Review Article

Drug Therapy

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PHARMACOLOGIC TREATMENT OF CANCER PAIN

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PAIN from cancer is a major health care problem.[1-3] Thirty percent of patients with cancer have pain at the time of diagnosis, and 65 to 85 percent have pain when their disease is advanced.[2,4-6] The impact of cancer pain is magnified by the interaction of pain and its treatments with other common cancer symptoms: fatigue, weakness, dyspnea, nausea, constipation, and impaired cognition.[4,6] Cancer pain can be effectively treated in 85 to 95 percent of patients with an integrated program of systemic, pharmacologic, and anticancer therapy.[7,8] Many of the remaining patients can be helped by the appropriate use of invasive procedures.[9-11] In the final days of life, pain not controlled by therapies aimed at both comfort and function can be relieved by intentional sedation.[12-14] No patient with cancer needs to live or die with unrelieved pain.

There are three basic approaches to the control of pain: modifying the source of the pain, altering the central perception of pain, and blocking the transmission of the pain to the central nervous system.[15] The optimal use of these approaches in the control of cancer pain requires a thorough assessment of each patient's pain, cancer, concurrent medical problems, and psychosocial status.[16-18] An individualized plan of care must be established, implemented, reassessed, and modified on a regular basis to maximize both the quality and duration of life. The pain of the vast majority of patients with cancer can be relieved through direct and indirect modification of the source of the pain combined with pharmacologic and nonpharmacologic alteration of the patients' perception of pain.[7,8,17,18] This paper reviews the pharmacologic treatment of cancer pain in a guideline format to facilitate the translation of current knowledge into clinical practice (Table 1). Readers are referred to more extensive review articles,[16,18,19] guidelines,[17,20] and textbooks[9,10,21,22] to integrate pharmacologic therapy with anticancer therapies, physical and psychosocial therapies, and procedural interventions to optimize patients' comfort and their ability to function.

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SELECTION OF THE APPROPRIATE ANALGESIC THERAPY

The selection of the appropriate analgesic therapy is based on the interplay of the intensity of each patient's pain and current analgesic therapy. Pain intensity can be measured reliably with the use of written or verbal numerical rating scales.[23-25] Pain that is rated 5 or higher on a scale of 0 to 10 interferes substantially with the quality of life and is defined as substantial pain.[23] Pain ratings of 1 to 4 correspond to mild pain; of 5 to 6, to moderate pain; and of 7 to 10, to severe pain.[26] The Three-Step Analgesic Ladder of the World Health Organization uses these three categories of pain to guide analgesic-drug therapy (Fig. 1).[27] Patients receiving no analgesic therapy who have mild-to-moderate pain should be treated with nonopioid analgesic drugs (step 1). If a patient has mild-to-moderate pain despite taking a nonopioid analgesic, the dose of the nonopioid analgesic should be maximized and a step 2 opioid analgesic should be added (Table 2). Patients who have moderate-to-severe pain despite therapy with step 2 opioids require an increase in the dose of the opioid or, if that is not feasible, a change to a step 3 opioid. This method can effectively relieve pain in 80 to 90 percent of patients.[7,8] Many experts recommend a step 2 opioid as initial therapy for patients with moderate pain[17,18,22] and may initiate therapy with a step 3 opioid when pain is severe. Patients who have mild-to-moderate pain while taking a step 3 opioid should have the dose of that opioid increased to an effective level.

Nonopioid, step 1 analgesic drugs include acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs). These drugs are of limited value to patients with pain from advanced cancer because of their relatively low maximal efficacy.[17,18,20] The dose of acetaminophen should not exceed 4 to 6 g per day to prevent liver damage.[22,28,29] Patients with cancer are not often given aspirin because of the high incidence of gastropathy and aspirin's ability to inhibit platelet aggregation.[30] The risk of bleeding problems can be minimized by using nonacetylated salicylates, such as choline magnesium trisalicylate, which do not interfere with platelet

TABLE 1. PHARMACOLOGIC TREATMENT OF CANCER PAIN.

