The Pharmacologic Management of Cancer Pain

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The management of cancer pain requires familiarity with a range of therapeutic strategies, including antineoplastic therapies, analgesic pharmacotherapy, and anesthetic, neurosurgical, psychological, and rehabilitation techniques. Successful pain management is characterized by implementation of the techniques with the most favorable therapeutic index for the prevailing circumstances, along with provision for repeated evaluations, so that a favorable balance between pain relief and adverse effects is maintained. For most patients, pain management involves the administration of specific analgesic approaches. In all cases, these analgesic treatments must be skillfully integrated with the management of other symptoms.

There is a wide consensus that analgesic pharmacotherapy is the mainstay of cancer pain management. A commonly recommended approach is the "three-step analgesic ladder" of the World Health Organization, which advocates three basic steps of therapy according to the severity of the presenting pain problem (Figure 1).[1] This approach emphasizes the principle of using analgesics appropriate to the severity of the prevailing pain problem; it emphasizes the centrality of opioid pharmacotherapy. Combined with appropriate dosing guidelines, this approach provides adequate relief to 70% to 90% of patients.[2-7] Systemic Analgesic Pharmacotherapy Nonopioid Analgesics

The nonopioid analgesics (aspirin, acetaminophen, and the nonsteroidal anti-inflammatory drugs [NSAIDs]) are useful alone for mild to moderate pain (step 1 of the WHO analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe pain.[8] They are useful in a broad range of pain syndromes of diverse mechanisms, but there are no data to support therapeutic superiority to alternative options in any particular setting other than inflammation.[8] Unlike opioid analgesics, the nonopioid analgesics have a "ceiling" effect for analgesia and produce neither tolerance nor physical dependence. The nonopioid analgesics constitute a heterogeneous group of compounds that differ in chemical structure but are all competitive blockers of cyclooxygenase. The relatively selective cyclooxygenase-2 drugs are equianalgesic with the non-selective inhibitors, and they are associated with less mucosal morbidity.[9-11] Despite the advances presented by the development of cyclooxygenase-2 selective agents, the coadministration of a conventional NSAID with a gastroduodenal protective agent (such as omeprazole (Prilosec), pantoprazole (Protonix), misoprostol (Cytotec), or high-dose famotidine remains a valid therapeutic option.[12] With the administration of all of these agents, particular caution is required for patients at increased risk for adverse effects, including the elderly and those with predilection to peptic ulceration, impaired renal function, and concurrent corticosteroid therapy. Acetaminophen rarely produces gastrointestinal toxicity and there are no adverse effects on platelet function; hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses.[13]
A trial of systemic opioid therapy should be administered to all cancer patients with pain of moderate or greater severity regardless of the pain mechanism. Although both somatic and visceral pain appear to be relatively more responsive to opioid analgesics than neuropathic pain, a neuropathic
mechanism does not confer opioid resistance; appropriate dose escalation will identify many patients with neuropathic pain who can achieve adequate relief.[14,15] Optimal use of opioid analgesics requires a sound understanding of the general principles of opioid pharmacology, the pharmacologic characteristics of each of the commonly used drugs, and principles of administration, including drug selection, routes of administration, dosing and dose titration, and the prevention and management of adverse effects. **Important Principles in Opioid Drug Therapy**

- **Classification**- Opioid compounds can be divided into agonist, agonist-antagonist, and antagonist classes based on their interactions with the various receptor subtypes (Table 1). In the management of cancer pain, the pure agonists are most commonly used. Recently, with the advent of a transdermal route of administration, there has been increased interest in the use of the partial agonist opioid buprenorphine in the management of moderate pain.

- **Dose-Response Relationship**- The pure agonist drugs do not have a ceiling dose. As the dose is raised, analgesic effects increase in a semilog-linear function until either analgesia is achieved or the patient develops dose-limiting adverse effects such as nausea, vomiting, confusion, sedation, myoclonus, or respiratory depression.

- **The Equianalgesic Dose Ratio**- Relative analgesic potency of opioid is commonly expressed in terms of the equianalgesic dose ratio. This is the ratio of the dose of two analgesics required to produce the same analgesic effect. By convention, the relative potency of each of the commonly used opioids is based upon a comparison to 10 mg of parenteral morphine.[16] Equianalgesic dose information and dose conversion tables (Table 2) provide guidelines for dose selection when the drug or route of administration is changed.

