STRATEGIES FOR THE MANAGEMENT OF OPIOID-INDUCED ADVERSE EFFECTS

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ABSTRACT

Opioids have the potential to produce a broad range of adverse events, including sedation, respiratory depression, nausea, vomiting, and constipation. Many of these adverse effects diminish over time as tolerance develops, although tolerance to some effects develops very slowly or not at all. The adverse event profiles of the various opioids are generally similar when administered at equianalgesic doses, although individual patients may respond differently to the various agents. In addition, some opioids (eg, meperidine and propoxyphene) are associated with relatively high rates of adverse events, and are not recommended as first-line analgesics. Sedation and nausea are common with opioid initiation or dose escalation, and may be exacerbated by a number of other medications or comorbid conditions. Opioids produce a number of central and peripheral effects that contribute to nausea and vomiting. Constipation is very common with opioid therapy, and is generally not significantly relieved by the development of tolerance. A bowel regimen that includes a stool softener and a stimulant laxative is essential for every patient who is using an opioid analgesic. Bulk-forming laxatives are not recommended for patients taking opioids. Strategies to reduce opioid-induced adverse events include cautious dosage titration, dose reduction, management of specific symptoms, opioid rotation, or using a different route of administration. Opioid conversion may be calculated using published conversion charts, but must be individualized on the basis of the patient's treatment history and other clinical characteristics. Pharmacists perform many essential roles in the management of acute pain, including patient education, ensuring the accuracy and safety of prescribed medications, and performing regular assessment of the efficacy and safety of opioid therapy.

(*Adv Stud Pharm.* 2008;5(2):52-57)

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An important goal of pain management is to provide adequate pain relief while ensuring patient safety. Opioids are powerful analgesics that are generally well tolerated for the treatment of acute pain in many different clinical settings. They also have the potential to produce a broad range of adverse effects, including sedation, respiratory depression, nausea and vomiting, and constipation. Opioid-induced adverse events are often difficult for patients to tolerate, and may interfere with treatment adherence and relief from pain. However, tolerance to many of these adverse events develops relatively quickly, and others may be effectively managed by adjunctive therapies, many of which are available without a prescription. Patient education is essential to reduce the risk of opioid-related adverse events and to help patients attain the greatest possible pain relief.

Several factors influence the risk of opioid-related adverse events. There is little evidence that any particular opioid is associated with a significantly lower risk of adverse events in general when administered at equianalgesic doses, although the responses of individual patients to the different agents may vary.[1] Most adverse events are dose related, including respiratory depression and sedation,[2] whereas other adverse effects (eg, constipation) are less closely related to the opioid dose. Many patients take other medications that produce additive or even synergistic adverse effects. Patient factors that influence the risk of adverse effects include genetic variability, comorbid conditions, and age. Older patients in particular are more likely to experience pain

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due to higher rates of surgical procedures, injuries, or painful medical conditions; they are more likely to have comorbid conditions that may complicate therapy; and they are more likely to experience adverse effects of treatment.[3] Patients with renal impairment may have higher rates of adverse events with opioids that produce toxic metabolites that are renally excreted. For example, renally excreted metabolites of morphine or meperidine (morphine-3-glucuronide and normeperidine, respectively) contribute to the adverse events associated with these medications.[1]

In general, strategies to reduce adverse effects include reducing the opioid dose, symptom management by the addition of other medications, opioid rotation, or switching to another route of administration. Gradual dose reduction is usually attempted for patients with well-controlled pain who are experiencing dose-related adverse effects. Numerous symptomatic treatments are used for patients with opioid-related adverse effects, several of which are described in detail below. However, polypharmacy also increases the risk of drug interactions and new adverse effects. Many studies have demonstrated that rotation to a different opioid often helps to improve tolerability, which may reflect patient-to-patient variation in genetics, comorbid conditions, or accumulation of metabolites.[4,5] Individual opioids may also possess subtle differences in their agonist or antagonist effects at different receptor subtypes that influence the likelihood of adverse events. This possibility is supported by studies that have demonstrated incomplete cross-tolerance to different opioids.[6]

