Current Management of Opioid-Related Side Effects

ABSTRACT: The optimal management of opioid-related side effects is hampered by a lack of comparative studies of management strategies. The prevalence of such side effects is influenced by the extent of disease, the patient's age, the presence of coexistent renal and hepatic disease, pulmonary disease, and cognitive dysfunction, a prior opioid history, use of polypharmacy, dose of opioid drug being administered, and the route of administration. The most common opioid-related side effects are constipation, sedation, nausea, vomiting, and cognitive disturbance. Less frequent side effects include urinary retention, perceptual distortion, respiratory depression, and myoclonus. In an era emphasizing quality of life in cancer care, clinicians need to be aware of (1) factors that influence the prevalence of opioid-related side effects, (2) effective management strategies, and (3) how to recognize when symptoms are opioid related as opposed to caused by other etiologies, such as the patient's disease process or treatment approaches. The use of validated instruments and repeated assessment enhances such an evaluation and subsequent treatment. This article delineates the current optimal management of opioid-related nausea and vomiting, constipation, cognitive side effects, myoclonus, and respiratory depression. [ONCOLOGY 15(1):61-82, 2001]

Introduction

Opioid use is associated with a wide range of side effects, the most common of which are constipation, sedation, nausea, vomiting, and cognitive disturbance. Less frequent side effects include urinary retention, perceptual distortion, respiratory depression, and myoclonus. Adding to the complexity of the assessment and management of these side effects is the multifactorial etiology of many of these symptoms in the cancer patient. TABLE 1

In day-to-day clinical practice, the management of opioid-related side effects is heuristic, based on clinical experience rather than research. Few studies have compared the incidence of the side effects associated with one narcotic vs another or have explored the role of the route of administration in provoking side effects.[1-9] Several studies of opioids are summarized in Table 1. Much of the available comparative data, however, comes from surveys that lack information on the doses used.

Altering the Opioid Regimen
A prospective study of 100 cancer patients evaluated by a pain and palliative care service found that alterations in the opioid regimen, including changes in the drug and/or route of administration, were made in 80% of patients. Of these alterations, 17.7% were instituted to simultaneously improve pain control and decrease opioid toxicity, while 25% were aimed at diminishing side effects in the setting of controlled pain.

About 31% of the alterations in pain management approaches were made for the convenience of the patient in the setting of controlled pain—for example, the conversion of a patient’s opioid medication from a parenteral patient-controlled analgesia delivery system to an oral or transdermal route of administration in order to simplify a hospital discharge plan. An additional 19% of changes were made to reduce the invasiveness of therapy in the setting of controlled pain, such as conversion from parenteral to oral opioid medication regimens.[10]

**Goals of Care**

The personal impact of an individual side effect often depends on the stage of a patient’s illness and the goals of care. For example, opioid-related sedation may cause minimal distress to a patient in the last days of life, and in fact, may be desirable. However, its occurrence earlier in the course of a patient’s illness may be a source of distress to the patient and family, leading to noncompliance with a given medication. Having a clear understanding of the goals of care for the patient will dictate the decision to aggressively work-up an individual symptom or side effect or to change the management approach, switching, for example, to a different opioid or route of administration.

Unfortunately, in a patient who is receiving opioid therapy, nausea, vomiting, constipation, sedation, cognitive and perceptual disturbances, respiratory depression, and myoclonus are too often dismissed as being opioid related, without further assessment for other possible etiologies. In addition to missing potentially serious and treatable diagnoses, this approach may result in a decreased dose or premature discontinuation of the opioid and, therefore, increased pain and suffering for the patient. A patient may also be converted unnecessarily from a convenient, economical route of drug delivery to a more cumbersome and costly route. TABLE 2

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**TABLE 2**

Role of Polypharmacy, Patient Age, and Comorbidities in Opioid Side Effects

Our understanding of the mechanisms underlying opioid-related side effects is hampered by a deficit of studies in this area. These side effects are known to occur in patients with advanced disease, the elderly, those with coexisting renal, hepatic, pulmonary, and cognitive dysfunction, and patients who have been receiving opioids for an extended period of time (Table 2).[11-23] In addition, clinical observations have associated the route of opioid administration with the occurrence of side effects. For example, nausea, vomiting, and constipation may occur more frequently when opioid medications are administered orally.