Several principles are critical in interpreting the data presented in such tables. The commonly quoted values do not reflect the substantial variability that is observed in both single-dose and multidose crossover studies. Numerous variables may influence the appropriate dose for the individual patient, including pain severity, prior opioid exposure (and the degree of cross-tolerance this confers), age, route of administration, level of consciousness, and genetically determined metabolic or receptor heterogeneity. For most opioids the equianalgesic dose relationship to morphine is linear. For methadone, however, the relationship appears to be curvilinear, with the equianalgesic dose ratio falling as the dose of prior morphine increases: at low doses of morphine (30 to 300 mg oral morphine) the equianalgesic ratio for oral methadone to oral morphine is 1:4 to 1:6 and at high doses (> 300 mg oral morphine) it is 1:10 to 1:12.[17]
The factors that influence opioid selection in chronic pain states include pain intensity, pharmacokinetic and formulatory considerations, previous adverse effects, and the presence of coexisting disease. Traditionally, patients with moderate pain have been conventionally treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene. The doses of these combination products can be increased until the maximum dose of the nonopioid coanalgesic is attained (eg, 4,000 mg acetaminophen). Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled-release formulations of codeine, dihydrocodeine, oxycodone, morphine, and tramadol in dosages appropriate for moderate pain, and most recently, patches of buprenorphine. Patients who present with strong pain are usually treated with morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, or methadone. Of these, the short half-life opioid agonists (morphine, hydromorphone, fentanyl, oxycodone, or oxymorphone) are generally favored because they are easier to titrate than the long half-life drugs that require a longer period to approach steady-state plasma concentrations. If the patient is currently using an opioid that is well tolerated, it is usually continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. A switch to an alternative opioid is considered if the patient develops dose-limiting toxicity that precludes adequate relief of pain without excessive side effects, or if a specific formulation, not available with the current drug, is either needed or may substantially improve the convenience of opioid administration. Some patients will require sequential trials of several different opioids before a drug which is effective and well tolerated is identified.[18,19] This strategy has been variably labeled opioid rotation, or opioid switching. The existence of incomplete cross-tolerance to various opioid effects (analgesia and side effects) may explain the utility of these sequential trials. It is strongly recommended that clinicians be familiar with at least three opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data when switching between drugs. **Selecting the Appropriate Route of Systemic Opioid Administration**

Opioids should be administered by the least invasive and safest route capable of providing adequate...
analgesia. The oral route is usually preferred. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia, and those who are unable to manage either the logistics or side effects associated with the oral route. Transdermal fentanyl (Duragesic) often provides a convenient and noninvasive alternative to oral administration. Transdermal patches capable of delivering 25, 50, 75, and 100 ?g/h are available. The dosing interval for each patch is usually 72 hours,[20] but some patients require a 48-hour schedule.[21] Data from controlled studies suggest that the transdermal administration of fentanyl is associated with a lesser incidence of constipation than oral morphine.[22-24] Other noninvasive routes are less commonly used. Rectal suppositories containing oxycodone, hydromorphone, oxymorphone, and morphine have been formulated, and controlled-release morphine tablets can also be administered per rectum.[25,26] The potency of opioids administered rectally is approximately equivalent to that achieved by the oral route.[27] The sublingual route has limited value due to the lack of formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl (Actiq), which incorporates the drug into a candy base, has been approved for use in the management of breakthrough pain.[28,29]

- **Invasive Routes**- A parenteral route may be considered when the oral route is precluded or there is a need for rapid onset of analgesia or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes, provides the most rapid onset and shortest duration of action. Parenteral boluses are most commonly used to treat very severe pain, in which case doses can be repeated at an interval as brief as that determined by the time to peak effect until adequate relief is achieved.[30] Repeated bolus doses without frequent skin punctures can be accomplished through the use of an indwelling IV or SC infusion device such as a 25- to 27-gauge infusion device (a "butterfly") that can be left under the skin for up to a week.[31] Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Longterm infusions may be administered IV or SC. In practice, the major indication for continuous infusion occurs in patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical. Ambulatory patients can easily use continuous SC infusion. A range of pumps are available, varying in complexity, cost, and ability, to provide patient-controlled "rescue doses" as an adjunct to a continuous basal infusion.[31] There are data indicating that when available, Teflon- or Vialon-coated nonmetal cannulae are preferred to butterfly needles.[32] Opioids suitable for continuous SC infusion must be soluble, well absorbed, and nonirritating. Extensive experience has been reported with heroin, hydromorphone, oxymorphone, morphine, and fentanyl. Methadone appears to be relatively irritating and is generally not recommended. To maintain the comfort of an infusion site, the SC infusion rate should not exceed 3 to 5 mL/h. Patients who require high doses may benefit from the use of concentrated solutions such as hydromorphone at 10 mg/mL or morphine tartrate, which is available in some countries as an 80 mg/mL solution.

- **Changing Routes of Administration**- The switch between oral and parenteral routes should be guided by knowledge of relative potency (Table 2) to avoid subsequent overdosing or underdosing. In calculating the equianalgesic dose, the potencies of the IV, SC, and IM routes are considered equivalent. In recognition of the imprecision in the accepted opioid dose conversion tables and the risk of toxicity from potential overdose, a modest reduction in the calculated dose is prudent.

**Scheduling of Opioid Administration**
The schedule of opioid administration should be individualized to optimize the balance between patient comfort and convenience. "Around-the-clock" dosing and "as-needed" (PRN) dosing both have a place in clinical practice.

- **Around-the-Clock Dosing With Rescue Doses**- Around-the-clock dosing provides the chronic pain patient with continuous relief by preventing the pain from recurring. This is usually achieved with controlled-release preparations of opioids. Patients should also be provided a so-called "rescue dose," which is a supplemental dose offered on an as-needed basis to treat pain that breaks through the regular schedule.[27] The frequency with which the rescue dose can be offered depends on the route of administration and the time to peak effect.
effect for the particular drug. Oral rescue doses are usually offered up to every 1 to 2 hours and parenteral doses can be offered as frequently as every 15 to 30 minutes. Clinical experience suggests that the initial size of the rescue dose should be equivalent to approximately 50% to 100% of the dose administered every 4 hours for oral or parenteral bolus medications, or 50% to 100% of the hourly infusion rate for patients receiving continuous infusions. Alternatively, this may be calculated as 5% to 15% of the 24-hour baseline dose. The magnitude of the rescue dose should be individualized and some patients with low baseline pain but severe exacerbations may require rescue doses that are substantially higher.[33] The drug used for the rescue dose is usually identical to that administered on a scheduled basis. This approach provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who require more than four to six rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment. Alternatively, each dose increment can be set at 33% to 50% of the preexisting dose. In all cases, escalation of the baseline dose should be accompanied by a proportionate increase in the rescue dose, so that the size of the supplemental dose remains a constant percentage of the fixed dose.