Select the appropriate analgesic drug.
Prescribe the appropriate dose of the drug.
Administer the drug by the appropriate route.
Schedule the appropriate dosing interval.
Prevent persistent pain and relieve breakthrough pain.
Titrate the dose of the drug aggressively.
Prevent, anticipate, and manage the side effects of the drug.
Consider sequential trial of analgesic drugs.
Use appropriate adjuvant drugs.

function.[31,32] Patients taking any NSAID should be monitored for gastropathy, renal failure, hepatic dysfunction, and bleeding.[20,33,34] Gastric distress may be ameliorated by the use of a histamine H_2 antagonist or sucralfate.[35] Misoprostol, in a dose of 200 μg taken orally twice daily, is more effective than 150 mg of ranitidine taken orally twice daily in preventing asymptomatic, NSAID-induced gastric ulceration.[36]

Tramadol, a centrally acting analgesic that binds to μ-opioid receptors and inhibits the reuptake of norepinephrine and serotonin, has recently been approved in the United States for the treatment of moderate to moderately severe pain.[37,38] The analgesic efficacy of 50 mg of tramadol is equivalent to that of 60 mg of codeine or 30 mg of codeine plus 650 mg of acetaminophen in patients with procedure-induced pain and cancer pain.[37,38] In contrast, 50 or 100 mg of oral tramadol was no better than placebo in controlling pain after orthopedic surgery and caused more emesis than 60 mg of codeine.[39] The adverse effects of tramadol include nausea, dizziness, constipation, sedation, and headache. Patients with cancer who are most likely to benefit from tramadol are those with mild-to-moderate pain not relieved by acetaminophen who cannot tolerate NSAIDs and who wish to defer opioid therapy.

When switching from one opioid analgesic drug to another, one must know the dose equivalences between one drug and another and between one route of administration and another.[17,19,20] Tolerance to the analgesic effects of opioids is rare and can be managed by appropriate titration.[17,19,22,40] Physical dependence occurs when opioids are administered for long periods, but it can be managed by a gradual dose reduction in patients in whom the cause of the pain has been eliminated or the transmission of the pain message has been blocked. Addiction or psychological dependence is rare in patients with cancer.[17,18,20,22,41]

The step 2 opioids used to treat moderate pain include codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene (Table 2). Step 2 opioids are restricted to the treatment of moderate pain because of dose-limiting side effects or because they are prepared in fixed combinations with nonopioid analgesics. Propoxyphene is not recommended for routine use because of its long half-life and the risk of accumulation of norpropoxyphene, a toxic metabolite.[17,22] The value of codeine is limited by the increasing incidence of side effects at doses above 1.5 mg per kilogram of body weight.[17,19,22] The usefulness of hydrocodone and oxycodone is limited by their being prepared in fixed combinations with acetaminophen. In order not to exceed 6 g of acetaminophen per day, patients receiving these combination products cannot take more than 15 mg of hydrocodone or oxycodone every four hours. Patients with a deficiency of CYP2D6 enzymes or those taking inhibitors of CYP2D6, such as quinidine, cimetidine, or fluoxetine, may not be able to convert codeine into morphine and therefore may get little or no analgesic effect from codeine.[42,43]

Step 3 opioids commonly prescribed for the relief of moderate-to-severe cancer pain include morphine, oxycodone, hydromorphone, and fentanyl (Table 2). These opioids should be used one at a time to capitalize on idiosyncratic differences in patients' responses.[44-46] Morphine is the step 3 opioid most commonly used to control severe pain, because of its wide availability, varied formulations, and well-char-

