Management of Pain and Spinal Cord Compression in Patients with Advanced Cancer

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General internists often care for patients with advanced cancer. These patients have substantial morbidity caused by moderate to severe pain and by spinal cord compression. With appropriate multidisciplinary care, pain can be controlled in 90% of patients who have advanced malignant conditions, and 90% of ambulatory patients with spinal cord compression can remain ambulatory. Guidelines have been developed for assessing and managing patients with these problems, but implementing the guidelines can be problematic for physicians who infrequently need to use them. This paper traces the last year of life of Mr. Simmons, a hypothetical patient who is dying of refractory prostate cancer. Mr. Simmons and his family interact with professionals from various disciplines during this year. Advance care planning is completed and activated. Practical suggestions are offered for assessment and treatment of all aspects of his pain, including its physical, psychological, social, and spiritual dimensions. The methods of pain relief used or discussed include nonpharmacologic techniques, nonopioid analgesics, opioids, adjuvant medications, radiation therapy, and radiopharmaceutical agents. Overcoming resistance to taking opioids; initiating, titrating, and changing opioid routes and agents; and preventing or relieving the side effects they induce are also covered. Data on assessment and treatment of spinal cord compression are reviewed. Physicians can use the techniques described to more readily implement existing guidelines and provide comfort and optimize quality of life for patients with advanced cancer.

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General internists often care for patients with advanced cancer. Pain and spinal cord compression are two of the most distressing and disabling problems that these patients experience. Evidence-based guidelines (1–7) and comprehensive reviews of pain assessment and pain management (8–14) show that the right combination of nonpharmacologic techniques and therapeutic agents can control pain in 85% to 95% of patients. Early recognition and treatment of spinal cord compression will preserve ambulation and continence; guidelines for management are available (15). Physicians who do not encounter many patients with moderate to severe cancer-related pain or with spinal cord compression may be unfamiliar with how to implement these guidelines in their practices. In this paper, the case of Mr. Simmons, a hypothetical patient dying of refractory metastatic prostate cancer, is used to illustrate an evidence-based approach to the most common clinical challenges such patients present.

Mr. Simmons is a 72-year-old consultant who was found to have locally extensive prostate cancer 4 years ago. He received radiation therapy, and, later, underwent orchiectomy and received flutamide for recurrence. The disease has become refractory to all therapies.

At the time of a routine appointment with his general internist, Mr. Simmons reports generalized aching pain "in my bones." This pain is almost always present and is exacerbated by movement. He has a history of ulcer disease. He takes acetaminophen, 1000 mg four times daily. A recent bone scan revealed diffuse bony metastases in his skull, spine, hips, and femurs, with spotty involvement of his ribs. Magnetic resonance imaging showed no extension of tumor into the spinal canal. His wife reports that he is sleeping badly, is irritable, is almost confined to his recliner, and cannot attend church regularly. Mr. and Mrs. Simmons hope to join their family on a month-long cruise, and she is worried that he won't enjoy the trip.

Pain Assessment

No further diagnostic studies are needed to determine the cause of Mr. Simmons' pain; it results from his refractory metastatic prostate cancer. The functional consequences are also apparent: He is irritable, cannot sleep, and is confined to a chair. The physician should assess the intensity of the pain to determine the appropriate pharmacologic agents for initial therapy. The World Health Organization Analgesic Ladder (a repeatedly validated method for controlling pain in patients with cancer [1, 2]) and the Agency for Health Care Policy and Research guidelines for treatment of cancer pain (3) recommend starting with nonopioid agents for mild pain (step 1) and adding other agents, including opioids, for moderate (step 2) or severe (step 3) pain. After therapy with pain medication is begun, repeated assessment of pain intensity enables dose adjustments in much the same way as the blood glucose level guides adjustment of the insulin dose.

Patients with chronic pain do not manifest the tachycardia, elevated blood pressure, facial grimacing, or emotional reactions typical of patients with acute pain (10). The only reliable way to determine the intensity of their pain is to ask them. Family members, physicians, and nurses regularly underestimate the intensity of pain in patients with cancer (9, 16–18) or AIDS (19, 20). Hispanic and black patients with cancer, elderly persons, cognitively impaired persons, women, and patients with a history of drug abuse are even more likely than other groups to have the severity of their pain underestimated and to be undertreated by physicians (16, 18, 20, 21).