- **As-Needed Dosing**- Opioid administration on an as-needed basis, without an around-the-clock dosing regimen, may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or therapy with a long half-life opioid such as methadone or levorphanol is begun. As-needed dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pain separated by pain-free intervals.

- **Patient-Controlled Analgesia**- Patient-controlled analgesia (PCA) generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug "on demand" according to parameters set by the physician. Long-term PCA in cancer patients is most commonly accomplished via the subcutaneous route using an ambulatory infusion device.[34] In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose.[34] Rare patients have benefited from PCA alone to manage episodic pains characterized by an onset so rapid that an oral Dose Calculation protocol efficiently prompt relief.

- **Selecting a Starting Dose**- A patient who is relatively nontolerant, having had only some exposure to an opioid typically used on the second rung of the analgesic ladder for moderate pain, should generally begin one of the opioids typically used for severe pain at a dose equivalent to 5 to 10 mg morphine IM every 4 hours.[27] If morphine is used, anoral-to-IM relative potency ratio of 2:1 to 3:1 is conventional.[27]

- **Dose Adjustment**- Inadequate relief should be addressed through gradual dose escalation until adequate analgesia is reported or excessive side effects supervene. Because opioid response increases linearly with the log of the dose, a dose increment of less than 30% to 50% is not likely to significantly improve analgesia. The absolute dose is immaterial as long as administration is not compromised by excessive side effects, inconvenience, discomfort, or cost.

- **Rate of Dose Titration**- The rate of dose titration depends on the severity of the pain, the medical condition of the patient, and the goals of care. Patients who present with very severe pain are sometimes best managed by repeated parenteral administration of a dose every 15 to 30 minutes until pain is partially relieved. Patients with moderate pain may not require a loading dose of the opioid, but rather the initiation of a regular dose with provisions for rescue doses and gradual dose titration. In this situation dose increments of 30% to 50% can be administered at intervals greater than that required to reach steady state following each change. The dose of morphine (tablets or elixir), hydromorphone, or oxycodone can be increased on a twice-daily basis, and the dose of controlled-release oral morphine or transdermal fentanyl can be increased every 24 to 48 hours.

**Management of Opioid Adverse Effects**
Successful opioid therapy requires that the benefits of analgesia clearly outweigh treatment-related adverse effects.[35] This implies that a detailed understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in cancer pain management. Among adverse effects there is substantial variability in dose response. A
The dose-response relationship is most commonly evident with regard to the central nervous system adverse effects of sedation, cognitive impairment, hallucinations, myoclonus, and respiratory depression. Even among these, however, there is very substantial interindividual variability to many of these effects. Additionally, as tolerance develops to some effects, the spectrum of adverse effects varies with prolonged use. Commonly, patients who have had prolonged opioid exposure have a lesser tendency to develop sedation or respiratory depression, and the predominant central nervous system effects become the neuroexcitatory ones of delirium and myoclonus. Gastrointestinal adverse effects generally have a weaker dose-response relationship. Some, like nausea and vomiting, are common with the initiation of therapy but are subsequently unpredictable, with resolution among some patients and persistence among others. Constipation is virtually universal and it demonstrates a very weak dose relationship. Adverse changes in patient wellbeing among patients taking opioids are not always caused by the opioid. The appearance of a new adverse change in patient well-being that occurs in the setting of stable opioid dosing is rarely caused by the opioid. An alternate explanation should be vigorously sought, as adverse effects may result from other causes of comorbidity that may develop in the treated patient, or from drug interactions. Common causes of comorbidity that may mimic opioid-induced adverse effects are presented in Table 3. Since polypharmacy is common in patients with advanced cancer, it is essential to scrutinize medication records and the patient's report of self-medication to evaluate for possible drug interactions or some other drug-related explanation for the reported symptoms.

Overview of the Alternative Approaches to Treating Opioid Adverse Effects

In general, four different approaches to the management of opioid adverse effects have been described:

- **Dose Reduction of Systemic Opioid** - Reducing the dose of administered opioid usually results in a reduction in dose-related adverse effects. When patients have well-controlled pain, gradual reduction in the opioid dose will often result in the resolution of dose-related adverse effects with preservation of adequate pain relief. When opioid doses cannot be reduced without the loss of pain control, reduction in dose must be accompanied by the addition of an accompanying synergist approach. Extensive experience has been reported with four accompanying approaches:
  1. The addition of a nonopioid coanalgesic: The analgesia achieved from nonopioid coanalgesics from the nonsteroidal anti-inflammatory class of agents is additive and often synergistic with that achieved by opioids.
  2. The addition of an adjuvant analgesic that is appropriate to the pain syndrome and mechanism: Adjuvant analgesics (see below) may be combined with primary analgesics to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. There is great interindividual variability in the response to all adjuvant analgesics, and for most, the likelihood of benefit is limited. Furthermore, many of the adjuvant analgesics have the potential to cause side effects that may be additive to the opioid-induced adverse effects that are already problematic. In evaluating the utility of an adjuvant agent in a particular patient setting, one must consider the likelihood of benefit, the risk of adverse effects, the ease of administration, and patient convenience.
  3. The application of a therapy targeting the cause of the pain: Specific antitumor therapies—such as radiotherapy, chemotherapy, or surgery—targeting the cause of cancer-related pain can provide substantial relief and thus lower the need for opioid analgesia. Radiotherapy is of established benefit in the treatment of painful bone metastases, epidural neoplasm, and headache due to cerebral metastases. In other settings there is a lack of well-established supportive data, and the use of radiotherapy is largely anecdotal. Despite a paucity of evidence concerning the specific analgesic benefits of chemotherapy, there is a strong clinical impression that tumor shrinkage is generally associated with relief of pain. Although there are some reports of analgesic value even in the absence of significant tumor shrinkage, the likelihood of a favorable effect on pain is generally related to the likelihood of tumor response. Surgery may play a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures, and compression of neural tissues.
  4. The application of a regional anesthetic or neuroablative intervention: The results of the WHO analgesic ladder validation studies suggest that 10% to 30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone without unacceptable drug toxicity. Anesthetic and neurosurgical approaches...
techniques may reduce or eliminate the requirement for systemically administered opioids to achieve adequate analgesia. In general, regional analgesic techniques such as intraspinal opioid and local anesthetic administration, or intrapleural local anesthetic administration, are usually considered first because they can achieve this end without compromising neurologic integrity. Neurodestructive procedures, however, are valuable in a small subset of patients; some of these procedures, such as celiac plexus blockade in patients with pancreatic cancer, may have a favorable enough risk-benefit ratio that early treatment is warranted.

- **Symptomatic Management of the Adverse Effect**-Symptomatic drugs used to prevent or control opioid adverse effects are commonly employed. Most of these approaches are based on cumulative anecdotal experience. With few exceptions, the literature describing these approaches is anecdotal or “expert opinion.” Very few studies have prospectively evaluated efficacy and no studies have evaluated the toxicity of these approaches over the long term. In general, this approach involves the addition of a new medication, adding to medication burden and incurring the associated risks of adverse effects or drug interaction.

- **Opioid Rotation**-Over the past 10 years numerous clinicians and cancer pain services have reported successful reduction in opioid side effects by switching to an alternative opioid.\[18,19,45-57\] Improvements in cognitive impairment, sedation, hallucinations, nausea, vomiting, and myoclonus have been commonly reported. This approach requires familiarity with a range of opioid agonists and with the use of equianalgesic tables to convert doses when switching between opioids. While this approach has the practical advantage of minimizing polypharmacy, outcomes are variable and unpredictable. When switching between opioids, even with prudent use of equianalgesic tables, patients are at risk for under- or overdosing by virtue of individual sensitivities. The biologic basis for the observed intraindividual variability in sensitivity to opioid analgesia and adverse effects is multifactorial. Preclinical studies show that opioids can act on different receptors or subtype receptors,\[19,58-60\] and individual receptor profiles may influence the analgesia as well as the side effects. The genetic makeup of the individual plays an important role in analgesia for some opioids\[61-67\] and similar phenomena may contribute to variability in adverse effect sensitivity.
• **Switching Route of Systemic Administration**- Limited data indicate that some adverse side effects among patients receiving oral morphine can be relieved by switching the route of admission to the subcutaneous route. In one small study, this phenomenon was reported for nausea and vomiting[ 68]; in another study there was less constipation, drowsiness, and nausea.[69]

**Gastrointestinal Side Effects**
The gastrointestinal adverse effects of opioids are common. In general they are characterized by a weak doseresponse relationship.

| Table 4 |
|------------------|------------------|
| Management of Opioid-Induced Delirium |
| (1) Discontinue nonessential centrally acting medications |
| (2) If analgesia is satisfactory, reduce opioid dose by 25% |
| (3) Exclude sepsis or metabolic derangement |
| (4) Exclude central nervous system involvement by tumor |
| (5) If delirium persists, consider: |
| • trial of neuroleptic (eg, haloperidol) |
| • change to an alternative opioid drug |
| • a change in opioid route to the intraspinal route (± local anesthetic) |
| • a trial of other anesthetic or neuromuscular blocking agent |

• **Multifocal Myoclonus**-All opioid analgesics can produce myoclonus. Mild and infrequent myoclonus is common. In occasional patients, however, myoclonus can be distressing or contribute to breakthrough pain that occurs with the involuntary movement. If the dose cannot be reduced due to persistent pain, consideration should be given to switching to an alternative opioid or to symptomatic treatment with a benzodiazepine (particularly clonazepam or midazolam), dantrolene (Dantrium), or an anticonvulsant[ 74].

• **Urinary Retention**-Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an increase in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly but catheterization may be necessary to manage transient problems. Successful opioid therapy requires that the benefits of analgesia and other desired effects clearly outweigh treatment-related adverse effects. Thus a detailed understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in cancer pain management.

