Management of Common Opioid-Induced Adverse Effects

JOHN M. SWEGLE, PHARM.D., *Mercy Family Medicine Residency Program, Mason City, Iowa*
CRAIG LOGEMANN, PHARM.D., *Urbandale Family Physicians, Urbandale, Iowa*

Opioid analgesics are useful agents for treating pain of various etiologies; however, adverse effects are potential limitations to their use. Strategies to minimize adverse effects of opioids include dose reduction, symptomatic management, opioid rotation, and changing the route of administration. Nausea occurs in approximately 25 percent of patients; prophylactic measures may not be required. Patients who do develop nausea will require antiemetic treatment with an antipsychotic, prokinetic agent, or serotonin antagonist. Understanding the mechanism for opioid-induced nausea will aid in the selection of appropriate agents. Constipation is considered an expected side effect with chronic opioid use. Physicians should minimize the development of constipation using prophylactic measures. Monotherapy with stool softeners often is not effective; a stool softener combined with a stimulant laxative is preferred. Sedation and cognitive changes occur with initiation of therapy or dose escalation. Underlying disease states or other centrally acting medications often will compound the opioid's adverse effects. Minimizing unnecessary medications and judicious use of stimulants and antipsychotics are used to manage the central nervous system side effects. Pruritus may develop, but it is generally not considered an allergic reaction. Antihistamines are the preferred management option should pharmacotherapy treatment be required. (Am Fam Physician 2006;74:1347-54. Copyright © 2006 American Academy of Family Physicians.)

Opioids are useful agents for managing acute and chronic pain.[1] When prescribing these medications, an understanding of the risks and benefits is essential. Many organizations, including the American Pain Society and the American Academy of Pain Management, have educational materials and other resources available for physicians.[1,2] In addition, the European Association of Palliative Care (EAPC) Research Network has developed recommendations for treating opioid-induced adverse effects.[3]

The development of adverse effects from opioids may cause physicians to weigh the treatment risks against the benefits. Anticipating potential adverse effects in relation to predisposing patient factors is critical when addressing this problem. The mechanisms by which opioids cause these adverse effects are not always completely understood.

Sex, race, and increasing age are all factors shown to influence the development of adverse effects.[4] Reductions in renal function associated with aging may lead to accumulation of opioids and their metabolites.[5] To reduce the risk of developing adverse effects, downward dose adjustments or prolonging the opioid interval should be anticipated for persons older than 70 years.[1,5] Nausea and vomiting are less likely to occur in men than in women and are less likely in whites than in blacks.[4,6] The EAPC working group identified four general approaches to consider when encountering adverse effects caused by opioids: dose reduction of systemic opioid, symptomatic management of the adverse effect, opioid rotation, and switching the route of systemic administration.[3]

If pain is well controlled, small reductions in the dose of opioid may help resolve the adverse effect while maintaining pain control.[3] Addition of nonopioid analgesics, use of adjuvant agents (e.g., tricyclic antidepressants), or treatments directed toward the source of pain are all options for providing a synergistic approach to pain management.[3]

Opioids have subtle differences in binding to the mu, kappa, and sigma receptors; the clinical effects can vary from one agent to another.[7,8] Opioid rotation is a concept in which one opioid is exchanged for another to improve pain control or manage certain adverse effects. Pain experts support the clinical use of opioid rotation as a reasonable strategy.[8-10] Patient response to opioid therapies can be highly variable, so physicians should be knowledgeable about different

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Opioid rotation may be used for managing opioid-induced adverse effects.	C	8, 9
Because no antiemetic has been shown to be superior to another in this setting, cost can be used to determine the treatment method of opioid-induced nausea.	C	3, 16
Monotherapy with stool softeners for constipation is not recommended.	C	1
Transdermal fentanyl (Duragesic) is an option for pain control in patients with constipation from oral opioids.	B	21-23

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1263 or http://www.aafp.org/afpsort.xml.

opioids and also understand the fundamentals of proper equianalgesic conversion.

A MEDLINE search (1966-2005) was performed to identify evidence-based approaches for managing opioid-induced adverse effects. In addition, evaluation of consensus guidelines and various working groups providing expert opinion were used in developing this review. Few randomized comparative studies have evaluated the safety and effectiveness of various treatment regimens to manage adverse effects of opioids. Many of the recommendations for management are based on consensus opinion and clinical experience.