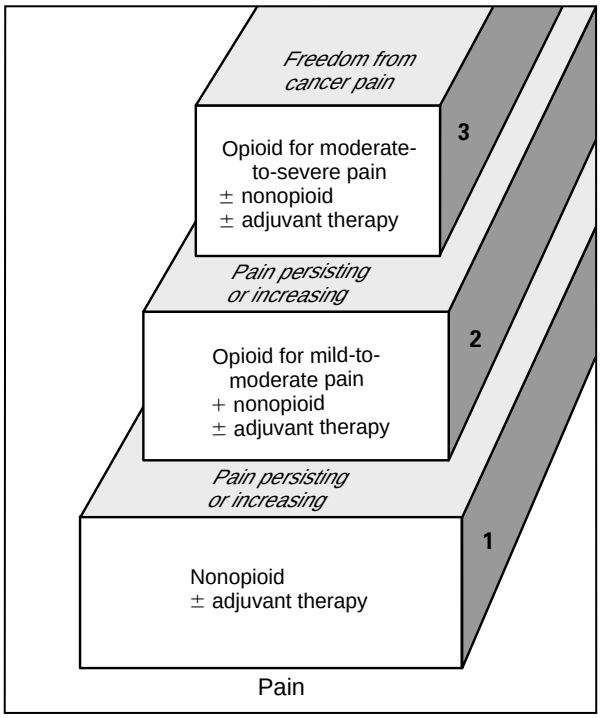

Figure 1. Three-Step Analgesic Ladder of the World Health Organization.

Reproduced from a report of the World Health Organization[27] with the permission of the publisher.

TABLE 2. ORAL AND PARENTERAL DOSE EQUIVALENTS OF OPIOID ANALGESIC DRUGS.

DRUG	DOSE*	
	ORAL	PARENTERAL
Recommended for routine use		
Step 2 opioids		
Codeine†	100 mg every 4 hr	50 mg every 4 hr
Dihydrocodeine	50–75 mg every 4 hr	NA
Hydrocodone	15 mg every 4 hr	NA
Oxycodone‡§	7.5–10 mg every 4 hr	NA
Step 3 opioids		
Morphine§	15 mg every 4 hr	5 mg every 4 hr
Oxycodone‡§	7.5–10 mg every 4 hr	NA
Hydromorphone¶	4 mg every 4 hr	0.75–1.5 mg every 4 hr
Fentanyl‖	NA	50 μg/hr every 72 hr
Not recommended for routine use		
Propoxyphene	180 mg every 4–6 hr	NA
Meperidine	150 mg every 2–3 hr	50 mg every 2 hr
Methadone	10 mg every 6–8 hr	5 mg every 6 hr
Levorphanol	2 mg every 6–8 hr	1 mg every 6–8 hr

*Values are dose equivalents for around-the-clock analgesic therapy for chronic pain. NA denotes not available.

†Doses above 1.5 mg per kilogram of body weight are not recommended because of increased toxicity.

‡Parenteral oxycodone is available in some countries. The equivalent parenteral dose is 50 percent of the oral dose.

§This drug is available in tablets and liquids taken every 4 hours and in controlled-release tablets taken every 12 hours. The 12-hour dose is three times the 4-hour dose.

¶The ratio of oral to parenteral doses has been reported to be as high as 2:1.

‖The microgram-per-hour dose of transdermal fentanyl is equal to one half of the milligram-per-day dose of oral morphine.

acterized pharmacologic properties.[17,18,20,22] Controlled-release formulations of morphine for oral administration at 12-hour intervals have been the mainstay of the control of chronic cancer pain for the past decade because of the ease of their administration and titration.[47-49] Oxycodone is a step 3 opioid when it is used in preparations that do not contain aspirin or acetaminophen and may have fewer side effects than morphine.[50,51] A controlled-release formulation of oxycodone administered at 12-hour intervals is now available and is a useful alternative to controlled-release morphine.[52,53]