**Adjuvant Analgesics** The term "adjuvant analgesic" describes a drug that has a primary indication other than pain but is analgesic in some conditions. In the cancer population, these drugs may be combined with primary analgesics in any of the three steps of the analgesic ladder to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. In the management of cancer pain, adjuvant analgesics can be broadly classified based on conventional use. Four groups are distinguished: (1) multipurpose adjuvant analgesics, (2) adjuvant analgesics used for neuropathic pain, (3) adjuvant analgesics used for bone pain, and (4) adjuvant analgesics used for visceral pain. **Multipurpose Adjuvant Medications**

• **Corticosteroids**-Corticosteroids are among the most widely used adjuvant analgesics.[75,76] They have been demonstrated to have analgesic effects, to significantly improve quality of life, and to have beneficial effects on appetite, nausea, mood, and malaise in the cancer population. Painful conditions that commonly respond to corticosteroids include...
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raised intracranial pressure headache, acute spinal cord compression, superior vena cava syndrome, metastatic bone pain, neuropathic pain due to infiltration or compression by tumor, symptomatic lymphedema, and hepatic capsular distention. The mechanism of analgesia produced by these drugs may involve antiedema effects and anti-inflammatory effects, and may have a direct influence on the electrical activity in damaged nerves.[77] The most commonly used drug is dexamethasone, a choice that gains theoretical support from the relatively low mineralocorticoid effect of this agent. Dexamethasone also has been conventionally used for raised intracranial pressure and spinal cord compression. Patients with advanced cancer who experience pain and other symptoms may respond favorably to a relatively small dose of corticosteroid (eg, dexamethasone at 1 to 2 mg twice daily). In some settings, however, a highdose regimen may be appropriate. For example, patients with spinal cord compression or an acute episode of very severe bone pain or neuropathic pain that cannot be promptly reduced with opioids may respond dramatically to a short course of relatively high doses (eg, dexamethasone at 100 mg, followed initially by 96 mg/d in divided doses[76,78]). This dose can be tapered over weeks concurrent with initiation of other analgesic approaches, such as radiotherapy. Although the effects produced by corticosteroids in patients with advanced cancer are often very gratifying, side effects are potentially serious and increase with prolonged usage.[ 79] The most common adverse effects include oropharyngeal candidiasis, edema or cushingoid habitus, dyspepsia, weight gain, neuropsychological changes, ecchymoses, hyperglycemia, and myopathy. The risk of peptic ulcer is approximately doubled in patients chronically treated with corticosteroids, and coadministration of corticosteroids with aspirin or an NSAID further increases the risk of gastroduodenopathy and is not recommended.[ 80] Active peptic ulcer disease, systemic infection, and unstable diabetes are relative contraindications to the use of corticosteroids as adjuvant analgesics.

**Topical Local Anesthetics**—Topical local anesthetics can be used in the management of painful cutaneous and mucosal lesions, and as a premedication prior to skin puncture. Eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA) is effective in reducing pain associated with venipuncture, lumbar puncture, and arterial puncture. It has also been used for painful ulcerating skin lesions. Viscous lidocaine is frequently used in the management of oropharyngeal ulceration. Although the risk of aspiration appears to be very small, caution with eating is required after oropharyngeal anesthesia.