NAUSEA

Nausea has been reported to occur in approximately 25 percent of patients treated with opioids; prophylactic measures generally are not required at the initiation of therapy.[4,11] Mechanisms for nausea may include direct stimulation of the chemoreceptor trigger zone (CTZ), reduced gastrointestinal motility, or enhanced vestibular sensitivity.[7,12,13] An understanding of these mechanisms will aid physicians in the selection of antiemetic agents to target the underlying cause. Nausea that results from opioids usually is transient; however, treatment should be made available if substantial nausea and vomiting develop.[13]

The initial antiemetic choice will depend on patient characteristics including concomitant disease states and likelihood of adverse reactions or drug interactions. Available options include antipsychotics, metoclopramide (Reglan), serotonin antagonists, antihistamines, and corticosteroids. These agents are used alone or in combination. There is no proven clinical benefit of one antiemetic over another.[3] An understanding of the potential mechanism for the opioid-induced nausea should factor into selection.

Antipsychotics are inexpensive agents that block dopamine receptors within the CTZ.[14] Haloperidol (Haldol) and prochlorperazine (Compazine) are considered first-line options, primarily based on expert opinion.[3,10] Adverse effects such as akathisia, dystonic reactions, sedation, and orthostatic hypotension may occur with antipsychotic use. Another option is metoclopramide, which will block dopamine receptors in the CTZ and promote peristalsis through enhanced release of acetylcholine.[15] Central nervous system (CNS) effects (e.g., sedation and extrapyramidal effects) often limit the use of metoclopramide.

Serotonin antagonists block serotonin release, primarily within the gastrointestinal tract, but they have secondary effects on blocking serotonin centrally.[15] These agents are more useful in preventing nausea resulting from highly emetogenic chemotherapy, radiation, and postoperative sickness.[16] Although they are free of extrapyramidal adverse effects, routine use of serotonin antagonists in managing opioid-induced nausea often is cost prohibitive. Because of this, these products typically are not considered

first-line agents, although they are possible alternatives when other products are ineffective or not well tolerated.[16]

Antihistamines and anticholinergic agents reduce opioid-induced vestibular sensitivity. Patients experiencing nausea related to ambulation are most likely to benefit from medications that antagonize the effects of acetylcholine and histamine.[17] The use of these medications often is limited by sedation and orthostatic changes. Corticosteroids have an unclear mechanism of action for treating nausea caused by opioids. Jitteriness, confusion, and increased appetite are adverse effects that need to be considered before starting corticosteroids. An overview of agents used for treating nausea and vomiting is listed in *Table 1*.[14-16]

CONSTIPATION

Constipation is the most common adverse effect occurring with chronic opioid use. Prophylactic treatments are essential to minimize this complication. Opioids have various

TABLE 1
Selected Medications for Treating Opioid-Induced Nausea

Classification	*Medication and adult dose*	*Cost**	*Comments*
Antihistamines	Diphenhydramine (Benadryl) 25 to 50 mg orally or IV every four to six hours	Oral: $0.16 to $0.24 (generic) or $0.69 to $1.05 (brand) per day IV: $1.86 per 50-mg vial (brand)	These agents more useful if nausea related to ambulation
	Meclizine (Antivert) 12.5 to 25 mg orally every six to eight hours	Oral: $0.12 to $1.05 (generic) or $1.58 to $3.35 (brand) per day	
Antipsychotics and related agents	Haloperidol (Haldol) 0.5 to 2 mg orally two to four times per day	Oral: $0.50 to $2.05 per day	Reasonable agent for treating nausea; multiple uses for haloperidol in palliative medicine
	Prochlorperazine (Compazine) 5 to 10 mg oral or IV every six to eight hours or 25 mg rectally every 12 hours	Oral: $2.67 to $3.24 (generic) or $3.21 to $4.28 (brand) per day IV: $6.70 per 10-mL vial Suppository: $6.44 to $13.78 (generic) or $7.68 (brand) per day	Prochlorperazine less sedating than promethazine
	Promethazine (Phenergan) 12.5 to 25 mg orally, IV, or rectally every four to six hours	Oral: $1.74 to $3.06 (generic) or $17.49 to $26.24 (brand) per day IV: $2.29 (generic) or $2.97 (brand) per 25-mg vial Suppository: $3.37 to $4.46 per dose	Dopamine-blocking properties less than prochlorperazine; more antihistaminic qualities
Prokinetic agents	Metoclopramide (Reglan) 5 to 10 mg orally or IV four times per day	Oral: $0.42 to $1.70 (generic) or $3.12 to $5.04 (brand) per day IV: $0.84 (generic) or $2.26 (brand) per 10-mg vial	Lower doses preferred in older patients; more useful if early satiety is the presenting problem
Serotonin antagonists	Granisetron (Kytril) 1 mg orally or IV twice per day	Oral: $104.24 per day IV: $195.20 per 1-mg single-dose vial	Because of cost, this class best reserved for treatment failures; other serotonin antagonists also available
	Ondansetron (Zofran) 4 mg orally or IV two to four times per day	Oral: $48.47 to $96.94 per day IV: $25.60 per 2-mg single-dose vial	

