Opioid side effects should be anticipated and treated preemptively. Nearly all patients experience constipation that can be debilitating (see below). Failure to prevent constipation often results in noncompliance with opioid therapy. Methylnaltrexone is a drug that targets opioid-induced constipation by blocking peripheral opioid receptors but not central receptors for analgesia. In placebo-controlled trials, it has been shown to cause laxation within 24 h of administration. As with the use of opioids, about a third of patients using methylnaltrexone experience nausea and vomiting, but unlike constipation, tolerance develops, usually within a week. Therefore, when one is beginning opioids, an antiemetic such as metoclopramide or a serotonin antagonist often is prescribed prophylactically and stopped after 1 week. Olanzapine also has antinausea properties and can be effective in countering delirium or anxiety, with the advantage of some weight gain.

Drowsiness, a common side effect of opioids, also usually abates within a week. During this period, drowsiness can be treated with psychostimulants such as dextroamphetamine, methylphenidate, and modafinil. Modafinil has the advantage of everyday dosing. Pilot reports suggest that donepezil may also be helpful for opiate-induced drowsiness as well as relieving fatigue and anxiety. Metabolites of morphine and most opioids are cleared renally; doses may have to be adjusted for patients with renal failure.

Seriously ill patients who require chronic pain relief rarely if ever become addicted. Suspicion of addiction should not be a reason to withhold pain medications from terminally ill patients. Patients and families may withhold prescribed opioids for fear of addiction or dependence. Physicians and health care providers should reassure patients and families that the patient will not become addicted to opioids if they are used as prescribed for pain relief; this fear should not prevent the patient from taking the medications around the clock. However, diversion of drugs for use by other family members or illicit sale may occur. It may be necessary to advise the patient and caregiver about secure storage of opioids. Contract writing with the patient and family can help. If that fails, transfer to a safe facility may be necessary.

Tolerance is the need to increase medication dosage for the same pain relief without a change in disease. In the case of patients with advanced disease, the need for increasing opioid dosage for pain relief usually is caused by disease progression rather than tolerance. Physical dependence is indicated by symptoms from the abrupt withdrawal of opioids and should not be confused with addiction.

Adjuvant analgesic medications are nonopioids that potentiate the analgesic effects of opioids. They are especially important in the management of neuropathic pain. Gabapentin and pregabalin, calcium channel alpha 2-delta ligands, are now the first-line treatments for neuropathic pain from a variety of causes. Gabapentin is begun at 100–300 mg bid or tid, with 50–100% dose increments every 3 days. Usually 900–3600 mg/d in two or three doses is effective. The combination of gabapentin and nortriptyline may be more effective than gabapentin alone. One potential side effect of gabapentin to be aware of is confusion and drowsiness, especially in the elderly. Pregabalin has the same mechanism of action as gabapentin but is absorbed more efficiently from the GI tract. It is started at 75 mg bid and increased to 150 mg bid. The maximum dose is 225 mg bid. Carbamazepine, a first-generation agent, has been proved effective in randomized trials for neuropathic pain. Other potentially effective anticonvulsant adjuvants include topiramate (25–50 mg qd or bid, rising to 100–300 mg/d) and oxcarbazepine (75–300 mg bid, rising to 1200 mg bid). Glucocorticoids, preferably dexamethasone given once a day, can be useful in reducing inflammation that causes pain while elevating mood, energy, and appetite. Its main side effects include confusion, sleep difficulties, and fluid retention. Glucocorticoids are especially effective for bone pain and abdominal pain from distention of the GI tract or liver. Other drugs, including clonidine and baclofen, can be effective in pain relief. These drugs are adjuvants and generally should be used in conjunction with—not instead of—opioids. Methadone, carefully dosed because of its unpredictable half-life in many patients, has activity at the *N*-methyl-D-aspartamate (NMDA) receptor and is useful for complex pain syndromes and neuropathic pain. It generally is reserved for cases in which first-line opioids (morphine, oxycodone, hydromorphone) are either ineffective or unavailable.

Radiation therapy can treat bone pain from single metastatic lesions. Bone pain from multiple metastases can be amenable to radiopharmaceuticals such as strontium-89 and samarium-153. Bisphosphonates (such as pamidronate [90 mg every 4 weeks]) and calcitonin (200 IU intranasally once or twice a day) also provide relief from bone pain but have an onset of action of days.

Constipation • ***FREQUENCY*** Constipation is reported in up to 87% of patients requiring palliative care.

ETIOLOGY Although hypercalcemia and other factors can cause constipation, it is most frequently a predictable consequence of the use of opioids for the relief of pain and dyspnea and of tricyclic antidepressants, from their anticholinergic effects, and of the inactivity and poor diet that are common among seriously ill patients. If untreated, constipation can cause substantial pain and vomiting and also is associated with confusion and delirium. Whenever opioids and other medications known to cause constipation are used, preemptive treatment for constipation should be instituted.

ASSESSMENT The physician should establish the patient's previous bowel habits, including the frequency, consistency, and volume. Abdominal and rectal examinations should be performed to exclude impaction or acute abdomen. A number of constipation assessment scales are available, although guidelines issued in the *Journal of Palliative Medicine* did not recommend them for routine practice. Radiographic assessments beyond a simple flat plate of the abdomen in cases in which obstruction is suspected are rarely necessary.

INTERVENTION Intervention to reestablish comfortable bowel habits and relieve pain and discomfort should be the goals of any measures to address constipation during end-of-life care. Although physical activity, adequate hydration, and dietary treatments with fiber can be helpful, each is limited in its effectiveness for most seriously ill patients, and fiber may exacerbate problems in the setting of dehydration and if impaired motility is the etiology. Fiber is contraindicated in the presence of opioid use. Stimulant and osmotic laxatives, stool softeners, fluids, and enemas are the mainstays of therapy **(Table 10-5)**. In preventing constipation from opioids and other medications, a combination of a laxative and a stool softener (such as senna and docusate) should be used. If after several days of treatment, a bowel movement has not occurred, a rectal examination to remove impacted stool and place a suppository is necessary. For patients with impending bowel obstruction or gastric stasis, octreotide to reduce secretions can be helpful. For patients in whom the suspected mechanism is dysmotility, metoclopramide can be helpful.

Nausea • ***FREQUENCY*** Up to 70% of patients with advanced cancer have nausea, defined as the subjective sensation of wanting to vomit.

ETIOLOGY Nausea and vomiting are both caused by stimulation at one of four sites: the GI tract, the vestibular system, the chemoreceptor trigger zone (CTZ), and the cerebral cortex. Medical treatments for nausea are aimed at receptors at each of these sites: the GI tract contains mechanoreceptors, chemoreceptors, and 5-hydroxytryptamine type 3 (5-HT_3) receptors; the vestibular system probably contains histamine and acetylcholine receptors; and the CTZ contains chemoreceptors, dopamine type 2 receptors, and 5-HT_3 receptors. An example of nausea that most likely is mediated by the cortex is anticipatory nausea before a dose of chemotherapy or other noxious stimuli.

Specific causes of nausea include metabolic changes (liver failure, uremia from renal failure, hypercalcemia), bowel obstruction, constipation, infection, GERD, vestibular disease, brain metastases, medications (including antibiotics, NSAIDs, proton pump inhibitors, opioids, and chemotherapy), and radiation therapy. Anxiety can also contribute to nausea.

INTERVENTION Medical treatment of nausea is directed at the anatomic and receptor-mediated cause that a careful history and physical examination reveals. When a single specific cause is not found, many advocate beginning treatment with a dopamine antagonist such as haloperidol or prochlorperazine. Prochlorperazine is usually more