**Adjuvants Used for Neuropathic Pain**
Neuropathic pain is generally less responsive to opioid therapy than nociceptive pain, and in many cases the outcome of pharmacotherapy may be improved by the addition of an adjuvant analgesic. Antidepressant drugs are commonly used to manage continuous neuropathic pain. The evidence for analgesic efficacy is greatest for the tertiary amine tricyclic drugs, such as amitriptyline, doxepin, and imipramine.[ 81] The secondary amine tricyclic antidepressants (such as desipramine, clomipramine, and nortriptyline) have fewer side effects and are preferred when concern about sedation, anticholinergic effects, or cardiovascular toxicity is high. There is less evidence for the analgesic effectiveness of selective serotonin uptake inhibitor antidepressants, but given their reduced tendency to adverse effects they may be considered in the management of neuropathic pain.[82] Selected anticonvulsant drugs may be effective for diverse types of neuropathic pain. Although the evidence is best for carbamazepine, the potential for adverse hematologic effects associated with this drug has limited its use in medically ill patients. Due to its proven analgesic effect in several neuropathic pains, its good tolerability, and a paucity of drug-drug interactions, gabapentin (Neurontin) has been recommended as a first-line agent for the treatment of neuropathic pain of diverse etiologies.[83] A number of the newer anticonvulsants such as lamotrigine (Lamictal), topiramate (Topamax), felbamate (Felbatol), and oxcarbazepine (Trileptal) are also promising. Occasionally, systemically administered local anesthetic drugs may be useful in the management of neuropathic pains characterized by either continuous or lancinating dysesthesias. It is reasonable to undertake a trial with an oral local anesthetic in patients with continuous dysesthesias who fail to respond adequately, or who cannot tolerate, the tricyclic antidepressants, and in patients with lancinating pains refractory to trials of anticonvulsant drugs and baclofen. Long-term systemic local anesthetic therapy is now usually accomplished using an oral formulation such as flecainide, tocainide (Tonocard), or mexiletine (Mexitil). Analgesic response to a trial of intravenous lidocaine (5 mg/kg over 45 minutes) may predict for likelihood of response to oral mexiletine.[84] Less compelling data support the use of clonidine, baclofen, calcitonin, and subcutaneously administered...
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The management of bone pain frequently requires the integration of opioid therapy with multiple ancillary approaches. Although a metaanalysis of NSAID therapy in cancer pain that reviewed data from 3,084 patients in 42 trials found no specific efficacy in bone pain and analgesic effects equivalent only to "weak" opioids,[ 8] some patients appear to benefit greatly from the addition of such a drug. Corticosteroids are often advocated in difficult cases.[75] Bisphosphonates are analogs of inorganic pyrophosphate that inhibit osteoclast activity and reduce bone resorption in a variety of illnesses. Controlled trials of intravenous pamidronate and clodronate in patients with advanced cancer have demonstrated reduction of bone pain.[86] The analgesic effect of pamidronate appears to be dose and schedule dependent, a dose response is evident at doses between 15 and 30 mg/wk, and it has been noted that 30 mg every 2 weeks is less effective than 60 mg every 4 weeks.[87] Similar effects have been observed with orally administered intravenous zoledronate (Zometa)[88] and oral ibandronate (Boniva).[89,90] Radiolabeled agents that are absorbed into areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. It has the advantages of addressing all sites of involvement and relatively selective absorption, thus limiting radiation exposure to normal tissues. Excellent clinical responses with acceptable hematologic toxicity have been observed with a range of radiopharmaceuticals. The best studied and most commonly used radionuclide is strontium-89. Large, prospectively randomized clinical trials have demonstrated its efficacy as a first-line therapy.[91,92] Its role as an adjuvant to external-beam radiotherapy is controversial and the data are conflicting.[ 93,94] This approach is contraindicated with patients who have a platelet count < 60,000 or a white cell count < 2.4, and is not advised for patients with very poor performance status.[95] Using another approach, bone-seeking radiopharmaceuticals that link a radioisotope with a bisphosphonate compound have been synthesized. Positive experience has been reported with samarium-153-ethylendiaminetetramethylene phosphonic acid,[96] samarium-153-lexidronam,[97] and rhenium-186-hydroxyethylidene diphosphonate.[98] Adjuvant Analgesics for Visceral Pain There are limited data that support the potential efficacy of a range of adjuvant agents for the management of bladder spasm, tenesmoid pain, and colicky intestinal pain. Oxybutynin chloride, a tertiary amine with anticholinergic and papaverine-like direct muscular antispasmodic effects, is often helpful for bladder spasm pain,[99] as is flavoxate (Urispas).[100] Based on limited clinical experience and in vitro evidence that prostaglandins play a role in bladder smooth muscle contraction, a trial of NSAIDs may be justified for patients with painful bladder spasms.[102] Limited data support a trial of intravesical capsaicin.[103,104] There is no well-established pharmacotherapy for painful rectal spasms. A recent double-blind study demonstrated that nebulized salbutamol can reduce the duration and severity of attacks.[105] There is anecdotal support for trials of diltiazem,[106,107] clonidine,[108] chlorpromazine,[109] and benzodiazepines.[110] Colicky pain due to inoperable bowel obstruction has been treated empirically with intravenous scopolamine (hyoscine) butylbromide[111- 113] and sublingual scopolamine (hyoscine) hydrobromide.[114] There are also data supporting the use of octreotide (Sandostatin) for this indication.[115,116] Other Noninvasive Analgesic Techniques Psychological Therapies in Cancer Pain Psychological approaches are an integral part of the care of the cancer patient with pain. All patients can benefit from psychological assessment and support, and some are good candidates for specific psychological interventions including those commonly used in the management of pain. Cognitive-behavioral interventions can help some patients decrease the perception of distress engendered by pain through the development of new coping skills and the modification of thoughts, feelings, and behaviors.[117,118] Relaxation methods may be able to reduce muscular tension and emotional arousal, or enhance pain tolerance.[119] Successful implementation of these approaches in the cancer population requires a cognitively intact patient and a dedicated, well-trained physician. Physiatric Techniques Physiatric techniques can be used to optimize the function of the patient with chronic cancer or enhance analgesia through application of modalities such as electrical stimulation, heat, or cryotherapy. The treatment of lymphedema by the use of wraps, pressure stockings, or pneumatic pump devices can both improve function and relieve pain and heaviness.[120,121] The use of orthotic devices can immobilize and support painful or weakened structures, and assistive devices can be of great value to patients with pain precipitated by weight-bearing or ambulation. Transcutaneous Electrical Nerve Stimulation The mechanisms by which transcutaneous electrical nerve stimulation (TENS) reduces pain are not well defined; local neural blockade and activation of central inhibitory systems have been proposed.
as explanations. Accumulated anecdotal evidence suggests that TENS may have a role in relieving pain in general and cancer pain in particular. There is, however, little research to support this belief.[122,123] Given the potential for patient benefit and its low intrinsic morbidity, it can be adopted for cancer patients who are in pain as a supplement to pharmacologic treatment. **Invasive Analgesic Techniques**

