

CHAPTER 6

MANAGEMENT OF ADVERSE EFFECTS

One of the goals of opioid therapy is to maintain a favorable balance between analgesia and side effects. Effective treatment of side effects increases the likelihood of a favorable outcome and potentially allows the use of higher opioid doses, which may be necessary to control pain. Moreover, unrelieved side effects can themselves substantially impair quality of life, negating benefits derived from pain control. If intolerable side effects occur, the analgesic regimen has failed, reassessment is necessary, and an alternative therapy is indicated.

Unfortunately, studies designed to improve the management of opioid-related side effects have been limited. Management strategies are largely anecdotal and most of the recommended approaches represent an extrapolation of treatments directed against similar symptoms caused by different pathophysiologic conditions. Broad guidelines based on clinical experience also do not capture the nuances encountered in the clinical setting, such as the extent to which side effects may be influenced by expectation and learning.

These limitations notwithstanding, strategies to address the common side effects associated with opioid analgesics can be developed. Ongoing assessment and treatment of these problems are an essential element in the effort to optimize outcomes.

Constipation

The most common and persistent side effect from opioid analgesics is bowel dysmotility, leading to constipation. Diminished frequency of defecation associated with difficult or painful elimination may also contribute to abdominal discomfort, bloating and distention, and sometimes nausea and anorexia. Rarely, constipation progresses to the serious complications of obstipation and bowel obstruction.

The clinical evaluation of the patient with constipation depends on the time course of its development and on the medical setting. Without prophylaxis of some sort, most patients develop some degree of constipation after initiation or escalation of opioid therapy. Often, the relationship to the drug is clear, and other contributing factors, such as inactivity or dehydration, are apparent. In such cases, further evaluation may not be warranted

unless the clinician strongly suspects another cause that may be amenable to treatment. However, when constipation develops or worsens without a clear precipitant, a thorough evaluation of potential etiologies is necessary. Depending on the clinical situation, the history taking and physical examination (including rectal examination) may be supplemented by a laboratory evaluation, a plain radiograph of the abdomen, other imaging approaches (computed tomography, magnetic resonance imaging, or ultrasound), or a colonoscopy.

Management of opioid-induced constipation

Tolerance to the effects of opioids develops very slowly, and a large proportion of patients require laxative therapy as long as they are receiving opioid therapy. Some patients are able to improve bowel function by dietary modifications, and others may habituate to the constipating effects of these drugs and require no intervention.

The epidemiology of opioid-induced constipation is not well understood, but it is likely that younger, active patients without concurrent risk factors for constipation are least likely to have problems, whereas older patients and those with other risk factors, such as inactivity, use of other constipating drugs, and intrinsic bowel disease, are more likely to encounter difficulties. Because the use of laxatives can be expensive and burdensome, it is reasonable to limit constipation prophylaxis to patients with these other risk factors. Those who are likely at the lowest risk for this side effect can be managed expectantly.

For some patients with opioid-induced bowel dysfunction, nonpharmacologic interventions are sufficient. If possible, dietary fiber intake should be increased by adding fruits or high-fiber cereals or by using a commercially available fiber supplement. Fiber or bulking agents should be avoided if the patient is debilitated, fluid intake is limited, partial bowel obstruction is suspected, or a change in diet is impeded by anorexia or some other intercurrent medical problem. If fiber worsens symptoms, it should be discontinued.

Patients with opioid-induced constipation should be encouraged to increase their fluid intake irrespective of their fiber consumption. Generally, an intake of 2 to 3 L per day should be adequate. Whenever possible, patients who receive opioids should be encouraged to increase their activity level. Inactivity has been associated with decreasing colonic motility, and regular exercise can be important in the prevention of constipation. Patient comfort, privacy, and convenience during defecation should be ensured. In the institutional setting, use of a bedside commode

and prompt nursing response may be beneficial. Patients with limited self-reporting ability should undergo evaluation for anal fissures or hemorrhoids.

Given the individual variation in the response to different opioid analgesics, a switch from one opioid to another (opioid rotation) should be considered among the strategies used for refractory constipation. Recent surveys suggest that the transdermal fentanyl system may produce less constipation than oral morphine, and this formulation may be preferred for a trial in this setting. Very rarely, severe and refractory constipation may require the use of an alternative means of pain control (eg, neuraxial techniques) to reduce or eliminate the need for systemic opioids. In these cases, consideration must be given to the patient's overall quality of life and goals of care.