Sedation

Sedation commonly occurs with the initiation of opioid therapy or with dosage increases, and may be accompanied by transient drowsiness or cognitive impairment. The likelihood of sedation is increased by several comorbid medical conditions (eg, dementia, metabolic encephalopathy, and metastases of the brain in patients with cancer) or by other medications (eg, antidepressants, anticonvulsants, and muscle relaxants).[7] There are several options for the management of opioid-related sedation, including assessing and managing any comorbid conditions that may contribute to sedation, discontinuing or reducing the doses of other sedating medications, opioid rotation, or the addition of a psychostimulant (eg, caffeine, dextroamphetamine, methylphenidate, or modafinil).[8]

Respiratory Depression

Respiratory depression with opioid treatment is potentially the most dangerous opioid-related adverse event, often occurring in first-time opioid users who receive a short course of oral opioids.[2] Tolerance to the respiratory effects of opioids usually develops within a few days to several weeks. Respiratory depression may be managed by reducing the opioid dose or dosing frequency. In severe cases, an opioid antagonist may be required to rapidly reverse respiratory depression. Sudden, severe sedation is often a warning sign of an increased risk of dangerous respiratory depression, and indicates the need for opioid dose reduction or an increased period between doses.

Opioids may also complicate sleep apnea. A recent observational study of 140 patients with chronic pain who were receiving stable doses of opioids included an assessment of a night's sleep using overnight polysomnography.[9] Obstructive or central sleep apnea occurred in 75% of the patients, which is significantly higher than the rate of sleep apnea among the general population (approximately 2%–4%). An index of apnea or hypopnea was directly related to the daily dosage of methadone, and was also higher in opioid-treated patients who received benzodiazepines. Although sleep apnea has primarily been studied in patients with chronic pain, acute opioid treatment has also been shown to exacerbate sleep apnea.[10,11]

Nausea and Vomiting

Nausea and vomiting affect an estimated 30% to 60% of patients who are treated with opioids, and are described by patients as highly distressing.[7] Opioids produce nausea and vomiting by several distinct mechanisms. Nausea and vomiting are influenced by several different sensory pathways that converge on a "vomiting center" in the brain stem.[12] These include the chemoreceptor trigger zone (CTZ), a region of the brain that is especially sensitive to toxins; the vestibular apparatus of the ear, which regulates balance and causes nausea during motion sickness or in individuals with vestibular disease; and the vagus nerve and gastrointestinal tract, which respond to gastric irritation, intestinal distention, or to stimulation of the gag reflex. The opioids contribute to nausea and vomiting by activating all of these mechanisms, including stimulation of the CTZ, gastric stasis, and enhanced vestibular sensitivity. Tolerance to nausea and vomiting develops slowly. Nausea and vomiting may be exacerbated by comorbid conditions such as hypercalcemia, increased intracranial pressure, or the use of emetogenic drugs (eg, digoxin, antibiotics, iron, and cytotoxic agents). Options for the medical management of nausea and vomiting include dopamine antagonists (eg, haloperidol and prochlorperazine),

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serotonin antagonists, prokinetic agents (eg, metoclopramide), or agents that are used to treat motion sickness (eg, diphenhydramine and scopolamine).[13-15]

Constipation

Constipation is among the most common adverse effects of opioid therapy. The binding of endogenous or exogenous opioids to opioid receptors in the gastrointestinal tract suppresses intestinal peristalsis and decreases the release of mucosal secretions, resulting in impaired defecation response, increased fluid reabsorption, and the formation of dry, hard stools.[12,16] In contrast with most other opioid-related adverse events, tolerance does not develop to opioid-induced constipation. Other factors that contribute to constipation in opioid-treated patients include physical inactivity, dehydration, or the use of other drugs. The US National Health and Wellness Survey examined the impact of constipation among patients using opioid medications for the relief of chronic pain. Constipation was the most common and persistent side effect of opioid therapy, and was associated with patient self-reported impairment of the ability to work or carry out other normal activities.[17] A related condition, opioid bowel dysfunction (OBD), is characterized by abdominal pain and distension, nausea and vomiting, urinary retention, confusion, hard stools, straining, pseudodiarrhea (increased stool frequency but reduced stool mass), anorexia, and gastro-esophageal reflux.[18,19]