As described previously, 10% to 30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone with out unacceptable drug toxicity; for some of these patients anesthetic and neurosurgical techniques may help prove relief. Consideration of invasive approaches requires a word of caution. Interpretation of data regarding the use of alternative analgesic approaches and extrapolation to the presenting clinical problem requires care. The literature is characterized by a lack of uniformity in patient selection, inadequate reporting of previous analgesic therapies, inconsistencies in outcome evaluation, and paucity of long-term follow-up. Furthermore, reported outcomes in the literature may not predict the outcomes of a procedure performed on a medically ill patient by a physician who has more limited experience with the techniques involved. For most pain syndromes there exists a range of techniques that may theoretically be applied. In choosing from a range of procedures the following principles are salient:

- Ablative procedures are deferred as long as pain relief is obtainable by nonablative modalities.
- The procedure most likely to be effective should be selected. If there is a choice, however, the one with the fewest and least serious adverse effects is preferred.
- In progressive stages of cancer, pain is likely to be multifocal. A procedure aimed at a single locus of pain, even if completed flawlessly, is unlikely to yield complete relief of pain until death. A realistic and sound goal is a lasting decrease in pain to a level that is manageable by pharmacotherapy with minimal side effects.
- Whenever possible, somatic neurolysis should be preceded by the demonstration of effective analgesia with a local anesthetic prognostic block.
- Since there is a learning curve with all of the procedures, performance by a physician who is experienced in the specific intervention may improve the likelihood of a successful outcome.

In general, regional analgesic techniques such as intraspinal opioid and local anesthetic administration or intrapleural local anesthetic administration are usually considered first because they can achieve this end without compromising neurological integrity. Neurodestructive procedures, however, are valuable in a small subset of patients; some of these procedures, such as celiac plexus blockade in patients with pancreatic cancer, may have a favorable enough risk-benefit ratio that early treatment is warranted. **Regional Analgesia**

- **Epidural and Intrathecal Opioids** - The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. In the one randomized trial comparing intraspinal opioid therapy to routine systemic therapy, the intraspinal route was found to have advantages in terms of better analgesia and fewer adverse effects.[124] In general, intrathecal administration is preferred to epidural. Opioid selection for intraspinal delivery is influenced by several factors. Hydrophilic drugs, such as morphine and hydromorphone, have a prolonged half-life in cerebrospinal fluid and significant rostral redistribution.[125] Lipophilic opioids, such as fentanyl and sufentanil (Sufenta), have less rostral redistribution and may be preferable for segmental analgesia at the level of spinal infusion. The addition of a low concentration of a local anesthetic, such as 0.125% to 0.25% bupivacaine[126-128] has been demonstrated to increase analgesic effect without increasing toxicity. Other agents have also been coadministered with intraspinal opioids, including clonidine,[129] octreotide,[130] ketamine,[131,132] and calcitonin,[133] but additional studies are required to assess their potential utility.

- **Intraventricular Opioids** - A growing international experience suggests that the administration of low doses of an opioid (particularly morphine) into the cerebral ventricles can provide long-term analgesia in selected patients.[134,135] This technique has been used for patients with upper body or head pain, or severe diffuse pain, and has been generally very well tolerated. Schedules have included both intermittent injection via an Ommaya reservoir[134,135] and continual infusion using an implanted pump.[136]
Regional Local Anesthetic - Several authors have described the use of intrapleural local anesthetics in the management of chronic post-thoracotomy pain [137] and cancer-related pain involving the head, neck, chest, arms, and upper abdominal viscera.[138,139] For patients with localized upper limb pain, intermittent infusion of bupivacaine through an interscalene brachial plexus catheter may be of benefit.[140]

Celiac Plexus Block - Neurolytic celiac plexus blockade may be helpful in the management of pain caused by neoplastic infiltration of the upper abdominal viscera, including the pancreas, upper retroperitoneum, liver, gall bladder, and proximal small bowel.[141,142] Reported analgesic response rates in patients with pancreatic cancer are 50% to 90%, and the reported duration of effect is generally 1 to 12 months.[141-143] Given the generally favorable response to this approach, and supportive data from two small studies,[144,145] some clinicians recommend this intervention at an early stage[143]; other experts differ and recommend celiac plexus block only for patients who do not maintain an adequate balance between analgesia and side effects from an oral opioid.[141] Common transient complications include postural hypotension and diarrhea. Traditionally, celiac plexus block has been performed under fluoroscopic or CT control; more recently, a transgastric approach has been developed using accurate anatomic localization with endoscopic ultrasound.[146,147]

Sympathetic Blocks for Pelvic Visceral Pain - Limited anecdotal experience has been reported with two techniques. Phenol ablation of the superior hypogastric nerve plexus has been reported to relieve chronic cancer pain arising from the descending colon, rectum, and the lower genitourinary structures.[148,149] Similarly, neurolysis of the ganglion impar (ganglion of Walther), a solitary retroperitoneal structure at the sacrococcygeal junction, has been reported to relieve visceral sensations referred to the rectum, perineum, or vagina.[150-152]

Sympathetic Blockade of Somatic Structures - Sympathetically maintained pain syndromes may be relieved by interruption of sympathetic outflow to the affected region of the body. Lumbar sympathetic blockade should be considered for sympathetically maintained pain involving the legs, and stellate ganglion blockade may be useful for sympathetically maintained pain involving the face or arms.[153]