Pharmacologic strategies for constipation vary with the medical status, expectations, and responses of the patient. Various options should be discussed with the patient and treatments that are consistent with patient preference should be initiated (table 13). If the response to one approach is not favorable, an alternative should be selected.

Laxative therapy should not be initiated in patients with existing severe constipation until serious problems, such as bowel obstruction, have been excluded and the clinician is reasonably certain that impaction is not present. Examination of the rectum can reveal low impaction, but high impaction requires abdominal imaging for evaluation. Management of impaction may require physical disimpaction, repeated enemas, and a combination of rectal and oral laxatives. Routine laxative therapy can begin once impaction is ruled out or cleared.

Rectal therapies. Rectal therapies are not generally recommended for long-term management of constipation because of the inconvenience, the potential for local trauma, and the efficacy of alternative oral therapies. Enemas and suppositories are typically used for acute short-term management of more severe episodes of constipation. Nonetheless, some patients prefer the regular use of rectally administered therapy, and these measures should be available to them.

Rectal suppositories may contain an inert (eg, glycerine) or active (eg, bisacodyl) ingredient. Inert suppositories draw fluid into the rectum and act as a stimulus to defecation. Active suppositories contain a contact cathartic. Enemas may consist of a small volume containing sodium phosphate or oil or may consist of a large volume containing tap water, soap suds, or saline (table 14).

Oral therapies. Selection of a laxative therapy is largely a trial-and-error process and must be based on a comprehensive

Table 13. Stepwise approach for managing opioid-induced constipation

1. Nonpharmacologic approaches for all patients
 - Increase fluid intake as tolerated
 - Increase dietary fiber as tolerated (unless patient is severely debilitated or bowel obstruction is suspected)
 - Encourage mobility and ambulation if appropriate
 - Ensure comfort and privacy for defecation
 - Encourage bowel movements at the same time each day
 - Rule out or treat impaction
2. Consider pharmacologic interventions and discuss approaches with patient
 - Intermittent use (every 2-3 days) of an osmotic laxative, such as magnesium hydroxide, magnesium citrate, or sodium phosphate
 - Trial of a daily softening agent (sodium docusate) alone
 - Intermittent use (every 2-3 days) of a contact cathartic, such as senna or bisacodyl
 - Daily use of a contact cathartic preparation (with or without a concurrent softening agent)
 - Daily use of lactulose or sorbitol
 - Daily use of polyethylene glycol
3. Adjust dose and dosing schedule of selected therapy to optimize effects
4. Switch or combine conventional approaches if initial therapy is inadequate

assessment of the patient's medical needs, capabilities, and expectations. Currently available oral laxatives include bulk-forming agents, osmotic agents, lubricants, surfactants, contact cathartics, prokinetic drugs, agents for colonic lavage, and oral naloxone (table 15). Dosing guidelines for oral agents are summarized in table 16.

The contact cathartics are most commonly used for long-term treatment of opioid-induced constipation. Castor oil acts on the small bowel and is often poorly tolerated. The clinical experience with senna and bisacodyl is extensive, and these drugs are available over the counter. Treatment should begin with a relatively low dose (eg, 1 senna tablet at bedtime), which can then be increased every 2 to 3 days (at bedtime or in divided doses) until constipation is relieved, the patient reports side effects, or the therapy becomes too burdensome or costly to continue. Some patients prefer to use a contact cathartic intermittently, such as every 3 to 4 days if needed.

Although sodium docusate is a contact cathartic at relatively high doses, the doses used clinically only produce a surfactant effect that allows fat to mix with feces, softening the stool. This drug may be used alone or in combination with another type of laxative.

