hours and is likely to improve patient compliance. Bypassing generic morphine for expensive new opioids or opioid formulations in individuals with limited incomes is not economically responsible prescribing and is likely to lead to primary prescription failures, as individuals weigh the benefits of food on the table or paying out of pocket for opioid analgesics.

### Table 5

**Seven Basic Prescribing Principles**

- Equitable
- Economically responsible
- Efficacious
- Efficient
- Patient-centered
- Safe (risk minimized)
- Timely

### Acute Cancer Pain

Acute, severe pain arises from either a cancer complication (fracture, bowel perforation) or rapidly progressive cancer. The most effective dosing strategy involves small frequent doses of potent short-acting opioids until pain is controlled, followed by maintenance therapy.[79-83] Treatment of acute pain with either oral opioids, patient-controlled analgesia, or continuous infusion without titration will delay effective analgesia.[79,80]

Several strategies for managing acute cancer pain have been published. Mercadante and colleagues used 2 mg of intravenous morphine every 2 minutes until significant pain relief.[84] We have used intravenous morphine at 1 mg per minute for 10 minutes followed by a 5-minute respite, repeated twice until significant pain relief.[85] Harris and Kumar used 1.5 mg of intravenous morphine every 10 minutes. Responses usually occur within the hour.[82,83]

If intravenous access is impractical or not feasible, then 2 mg of morphine can be given subcutaneously every 5 minutes. The maintenance dose is either one-third of the titrated dose as an hourly infusion or three times the titrated dose given orally every 4 hours as immediate-release morphine.[79,84,85] Alternatives to morphine are hydromorphone at 0.2 mg or fentanyl at 20 µg for intravenous titration, or hydromorphone at 0.4 mg or fentanyl at 40 µg for subcutaneous titration. If patients are on chronic morphine prior to titration, then the pretitration ATC dose should be added to the maintenance dose determined by titration.

An oral loading dose of immediate-release morphine, 5 mg, every 30 minutes can be used in the opioid-naive patient. Alternatives to morphine are oral hydromorphone, 1 mg, or oxycodone, 5 mg, at 30-minute intervals. This dosing interval correlates with onset to analgesia seen with immediate-release opioids.[86]

### Chronic Cancer Pain

Cancer pain has two temporal patterns—continuous and intermittent—in most individuals. Intermittent pain may be precipitated by activity (incident pain), not spontaneous (breakthrough pain), or at the end of an opioid dosing interval (end-of-dose-failure pain).[25,87-90] In the frail or elderly, intravenous morphine at 0.5 mg/h, fentanyl at 20 µg/h, or hydromorphone at 0.2 mg/h are safe initial doses for continuous pain.[90] Younger, more robust patients who are opioid-naive can be
started on 1mg/h of morphine safely. Median dose requirements are between 2 and 4 mg/h. Appropriate oral morphine doses in the opioid-naive are either 5 mg of immediate-release morphine every 4 hours or 15 mg of sustained-release morphine every 12 hours.[87] Younger, more robust individuals may be started on 10 mg of morphine every 4 hours.[92]

Most patients require rescue opioid doses in addition to the ATC dose. Recommended oral rescue doses include the same dose used every 4 hours, 25% to 50% of that dose, and 5% to 10% of the total daily morphine dose.[25,87,90] No randomized controlled trials have shown evidence of an optimal rescue dose or timing interval between rescue doses. For end-of-dose failure or breakthrough pain, the ATC dose is increased by adding rescue doses.[87,90] This implied relationship between pain episodes and the ATC opioid dose may not hold true for incident pain.[87,88]

If chronic pain is under control but the patient is experiencing significant incident pain, short-acting opioids should be dose-adjusted to the severity of incident pain but not added to the ATC doses, to avoid opioid toxicity during rest. If incident pain responds > 50% but still limits function, doses of immediate-release rescue morphine should be increased 50%. If incident pain responds but < 50%, the rescue dose should be doubled.[91]

Other techniques to control incident pain include the use of parenteral patient-controlled analgesia and sublingual/buccal fentanyl (Fentora), which has a quick onset of action compared with oral or sublingual morphine. A recent study found that both parenteral morphine and oral transmucosal fentanyl were effective as rescue opioids. A dose proportionality was found to the basal (ATC) opioid doses in this study. Either 20% of the oral total daily morphine dose converted to parenteral (4 mg for 60 mg of oral morphine per day) or transmucosal fentanyl at 200 µg for each 60 mg of morphine per day were equally effective at 15 and 30 minutes after dosing.[89,93]