Hydromorphone's main advantage is that it is six times as soluble in aqueous solutions as morphine and four times as potent, allowing for smaller injection or infusion volumes in patients who require opioids to be administered parenterally.[17,54] A long-acting formulation of hydromorphone has been developed but is not yet available in the United States.[55] Fentanyl delivered by means of transdermal patches can control chronic cancer pain for 72 hours and is particularly useful in patients with stable pain who cannot take oral medications.[56,57] Methadone and levorphanol may also be considered for the relief of severe cancer pain but are not recommended for initial therapy because of their long half-lives and the risk of drug accumulation.[18-20,22]

Opioids not recommended for use in the control of moderate-to-severe cancer pain include meperidine, buprenorphine, pentazocine, butorphanol, dezocine, and nalbuphine. Meperidine should not be given, because its half-life is short and its metabolite, normeperidine, is toxic.[17,18,20,22] Partial opioid agonists such as buprenorphine are of limited benefit because of their low maximal efficacy. Above a certain dose, they are toxic without additional analgesia.[17,18,20,22] Mixed-opioid agonists–antagonists such as pentazocine, butorphanol, dezocine, and nalbuphine are not recommended because of their low maximal efficacy and their potential to reverse analgesia and even cause a physical-withdrawal syndrome when taken by patients already receiving full agonists such as morphine.[17,18,20,22]

APPROPRIATE ANALGESIC DOSAGE

There is no one optimal or maximal dose of a step 3 opioid analgesic drug.[17-20,22] The appropriate dose is one that relieves a patient's pain throughout its dosing interval without causing unmanageable side effects. The initial dose should be based on the patient's level of pain and the efficacy of prior analgesic therapy. Subsequent therapy should be based on a continuing assessment of the efficacy of therapy, with the dosage titrated upward as needed. Although pain can be controlled in most patients with 240 mg of oral morphine per day or less,[7,8] patients with severe cancer pain may require 1200 to 1800 mg of oral morphine per day,[4,40,58] and a few patients may require 1000 to 4500 mg of parenteral morphine per hour.[4,40]

ROUTE OF ADMINISTRATION OF ANALGESIC DRUGS

Most patients with cancer who have chronic pain should receive oral analgesic therapy, because it is simpler, easier to use, and less expensive than parenteral therapy.[17-20,22,59] If a patient cannot swallow tablets or liquids, morphine concentrates and soluble tablets can be administered sublingually.[18,19,22] The usefulness of prolonged sublingual administration is limited by the low dosage of available formulations and the need to repeat the dose every four hours. Fentanyl citrate can be administered buccally for episodic, breakthrough pain.[60] Morphine and hydromorphone may also be administered rectally,[17,20,61] but the regular use of this route is limited by physical and psychosocial constraints. The bioavailability of morphine is similar when given by any enteral route.[17,20,61] Transdermally administered fentanyl is an excellent alternative for patients with chronic cancer pain who cannot be treated with oral medication.[56]

Subcutaneous or intravenous administration of

morphine or hydromorphone is preferable to transdermal administration of fentanyl in patients who are unable to take oral medications for 24 to 48 hours, patients with frequent episodes of incident pain, and patients with acute, severe pain in whom injections or infusions facilitate escalating the dose. Since the bioavailability of parenterally administered morphine is three times that of oral morphine (Table 2),[17,19,20,22] the dosage must be changed when the route is switched from one to the other. Subcutaneous or intravenous administration of opioid analgesics by means of patient-controlled analgesia pumps expedites individualized pain relief.[62] Intramuscular opioid therapy is not recommended, because it is painful and harder for family care givers to administer.[17,20]

Spinal administration of opioids, alone or in combination with local anesthetics, should be reserved for patients in whom systemic analgesic therapy is unacceptably or unmanageably toxic.[17-19,63,64] The potency of opioids administered epidurally is 5 to 10 times that of opioids administered parenterally. The intrathecal route is 10 times more potent than the epidural route. Individualized dose titration typically results in better pain relief with fewer central side effects.[63-66] Intraventricular administration can be advantageous in patients with pain from head and neck cancers or from tumors invading the brachial plexus.[67]