Table 14. Types of enemas

Enema	Mechanism	Indications/comments
Small volume		
Sodium phosphate	Stimulates lower bowel	May be used 1-3 times per week
Oil retention	Softens hard, impacted stool	Best if oil can be retained; administered before large-volume enema
Milk and molasses	Stimulates lower bowel; sugar in the molasses is an irritant to bowel lining and can lead to gas production that distends bowel and causes pressure, peristalsis, and evacuation	Softens hard, impacted stool
Large volume		Helpful to warm the solution; mineral oil may be added to any large-volume enema to soften stool; difficult to self-administer
Tap water	Induces peristalsis	
Soap suds	Stimulates lower bowel, promotes evacuation	Can be irritating
Saline	Stimulates lower bowel, promotes evacuation	
Harris flush (up-and-down flush)	Provides lower-bowel irrigation, promotes expulsion of flatus	Useful postoperatively

Adapted from Derby S, Portenoy RK. Assessment and management of opioid-induced constipation. In: Portenoy RK, Bruera E, eds. Topics in Palliative Care. New York: Oxford Univ Press; 1997:95-112.

The risks associated with short-term use of a contact cathartic are minimal. Long-term ingestion, however, may result in a syndrome that has been termed laxative bowel and cathartic bowel, a condition characterized by dependence on laxatives for bowel function. Risk of this syndrome is not a contraindication to therapy in the setting of advanced disease, but it should be considered in patients with long life expectancies. In the latter situation, an alternative approach to constipation—or alternate use of the contact cathartics with laxatives that have other mechanisms of action—should be considered.

Long-term treatment of constipation also may be accomplished by regular oral administration of a highly osmotic sugar,

Table 15. Agents used for opioid-induced constipation									
Class	Bulk-forming laxatives (cellulose, psyllium seeds)	Osmotic/saline cathartics (magnesium salts, sodium salts, lactulose, sorbitol)	Lubricants (mineral oil)	Surfactants (docusate sodium)	Oral lavage (polyethylene glycol)	Contact cathartics Diphenylmethane (bisacodyl), anthraquinones (cascara, senna)	Contact cathartics Castor oil	Contact cathartics Prokinetic agents (metoclopramide, domperidone)	Oral naloxone
Mechanism	<ul style="list-style-type: none"> • Increase mass and water content of stool • Decrease transit time 	<ul style="list-style-type: none"> • Increase water in bowel • Decrease transit time • Lactulose and sorbitol attract water into colon, acidify contents 	<ul style="list-style-type: none"> • Soften stool 	<ul style="list-style-type: none"> • Facilitate mixture of fat and stool 	<ul style="list-style-type: none"> • Flushes colon 	<ul style="list-style-type: none"> • Increase peristalsis • Reduce absorption of water and electrolytes from intraluminal contents 	<ul style="list-style-type: none"> • Increases secretions 	<ul style="list-style-type: none"> • Promote transit through gastrointestinal tract 	<ul style="list-style-type: none"> • Opioid antagonist
Use	<ul style="list-style-type: none"> • Should be added to most laxative regimens • May be useful in changing character of effluent from functioning stoma 	<ul style="list-style-type: none"> • Often used for bowel cleansing before medical procedures • Long-term use may be beneficial for some patients, but others find rapid onset inconvenient • Lactulose and sorbitol have slower onset and greater flexibility than magnesium or sodium salts 	<ul style="list-style-type: none"> • Not generally recommended for chronic constipation • May be used for acute constipation or fecal impaction 	<ul style="list-style-type: none"> • Doses used clinically (usually 200-400 mg/day) produce surfactant effect rather than contact cathartic effect • Usually combined with contact cathartic as first-line therapy for opioid-induced constipation 	<ul style="list-style-type: none"> • Often used for bowel cleansing before medical procedures • Available powdered formulation can be used daily for long-term management 	<ul style="list-style-type: none"> • Generally recognized as safe and well tolerated for management of chronic constipation 	<ul style="list-style-type: none"> • Not generally recommended for long-term use 	<ul style="list-style-type: none"> • Experience is limited, and trial should be considered only when constipation has responded poorly to more conventional measures 	<ul style="list-style-type: none"> • May ameliorate opioid-induced constipation without causing systemic opioid withdrawal • Should be used only if other therapies have failed • Treatment should incorporate dose escalation that identifies a dose that produces bowel withdrawal without concurrent systemic withdrawal
Problems/ comments	<ul style="list-style-type: none"> • May worsen flatulence, distention, bloating, or abdominal pain in patients with intra-abdominal disease • Avoid use in patients who are severely debilitated or have partial bowel obstruction • Significant allergies have been reported 	<ul style="list-style-type: none"> • Risks are generally minor • Severe diarrhea and dehydration may occur with overuse • Rarely, cause serious electrolyte disorders or volume overload • Patients with renal insufficiency or cardiac failure must be carefully monitored • Lactulose and sorbitol may increase flatulence 	<ul style="list-style-type: none"> • Long-term use impairs absorption of fat-soluble vitamins • Irritation of perianal area may occur • Potential for serious lipid pneumonia if aspiration occurs 	<ul style="list-style-type: none"> • Minimal risks 	<ul style="list-style-type: none"> • Diarrhea and dehydration are possible side effects 	<ul style="list-style-type: none"> • Risks associated with short-term use are minimal • Long-term use may result in laxative bowel, a condition characterized by dependence on laxatives for bowel function • Allergies to these substances have been reported • Overuse may produce dehydration 	<ul style="list-style-type: none"> • Cramping and diarrhea are common with long-term use, malabsorption of nutrients may occur 	<ul style="list-style-type: none"> • Some patients absorb sufficient naloxone and experience uncomfortable signs of abstinence 	