**Role of Opioid Receptors**

Certain opioid side effects may be mediated by specific opioid receptors. For example, activation of the mu-1 receptor may be associated with pruritus, whereas activation of the mu-2 receptor may mediate cardiovascular effects, delayed gastrointestinal tract transit time, and respiratory depression. Most mu receptors are found in the areas of the brain responsible for opioid-induced analgesia. None of the opioid agonists—morphine, meperidine, hydromorphone, oxymorphone (Numorphan), levorphanol (Levo-Dromoran), fentanyl, sufentanil, alfentanil (Alfenta), and methadone—selectively activate the mu-1 receptor without activating the mu-2 receptor. The opioid agonist-antagonists—butorphanol (Stadol), nalbuphine, and pentazocine (Talwin)—are weak mu-receptor antagonists and weak delta-receptor agonists. Both butorphanol and pentazocine act as agonists at the kappa receptor but nalbuphine is a partial kappa-receptor antagonist. The analgesia obtained from the agonist-antagonist medications mainly derives from kappa-receptor activation.
Because the opioid agonist-antagonist medications (ie, butorphanol, nalbuphine, pentazocine) can cause withdrawal symptoms in patients who exhibit tolerance to the effects of pure opioid agonist medications (ie, morphine, meperidine, hydromorphone, oxymorphone, levorphanol, fentanyl, sufentanil, alfentanil, methadone), they are not commonly used in patients with cancer pain who are likely to need chronic opioid therapy. Importantly, when there is a prevalence of side effects, kappa-receptor activation appears to be associated with sedation and psychotomimetic effects, including dysphoria and hallucinations, miosis, and mild respiratory depression.[24]

The assessment and management of opioid-related nausea and vomiting, constipation, cognitive changes, myoclonus, and respiratory depression are reviewed below.

**Nausea and Vomiting**

Nausea and vomiting are not uncommon at the start of opioid therapy. Tolerance to this effect typically occurs within days to weeks. Opioid-associated nausea usually does not require treatment or requires only temporary treatment, although a minority of patients will require opioid rotation or a change in route of administration for management. Anecdotal experience suggests that this side effect occurs more frequently with lower doses of morphine than with higher doses. Survey data show small differences in the overall prevalence of nausea from one opioid to another. There is currently no evidence to suggest that mu-receptor agents such as codeine, dextropropoxyphene, morphine, hydromorphone, meperidine, levorphanol, fentanyl, and methadone are less emetogenic than other opioids. In a study of 260 patients treated with opioids for cancer pain, 8.3% of those who received buprenorphine (Buprenex) developed nausea at the onset of therapy, compared with 18.3% of patients treated with morphine, 16.2% treated with codeine, and 10% treated with oxycodone. At 72 hours, these percentages rose to 22.7%, 28%, 29.7%, and 18%, respectively. Refractory nausea and vomiting led to the use of an alternative opioid in 22% of patients after 72 hours. This study did not control for starting dose.[25]

Opioid-induced nausea may be triggered by afferent input to the medullary emesis center from gastrointestinal receptors, vestibular centers, the cerebral cortex, and the chemoreceptor trigger zone. Nausea that occurs primarily with movement can be assumed to be generated by input from the vestibular center. Nausea and vomiting that is postprandial and associated with a feeling of bloating and satiety suggests a gastrointestinal etiology.