APPROPRIATE INTERVALS OF ANALGESIC DOSING

Analgesic drugs should be scheduled at intervals that prevent the recurrence of pain and minimize the number of daily doses. The appropriate dosing interval is determined by the opioid used and its route of administration. The analgesic effects of short-acting oral opioids such as morphine, hydromorphone, and oxycodone begin within a half hour after their administration and should last for four hours.[19,22] If pain returns sooner, the dose should be increased until the pain continues to be relieved without toxicity during the four-hour dosing interval. In patients given controlled-release formulations of morphine or oxycodone, relief should begin in 1 hour, peak in 2 to 3 hours, and last for 12 hours.[47,48,52,68] If the analgesia from these drugs does not last for 12 hours, the dose should be increased.

The analgesic effect of transdermal fentanyl begins approximately 12 hours after the application of the patch, peaks in 24 to 48 hours, and lasts for about 72 hours.[56] If the analgesic effect of transdermal fentanyl does not last for 72 hours, the dose should be increased. In patients given morphine or hydromorphone subcutaneously, analgesia begins within 10 to 15 minutes and lasts for 3 to 4 hours.[17,22] In patients given these opioids intravenously, pain relief should begin within 5 minutes and last for 1 to 2 hours.[17,22]

PREVENTION OF PERSISTENT PAIN AND RELIEF OF BREAKTHROUGH PAIN

The goal of treating chronic cancer pain is not simply pain relief but also pain prevention.[17-20,22] For sustained analgesia in most cases, around-the-clock dosing can be instituted or it can be initiated after the patient has been given a few doses on an as-needed basis to allow an effective dose to be determined. Supplemental, rescue doses of analgesic drugs should be available to patients for breakthrough pain due to activity, stress, or progressive disease.[17-19,69] As a guide, the total dose of as-needed rescue medication available in a specific interval should be equal to the regular dose given during that interval. For example, a patient taking 90 mg of controlled-release morphine every 12 hours should be given 30 mg of immediate-release morphine every 4 hours for unrelieved, breakthrough pain.

Pain prevention is also an appropriate goal in the treatment of acute moderate-to-severe pain that is expected to last more than 24 hours.[70] Resolution of the source of the acute pain should be anticipated with regular downward dose titration if the pain is well controlled without the need of additional analgesics. Initial therapy of acute pain that is not expected to last more than 24 hours can consist solely of treatment on an as-needed basis.

TITRATION OF ANALGESIC-DRUG DOSES

The optimal management of cancer pain requires aggressive upward dose titration. The repeated occurrence of breakthrough pain and the frequent need for rescue doses of analgesic indicate the need for an increase in the patient's around-the-clock dose. In contrast, patients who need extra doses for brief, infrequent, or activity-related pain may have fewer side effects if they continue receiving the extra doses and their around-the-clock dosage is not increased.[61,69] On the basis of the steady-state pharmacokinetics of morphine, patients with severe, unrelieved chronic pain should have their total daily dose of morphine increased by 50 to 100 percent every 24 hours.[17-19,22] Moderate unrelieved pain can be treated with daily increases of 25 to 50 percent to reduce the risk of overmedication.

Aggressive downward dose titration is important in patients whose pain is diminished because its cause has been effectively treated or because its transmission has been successfully blocked by neurolysis or neurosurgery.[17,20] The dose of opioid should be decreased by 25 to 50 percent each day in these patients, depending on whether the pain has subsided, whether the patient no longer needs additional doses for breakthrough pain, and whether there are opioid side effects. Patients with substantial side effects may need to have one or two doses withheld and subsequent doses reduced by 50 to 75 percent. After a period of

TABLE 3. MANAGEMENT OF OPIOID-INDUCED CONSTIPATION.