Several validated pain assessment scales (3, 9) can provide an accurate measure of Mr. Simmons' pain intensity. For adults, there are three useful choices: a verbal numerical scale, a word scale (3), and visual analogue scales (**Figure 1**). A scale that both the physician and the patient and his or her family are comfortable with should be chosen and used each time pain is reassessed. On a 0 to 10 scale, 1 to 4 represents mild pain, 5 to 6 represents moderate pain, and 7 to 10 represents severe pain.

Sitting quietly in a chair in the office and appearing tired but not in distress, Mr. Simmons surprisingly reports that his pain level is now at 9, the average intensity of his pain is 9, and his worst pain is at least 10. For a few hours after he takes acetaminophen, his pain level falls to 8.

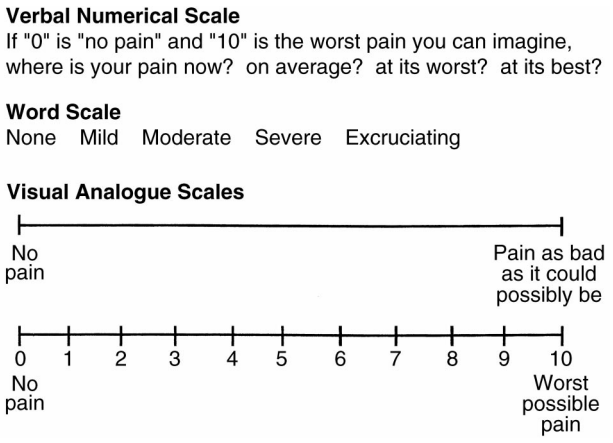

Figure 1. Pain assessment scales. The verbal numerical scale, word scale, and the two visual analogue scales shown are four validated, commonly used scales for pain assessment. On a visual analogue scale, the patient marks the point that represents the intensity of his or her pain now, on average, at its worst, and at its best. See reference 3 for more information.

Therapy for Bone Pain

Mr. Simmons' bone pain is too diffuse for standard radiation of the most painful metastases. In this case, because none of the remedies discussed below is curative and each has different risks, benefits, and costs, the patient's preferences should be sought before one is chosen.

Pharmacologic Therapy

Adjuvant therapy with acetaminophen can be continued (3, 22). Considering Mr. Simmons' age and ulcer history, standard nonsteroidal anti-inflammatory drugs, which have a high incidence of inducing gastrointestinal toxicity in this population (22–25), should not be used. If a nonsteroidal anti-inflammatory drug is used, misoprostol or omeprazole is also indicated (26, 27).

The mainstay of therapy for severe pain is a step 3 opioid (3, 28–42) (**Table 1**) and a laxative (2, 43–45) (**Figure 2**). When opioids are used in pain management, the following should be done:

1. Use the World Health Organization analgesic ladder. Advance up the ladder if pain persists.

2. Prescribe doses high enough to relieve the pain and give them frequently enough to prevent recurrence of pain (3–5, 11).

3. Provide a "rescue" dose of a short-acting opioid for unexpected pain exacerbations (3, 46). This dose should be 10% of the total daily opioid dose (13). Sustained-release preparations of oxycodone or morphine, as well as transdermal fentanyl (47, 48) can be used to control continuous baseline pain. Transdermal fentanyl diffuses into a skin reservoir from which it enters the bloodstream (33). There is, therefore, a 12- to 24-hour delay in onset of pain relief and, should toxicity occur, a similar delay in its resolution (49). Because of this, immediate-release opioids are routinely required for opioid-naive patients in whom therapy with transdermal fentanyl is begun (33).