Studies of opioid-treated animals have demonstrated reversal of the emetic response following administration of the mu-opioid antagonist naltrexone (ReVia, Depade).[26]

**Assessment**

Clinicians should investigate nausea and vomiting as separate issues, since either symptom may occur in isolation. Assessing the severity of nausea/vomiting is often difficult. Observer-rated measures of nausea tend to underestimate its frequency. Indirect measures, such as the patient’s appetite and food intake, tend to be confounded by disease stage. The patient’s visual analog scale reports of nausea, especially in those with advanced disease, may be compromised by cognitive impairment occurring in conjunction with the symptom or its treatment. **FIGURE 1**

Furthermore, some of the therapies available for the treatment and/or prevention of nausea and vomiting (eg, phenothiazine, butyrophenones, benzodiazepines) may exacerbate cognitive impairment, further limiting assessment. The most practical quantification of emesis is observer assessment of the number of episodes and duration of emesis. The association of nausea or vomiting with an opioid may be validated by eliciting a temporal relationship between the two.[27]
The extent of the work-up in a patient complaining of nausea and/or vomiting who is receiving opioid therapy for pain is dictated by the clinical setting and the goals of care (Figure 1). Given the potential for intestinal obstruction in many of these patients, the work-up, at a minimum, includes examination for abdominal distension, organomegaly, and bowel sounds. A neurologic examination should also be performed, given the association between refractory nausea and intracranial pathology.

The appearance of nausea in conjunction with a recent dose escalation or the initiation of opioid therapy, particularly when the nausea responds to conservative measures, should not prompt a work-up for alternative etiologies. However, nausea and vomiting occurring during a time of stable opioid dosing should be investigated further, especially if these symptoms are refractory to therapy or associated with abnormalities on physical examination.

Assessment of electrolytes and calcium levels may be indicated. If the physical examination is suggestive of focal pathology, computed tomography (CT) scans of the head or abdomen should be performed, as dictated by the goals of care. Any nonessential medications with emetogenic potential (eg, serotonin-reuptake inhibitors, antibiotics, and nonsteroidal anti-inflammatory drugs [NSAIDs]) should be discontinued or their doses adjusted.

**Management**

An immediate clinical decision concerns whether to treat the side effect or switch opioids and/or the route of administration with the goal of eliminating or decreasing the symptom. Because nausea and vomiting is not uncommon at the start of opioid therapy and tolerance to this effect typically develops within days to weeks, only a minority of patients will require opioid rotation or a change in the route of drug administration. The following discussion focuses on the treatment of the symptom rather than on changing the opioid or route of administration.

**Treating the Symptom:** In patients with dyspepsia who are being treated with NSAIDs, consideration should be given to discontinuing the NSAID. If the NSAID is an important part of the patient’s therapy, adding a histamine-2-receptor antagonist such as ranitidine, nizatidine (Axid) or prostaglandin analogs such as misoprostol (Cytotec) may be appropriate. In patients who are constipated, optimizing their bowel regimen may improve or eliminate the symptom. Patients with bloating and postprandial nausea may benefit from small, more frequent meals, and patients with a compromised biliary system may find that their symptoms improve with low-fat meals.

Most patients will respond to antiemetics that are active at the chemoreceptor trigger zone. These include the phenothiazine antiemetics, such as prochlorperazine and chlorpromazine, and the butyrophenones, haloperidol, and droperidol. These agents should be administered at the standard dose initially, with the dose doubled as indicated by clinical response. There is wide individual variability in response to these agents and, therefore, assessment and reassessment of treatment efficacy is essential. Haloperidol appears to be the most active of the dopamine-receptor antagonists at the chemoreceptor trigger zone.