Prevention*
100 mg of docusate sodium plus 17.2 mg of sennosides orally twice a day
10 mg of bisacodyl orally at bedtime as needed if no bowel movement in previous 24 hr; repeat in the morning if still no bowel movement
Titration†
100–200 mg of docusate sodium plus 17.2–34.4 mg of sennosides orally two to three times a day
10–15 mg of bisacodyl orally two to three times a day
Obstipation‡
30–60 ml of milk of magnesia plus 15–30 ml of mineral oil orally once or twice a day
30–60 ml of lactulose orally two to four times a day
8 oz (240 ml) of citrate of magnesia orally once a day
Phosphosoda enema once a day

*The therapeutic goal of one soft bowel movement every one to two days is best achieved by regularly administering both a stool softener and a bowel stimulant, with additional stimulants as needed. The preventive regimen outlined is recommended for patients taking the equivalent of 120 mg of morphine orally per day. Common doses are 50 mg of docusate sodium plus 8.6 mg of sennosides per tablet, and 5 mg of bisacodyl per tablet.

†The preventive regimen should be titrated to meet the therapeutic goal without causing cramps or requiring straining. The dose of docusate and sennosides should be escalated before the bisacodyl dose is escalated, to minimize cramping.

‡Any patient who does not have a bowel movement in any three-day period should be evaluated for impaction and should be disimpacted, if indicated, before taking additional oral laxatives.

regular use of an opioid, patients without pain whose doses are being tapered should be given at least 25 percent of their previous day's doses to prevent a physical-withdrawal syndrome.[17]

SIDE EFFECTS OF ANALGESIC DRUGS

Pain prevention must be accompanied by the prevention of side effects.[17,18,20-22] Unavoidable side effects require specific therapy and may require a trial of other opioids[44-46] or anesthesiologic or neurosurgical intervention.[9-11] Nonanalgesic causes for these symptoms must be sought and specifically treated. Almost all patients receiving around-the-clock opioid therapy need regular laxative therapy (Table 3).[22,71,72] Opioid-associated nausea is often caused by constipation but may require treatment with a centrally acting antiemetic drug such as prochlorperazine, haloperidol, or metoclopramide.[17-19,22] Sedation and cognitive impairment can usually be managed by allowing time for tolerance to develop after therapy is initiated or the dose is escalated,[19,73,74] and by the use of opioid-sparing, nonsedating drugs used in combination with analgesic drugs (Tables 4 and 5).[18,19,22] Persistent sedation and cognitive dysfunction due primarily to opioid analgesia can be reduced with caffeine[75] or methylphenidate.[76] The usual dose of

TABLE 4. DRUGS COMMONLY USED IN COMBINATION WITH ANALGESIC DRUGS FOR CANCER PAIN.

TYPE OF PAIN	DRUGS
Bone metastasis, soft-tissue infiltration, serositis, arthritis	NSAIDs: 1500 mg of choline magnesium trisalicylate orally twice a day, 800 mg of ibuprofen orally every 8 hr, 550 mg of naproxen sodium orally two to three times a day, 150–200 mg of sulindac orally every 12 hr
Postoperative pain	NSAIDs: 50 mg of indomethacin rectally every 6–8 hr, 15–30 mg of ketorolac intravenously every 6 hr*
Soft-tissue infiltration, acute nerve compression, visceral distention, increased intracranial pressure	Corticosteroids†: 4–8 mg of dexamethasone orally two to three times a day, 16–32 mg of methylprednisolone orally two to three times a day, 20–40 mg of prednisone orally two to three times a day
Acute spinal cord compression; acute, severe increased intracranial pressure	Corticosteroids†: 10–20 mg of dexamethasone intravenously every 6 hr‡, 40–80 mg of methylprednisolone intravenously every 6 hr
Neuropathic pain	Tricyclic antidepressant drugs§¶: 50–150 mg of amitriptyline orally at bedtime, 50–150 mg of nortriptyline orally at bedtime, 50–200 mg of desipramine orally at bedtime Anticonvulsant drugs: 200 mg of carbamazepine§¶ two to four times a day, 0.5–1.0 mg of clonazepam§ orally three times a day

*Ketorolac should be given for no more than five days.