A bowel regimen is essential for every patient who is using opioid therapy. Pharmacotherapy for opioid-induced constipation includes the use of softening agents (eg, docusate 200 mg per day), osmotic laxatives (eg, lactulose and sorbitol 15–30 mL twice daily, administered orally or rectally), and stimulant laxatives (eg, biscadoyl or senna, combined with a stool softener).[12] Because of the suppression of peristalsis by opioids, bulk-forming laxatives or the use of a stool softener without a stimulant laxative should be avoided.[12] Traditional laxative therapies alone may not be adequate for patients with OBD. It is also be possible to reduce the impact of OBD by modifying the effects of opioids on the bowel using opioid antagonists that target opioid receptors in peripheral tissues. Several studies have demonstrated that oral naloxone relieves at least some opioid-induced constipation,[20,21] although the use of naloxone may require an increase in the opioid dose. Methylnaltrexone bromide was recently approved for the restoration of bowel function in patients with late-stage, advanced illness who are receiving opioids on a continuous basis for pain relief.[22] Other peripheral opioid antagonists are being studied for the prevention of OBD.[23] Finally, novel opioid pain relievers that are currently in development may provide pain relief with less risk of constipation. A recent phase III clinical trial examined the efficacy and safety of tapentadol—a novel μ opioid receptor agonist and norepinephrine reuptake inhibitor—in patients with severely painful joint conditions.[24] At the end of 5 days of treatment, tapentadol doses of 50 mg or 75 mg produced pain relief that was similar to that of a relatively low dose of oxycodone (10 mg), but with a lower incidence of gastrointestinal adverse events. Constipation was noted for 18% and 21% of patients with tapentadol 50 mg and 75 mg, respectively, compared to 41% of patients who received oxycodone.

Other Adverse Effects of Opioid Therapy

Opioid therapy has the potential to produce a range of other adverse effects that can be troubling for patients. Delirium—an acute confusional state—sometimes occurs with initiation of opioid therapy or when the dosage is increased. In some cases, delirium may cause significant disturbance of consciousness and comprehension. Delirium may also be exacerbated by comorbid conditions or other drug therapy. The risk of delirium may be greater with highly lipophilic opioids, which produce more rapid receptor occupancy. Management of delirium in an opioid-treated patient includes an assessment of other potential causes, discontinuation or dose reduction of other medications, or switching to a different opioid.[25,26] In severely ill patients (eg, patient with acquired immune deficiency syndrome), delirium may be improved by the addition of an antipsychotic (eg, haloperidol and chlorpromazine) to the treatment regimen.[26]

Myoclonus (brief, uncontrolled movements, especially of the arms and legs) has been noted with several opioid medications (including meperidine, morphine, hydromorphone, methadone, and fentanyl), and is more common with high opioid doses.[13] The mechanism of action is not well established, but may be related to metabolites formed during opioid metabolism. Most patients who experience myoclonus exhibit relatively mild twitching, whereas others develop involuntary limb movements, spasms, or pain. Myoclonus may be alleviated by reducing the dose of opioid, increasing the dose of adjunctive pain relievers, switching to a different opioid, or by adding a benzodiazepine or a muscle relaxant (eg, dantrolene).[27,28] Finally, pruritus is often a problem with opioid medications. Although it is especially common among patients who receive intrathecal opioids, it may be encountered with any route of administration. Pruritus is thought to be caused by opioid-induced

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release of histamine from mast cells, but some agents (eg, fentanyl) appear to cause itching without stimulating histamine release.[1] Pruritus may be managed using antihistamines, opioid rotation to an agent with less histamine release (eg, fentanyl and oxymorphone), or the serotonin 5-HT3 antagonist ondansetron.[8]

Patients who are using opioids require close monitoring of both efficacy and adverse events. Table 1 shows important assessments for the subjective and objective outcomes for both efficacy and safety. Table 2 summarizes strategies to manage some of the most common adverse effects of opioid therapy.