Table 16. Dosing guidelines for agents used in opioid-induced constipation

Class of agent	Starting dose	Effects/comments
Bulk-forming laxatives		
Psyllium	1 tbsp tid	2-4 days Must be taken with at least 8 oz of water
Methyl cellulose	1 tbsp tid	2-4 days Must be taken with fluids
Osmotic (saline) cathartics		
Magnesium citrate	1/2-1 bottle	3-6 hr
Magnesium sulfate (Epsom salts)	5-15 g	3-6 hr
Magnesium hydroxide	30-60 mL	30 min-6 hr
Sodium phosphate	45 mL	30 min-6 hr Useful as prep for colonoscopy
Lactulose, sorbitol	30 mL	24-48 hr
Polyethylene glycol	1 capful/day	Variable
Lubricants		
Mineral oil	1-2 tbsp	1-3 days
Surfactants		
Docusate	300 mg	1-3 days
Contact cathartics		
Diphenylmethane Bisacodyl	1-2 tabs	6-12 hr
Anthraquinones Cascara, senna	1-2 tabs	6-12 hr
Castor oil	1-2 tbsp	3-6 hr
Prokinetic agents		
Metoclopramide	10 mg qid	
Oral naloxone	1 mg bid	Titrate dose; monitor for withdrawal symptoms

specifically lactulose or sorbitol. Some patients are unable to tolerate this approach because of unpalatability or the occurrence of flatulence and bloating. An alternative strategy is daily use of a powdered form of polyethylene glycol. This compound is an oral lavage agent that is not absorbed and can flush the colon. Consumption of a large volume of polyethylene glycol fluid is used for colonic lavage before bowel procedures. Both the osmotic sugars and polyethylene glycol require dose titration in an effort to find a level associated with comfortable laxation.

In patients whose condition has been refractory to other types of laxative therapy, several other treatment approaches should be considered. Oral naloxone may ameliorate opioid-induced

constipation with little risk of systemic withdrawal. The compound is about 3% bioavailable. Dosing usually starts with 1 mg twice daily and is then increased gradually; some patients do not benefit until doses above 20 mg per day are reached. Use of naloxone is not without risk; some patients develop painful cramping while others absorb enough of the drug to have symptoms of systemic abstinence. This outcome is more likely to occur in patients receiving high doses of an opioid.

Although not yet commercially available, 2 promising agents are currently undergoing investigation for reversing opioid-induced bowel dysfunction without reversing analgesia or precipitating abstinence. Methylnaltrexone and alvimopan are quaternary opioid antagonists with activity that is restricted to peripheral receptors. Early studies have indicated that these agents are effective at normalizing bowel function in opioid-treated patients without affecting analgesia. If clinical trials continue to demonstrate the safety and efficacy of these products, they may allow for more aggressive use of opioid analgesics with fewer adverse effects and eliminate the need for more complicated and burdensome bowel regimens.