IV = intravenously.

**—Estimated cost to the pharmacist based on average wholesale cost in Red Book, Montvale, N.J.: Medical Economics Data, 2006. Cost to patient will be higher, depending on prescription filling fee.*

Information from references 14 through 16.

effects on the gastrointestinal tract, including decreases in motility, secretions, and blood flow, which lead to hard, dry feces.[18-20] The constipating effects of opioids are considered to be dose-related, and tolerance to this symptom rarely develops. A common goal of therapy is for patients to have one bowel movement every one to two days.[19]

Nondrug treatments, such as increasing fluid and dietary fiber intake, increasing physical activity, and establishing a toileting routine, should be implemented to minimize the risk of constipation.[21] Monotherapy with stool softeners is considered ineffective, and use of a scheduled stimulant laxative often is required.[1] There are no studies showing superiority of one laxative over another. However, one common approach is the scheduled use of senna with or without a stool softener.[1,3] If patients do not have an adequate response, a trial of an osmotic agent (e.g., sorbitol) may be used. Bulk-forming laxatives also are an option, although these agents require adequate fluid intake that may not be appropriate in all patient populations.[19] Periodic use of saline laxatives or administration of suppositories or enemas may be needed.

Constipation is the most common adverse effect occurring with chronic opioid use.

Transdermal fentanyl (Duragesic) is considered an option for patients who have difficulty with the constipating effects of oral opioids. Although not free of constipating adverse effects, transdermal fentanyl has been shown to have fewer such effects compared with various oral opioids.[21-23] A retrospective cohort study found a significantly higher risk of developing constipation with oral oxycodone (Roxicodone) compared with transdermal fentanyl.[22] A randomized crossover trial found a significant reduction in constipation in the transdermal fentanyl group compared with sustained-release oral morphine (29 and 48 percent, respectively).[23] *Table 2*[19,24] lists selected agents used to treat constipation.

One concept to reduce the adverse effects of opioids is the use of very small doses of opioid antagonists.[25-28] The rationale is that agents such as naloxone (Narcan) have a biphasic effect whereby very low doses reduce the incidence of opioid adverse effects and may augment the analgesic effect.[25,28] Much of the data are limited to the inpatient setting with intravenous administration of the opioid antagonist.[25-27] Concomitant administration of intravenous naloxone with morphine infusions has been studied, but the results have been mixed.[25-27] More research is needed before this treatment is implemented as part of routine practice.

CNS ADVERSE EFFECTS

Sedation and decreased cognition are examples of CNS adverse effects associated with opioid use. Most of the these effects are transient, although some patients require additional therapy to help cope with the unwanted effects. An initial step is to identify and eliminate unnecessary medications that may worsen underlying sedation or cognitive function.

The reported incidence of sedation is between 20 and 60 percent.[3] It commonly presents with initiation of opioid therapy or with dose increases.[7] Pharmacologic management of sedation through the use of psychostimulants (e.g., methylphenidate [Ritalin]) may be considered, although data supporting their use are lacking in clinical trials.[1,29] In addition, potential side effects of psychostimulants warrant judicious prescribing in this setting.