The physician should also prescribe immediate-

Table 1. Opioids for Step 3 (Severe) Pain*

Opioid	Initial Dose†		Dose Interval	Preparations Available
	Oral	Parenteral		
	mg		*h*	
Morphine				
Immediate release	15–30	10	3–4	Intravenous, intramuscular, subcutaneous, tablet, rectal, liquid, liquid concentrate
Sustained release	30–60	NA	8–12	Tablet
Sustained release	60–120	NA	12–24	Capsule with pellets
Hydromorphone (immediate release)	6	1.5	3–4	Intravenous, intramuscular, subcutaneous, tablet, rectal
Oxycodone plus level 1 agents	10	NA	3–4	Tablet, liquid
Oxycodone	10–20	NA	3–4	Tablet, liquid, liquid concentrate
Oxycodone (sustained release)	30–60	NA	12	Tablet
Fentanyl	NA	50‡	72	Transdermal
	200‡	NA	4	Transmucosal oralet
Methadone	20	10	6–8	Intramuscular, intravenous, subcutaneous§, tablet, liquid
Meperidine¶	300	100	3	Intramuscular, intravenous, tablet

* References 3, 28–30, 32, 33, 36–42. NA = not applicable.
† For patients weighing more than 110 lb who have moderate to severe pain. From Management of Cancer Pain: Adults. AHCPR 94-0592. Initial doses should be halved for opioid-naive patients, elderly persons, or medically frail persons.
‡ Values given are μg/h.
§ Least-recommended route; pain and pruritus often develop at the infusion site.
¶ Not recommended for patients with advanced cancer.

release opioids at this time to treat unexpected exacerbations of pain or pain that occurs only with movement. These rescue doses (3, 46) of morphine, oxycodone, or hydromorphone start at 10% of the total daily opioid dose and are given every 1 to 2 hours as needed (13). The dose of the oral transmucosal fentanyl lozenge must be individually determined (38–42).

Meperidine is not indicated for repeated dosing in patients with chronic severe pain (3, 8). It has poor oral bioavailability and a short therapeutic half-life. Toxic levels of its metabolite, normeperidine, accumulate with repeated dosing or in patients with renal insufficiency and can cause dysphoria, myoclonic jerks, and seizures (50).

Nonpharmacologic Therapy

Several physical and cognitive therapies can diminish patients' experience of pain (51–59). Physiatrists and physical and occupational therapists use positioning, exercise, and assist devices (such as lift chairs) (52, 53), and prescribe cold, heat, and massage (51, 52, 54) for nerve injury, muscle spasm, or inflamed joints. Acupuncture therapy has not been extensively studied in patients like Mr. Simmons. Transcutaneous electrical nerve stimulation is most effective for dermatomal pain (51).

The cognitive therapies progressive muscle relaxation (55, 56) and hypnosis (57) have been shown in controlled trials to decrease cancer pain (55, 57). Patients should also be screened for social, psychological, or spiritual concerns (56) and should be referred to social workers or spiritual or psychological counselors when needed (58, 59).

Other Therapeutic Options

Bisphosphonates greatly relieve pain in patients with multiple myeloma and breast cancer (60–64). Small trials indicate efficacy in patients with prostate cancer (65), and phase III trials are under way (62). Phase III double-blind, placebo-controlled trials have documented the efficacy of the radiopharmaceutical agents ^{89}strontium (66–70) and samarium (71) in relieving pain from blastic metastases; studies of rhenium are under way (68). Hemibody radiation, which is more difficult to deliver, relieves lower-body bone pain (67) in as many as 80% of patients with prostate cancer. Toxicity to viscera and bone marrow exceeds that caused by radiopharmaceutical agents (67, 70).

Mr. Simmons' physician presents Mr. and Mrs. Simmons with what she feels are the best initial options: opioid therapy and nonpharmacologic methods. They accept lift and bath chairs and a new heating pad. They have begun regular discussions with their pastor and feel that he provides adequate psychological support. But Mr. Simmons refuses the opioid prescription.

Patients' Reluctance To Take Opioids

Like many other patients with cancer, Mr. Simmons probably harbors numerous misconceptions about opioids: fear of becoming an addict, "feeling high," using up the effective agents and having nothing left if the pain gets worse, and developing refractory constipation (3, 14). To explore patients' fears and enhance compliance, physicians must help patients understand several aspects of opioid use.

First, there is the distinction among tolerance, physical dependence, and psychological addiction. Second, the chances of addiction are less than 1% (72–75). Third, patients will not "feel high" on effective doses of opioids; moreover, a feeling of euphoria does not imply that the patient is misusing the medication. Finally, even if the patient takes medication now, he or she will still be able to achieve pain relief by using higher doses should the pain worsen.