Nausea and vomiting

Nausea may occur after the administration of an opioid. However, tolerance usually develops rapidly, and routine prophylactic administration of an antiemetic agent is not typically indicated except in patients with a history of severe opioid-induced nausea. Some patients experience symptoms severe enough to interrupt treatment, and a small proportion have symptoms that are persistent and difficult to manage despite a trial of different agents.

Nausea and vomiting have many etiologies, and potential contributing factors should be evaluated if it is suspected that the opioid is not the entire explanation. If the assessment suggests that factors other than opioid use are contributing to the problems, antiemetic therapy may be combined with specific interventions to reverse or minimize these factors. If possible, nonessential drugs that may contribute to nausea, such as nonsteroidal anti-inflammatory drugs, should be eliminated. Constipation should be treated. Other abnormalities, such as electrolyte disturbances, gastritis, gastroesophageal reflux, or other intra-abdominal pathology, also should be addressed.

Several opioid effects may interact to produce nausea. These include direct effects on the chemoreceptor trigger zone in the lower brainstem, enhanced vestibular sensitivity, and delayed gastric emptying. Based on clinical observations, it is possible to postulate a link between the specific complaints of the patient

and the putative mechanism underlying the problem. Specifically, nausea associated with enhanced vestibular sensitivity may be accompanied by vertigo or may worsen markedly with movement. Nausea associated with delayed gastric emptying may be most severe postprandially and be associated with early satiety and bloating. These symptoms, in turn, may suggest the utility of specific treatment approaches.

Management of opioid-related nausea and vomiting

Nausea is highly noxious and must be treated promptly. Beyond the immediate benefits to the patient, prompt treatment may reduce the likelihood of conditioned responses that can complicate future management of symptoms. Conditioned nausea is suggested if the symptoms occur from the mere sight or taste of the opioid. The conditioned response may become generalized to the extent that other therapies or characteristics of the clinical situation or surroundings induce nausea. Once established, conditioned nausea can mimic pharmacologic outcomes and contribute to a poor therapeutic response.

For most patients, opioid-related nausea is adequately managed by the administration of an antiemetic agent at the time the nausea occurs, assuming that this treatment can be initiated promptly. Because opioid-induced nausea typically wanes in a period of days to weeks, interventions that may not be feasible for the long term can be tried as short-term therapeutic strategies. For example, some patients experience relief from a change in diet, including consumption of smaller, more frequent, and less spicy or pungent meals. This approach to managing opioid-induced nausea is obviously inappropriate if the symptom persists, but it may be tolerable for a period of days to weeks. If symptoms do not gradually improve during this time, the therapy must be changed.

Antiemetic therapy can be administered on either an as-needed or fixed-schedule basis. If nausea is intermittent and relatively mild, access to a drug on an as-needed basis may be sufficient. However, if the symptom is persistent and severe, continuous dosing is preferred. Should nausea be entirely controlled in the latter setting, the dose should be tapered after 1 week to determine whether tolerance has developed to the emetogenic effects of the opioid. If nausea returns as the dose is lowered, treatment should be resumed and continued for another week or so before a trial without the antiemetic is again undertaken.

There are numerous options when selecting a medication for treatment of opioid-induced nausea (table 17). However, no comparative trials have been conducted on these options, and

aside from a rationale for drug selection based on putative mechanisms (table 18), the decision to try one agent over another is based on clinical judgment, patient preference, availability, and cost. The dose-response relationships of the antiemetic drugs are not known, and treatment should explore this relationship at least to the extent of doubling the standard starting dose if the initial antiemetic response is inadequate and no adverse effects are noted. Patients differ substantially in their response to different medications, and sequential trials are sometimes needed to identify the most salutary treatment.

Based on the observation that antiemetic drugs differ in their mechanisms of action, the use of drug combinations may be reasonable. It should be appreciated, however, that no controlled clinical trials have established the safety and efficacy of any specific combination therapy. The use of concurrent therapy from unrelated classes could be justified on theoretical grounds in difficult cases.