Cognitive changes may present, especially in patients who have cognitive dysfunction at baseline. Similar to sedation, this adverse effect appears to be related to initiation of an opioid or dose increases.[30] Persistent confusion often is compounded in the presence of infection, dehydration, metabolic abnormalities, or advanced cancer.[31] Treatment of cognitive impairment may involve the use of antipsychotics, with most of the evidence based on clinical experience in managing delirium in medically ill patients.[3] A recent Cochrane review evaluated the use of medications for treating terminally ill patients with delirium.[32] Only one study of terminal patients with acquired immunodeficiency

TABLE 2

Selected Medications for Treating Opioid-Induced Constipation

Laxative	*Adult dose*	*Onset of action*	*Cost**	*Comments*
Bulk-forming				
Methylcellulose (Citrucel)	Oral (powder or caplets): one to three times per day	12 to 48 hours	$0.38 to $0.51 per day	Source of fiber; less gas formation compared with psyllium
Polycarbophil (Fibercon)	Oral (caplets): one to four times per day	12 to 48 hours	$0.12 to $0.48 (generic) or $0.14 to $0.56 (brand) per day	May be ineffective if patient has pre-existing constipation or if patient is nonambulatory
Psyllium (Metamucil)	Oral (powder, wafer, or capsule): one to three times per day	12 to 48 hours	Powder: $4.25 (generic) for 371 g or $8.17 (brand) for 390 g Capsule: $0.09 to $0.27 per day Wafer: $0.18 to $0.55 per day	Source of fiber; adequate water ingestion required (1,000 to 1,500 mL per day)
Osmotic				
Lactulose	Oral (liquid): 15 to 60 mL per day	24 to 48 hours	$10.51 to $32.40 per 480-mL bottle	More expensive than sorbitol
Polyethylene glycol (Miralax)	Oral (powder): 17 g (i.e., one capful) in 8 oz water daily	24 to 48 hours	$2.11 per day	Lacks salty taste, making it a good option; more expensive than sorbitol
Sorbitol	Oral (liquid): 15 to 60 mL per day	24 to 48 hours	$7.23 to $7.57 per 480-mL bottle	70% solution; sweet taste
Saline				
Magnesium citrate (Citroma)	Oral (liquid): 8 oz orally once; may repeat as needed	0.5 to 3 hours	$1.49 per 300-mL bottle	Saline laxatives more useful on an as-needed basis; electrolyte imbalances are possible with all of the saline laxatives; use caution when prescribing to patients with declining renal function
Magnesium hydroxide (Milk of Magnesia)	Oral (liquid): 15 to 60 mL once; may repeat as needed	0.5 to 3 hours	$3.05 (generic) or $3.53 (brand) per 360-mL bottle	
Sodium phosphate (Phospho-Soda)	Rectal: one adult enema	Within 30 minutes	$0.80 per bottle	
Stimulant				
Bisacodyl (Dulcolax)	Oral: 10 to 15 mg one to three times per day Rectal: one suppository (10 mg) per day	Oral: 6 to 12 hours Rectal: 15 to 60 minutes	Oral: $0.13 to $0.49 (generic) or $0.40 to $1.20 (brand) per day Rectal: $0.24 (generic) or $0.86 (brand) per suppository	Not often used for opioid-induced constipation
Senna	Oral (liquid or tablet): two tablets once per day to four tablets twice per day	6 to 12 hours	$0.20 to $3.50 per day	Good first-line choice in those receiving chronic opioids
Stool softener				
Docusate sodium (Colace)	Oral (capsule or liquid): 100 to 400 mg once or twice per day	24 to 72 hours	$0.03 to $0.28 (generic) or $0.26 to $0.52 (brand) per day	Not effective as monotherapy for opioid-induced constipation; often used in combination with other laxatives

**—Estimated cost to the pharmacist based on average wholesale cost in Red Book, Montvale, N.J.: Medical Economics Data, 2006. Cost to patient will be higher, depending on prescription filling fee.*

Information from references 19 and 24.

TABLE 3
Selected Medications for Treating Opioid-Induced Central Nervous System Symptoms

Symptom	*Medication/adult dose*	*Cost**	*Comments*
Delirium or reduced cognition	Haloperidol (Haldol) 0.5 to 2 mg orally twice per day	$0.50 to $2.05 per day	Often first choice; inexpensive; minimal sedation and cardiovascular effects
	Quetiapine (Seroquel) 25 to 50 mg orally twice per day	$4.08 to $8.16 per day	More sedating than haloperidol
	Risperidone (Risperdal) 0.25 to 1 mg orally twice per day	$6.94 to $8.10 per day	Other antipsychotics also are available options.
Sedation	Dextroamphetamine (Dexedrine) 2.5 to 5 mg orally twice per day	$0.27 to $0.54 (generic) or $0.52 to $1.04 (brand) per day	Judicious use advised; adverse effects include tremor, delirium, decreased appetite, and hallucinations.
	Methylphenidate (Ritalin) 2.5 to 5 mg orally twice per day	$0.30 to $0.84 (generic) or $0.63 to $1.26 (brand) per day	