Metoclopramide and domperidone (Motilium, investigational) have less dopamine-receptor antagonist function. Motility agents such as metoclopramide and domperidone are indicated in patients with postprandial fullness and a high likelihood of autonomic neuropathy (eg, patients with intra-abdominal disease, multiple surgeries, or recent chemotherapy). Because it penetrates the blood barrier to a lesser extent, domperidone is associated with fewer and less severe extrapyramidal side effects and central nervous (CNS) system toxicity than metoclopramide. Metoclopramide is thought to act by increasing gastrointestinal cholinergic activity through activation of a 5-HT receptor. Antiemetics should be administered on an around-the-clock dosing schedule if a trial of intermittent as-needed dosing is ineffective. Metoclopramide, prochlorperazine, and chlorpromazine are available in suppository formulations. Haloperidol can be given subcutaneously, whereas prochlorperazine and chlorpromazine cause subcutaneous irritation and should not be administered subcutaneously. TABLE 3

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**TABLE 3**

| Antiemetics Used in the Management of Opioid-Associated Nausea |}
and Vomiting

If nausea and vomiting fail to respond to the above measures and the pattern of nausea and vomiting suggests that it is movement related, a trial of an anticholinergic medication (eg, scopolamine or atropine) or an antihistamine (eg, meclizine or cyclizine [Marezine]) should be considered. Scopolamine and cyclizine can be administered subcutaneously. Refractory nausea may be treated with a combination of antiemetics from different drug classes (Table 3). However, because of their cost, the newer, more selective 5-HT-receptor antagonist medications (eg, ondansetron [Zofran], dolasetron [Anzemet], and granisetron [Kytril]) are considered second- and third-line drugs in the management of opioid-related nausea and vomiting. A trial of these drugs may be useful, for example, if the symptom persists or if the patient develops dystonic reactions or uncontrolled and distressing anticholinergic side effects from metoclopramide or prochlorperazine therapy.

Constipation

Constipation is defined as a reduction in the frequency of bowel movements to less than one every 3 days, or difficulty passing stool. It is perhaps the most prevalent of the opioid side effects and has the distinction of being the least likely major side effect to which patients develop tolerance. In one survey of hospitalized patients with cancer-related pain who were receiving opioids, 21.7% to 39.4% reported constipation.[10] Constipation may cause or compound abdominal pain, abdominal distension, and/or nausea, and thereby further compromise appetite. If left untreated, it can evolve to intestinal obstruction and ileus.

Opioids cause constipation in a variety of ways:
- They act directly on opioid receptors in the bowel as well as in the CNS.
- They decrease peristalsis and ileal and colonic motility.
- They decrease intraintestinal fluid volume by increasing fluid absorption.
- They increase sphincter tone.[28]
- They increase nonpropulsive segmental contractions.

Opioids activate myenteric plexus cholinergic, serotoninergic, and enkephalinergic receptors. This reduces peristalsis in both the small and large intestines and also increases nonpropulsive rhythmic segmental contractions.

In the upper gastrointestinal tract, there is reduced gastric motility and increased antral tone. In addition, there is increased sphincter tone throughout the gastrointestinal tract. It is unclear whether central or peripheral mechanisms predominate in the genesis of constipation. We do know that injection of morphine into the cerebral ventricles inhibits bowel motility, and that this is reversed by intraventricular administration of naloxone.[29]

Assessment

Constipation in the palliative care setting is common and usually multifactorial. Surveys of hospice patients indicate that at least 50% of patients not receiving opioids report constipation and require laxative therapy.[30] Constipation is thus a common problem in this population. Some studies have employed objective measures of constipation, such as small bowel transit time as assessed by the lactulose/hydrogen breath test.[31] Others apply numeric ratings to patient reports of stool frequency or form. In everyday practice, the question is usually addressed by simply asking the patient about stool frequency, hardness, and volume of bowel movement. FIGURE 2
As with other opioid-related side effects, the approach to the work-up of constipation should be appropriate to the goals of care for the patient. Constipation occurring shortly after an opioid dose escalation or the introduction of a new opioid may reasonably be attributed to the opioid escalation and does not necessarily require further work-up. However, refractory constipation in the face of stable opioid dosing, suggests a nonopioid etiology (Figure 2).