Table 17. Antiemetic medications used in opioid-induced nausea and vomiting

Class	Examples	Initial dose*
Neuroleptics		
Phenothiazines	Prochlorperazine	10 mg PO q6h; 25 mg PR q6h
	Chlorpromazine	12.5-25 mg PO q8h
Butyrophenones	Haloperidol	0.5 mg IV q6h; 1 mg PO q6h
Anticholinergic drugs	Scopolamine	1.5 mg q3d
Antihistamines	Promethazine	25 mg PO/PR q6h
	Meclizine	25 mg PO q6h
	Diphenhydramine	25 mg PO/IV q6h
	Dimenhydrinate	25 mg PO/IV q6h
	Hydroxyzine	25 mg PO/IV q6h
	Trimethobenzamide	250 mg PO; 200 mg PR q6h
Prokinetic drugs	Metoclopramide	10 mg PO/IV q6h
Corticosteroids	Dexamethasone	1-4 mg PO/IV q8h
Benzodiazepines	Lorazepam	0.5-1 mg SL/PO/IV q4-6h
Cannabinoids	Dronabinol	2.5 mg PO q12h
5-HT₃ receptor antagonists	Ondansetron	4-8 mg PO/SL/IV q8h
	Granisetron	1 mg PO/SL/IV q12h
	Dolasetron	50-100 mg PO/IV q12h

IV, intravenous; PO, by mouth; PR, parenteral; SL, sublingual.

* May start at lower dose in older patients.

Table 18. Putative mechanisms of nausea and vomiting and their respective treatments

Mechanism	Description	Treatment
Chemoreceptor trigger zone	Nausea is described in nonspecific terms, without associated symptoms.	A neuroleptic (eg, prochlorperazine, haloperidol) or a prokinetic drug with dopamine antagonist properties (eg, metoclopramide) is typically first-line therapy. If neuroleptics are ineffective at relatively high doses, other options include a trial with an alternative opioid or route of opioid administration or treatment with an alternative neuroleptic (eg, haloperidol, chlorpromazine), antihistamine (eg, diphenhydramine, hydroxyzine), benzodiazepine (eg, lorazepam), corticosteroid (eg, dexamethasone), or serotonin antagonist (eg, ondansetron).
Enhanced vestibular sensitivity	Nausea is markedly exacerbated by movement (eg, when patient arises from bed) or is associated with vertigo, reading, or watching television.	Patients may benefit from use of an anticholinergic drug (eg, scopolamine), an antihistamine (eg, meclizine, promethazine), or a benzodiazepine (eg, lorazepam).
Delayed gastric emptying	Nausea is most severe immediately after eating and may be associated with postprandial vomiting, early satiety, and bloating.	A prokinetic drug (eg, metoclopramide) is the most reasonable initial treatment.

Some patients with severe opioid-induced nausea benefit from a change in the opioid medication (opioid rotation) or in the route of opioid administration. Specifically, patients who become nauseated from an oral opioid sometimes benefit from a switch to transdermal or parenteral administration. If this strategy is successful, it should be continued for a week or so, at which time a trial of oral therapy can be reinstated if appropriate.

Patients who experience severe opioid-induced nausea and vomiting also should be considered for cognitive therapy, particularly if the nausea appears at least partly generated by behavioral factors. Cognitive therapies have established efficacy in treatment of chemotherapy-induced emesis, and the techniques developed for this setting may be adaptable to other situations.

Somnolence and cognitive impairment

Initiation of opioid therapy or significant dose escalation can cause somnolence or mental clouding, which typically wanes over a period of days or weeks. However, some patients continue to have problems, particularly if other contributing factors exist.

Somnolence can range from mild (merely a tendency to fall asleep when not active) to severe. Cognitive impairment may range from slight inattention or befuddlement to disorientation, severe memory impairment, or extreme confusion. Perceptual disorders may accompany confusion and be limited to increased dreaming or hypnologic illusions, or involve frank hallucinations. Some patients also experience mood disturbances associated with opioid use. These may be dysphoric (extending to depression) or euphoric (extending to episodes of hypomania) occurrences; dysphoria is more common.

As with other symptoms associated with opioid therapy, the decision to pursue additional evaluation is a clinical judgment influenced by the likelihood that other factors may be contributing. If the relationship to the drug or to other factors is clear, further evaluation may not be warranted. However, if the degree of impairment or its persistence is atypical, a thorough assessment of other potential etiologies is indicated.