†Dose recommendations are based on uncontrolled, anecdotal reports and clinical experience. After successful adjuvant therapy, the corticosteroid dose should be gradually tapered to the lowest possible effective dose or discontinued, if possible, to avoid long-term adverse effects.

‡Doses may be as high as 40 to 100 mg of dexamethasone when given as loading doses or when given every 6 hours for the first 24 to 72 hours of treatment.

§Therapy should be initiated at 50 percent of the lowest dose, and the dose should be titrated every few days until the optimal effect is achieved.

¶Serum drug concentrations should be monitored to assess compliance and to prevent unexpected toxicity.

TABLE 5. SUPPLEMENTAL DRUGS USED IN COMBINATION WITH ANALGESIC DRUGS.

TYPE OF PAIN	DRUG
Neuropathic pain	150–300 mg of mexiletine orally three times a day 4–18 ml (0.125–0.25%) of bupivacaine per hour epidurally 30 μg of clonidine per hour epidurally 5–30 mg of baclofen orally two or three times a day
Bone metastasis	90–120 mg of pamidronate intravenously every 3–6 wk 4 mCi of strontium chloride Sr 89 intravenously every 3 mo 200 IU of calcitonin intravenously or intranasally twice a day
Obstructed-bowel spasm	50–100 μg of octreotide subcutaneously two or three times a day

methylphenidate is 10 mg in the morning and 5 mg at noon, with an upper limit of 60 mg each morning and 30 mg at noon.[76] Patients with persistent confusion or delirium may respond to 0.5 to 1 mg of haloperidol, two to three times daily.[19,22] Opioid-induced myoclonic jerks can be treated with clonazepam, 0.25 to 0.5 mg orally three times daily.[77] Appropriate titration of the opioid dose rarely results in respiratory depression or cardiovascular collapse.[17,18,20,22] When these life-threatening complications do occur and do not respond to general supportive measures, naloxone (20 to 40 μg per minute intravenously) should be given[17-19,20,22] and subsequent doses of opioids delayed or reduced.

SEQUENTIAL TRIALS OF ANALGESIC DRUGS

In some patients, switching from one opioid to another can eliminate an unmanageable, idiosyncratic side effect of the initial drug.[44-46] In patients whose pain is well controlled, the initial dose of the new opioid should be 25 to 50 percent less than the estimated equivalent dose to allow for incomplete cross tolerance.[18,19] When morphine-induced side effects are thought to be due to true allergy to morphine, which is rare, patients should be switched to methadone or fentanyl.[19]

ADJUVANT THERAPY

Adjuvant drug therapy enhances the analgesic efficacy of opioids, treats concurrent symptoms that exacerbate pain, or produces independent analgesia for specific types of pain.[17] The early use of adjuvant drugs is aimed at optimizing patients' comfort and function by preventing or reducing the toxic effects of opioids. Cancer-pain syndromes most amenable to adjuvant therapy are those caused by bone metastasis, nerve compression, nerve damage, and visceral distention.[17-20,22] The drugs most commonly used in adjuvant therapy for the treatment of cancer pain are NSAIDs, corticosteroids, tricyclic antidepressant drugs, and anticonvulsant drugs (Table 4).[17-20,22]

NSAIDs are effective in the treatment of pain from bone metastasis, soft-tissue infiltration, arthritis, serositis, and recent surgery.[19,32] Beyond their value as step 1 nonopioid analgesics, NSAIDs can enhance the efficacy of opioid analgesia in patients with these kinds of inflammation-based pain.