**Management**

If indicated, the patient should be evaluated for a fecal impaction. A digital rectal examination can reveal a low impaction. However, confirmation of a high impaction may require an abdominal x-ray. When appropriate, simple measures, such as an increase in oral fluid and dietary fiber intake, should be encouraged. In addition, access to a bedside commode may facilitate bowel movements if pain and immobility deter the patient from venturing to the toilet. Nonessential constipating drugs (eg, calcium channel blockers such as verapamil, phenothiazenes, tricyclic antidepressants, ferrous sulfate, antacids, vinca alkaloids, antiepileptics) should be discontinued, and an evaluation of calcium levels, electrolytes, and thyroid function performed.

**Acute Impaction:** For the management of acute fecal impaction, it is important to administer systemic analgesics and perianal lidocaine gel prior to initiating enemas or manual disimpaction. Manual disimpaction can be extremely painful. Overall, patients with impaction tolerate stool softeners and cathartics better than lactulose. Personal clinical experience suggests that the combination of a stool softer and cathartic has the best efficacy. Once the acute episode has resolved, prevention is the best approach. Rectal suppositories and enemas are uncomfortable for many patients, and risk the precipitation of local trauma. The use of rectal suppositories and enemas is contraindicated in neutropenic or thrombocytopenic patients.

**Chronic Constipation:** There have been few comparative trials of agents for the management of chronic opioid-associated constipation. Strategies are again largely heuristic. One study of 91 patients in a palliative care unit who were receiving opioids for cancer pain found no difference in clinical outcomes between senna and lactulose use. The authors favored senna because of the cost differential.[32]

A study of loperamide-treated healthy volunteers compared the efficacies of lactulose, senna, and codanthrusate (a combination of stimulant and softening laxative). Volunteers who received the combination stimulant and cathartic had the best efficacy and least number of side effects. Senna was associated with the highest incidence of side effects (intestinal colic) and lactulose was poorly tolerated at effective doses by most subjects.[33] The lack of efficacy of lactulose in this study is supported by clinical research evidence in opioid-treated patients.[34] Given the prevalence of intestinal colic associated with effective bowel stimulants, clinicians may be reluctant to place patients on “bowel regimens” at the inception of around-the-clock opioid therapy, and patients may not wish to comply with such a regimen. Although some patients can avoid constipation with simple dietary modifications and adequate fluid intake alone, the majority of those on an around-the-clock opioid regimen require initiation of a bowel regimen. For patients receiving around-the-clock opioid therapy, initiating a bowel regimen for the prevention of constipation early in the course of treatment is considered standard practice.

If an initial trial of dietary modification alone does not ensure regular bowel movements, the patient should be placed on a bowel regimen promptly. The first step is introduction of a stool softener (eg, sodium docussate, 300 mg every other day initially, and increased to daily if needed). Second-line drugs include the cathartic medications (eg, senna, one tablet on alternate days increasing to two tablets daily if needed; the dose of senna can be increased gradually up to eight tablets a day if necessary). The stool softener should be continued after the cathartic medication is introduced. Intermittent use of a lubricant laxative (eg, magnesium hydroxide, magnesium citrate, or sodium phosphate) every 2 to 3 days is well tolerated by most patients and should be introduced if steps 1 and 2 have not produced results.

When the measures outlined above are not effective in relieving the patient’s constipation, a third-line approach including daily osmotic laxatives (lactulose or sorbitol) may be tried. Initial doses of lactulose at 15 mL twice daily can be increased to 30 mL three times a day if necessary. At effective doses, however, the osmotic laxatives may be accompanied by bloating, abdominal pain, flatulence, and nausea secondary to the sweet taste. Some patients are unable to tolerate the use of lactulose because of these unpleasant side effects, although the doses and dosing frequency can be individualized to the particular clinical situation.