High-Risk Agents

Some opioids are associated with greater risk of adverse events, and should be used with caution. Meperidine possesses a short duration of analgesic efficacy, but has a long-lasting neurotoxic metabolite (normeperidine) that can cause dysphoria, nervousness, tremors, myoclonus, and seizures.[1] Normeperidine is eliminated by the renal route, and the risk of adverse effects is greater for patients with diminished kidney function. Opioid antagonists such as naloxone should not be administered to a patient with meperidine-induced seizures. Naloxone does not antagonize the effect of normeperidine, and may actually exacerbate seizures.[1] The American Pain Society recommends that meperidine should be avoided for first-line therapy, that it should be reserved for patients who cannot tolerate or have allergies to other agents, and that it should not be used for more than 48 hours.[8] Meperidine should also be avoided in patients with impaired renal function, convulsive disorders, atrial flutter, or supraventricular tachycardia.[8] Similar to meperidine, the metabolism of propoxyphene yields a long-lasting metabolite (norpropoxyphene) that is renally excreted and that can cause several adverse effects, including cardiotoxicity, pulmonary edema, and cardiac arrhythmias.[1]

Opioid Conversion

As described earlier in this article, switching to a different opioid is a common management strategy for patients who having difficulty tolerating their pain medication. Opioid switching is also useful when patients no longer attain pain relief from their medication, patient status changes (eg, the patient is unable to use a particular formulation, or is moving from the inpatient to the outpatient setting), or because of pharmacokinetic properties of the different opioids (eg, switching a patient with renal failure to methadone or fentanyl, neither of which have pharmacologically active metabolites).[29] The patient's total daily opioid is determined, and an opioid conversion chart is used to determine an estimated dose for the

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Table 1. Subjective and Objective Assessment of Efficacy and Toxicity of Opioid Analgesics

Case Example: Mrs Smith is a 68-year-old woman with left hip replacement. She has been discharged from the hospital to a rehabilitation facility for physical therapy and continued pain management. She complains of pain in her left hip that can prevent her from participating in therapy, and frequently awakens her at night.

Once Mrs Smith is started on an appropriate analgesic regimen, the pharmacist would monitor for the following subjective and objective parameters of therapeutic effectiveness and potential toxicity:

	Subjective Parameters	Objective Parameters
Therapeutic effectiveness	• Pain rating (best in a 24-hour period, worst, and average) • Perceived abilities to perform activities of daily living (walking, sleeping, self-care, participating in therapy, etc)	• Distance able to walk • Time able to participate in therapy • Hours able to sleep without awakening
Potential toxicity	• Complaints of abdominal fullness, cramping, straining to defacate, and hard/dry stools • Complaints of sleepiness and confusion • Complaints of nausea • Complaints of itching	• Bowel movement frequency • Number of episodes of emesis • Mini-Mental State Examination • Signs of excoriation • Respiratory rate • Pupil size • Level of arousal (sedation scale) • Observed muscle twitching/jerking (myoclonus)

new opioid. Although an explanation of opioid conversion calculations is beyond the scope of this article, the practitioner would use an equianalgesic opioid chart, and calculate the appropriate dose of the new opioid that would be approximately equivalent to the original opioid. The dose is then individualized based on the patient's specific characteristics, and follow-up and reassessment are continued.