Constipation, the most common opioid-induced side effect, usually does not resolve with time (11, 43–45, 75). Daily laxatives prevent or at least improve opioid-induced constipation (11, 44, 75, 76). The most effective agents are senna (one or two tablets, once or twice daily; the dose can be increased as needed), senna combined with a stool softener, bisacodyl, milk of magnesia alone or with mineral oil, and lactulose (one to two tablespoons at bedtime; the dose can be increased as needed). Lactulose is the most expensive of these treatments (76). In selected patients, one tablespoon of polyethylene glycol in 4 ounces of water may be needed. Fiber intake should not be increased because as patients become more debilitated, fiber is more likely to exacerbate than to relieve the problem (75).

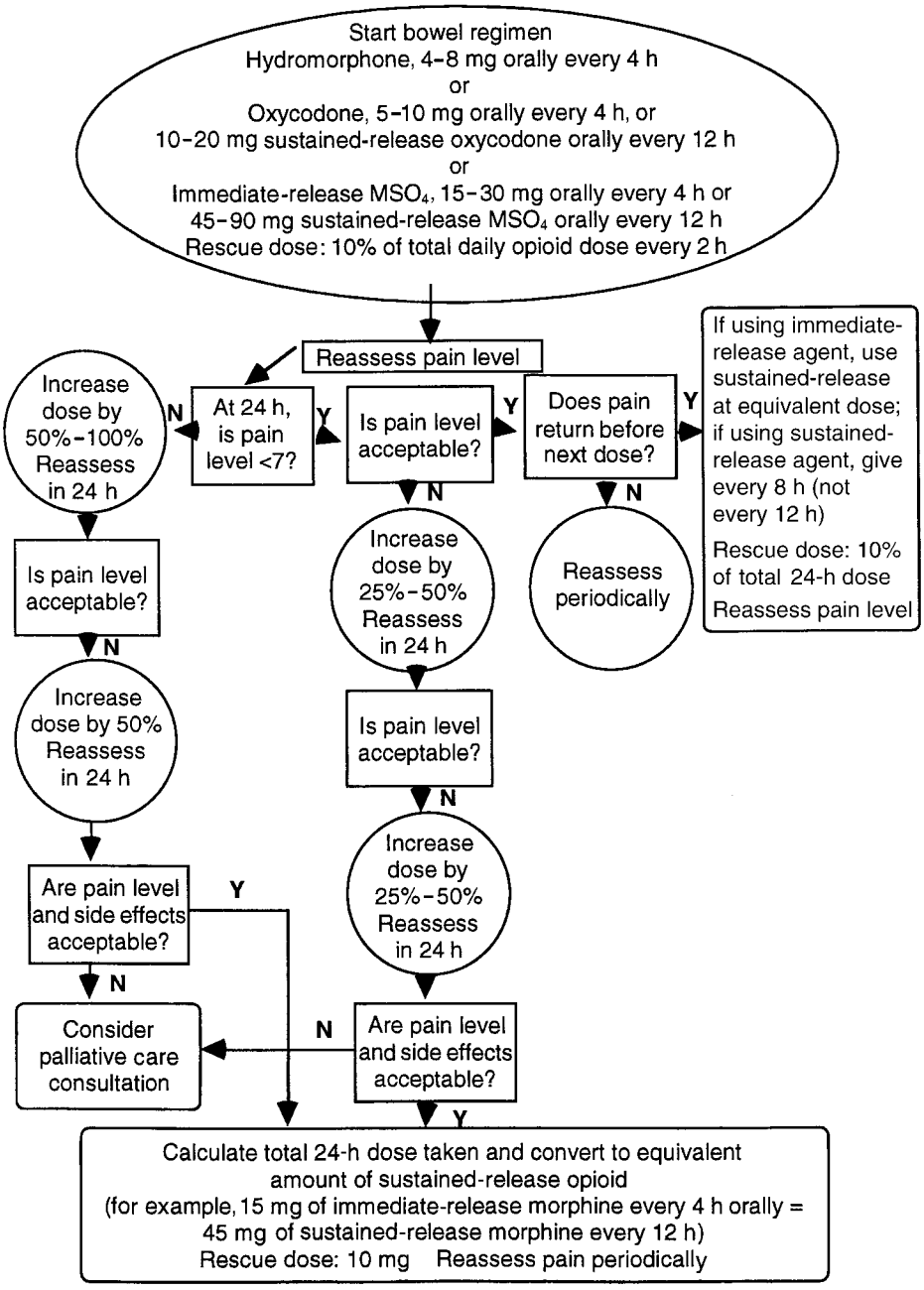

Figure 2. Management guidelines for severe cancer pain. MSO_4 = morphine sulfate.