Overall, laxatives can be switched or combined if initial therapy is unsuccessful. Before doing so,
however, adequate time should be allowed for the onset of action of the medication. TABLE 4

Oral Laxatives Used in the Therapy of Opioid-Induced Constipation

**Onset of Action:** The onset of action of bulk agents (eg, psyllium) is 2 to 4 days. The saline laxatives (magnesium hydroxide, magnesium citrate) have a latency of 1 to 6 hours. Osmotic laxatives (lactulose, sorbitol) require 1 to 2 days to take effect. The onset of action of the contact cathartics (senna, danthron, bisacodyl) is 6 to 12 hours. The surfactant laxatives (docusate, poloxamer) have a latency of 1 to 3 days.

There is considerable variation in response to cathartics from one patient to another, and tolerance develops over time. In addition, long-term therapy with the cathartic laxatives can cause toxicity to the myenteric plexus with resultant dependence on laxative therapy (Table 4).

In patients whose constipation is refractory to the above laxative regimens or who do not tolerate the side effects of the recommended laxatives, prokinetic agents such as domperidone or metoclopramide can be helpful. Intermittent enemas or suppositories should also be used if oral laxative therapies are ineffective in relieving constipation or are not tolerated. This is particularly important in moribund bed-bound patients. Intermittent colonic lavage with polyethylene glycol, 250 to 500 mL/d, can also be helpful.

Oral naloxone is currently available for refractory opioid-induced constipation as part of a clinical trial. Naloxone has a 3% bioavailability via the oral route but is nevertheless associated with a small risk of precipitating withdrawal in the opioid-dependent patient and, therefore, must be used with caution. Patients receiving higher doses of the opioid drugs are especially susceptible to the withdrawal syndrome. In the rare instances that opioid-induced constipation is refractory to other measures, the recommended starting dose of oral naloxone is 0.8 mg twice a day. The dose can be doubled every 2 to 3 days if the patient does not have a bowel movement.

Skye et al performed a randomized double-blind dose-finding study of naloxone in a cohort of healthy volunteer adults receiving loperamide therapy. They concluded that oral naloxone at doses of 20% or more of the 24-hour morphine dose is a potentially valuable therapy for opioid-induced constipation. The authors suggested that individual doses not exceed 5 mg because of the risk of systemic withdrawal.[35] In a second study of naloxone in the treatment of opioid-induced constipation, withdrawal symptoms occurred with dosing intervals of less than 3 hours and with area under the plasma concentration-time curves above 550 ng/min/mL. Titration up to a maximum dose of 12 mg at least 6 hours apart was recommended.[36] In the event of persistent constipation after aggressive laxative treatment, rotation to an alternate opioid or route of administration should be considered.

**Cognitive Side Effects**

Cognitive side effects of opioid medications include somnolence, mood changes, and disturbances in the sensorium. However, cognitive changes in the advanced cancer patient are often multifactorial, and opioid use may be only one of many contributing factors. Mood changes that may be associated with opioid therapy include dysphoria and euphoria. Changes in the sensorium that may occur with opioid therapy include visual and auditory illusions, hallucinations, hypnagogic and hypnopompic hallucinations, and delirium.

Morphine and its metabolites, morphine-3-glucuronide and normorphine, have been found to have central excitatory effects including agitation and seizures. In animal studies, morphine-3-glucuronide antagonizes the analgesic effect of morphine-6-glucuronide and induces hyperalgesia and convulsions. Clinically, this may account for the increase in pain severity and associated agitated delirium in occasional patients given high doses of opioid medications. The severity of both the agitation and pain increases as the dose of the opioid medication is increased. Tolerance to the analgesic and toxic effect of an individual opioid drug does not necessarily occur simultaneously, suggesting the possibility of a shift in receptor subtype density with time.