**—Estimated cost to the pharmacist based on average wholesale cost in Red Book, Montvale, N.J.: Medical Economics Data, 2006. Cost to patient will be higher, depending on prescription filling fee.*

Information from references 10 and 14.

syndrome met the criteria for the Cochrane review.[33] Haloperidol and chlorpromazine (Thorazine) were found to be effective in treating delirium in this population.[32,33] Low doses of haloperidol often are used first because of its effectiveness and low incidence of cardiovascular and anticholinergic effects.[3,10,31]

Benzodiazepines have been used with antipsychotics when severe agitation is present.[3] Although they may be used as adjunctive therapy, benzodiazepines could enhance the sedative effects and perhaps worsen cognition.[32]

An emerging concept is the use of acetylcholinesterase inhibitors for managing sedation and delirium associated with opioids. Theoretically, depression of central cholinergic activity is mediated partially through opioid use.[34] There is limited evidence supporting the use of donepezil (Aricept) for managing opioid-induced sedation and delirium.[35] *Table 3*[10,14] highlights medications used to treat the cognitive adverse effects of opioids.

TABLE 4
Selected Medications for Treating Opioid-Induced Pruritus

Medication/adult dose	*Cost**
Antihistamines†	
Cetirizine (Zyrtec) 10 mg orally once per day	$2.33 per day
Diphenhydramine (Benadryl) 25 to 50 mg orally every four to six hours	$0.16 to $0.24 (generic) or $0.69 to $1.05 (brand) per day
Fexofenadine (Allegra) 60 mg orally twice per day	$3.45 per day
Hydroxyzine (Atarax) 25 to 100 mg orally at bedtime as needed	$0.60 to $2.93 per day
Loratadine (Claritin) 10 mg orally once per day	$1.02 per day

**—Estimated cost to the pharmacist based on average wholesale cost in Red Book, Montvale, N.J.: Medical Economics Data, 2006. Cost to patient will be higher, depending on prescription filling fee.*

†—This is not an all-inclusive list. Any antihistamine can be used.

Information from reference 38.

PRURITUS

The likelihood of developing pruritus with opioid use ranges from 2 to 10 percent.[3] The probability is increased when opioids are given by epidural or intraspinal injections.[36] The postulated mechanism of pruritus is related to histamine release in the periphery or to a centrally mediated process. The pruritus associated with opioids most likely is an adverse effect rather than an allergic reaction.[7]

Prospective studies evaluating medications to treat opioid-induced pruritus are lacking. Antihistamines (e.g., diphenhydramine [Benadryl]) often are used to manage this symptom. Opioid rotation, dose reduction, or nondrug treatments such as cool compresses or moisturizers may be necessary for certain patients.[7] One case series has identified paroxetine (Paxil) as a possible treatment for pruritus in opioid-treated patients with cancer.[37] An overview is provided in *Table 4*.[38]

The Authors

JOHN M. SWEGLE, PHARM.D., is a clinical pharmacist at Mercy Family Medicine Residency Program in Mason City, Iowa, and assistant professor at the University of Iowa College of Pharmacy, Division of Clinical and Administrative Pharmacy, in Iowa City. Dr. Swegle received his doctor of pharmacy degree from the University of Iowa. He completed a pharmacy residency and a family medicine residency at the University of Iowa College of Pharmacy and the University of Iowa Hospitals and Clinics in Iowa City.

CRAIG LOGEMANN, PHARM.D., is a clinical pharmacist at Urbandale (Iowa) Family Physicians and is an adjunct associate professor at the University of Iowa College of Pharmacy, Division of Clinical and Administrative Pharmacy. Dr. Logemann received his doctor of pharmacy degree from the University of Minnesota in Minneapolis and completed a pharmacy residency at the University of Iowa Hospitals and Clinics.