Drug Interactions

Opioids interact with several other medications, which may result in decreased analgesic efficacy, increased sedation, and the risk of potentially serious adverse events.[30] The metabolism of meperidine is increased by phenobarbital and phenytoin, possibly resulting in decreased analgesic effect. Similarly, the metabolism of methadone is increased by phenytoin and rifampin, resulting in a lower serum methadone concentration. The bioavailability and half-life of morphine may be increased by clomipramine and amitriptyline, increasing both analgesic effect and sedation. For all of the opioids, increased sedation may occur with concomitant use of antihistamines, benzodiazepines, antidepressants, and antipsychotics.[1] Monoamine oxidase inhibitors or selective serotonin reuptake inhibitors have been associated with potentially fatal hyperpyrexia when administered with meperidine, and with seizures when administered with tramadol. Codeine, oxycodone, and hydrocodone are metabolized by the cytochrome P450 CYP2D6 enzyme, and drugs that inhibit the CYP2D6 enzyme may decrease the analgesic effects of these drugs.

The Role of the Community Pharmacist in Acute Pain Management

Many patients with pain first discuss their symptoms and potential treatment options with a pharmacist. Pharmacists are in an excellent position to identify patients who may be exceeding the maximum recommended dose of acetaminophen with combination analgesics (total of 4 g per day),[31] and to monitor the efficacy and safety of opioid therapy.

Other important roles of the pharmacist in pain management include:

- Compounding and dispensing to patients for analgesia and symptom control;
- Educating pharmacists and other clinicians about the pharmacotherapy of analgesia;
- Patient education, including obtaining medication histories, discussing medication use and adverse effects, and providing patients with correct and understandable printed materials;
- Ensuring continuity of care from hospitalization to postdischarge, including assessment of the

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Table 2. Overview of Adverse Effects and Their Management

Adverse Effect	Tolerance	Management
Constipation	No	• Patient education is essential. • Prescribe a stool softener (eg, docusate) and a laxative (eg, senna, MOM, bisacodyl, magnesium citrate, lactulose, or sorbitol) to be taken as needed.
Nausea, vomiting	Yes	• Tirate slowly. • Add or increase nonopioid or adjuvant analgesic so that the opioid dose can be reduced. • Prochlorperazine and metoclopramide are helpful.
Histamine reactions	Yes	• Add or increase nonopioid or adjuvant analgesic so that the opioid dose can be reduced. • Premedication with diphenhydramine 25–50 mg orally is helpful. • Switch to a different opioid.
Mental confusion, sedation	Yes	• Add or increase nonopioid or adjuvant analgesic so that the opioid dose can be reduced. • Withhold 1–2 doses and/or reduce opioid dose by 10%–25%. • Administer a lower dose more frequently to reduce peak concentrations. • Eliminate concomitant, nonessential CNS depressants.

CNS = central nervous system; MOM = milk of magnesia.
Adapted with permission from Oregon Health Science University. Guide to prescribing opioids for chronic nonmalignant pain. Available at: http://www.ohsu.edu/ahec/pain/part2sect8.pdf. Accessed February 10, 2008.[7]

patient's ability to pay for medications;
- Formulary management;
- Developing institutional policies and procedures to satisfy Joint Commission on Accreditation of Healthcare Organizations guidelines, in addition to state and federal regulatory requirements; and
- Participation in research regarding new treatments and patient outcomes.[30]

Conclusions

Adverse events that commonly occur among patients who are treated with opioid analgesics include sedation, respiratory depression, nausea and vomiting, constipation, and others. Many of these effects decrease over time as patients develop tolerance. Tolerance to constipation develops very slowly or not at all, and a bowel regimen is important for all patients who are using opioids. Several options are available to manage opioid-induced adverse events, including dose reduction, symptom management, and opioid rotation. Pharmacists carry out several tasks that are essential in the safe and effective use of opioid analgesics, including assessing treatment responses, monitoring for adverse events or potential drug interactions, educating patients about their opioid therapy, and helping patients to manage adverse events.

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