Table 2. Antiemetics*

Cause of Nausea	Drug	Dose	One-Month Supply, $†
Initiation of opioid therapy	Prochlorperazine	10 mg orally or 25 mg rectally 2 or 3 times daily	10–25
Stimulation of chemoreceptor	Haloperidol	1.5–5 mg orally 3 to 4 times daily or 2–10 mg intramuscularly twice or three times daily	10–25
Trigger zone by chemotherapy	Prochlorperazine	10 mg orally or 25 mg rectally 2 or 3 times daily	10–25
	Methotrimeprazine	2–6.25 mg intramuscularly 3 times daily or 6–25 mg over 24 h	Variable
Vertigo	Scopolamine (transdermal patch)	Apply 1 patch every 2–3 days	50–75
	Meclizine	50 mg orally or 25–50 mg intramuscularly three times daily	10–25
Delayed gastric emptying	Metoclopramide	10–20 mg 2 to 4 times daily or 1–3 mg/h intravenously	50–150 Variable
Bowel obstruction‡	Octreotide	50–100 μg subcutaneously 2 or 3 times daily or 300 μg over 24 h subcutaneously	7500–22 500 (that is, about 250 per 100 μg)
Multiple causes, refractory	Ondansetron	4–8 mg orally 2 or 3 times daily	750–1500
	Dexamethasone	2–4 mg orally 2 or 3 times daily	25–50

* References 11, 79–81.
† Reference 76.
‡ For treatment of symptoms when surgery is not possible.

Once a stable dose of opioid is reached, nausea and sedation will resolve, and the patient will be able to participate in usual activities, including driving (77).

Mr. Simmons admits that for him, accepting opioids means accepting death. He was also concerned about retaining his mental clarity and about what his children might think when they learned that he was "taking dope." But following his pastor's advice, he spoke with his children, who alleviated these concerns.

Mr. Simmons' pain is relieved by 30 mg of immediate-release morphine every 4 hours, and his therapy is switched to the equivalent dose of sustained-release morphine (90 mg every 12 hours) plus rescue doses of 15 mg of immediate-release morphine every 2 hours as needed; an equivalent is 60 mg of controlled-release oxycodone plus rescue doses of 10 mg of immediate-release oxycodone (Appendix Tables 1 and 2) (3, 36, 78). *Senna (two tablets twice daily) is added to Mr. Simmons' regimen, and prochlorperazine is available for nausea. Mr. Simmons mentions feeling mildly sedated, but his physician tells him that this effect will probably resolve by the end of the week.*

Two days later, Mr. Simmons reports that with his increased activity, he needed six rescue doses (90 mg) of morphine each day to maintain an average pain level of 6. He felt that this was too high.

Titrating an Opioid-Containing Regimen

Mr. Simmons took more than 25% of his daily scheduled morphine as rescue doses, suggesting that he needs a higher regularly scheduled morphine dose. Despite the rescue doses, his pain level remains moderate (level of 5 to 6); thus, he requires a 25% higher total daily morphine dose (**Figure 2**).

Mr. Simmons begins therapy with sustained-release morphine, 160 mg every 12 hours, plus rescue doses of immediate-release morphine, 30 mg (Appendix, Titration). *Twenty-four hours later, his pain level is 3, which is acceptable. He slept through the night and ambulates comfortably. He confides that when the pain was at its worst, he began to wonder what he had done to cause God to abandon him. Despite reassurances from his pastor, he felt a growing sense of despair and isolation from his family and his faith that began to resolve when he resumed attending Sunday church services.*

Three days later, Mr. Simmons' pain is still well controlled, but he has developed significant nausea that is unresponsive to oral prochlorperazine, 10 mg three times daily. He is not constipated, and the nausea is not positional or precipitated by the sight or smell of food. It is exacerbated by a rescue dose of immediate-release morphine.