Address correspondence to John Swegle, Pharm.D., Mercy Family Medicine Residency Program, 1000 4th St. SW, Mason City, IA 50401-2859 (e-mail: john-swegle@uiowa.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. Glenview, Ill.: American Pain Society, 2003.
2. Bowsell MV, Cole BE, Weiner RS, American Academy of Pain Management. Weiner's Pain Management: A Practical Guide for Clinicians. 7th ed. Boca Raton, Fla.: Taylor & Francis, 2006.
3. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol 2001;19:2542-54.
4. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther 2003;74:102-12.
5. Forman WB. Opioid analgesic drugs in the elderly. Clin Geriatr Med 1996;12:489-500.
6. Pleym H, Spigset O, Kharasch ED, Dale O. Gender differences in drug effects: implications for anesthesiologists. Acta Anaesthesiol Scand 2003;47:241-59.
7. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain 2003;4:231-56.
8. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. Cancer 1999;86:1856-66.
9. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995;10:378-84.
10. Hanks F, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny N, Calman K, eds. Oxford Textbook of Palliative Medicine. 3rd ed. New York, N.Y.: Oxford University Press, 2004:316-41.
11. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain 2001;93:247-57.
12. Sussman G, Shurman J, Creed MR, Larsen LS, Ferrer-Brechner T, Noll D, et al. Intravenous ondansetron for the control of opioid-induced nausea and vomiting. International S3AA3013 Study Group. Clin Ther 1999;21:1216-27.
13. Flake ZA, Scalley RG, Bailey AG. Practical selection of antiemetics. Am Fam Physician 2004;69:1169-74.
14. Baldessarini RJ, Tarazi FI. Drugs and the treatment of psychiatric disorders. In: Goodman LS, Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the Pharmacologic Basis of Therapeutics. 10th ed. New York, N.Y.: McGraw-Hill, 2001:485-520.
15. Pasricha PJ. Prokinetic agents, antiemetics, and agents used in irritable bowel syndrome. In: Goodman LS, Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the Pharmacologic Basis of Therapeutics. 10th ed. New York, N.Y.: McGraw-Hill, 2001:1021-36.
16. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Veder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441-51.
17. Ferris FD, Kerr IG, Sone M, Marcuzzi M. Transdermal scopolamine use in the control of narcotic-induced nausea. J Pain Symptom Manage 1991;6:389-93.
18. De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. Pharmacol Ther 1996;69:103-15.
19. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg 2001;182(5A suppl):11S-8S.
20. Herndon CM, Jackson KC II, Hallin PA. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacotherapy 2002;22:240-50.
21. Canty SL. Constipation as a side effect of opioids. Oncol Nurs Forum 1994;21:739-45.
22. Staats PS, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: a comparative study. South Med J 2004;97:129-34.
23. Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1154-8.

24. Jafri S, Pasricha PJ. Agents used for diarrhea, constipation, and inflammatory bowel disease; agents used for biliary and pancreatic disease. In: Goodman LS, Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the Pharmacologic Basis of Therapeutics. 10th ed. New York, N.Y.: McGraw-Hill, 2001:1037-58.
25. Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997;87:1075-81.
26. Sartain JB, Barry JJ, Richardson CA, Branagan HC. Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. Anesthesiology 2003;99:148-51.
27. Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirements but decreased incidence of opioid side effects. Pain 2004;107:41-6.
28. Hirayama T, Ishii F, Yago K, Ogata H. Evaluation of the effective drugs for the prevention of nausea and vomiting induced by morphine used for postoperative pain: a quantitative systematic review. Yakugaku Zasshi 2001;121:179-85.
29. Yee JD, Berde CB. Dextroamphetamine or methylphenidate as adjuvants to opioid analgesia for adolescents with cancer. J Pain Symptom Manage 1994;9:122-5.
30. Christo PJ. Opioid effectiveness and side effects in chronic pain. Anesthesiol Clin North Am 2003;21:699-713.
31. Cherny NI. The management of cancer pain. CA Cancer J Clin 2000;50:70-116.
32. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. Cochrane Database Syst Rev 2004;(2):CD004770.
33. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231-7.
34. Slatkin NE, Rhiner M. Treatment of opiate-related sedation: utility of the cholinesterase inhibitors. J Support Oncol 2003;1:53-63.
35. Bruera E, Strasser F, Shen L, Palmer JL, Willey J, Driver LC, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage 2003;26:1049-54.
36. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995;42:891-903.
37. Zylicz Z, Smits C, Krajnik M. Paroxetine for pruritus in advanced cancer. J Pain Symptom Manage 1998; 16:121-4.
38. Brown NJ, Roberts LJ. Histamine, bradykinin, and their antagonists. In: Goodman LS, Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's the Pharmacologic Basis of Therapeutics. 10th ed. New York, N.Y.: McGraw-Hill, 2001:645-67.