For patients experiencing "acute on chronic pain" (but not the severe, acute pain described earlier) rescue doses should be added to the ATC dose. For oral titration, divide the total morphine daily dose (rescue plus ATC dose) by 12 for the sustained-release dose, double the previous rescue dose, and give the new rescue dose every 30 minutes until pain is controlled.[91] Alternatively, the immediate-release morphine dose given every 4 hours could be given hourly.[25] If converting to parenteral morphine, add the ATC plus rescue doses, divide by 3, then divide by 24 for the hourly dose. Give twice the hourly dose as a loading dose, and repeat the hourly dose every 15 minutes until pain is controlled.[91] If chronic pain remains uncontrolled despite ATC and rescue doses, and a titration strategy as outlined above is not adopted, then the total morphine daily dose (rescue plus ATC) needs to be increased by 30% to 50%.[91]

Pain may resolve after a pain-relieving procedure, and this may result in a new onset of opioid toxicity if opioid doses are not reduced. Around-the-clock opioids should be tapered rather than discontinued. Opioid doses can be safely reduced by half without inducing withdrawal and subsequently reduced by half again every 3 days. However, the rescue dose should not be tapered simultaneously with the ATC dose, so that the patient may still be rescued if there is a resurgence of pain during the taper.[91]

Managing Opioid Overdose
The risk of respiratory depression is minimal with cautious opioid titration and frequent assessment for pain response and side effects. Respiratory depression can occur while individuals are on stable doses of morphine if there is a sudden dramatic reduction in pain from a neurolytic block, cord compression, or single fraction of radiation. Acute renal failure can cause respiratory depression if morphine doses are not adjusted downward.

To manage respiratory depression, dilute the standard 0.4-mg/mL naloxone vial with 10 mL of water and give 40 µg (1 mL) every 3 minutes parenterally or subcutaneously.[94] Discontinue this treatment once the patient's respiratory rate is > 10 per minute and he or she is arousable. The purpose of naloxone is to reverse respiratory depression, not analgesia. If the patient was on sustained-released morphine, transdermal fentanyl, or methadone, a continuous infusion of naloxone may be necessary due to naloxone's short half-life. The dose that successfully reverses respiratory depression is the hourly dose.[95]

Managing Pain Associated With Dose-Limiting Side Effects
Analgesia and its side effects should be initially evaluated at least every 24 hours with immediate-release and sustained-release morphine. Around-the-clock doses should not be changed for 20 to 24 hours with immediate-release morphine and for 48 hours with sustained-release morphine (at which time steady-state concentrations are reached).[25] Mild sedation is common and should be managed expectantly, with anticipated improvement over the next several days. Mild nausea may require antiemetics. Multiple classes of antiemetics have been used to manage...
opioid-induced nausea (Table 6).[27,96-111]

| Table 6 |
|---------------------|---------------------|---------------------|
| **Opioid-Induced Side Effects** | **Mechanism** | **Treatment** |
| **Gastrointestinal** | | |
| Constipation | Inhibit longitudinal muscle | Stool softener |
| | Disinhibits circular muscle | Laxatives |
| | Inhibits secretion | Enemas |
| | Increases absorption | Oral naltrexone |
| Nausea/vomiting | Stimulation of medullary central pattern generator | Cyclizine |
| | Gastric stasis | Haloperidol |
| | Stimulation of vestibular sensitivity | Ondansetron |
| **Endocrine** | | |
| Impotence | Hyogonadotropin | Hormone replacement |
| Amenorrhea | Hypogonadism | |
| **Respiratory** | | |
| Respiratory suppression | Opioid receptor (mu) blockade of medullary PCO₂-sensing neurons | Naloxone |
| | | Dose reduction |
| | | Buprenorphine |
| **Central nervous system** | | |
| Myoclonus | Antiglucogenic effect | Opioid dose reduction |
| | Dopaminergic upregulation | Opioid rotation |
| | Presynaptic release of glutamate by neuroactive metabolites | Clonazepam |
| Sedation | Inhibition of cholinergic neurotransmitter | Diazepam |
| | | Valproic acid |
| | | Baclofen |
| | | Dantrolene |
| | | Phenobarbital |
| Delirium | Inhibition of cholinergic neurotransmitter | Opioid dose reduction |
| | | Route conversion to epidural opioid |
| | | Opioid rotation |
| | | Haloperidol |
| | | Chlorpromazine |
| | | Add benzodiazepine to haloperidol |
| **Opioid-induced hyperalgesia/tolerance** | | |
| | Activation of N-methyl-D-aspartate (NMDA) receptors and reduced NMDA transport | Opioid dose reduction alone |
| | Uregulation of cholecystokinin in arcun stem | Opioid dose reduction with addition of an adjuvant analgesic |
| | Uregulation of dynorphine in spine | Opioid rotation |
| | Increased substance P and calcitonin G related peptide in spinal cord | NMDA receptor antagonist (ketamine)? |
| **Cutaneous** | | |
| Pruritus | Histamine release from most cells | Antihistamine |
| | Disinhibition of itch specific neurons | Ondansetron |
| | Central serotonin release | Propofol |