Therapy for Opioid-Induced Nausea

Mr. Simmons has not been receiving chemotherapy, and he has no evidence of vertigo, gastroparesis, or bowel obstruction (**Table 2**) (79–81). Morphine is the probable cause of his nausea, and changing from morphine to another opioid may eliminate it (82, 83); conversion techniques are described in the Appendix. Sustained-release oxycodone and transdermal fentanyl are easier to use but are more expensive than equianalgesic doses of methadone (76, 84–86).

Mr. Simmons refuses methadone therapy because "it's a drug for addicts" and refuses transdermal fentanyl because it is too visible. Therapy with sustained-release oxycodone, 70 mg every 12 hours (330 mg of sustained-release morphine = 220 mg sustained-release oxycodone; 2/3 of 220 mg of sustained-release oxycodone = 145 mg over 24 hours), is therefore started (Appendix, Conversion). *Three days later, he is no longer nauseated, and his pain level remains at 3; exacerbations are controlled by 15 mg of immediate-*

release oxycodone (10% of 140 mg = about 15 mg). He has no new adverse effects.

A week later, Mr. and Mrs. Simmons leave on their cruise, which turns out to be all they had hoped for. A month later, however, Mr. Simmons' pain with movement has increased, and he feels too sedated from the frequent oxycodone rescue doses. He accepts treatment with ^{89}strontium. Three weeks later, Mrs. Simmons reports that her husband is much more nauseated and somnolent. He has no pain at rest and has minimal pain when he changes position, and he has needed no rescue opioids. Laboratory studies show normal levels of electrolytes, calcium, and albumin and normal renal and hepatic function.

Treatment of Opioid-Induced Sedation

Mr. Simmons' opioid-induced sedation and nausea have most likely reemerged because therapy with ^{89}strontium decreased his bone pain. Naloxone is not needed to reverse these effects. Decreasing the oxycodone dose by approximately 50% (to 40 mg of sustained-release oxycodone every 12 hours plus 10-mg rescue doses) should alleviate the sedation. Naloxone would precipitate symptoms of opioid withdrawal (87) and reverse analgesia. If significant respiratory depression occurs (88), appropriate therapy would be just enough of the standard 0.4 mg of naloxone diluted in 10 mL of saline to reverse the respiratory depression (3).

Mr. Simmons' oxycodone dose is reduced as recommended, and within 36 hours, he is again alert, does not have nausea, and has an average pain level of 3, which is acceptable to him.

Three months later, Mr. Simmons visits the emergency department because of increasing discomfort in his mid-back region, with pain radiating to his right nipple. Comprehensive neurologic examination reveals normal finding, and no herpetic lesions are visible. Plain radiographs of the spine show diffuse blastic metastatic disease that includes the area of the pain. The dose of oral sustained-release oxycodone is increased to 60 mg every 12 hours, with a rescue dose of 10 mg. The next day, Mr. Simmons' back pain is at a level of 3 to 4. He continues to have normal bowel movements.

Assessment of Back Pain in Patients with Cancer

Mr. Simmons has thoracic spine pain, radiculopathy, and evidence on plain radiographs of metastatic disease in the area of his pain, a location typical for metastatic prostate cancer (89). There is a 90% probability that the prostate cancer has spread to the epidural space and that the spinal cord is in jeopardy (90–93). Even without the radiculopathy, the probability of epidural disease would be 60% to 70% (90–92). Normal findings on physical examination do not diminish this probability.

If a patient is treated while he or she is still ambulatory, the probability of remaining ambulatory is 89% to 94% (15, 67, 94–96). If a patient becomes paraparetic before therapy, the probability of regaining the ability to ambulate is only 39% to 51%; if he or she becomes paralyzed, it decreases to 10% (15, 67, 95). Emergency magnetic resonance imaging of the entire spine is probably preferable to computed tomographic myelography, which is potentially associated with more complications (95) and is no more sensitive or specific (89, 94).

Mr. Simmons undergoes magnetic resonance imaging of the spine, which reveals metastases to multiple thoracic vertebrae and epidural spread with early cord compression at T6.