Management of somnolence and cognitive impairment

The approach to persistent somnolence or cognitive impairment associated with opioid therapy is best taken in a stepwise fashion based on the assessment. First, contributing causes that may be relatively simple to address should be treated. This usually involves both the elimination of nonessential medications that can depress the central nervous system and treatment of metabolic disturbances, if any are found. Second, the opioid regimen should be evaluated. If analgesia is satisfactory, it may be possible to reduce the opioid dose. An empirical 25% reduction in dose will determine whether pain will worsen or side effects will clear. Third, drug treatment directed at the symptom should be considered.

There is a large body of clinical experience in the use of psychostimulants to treat opioid-induced cognitive impairment. The most extensive experience is with methylphenidate, which is usually initiated at a starting dose of 5 mg in the morning and at noon, or a comparable dose of one of the long-acting, modified-release formulations. The dose is gradually increased until benefits occur or side effects supervene. Most patients benefit at doses well below 60 mg per day, but some require considerably

higher doses. Therapeutic effects sometimes wane over time—a phenomenon that could reflect tolerance or the cumulative effects of higher opioid doses, other drugs, or intercurrent neurologic insults. Benefit can sometimes be regained after the dose is increased.

Other psychostimulants are also commonly tried. Patients seem to react more positively to one stimulant drug than another, and a trial of a different drug should be considered if the initial therapeutic response is poor, if benefits decline over time and cannot be regained by a modest dose increase, or if side effects occur. Dextroamphetamine and a compound of amphetamine congeners are dosed in a manner identical to methylphenidate. Modafinil, a newer drug, has less risk of sympathomimetic effects, and treatment is usually initiated at a dose of 100 to 200 mg per day and then titrated. Pemoline, an older drug, is used less commonly because of an association with a rare hepatopathy.

The potential for adverse effects during psychostimulant therapy must be carefully monitored. Consequences of toxicity include tremulousness, anorexia, anxiety or other mood disturbance, insomnia, and tachycardia or hypertension. Given the potential for these adverse effects, relative contraindications for therapy include preexisting anorexia, severe insomnia, psychiatric disorder characterized by anxiety or paranoid ideation, significant cardiac disease, or poorly controlled hypertension. Older patients and those with early dementing illness are especially susceptible to untoward psychotomimetic and cognitive disturbances.

Other strategies also should be considered. Any treatment that reduces the opioid requirement might allow a degree of dose reduction that would lessen or eliminate the somnolence or cognitive impairment. Accordingly, a patient with somnolence or cognitive disturbance should be considered for any of a variety of pharmacologic therapies (eg, addition of a nonopioid or adjuvant analgesic, a trial of neuraxial drugs) or nonpharmacologic therapies (eg, a psychologic approach, another interventional strategy), as suggested by the assessment.

Other side effects

Patients receiving opioid therapy for pain management may experience a variety of other adverse effects.

Myoclonus

Myoclonus is a common dose-related adverse effect of opioids. It is associated with somnolence and cognitive impairment and, like these problems, is often determined by multiple factors. If sponta-

neous muscle contractions or spasms interfere with usual functions, cause sleep disturbance, or are in any other way distressing, symptoms can be treated empirically with a low-dose benzodiazepine (eg, clonazepam, 0.5 mg PO q6-8h) or an anticonvulsant. Based on anecdotal observations, baclofen also may be tried if treatment is needed, starting with a 5-mg dose. Similar to treatment of other opioid-related symptom complexes, strategies such as opioid rotation or nonopioid treatments that allow lowering of the opioid dose also should be considered.

Pruritus

Pruritus can occur with any opioid and is believed to be caused by opioid-mediated release of histamine from mast cells. Studies have shown that fentanyl is relatively less likely to have this effect than other pure μ -agonists. Regardless of the opioid used, itch appears to be more likely during neuraxial administration than systemic administration. The pharmacologic management of opioid-induced pruritus begins with a trial of an antihistamine, such as diphenhydramine (25-50 mg PO/IV q6h) or hydroxyzine (25 mg PO q6h). If this is ineffective, empirical trials with other medications, administered on the basis of clinical experience, might be considered. These agents include sedative hypnotics (eg, lorazepam, 1 mg SL/PO/IV q6h) and selective serotonin reuptake inhibitors (eg, paroxetine). Opioid rotation and strategies to reduce the opioid requirement may be considered as well.