Nausea generally will resolve over several days, at which point antiemetics can be tapered in most individuals. Constipation and dry mouth occur independent of dose. Laxatives and stool softeners should be started with the first dose of ATC opioid therapy.[27,96,112] Dose-limiting side effects are usually neuropsychiatric (myoclonus, confusion, delirium, hallucination). In fact, opioid toxicity can mimic clinical symptoms of dying, which resolve with opioid rotation.[113] If pain is incompletely or poorly controlled, effective means of managing toxicity and maintaining analgesia include (1) route conversion (oral to parenteral or spinal), (2) opioid rotation to an alternative potent mu agonist, or (3) opioid dose reduction by 30% plus the addition of an adjuvant analgesic.[25,81,87,107,114-116] Nonpharmacologic approaches such as palliative radiation, surgery, kyphoplasty, or neurolytic blocks may also be opioid-sparing and allow for opioid dose
reduction. If pain has resolved, opioid doses should be reduced by 30%. For patients who have a short time to live or are extremely ill, and for whom spinal opioids or opioid rotation are not feasible, symptomatic management of side effects may be the only reasonable recourse (Table 6). Neuroleptics have been used to treat delirium in the terminally ill.[117] However, there is a paucity of evidence that opioid-induced delirium responds to neuroleptics.[96] In fact, opioid-induced delirium can occur while the patient is on atypical antipsychotics.[118] Medical management of opioid-induced myoclonus has been reported anecdotally. Successful management has been reported with baclofen, benzodiazepines (clonazepam, diazepam, midazolam), dantrolene, and valproic acid.[27,96,110,119-124] Sedation may respond to psychostimulants or donepezil (Aricept). Psychostimulants should not be used in those experiencing sedation and delirium.[96,125] Some patients limit their use of opioids due to intractable constipation. This can lead to nausea and vomiting, which may be attributed directly to the opioid as a central side effect rather than to unrelied constipation.[112] Oral naloxone has poor systemic bioavailability due to high first-pass hepatic clearance and can reverse the opioid bowel syndrome without loss of analgesia. Oral naloxone may also cause cramps and diarrhea.[112] Generally, doses > 10% of the daily morphine dose are needed.[126] Too high a dose leads to reduced analgesia or opioid withdrawal. Two investigational opioid peripheral-acting antagonists (methylnaltrexone and alvimopan) do not cross the blood-brain barrier and are reported to reverse the opioid bowel syndrome. Hopefully both will be available in the near future.[103,127] Pain Management in the Actively Dying Opioid therapy should be continued in the actively dying, most of whom will become delirious unrelated to opioids and may be unable to verbally report pain or its severity. Restlessness may be a manifestation of uncontrolled pain, terminal delirium, urinary retention, or fecal impaction. Assessment for urinary retention and fecal impaction is the first step to management. Family education about dying is important, as family members may mistake terminal delirium for opioid toxicity and demand that opioids be reduced or discontinued. A trial of a neuroleptic or a rescue dose of opioid and observed response (or lack of response) of restlessness will help decipher whether the restlessness is a pain behavior in the dying or delirious. Family members may be invaluable in determining response in this situation, since they are at the bedside for prolonged periods of time. Conclusions Opioids can be either a boon or a bane in the management of cancer pain, depending on the skill of the prescriber. Knowledge of opioid pharmacology and dosing strategies is fundamental to the education of any practicing oncologist. It is likely that in practice, the oncologist will be prescribing opioids at least as often as chemotherapy. Hence, his or her prescribing skills should be as good (if not better) in pain management as they are in chemotherapy. Disclosures: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article. References: 1. Parkin D, Bray F, Ferlay J, et al: Estimating the world cancer burden: Globocan 2000. Int J Cancer 94:153-156, 2001. 2. Rustoen T, Fossa SD, Skarstein J, et al: The impact of demographic and disease specific variables on pain in cancer patients. J Pain Symptom Manage 26:696-704, 2003. 3. Shvartzman P, Friger M, Shani A, et al: Pain control in ambulatory cancer patients—can we do better? J Pain Symptom Manage 26:716-722, 2003. 4. Forbes K: Opioids: Beliefs and myths. J Pain Palliat Care Pharmacother 20:33-35, 2006. 5. Kochhar R, Legrand SB, Walsh D, et al: Opioids in cancer pain: Common dosing errors. Oncology (Williston Park) 17:571-579 (incl discussion), 2003. 6. Burton AW, Cleeland CS: Cancer pain: Progress since the WHO guidelines. Pain Pract 1:236-242,


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