Corticosteroid Therapy for Malignant Spinal Cord Compression

Corticosteroid therapy decreases cord edema (97) and pain, helps preserve neurologic function, and improves overall outcome after specific therapy (98). High-dose dexamethasone (100-mg intravenous bolus followed by 24 mg orally four times daily for 3 days, then tapered over 10 days) is probably indicated for patients with impaired function of the spinal cord or cauda equina or with a high-grade radiologic lesion. At this dose, the drug substantially increases the number of these patients who remain ambulatory (81% compared with 63%) (98). Other patients usually receive lower-dose regimens (10-mg intravenous bolus followed by 4 mg intravenously four times daily, then tapered over 14 days), which are better tolerated (15) but may not improve the chance of remaining ambulatory (57.1% compared with 57.9%) (99).

Radiation Therapy with or without Surgery

Surgical decompression is advocated to establish the diagnosis (15); to treat a single site of suspected involvement (15); to treat progression despite radiation therapy (100); or to treat vertebral instability, collapse with bone impinging on the spinal cord, or displacement (15).

Surgery is not advocated for metastases from prostate or breast cancer, myeloma, and lymphoma, which are likely (70% to 88%) to respond to radiation therapy (95, 96). Back pain will resolve in 70% to 85% of cases (94, 95). Ambulatory patients

are equally likely to remain ambulatory with radiation therapy or surgery (101–103).

Mr. Simmons agrees to radiation therapy and corticosteroids because he hopes to "dance with my bride" at his 50th anniversary party. Three weeks later, further discussion with the Simmons family about their hopes, goals, and the burdens and benefits of hospitalization lead to enrollment in hospice, although Mr. Simmons still wishes to be resuscitated.

Mrs. Simmons later reports that the hospice team has markedly decreased her anxiety. An experienced nurse now evaluates her husband frequently; their eldest daughter agreed to be Mr. Simmons' health care proxy; and on the social worker's recommendation, the necessary financial and funeral arrangements have been made.

Mr. Simmons responds well to therapy, but over the next 6 weeks, his oral opioid requirements reach 100 mg of sustained-release oxycodone every 12 hours, and he is more sedated. Repeated laboratory testing reveals no contributing metabolic abnormalities. Psychiatric evaluation fails to detect evidence of depression. His anniversary party is only 1 week away, and he wants to be "sharp" then.

Further Treatment of Opioid-Induced Sedation

For patients in Mr. Simmons' circumstance, changing the adjuvant acetaminophen therapy to treatment with a nonsteroidal anti-inflammatory drug might allow the opioid dose to be reduced without sacrificing pain control. If this is insufficient, adding a psychostimulant without decreasing the opioid dose is likely to increase alertness (in Mr. Simmons' case, in time for him to enjoy the party) (104–107). Effective agents include methylphenidate or dextroamphetamine (initial dose, 2.5 to 5 mg orally in the morning and repeated at noon, if necessary) and pemoline, a chewable tablet (initial dose, 18.75 mg orally in the morning and repeated at noon) that is more expensive (76). Doses should be increased as needed. The patient might also be referred for instruction in hypnosis or relaxation techniques.

Mr. Simmons declines referral for hypnosis and relaxation instruction and is unable to tolerate the gastrointestinal side effects of low-dose ibuprofen. Therefore, he begins taking methylphenidate, 2.5 mg at 8 a.m. and noon. Three days later, without a change in opioid dose, he reports feeling "back to normal." After the party, Mr. Simmons' daughter calls the office to thank the physician for helping her parents fully enjoy their anniversary celebration.

Two weeks later, Mr. Simmons' pain again increases. When the physician visits their home, the pastor is present on one of his almost daily visits. He participates in the discussion with the Simmons family, in which Mr. Simmons reiterates his desire to die at home and states that he does not want resuscitation. Mr. Simmons asks the physician to limit his medications to pain relievers and laxatives. Over the next few weeks, he becomes less interactive, stays in bed more of the day, and asks for food less often. A hospice home health aide helps Mrs. Simmons with his care 2 hours a day, and volunteers from hospice sit with him while Mrs. Simmons does her marketing. A harpist who is a music therapist visits several times a week. Because of his decreased activity, Mr. Simmons now requires a sustained-release oxycodone dose of 160 mg every 12 hours.