Neuroablative Techniques for Somatic and Neuropathic Pain

Rhizotomy - Segmental or multisegmental destruction of the dorsal sensory roots (rhizotomy), achieved by surgical section, chemical neurolysis, or radiofrequency lesion, can be an effective method of pain control for patients with otherwise refractory localized pain syndromes. These techniques are most commonly used in the management of chest wall pain due to tumor invasion of somatic and neural structures.[154] Other indications include refractory upper limb, lower limb, pelvic, or perineal pain.[155] Satisfactory analgesia is achieved in about 50% of patients[154]; the average duration of relief is 3 to 4 months, but with a wide range of distribution. Specific complications of the procedure depend on the site of neurolysis. For example, the complications of lumbosacral neurolysis include paresis (5% to 20%), sphincter dysfunction (5% to 60%), impairment of touch and proprioception, and dysesthesias. Although neurologic deficits are usually transient, the risk of increased disability through weakness, sphincter incompetence, and loss of positional sense suggests that these techniques should be reserved for patients with limited function and preexistent urinary diversion. Patient counseling regarding the risks involved is essential.

Neurolysis of Primary Afferent Nerves or Their Ganglia - Neurolysis of primary afferent nerves may also provide significant relief for selected patients with localized pain. The utility of these approaches is limited by the potential for concurrent motor or sphincteric dysfunction. Refractory unilateral facial or pharyngeal pain may be amenable to trigeminal neurolysis (gasserian gangliolysis) or glossopharyngeal neurolysis.[156,157] Unilateral pain involving the tongue or floor of mouth may be amenable to blockade of the sphenopalatine ganglion.[158] Intercostal or paravertebral neurolysis are an alternative to rhizotomy for patients with chest wall pain. Unilateral shoulder pain may be amenable to suprascapular neurolysis.[159] Arm pain that is more extensive may be effectively relieved by brachial plexus neurolysis, but this approach will result in extreme motor weakness.[160]

Cordotomy - During cordotomy, the anterolateral spinothalamic tract is ablated to produce contralateral loss of pain and temperature sensibility.[161,162] This approach is generally reserved for patients with severe unilateral pain arising in the torso or lower
The percutaneous technique is generally preferred[161,162]; open cordotomy is usually reserved for patients who are unable to lie in the supine position or are not cooperative enough to undergo a percutaneous procedure. Significant pain relief is achieved in more than 90% of patients during the period immediately following cordotomy[161,162] but 50% patients have recurrent pain after 1 year.[163] Repeat cordotomy can sometimes be effective.

The complications of cordotomy include paresis, ataxia, and bladder and "mirror image" pain.[162] The complications are usually transient, but are protracted and disabling in approximately 5% of cases.[162] Rarely, patients with a long duration of survival (> 12 months) develop a delayed-onset dysesthetic pain.[163] The most serious potential complication is respiratory dysfunction, which may occur in the form of phrenic nerve paralysis or as sleep-induced dysfunction.[164,165] Because of the latter concern, bilateral high cervical cordotomies or a unilateral cervical cordotomy ipsilateral to the site of the only functioning lung are not recommended.

Sedation as Pain Therapy
Through the vigilant application of analgesic care, pain is often relieved adequately without compromising the sentience or function of the patient beyond that caused by the natural disease process itself. Occasionally, however, this cannot be achieved and pain is perceived to be "refractory."[166] In deciding that a pain is refractory, the clinician must perceive that the further application of standard interventions are either (1) incapable of providing adequate relief, (2) associated with excessive and intolerable acute or chronic morbidity, or (3) unlikely to provide relief within a tolerable time frame. In this situation, sedation may be the only therapeutic option capable of providing adequate relief. This approach is described as "sedation in the management of refractory symptoms at the end of life."[166] The justification of sedation in this setting is that it is goal appropriate and proportionate. At the end of life, when the overwhelming goal of care is the preservation of patient comfort, the provision of adequate relief of symptoms must be pursued even in the setting of a narrow therapeutic index for the necessary palliative treatments.[167-169] In this context, sedation is a medically indicated and proportionate therapeutic response to refractory symptoms, which cannot be otherwise relieved. Appeal to patients' rights also underwrites the moral legitimacy of sedation in the management of otherwise intolerable pain at the end of life. Patients have a right, recently affirmed by the Supreme Court, to palliative care in response to unrelieved suffering.[167] Once a clinical consensus exists that pain is refractory, it is appropriate to present this option to the patient or their surrogate. When presented to a patient with refractory symptoms, the offer of sedation can demonstrate the clinician's commitment to the relief of suffering. This can enhance trust in the doctor-patient relationship and influence the patient's appraisal of their capacity to cope. Indeed, patients commonly decline sedation, acknowledging that pain will be incompletely relieved but secure in the knowledge that if the situation becomes intolerable to them, this option remains available. Other patients reaffirm comfort as the predominating consideration and request the initiation of sedation. The published literature describing the use of sedation in the management of refractory pain at the end of life is anecdotal and refers to the use of opioids, neuroleptics, benzodiazepines, barbiturates, and propofol.[166] In the absence of relative efficacy data, guidelines for drug selection are empirical. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect. Conclusion The goal of analgesic therapy in the cancer population is to optimize analgesia with the minimum of side effects and inconvenience. Currently available techniques can provide adequate relief to a vast majority of cancer patients. Most will require ongoing pain treatment, and analgesic requirements often change as the disease progresses. Patients with refractory pain, or unremitting suffering related to other losses or distressing symptoms, should have access to specialists in pain management or palliative medicine who can provide an approach capable of addressing these complex problems.

Disclosures:
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