Corticosteroids can be helpful in patients with pain due to acute nerve compression, visceral distention, increased intracranial pressure, and soft-tissue infiltration.[17,19,20,78] Specific corticosteroid drugs and doses and their indications, based on anecdotal reports and clinical experience, are shown in Table 4. Short, tapering courses of drugs given in initially high doses are advised to optimize benefits and minimize long-term adverse effects, such as proximal myopathy and osteoporosis.[22]

Tricyclic antidepressant drugs are used as the first-line adjuvant therapy for neuropathic pain and may also improve underlying depression and insomnia.[17-20,22,79] Amitriptyline has been the most widely used drug of this type, but it has dose-limiting sedative and anticholinergic side effects.[79,80] Nortriptyline and desipramine cause fewer of these side effects, facilitating upward dose titration.[80,81] Low doses (10 to 25 mg) of either drug should be administered at night and titrated upward every few days as needed to a maximally tolerated dose. These drugs may be beneficial to patients with neuropathic pain in lower doses than those needed to treat patients with depression, but nightly doses of 100 to 150 mg of nortriptyline and 150 to 300 mg of desipramine may be needed to maximize their adjuvant effects. Serum drug measurements can be used to assess compliance, detect altered metabolism, and minimize toxicity. Pain relief usually takes two to four weeks after therapy is initiated.

An anticonvulsant drug can be useful in patients with neuropathic, lancinating, or tic-like pains[17-20,22,82-84] and may be added to a tricyclic antidepressant drug for neuropathic pains that are incompletely relieved by several weeks of full-dose antidepressant drug therapy. An anticonvulsant drug may be used alone in patients who cannot tolerate antidepressant drug therapy and in those with myoclonic jerks from opi-

oids. Carbamazepine[82] and clonazepam[83] are the preferred anticonvulsant drugs for neuropathic pain. Blood counts should be periodically monitored in patients receiving carbamazepine because of a potential risk of bone marrow suppression.

A variety of other drugs used in combination with analgesics can be considered in patients with neuropathic pain, bone metastasis, and bowel spasm (Table 5). Mexiletine and baclofen may relieve neuropathic pain.[85-87] The addition of either bupivacaine[88] or clonidine[89] to epidural morphine infusions has a synergistic effect in the control of neuropathic pain. Subcutaneous octreotide reduces intractable vomiting and bowel spasm in patients with intestinal obstruction.[90]

Patients with pain caused by bone metastasis may benefit from adjuvant therapy with pamidronate, strontium chloride Sr 89, or calcitonin. Initially developed for the control of hypercalcemia, pamidronate is a bisphosphonate that inhibits osteoclast activity and reduces pain or analgesic requirements by 20 to 50 percent in patients with pain caused by bone metastasis.[91,92] Pamidronate has recently been approved for adjuvant therapy in patients with multiple myeloma to reduce bone pain and the incidence of fractures.[88] Strontium chloride Sr 89, a beta-particle–emitting calcium analogue selectively taken up by osteoblasts, relieves pain or reduces the need for analgesic drugs in 60 to 95 percent of patients with osteoblastic bone metastases.[89,93] It may cause bone marrow depression, however, that can compromise subsequent anticancer therapy or necessitate transfusion support in patients with limited marrow reserves. Calcitonin, a polypeptide hormone that inhibits the activity of osteoclasts, may reduce pain from bone metastasis and phantom-limb pain.[94,95]

CONCLUSIONS

Pain relief in patients with cancer remains inadequate because it is not given priority and because there is a lack of education about and inappropriate attitudes toward the nature of pain and the appropriateness of opioid therapy among health care providers, patients, and patients' families.[2,3,17,96,97] Even if the ideal analgesic drug was discovered, it would probably be as underused as are current analgesic drugs if pain relief is not made a high priority throughout the health care delivery system.[17] We urgently need effective methods of training clinicians and holding them accountable for the adequate relief of pain.[98-100]

Drug therapy is the cornerstone of pain management in patients with cancer. Using the guidelines reviewed in this paper, most clinicians should be able to control most of the pain in the majority of their patients with cancer. Collaboration with pain experts should help the rest. Improving the alleviation of cancer pain will benefit thousands of patients and their families. It will also provide a model for better care of the even larger number of patients who have unrelieved pain due to illnesses other than cancer.[70,101]

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