Neuroendocrine effects

Opioids can interfere with the functioning of the hypothalamic-pituitary-adrenal axis and result in increased levels of prolactin or decreased levels of sex hormones, or both. The prevalence of clinically significant effects related to these changes, including sexual dysfunction, fatigue, accelerated bone loss, and mood disturbance, is only now coming under investigation. Further study is required to determine the need for systematic endocrine evaluation in these patients. Measurement of sex hormones and prolactin is reasonable should a patient describe symptoms that may be explained by these neuroendocrine effects. The role of replacement therapy is ill-defined, but again, a trial of replacement therapy could be justified if pain relief is satisfactory and symptoms that could be addressed by exogenous hormone therapy undermine quality of life.

Dysimmune effects

Opioid analgesics have effects on immune function, and studies indicate that these effects involve both cell-mediated and humoral

immunity. Peripheral effects may be mediated in some fashion by the now-confirmed existence of opioid receptors on lymphocytes. Other effects may be mediated centrally. Neither the durability (that is, the rapidity with which tolerance occurs) nor the clinical significance of opioid-related immunosuppression is yet understood. Confirmation in preclinical models that untreated nociception also suppresses immune functions, an outcome that can be reversed by opioid use, further complicates the interpretation of these effects. At present, the risk of clinically significant dysimmune effects has not been sufficiently established to recommend any change in guidelines for opioid therapy.

Respiratory depression

Respiratory depression is rarely a problem when opioids are administered according to accepted guidelines. Tolerance to this effect usually develops quickly, allowing rapid escalation of the dose by typical increments in the range of 30% to 100% of total daily dose. Combination of opioids with benzodiazepines, barbiturates, and other sleep-inducing or hypnotic drugs requires an added measure of caution because of synergistic blunting of hypoxic ventilatory drive. If the opioid dose is being increased too quickly, the risk of adverse respiratory effects is presaged by slowed respirations and other signs of central nervous system depression, including somnolence, cognitive impairment, and myoclonus. These signs usually provide a warning that the patient is at risk.

Tolerance notwithstanding, it also is true that some degree of opioid effect on respiratory function may persist over time, even if respiratory rate is normal. (Maintenance of respiratory rate is a normal compensatory mechanism and can occur even with significant shift in the carbon dioxide response curve.) The evidence for this effect is the occasional observation that patients receiving stable opioid therapy may experience respiratory depression after some other intervention that markedly reduces nociception and pain (eg, nerve block, radiotherapy to a painful metastasis, pharmacologic treatment such as high-dose steroids). To prepare for this possibility, it is prudent to monitor patients closely if this type of intervention is planned and, in the case of nerve blocks, to proactively lower the opioid dose by about 50% immediately after the procedure.

In the clinical setting, it is common for healthcare staff to attribute any respiratory problem experienced by opioid-treated patients to the opioid agent. This may lead to inadequate assessment of other contributing factors. It is important to understand that respiratory distress associated with tachypnea and anxiety is

never a primary opioid event. In this setting, an alternative explanation, such as pneumonia or pulmonary embolism, must be sought. Moreover, respiratory depression with bradypnea and somnolence that occurs in the setting of stable opioid dosing should never be assumed to be the result of the opioid alone. Even if naloxone reverses the effect, the occurrence of a problem during a stable period argues against a primary role for the opioid and should impel a search for some other cause, which may have combined with subclinical opioid effects.

Naloxone should be administered only for symptomatic respiratory depression, because of the risk of systemic withdrawal and the return of pain. If peak plasma levels of the opioid have already been reached and the patient is arousable, naloxone should not be administered; instead, the next opioid dose should be withheld and the patient monitored until improved. If the patient is becoming progressively obtund and is unarousable, naloxone should be administered using small bolus injections of dilute solution (eg, 1-mL doses of 0.4 mg of naloxone diluted in 10 mL of saline), which are titrated against respiratory rate. Patients receiving sustained-release opioid formulations or drugs with a long half-life (eg, methadone, levorphanol) may require a naloxone infusion to prevent recurrence of respiratory depression.

Suggested readings

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