When Mr. Simmons is closer to death and unable to swallow pills, his family is offered the choice of giving him hourly sublingual liquid oxycodone concentrate (0.66 mL of a 20-mg/mL solution each hour (320 mg of sustained-release oxycodone = 320 mg of immediate-release oxycodone in 24 hours; 320 mg ÷ 20 mg/mL = 16 mL in 24 hours) or a subcutaneous opioid infusion. Because they are unsure that he will remain comfortable while receiving the liquid opioid, the family requests an opioid infusion. Hydromorphone is chosen to minimize the amount of subcutaneous fluid required (Appendix Table 1). *Mr. Simmons dies peacefully the next day.*

Final Thoughts

Although treatments vary in efficacy, similar approaches are available for the other physical and mental disorders that afflict patients like Mr. Simmons. The roles of the health care team, social workers, and spiritual advisors and management strategies for fatigue, weakness, xerostomia, delirium, anxiety, depression, anorexia, and decubiti are reviewed in several recent textbooks (108–111), handbooks (112, 113), a case-based manual (114), and a resource document (115). With these resources and the information supplied by hospice and palliative care teams, general internists can relieve much of the distress in patients with advanced cancer.

Appendix Table 1. Opioid Equianalgesic Doses*

Drug	Oral	Parenteral
	mg	
Morphine	30	10
Hydromorphone	7.5	1.5
Oxycodone	20	NA
Levorphanol	4	2
Meperidine†	300	100

* References 3, 36, 37, 78. NA = not applicable.
† Not recommended.

Appendix Table 2. Equianalgesic Doses of Fentanyl and Morphine

Fentanyl	Morphine*	
	Oral	Parenteral
μg/h	*mg/24 h*	
25	30–90	10–30
50	91–150	31–50
75	151–210	51–70
100	211–270	71–90
125	271–330	91–110
150	331–390	111–130
200	451–510	151–170

* Reference 35.

Appendix

Believe the Patient's Report of Pain

1. To assess and manage the patient's pain, use a pain scale.

2. For mild pain (1 to 4 on a 0 to 10 scale), start with aspirin, acetaminophen, or a nonsteroidal anti-inflammatory drug.

3. If the pain is not relieved or is moderate (pain score, 5 to 6), add oxycodone, tramadol, or hydrocodone (or use a combination product that contains 5 mg of oxycodone or hydrocodone with aspirin, acetaminophen, or nonsteroidal anti-inflammatory drug).

4. For severe pain (pain score, 7 to 10), start therapy with oxycodone alone, hydromorphone, or morphine. If transdermal opioid is desired, consider using transdermal fentanyl after the effective opioid dose has been identified by using immediate-release agents.

5. Transdermal fentanyl has a 14- to 24-hour "on" and "off" time.

6. If the pain is excruciating (pain score $\geq$10), increase the opioid dose by 50% to 100% regardless of the amount of drug given, until pain is relieved.

7. For chronic pain, give around-the-clock therapy or "patient may refuse," not "as-needed therapy."

8. For pain between doses, give 10% of the total daily opioid dose in immediate-release form (for example, the rescue dose for 200 mg of opioid is 20 mg).

9. Always prescribe a laxative (such as senna with or without lactulose); do not give "as needed." Patient may need an antiemetic for 2 to 7 days.

10. Avoid benzodiazepine sleep medications.

Opioid Dose Titration

Current total dose = (90 mg every 12 hours) + rescue dose (15 mg $\times$ 6) = 180 mg + 90 mg = 270 mg.

Calculated new total dose = (270 mg) + (270 mg $\times$ 25% = 67.5 mg) = 337.5 mg.

Relevant available sustained-release morphine doses are 15, 30, 60, and 100 mg.

Actual new regimen = 160 mg every 12 hours to 175 mg every 12 hours, plus a 30-mg rescue dose.

Opioid Conversion

Determine the equinalgesic dose of new opioid (Appendix Table 1).

Prescribe two thirds of this dose to allow for incomplete cross-tolerance.

When using Appendix Table 2, prescribe full doses (data are from direct in vivo comparisons).

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