A study of steady-state morphine to morphine-6-glucuronide ratios in 109 cancer patients treated with oral and parenteral morphine found a correlation with oral opioid administration and the
presence of renal dysfunction and myoclonus. However, morphine to morphine-6-glucuronide ratios did not correlate with the presence of cognitive impairment and myoclonus. The presence of cognitive impairment was associated, however, with increased age, bilirubin, lactate dehydrogenase, creatinine, and the use of other centrally acting medications.[37]

Transient Nature of Cognitive Deficits

Anecdotal experience suggests that opioid-associated cognitive side effects tend to be transient, lasting up to 2 weeks after the introduction of a new opioid or an increase in the dose of an opioid medication. A study by Bruera et al demonstrated that short-acting opioids can cause transient cognitive deficits (eg, in the reverse memory of digits, finger tapping, arithmetic skills, or visual memory) in the context of dose increases. The investigators observed a marked reduction in these deficits after 1 week of treatment on a given dose of opioid medications.[38]

A second study suggested the persistence of delayed reaction times with long periods of stable dosing. However, statistical significance was not reached when opioid recipients were compared with a cohort of cancer patients who were not on opioids.[39] A third study examined continuous reaction times of cancer patients on a stable dose of oral opioids vs those on a stable dose of epidural opioids. The researchers failed to demonstrate a statistically significant difference in reaction times in either group.[40]

Effect of Different Opioids

Studies comparing the prevalence of cognitive side effects with different opioids are lacking. One Australian study demonstrated delirium in 25% of patients treated with morphine who were subsequently switched to continuous subcutaneous oxycodone infusions. Of 13 patients who were switched from morphine to oxycodone, 8 demonstrated improvement in mental status, and the other 5 showed no further deterioration. The improvement in mental status was progressive over 1 week, suggesting the involvement of a long-acting metabolite.[41]

Pinpointing the Cause of Cognitive Deficits

Caraceni et al reported on a series of 15 patients with organic brain syndromes who were receiving opioid medications for cancer-related pain. Of these 15 patients, 11 had concomitant conditions contributing to the organic brain syndrome. These conditions included a low albumin level, infections, metabolic derangements, and the use of anticholinergic and concomitant psychoactive drugs.[42] Reversal of cognitive impairment is unlikely when the etiology of the deficit cannot be identified.[43]

In a prospective study of 61 patients with advanced cancer who developed cognitive failure in the hospital, a specific cause was identified in only 44% of those evaluated, and treatment provided on the basis of this evaluation improved mental status in only 18%.[44] Bruera et al reported that subjective reports of improvement in patients’ cognitive status did not correlate with improvement in mental status examination scores following opioid rotation, suggesting that this is a heterogeneous population and that opioids are contributing factors rather than causative factors.[45] Anecdotal reports from clinicians suggest an increased incidence of opioid-related neuropsychiatric side effects in patients with underlying cognitive deficits such as dementia.

Assessment

The identification of opioid-associated cognitive side effects requires ongoing vigilance and the use of screening instruments. Conventional assessment tools for cognitive deficit lack sensitivity. In one study, a score of 24/30 or better on a Folstein Mini-Mental Status Exam was found to have poor negative-predictive value.[45] The Mini-Mental Status Exam also lacks specificity for delirium. Only the Confusion Assessment Method[46] and Delirium Symptom Interview[47] have been validated as reliable instruments for diagnosing delirium. The diagnostic criteria outlined in the third edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-III) or DSM-III-R are used with these tests. Patients must be questioned about these symptoms specifically. They may be misdiagnosed as being secondary to a primary affective or anxiety disorder if there is a temporal association with opioid dose changes or the introduction of a new opioid agent.

Multidimensional instruments for the assessment of sedation are difficult to administer in a population with advanced disease, asthenia, or cognitive impairment. A visual analog scale is usually more practical, although this measurement is also compromised by sedation and delirium. Again, the
diagnostic yield will be best if the patient is given the scale at the anticipated time of the particular opioid’s peak effect.

In patients showing symptoms of cognitive impairment, the possibility should be considered that they may be receiving other CNS-acting medications. In addition, the potential for drug-drug interactions with recently introduced medications should be examined. For example, in vitro studies have shown that ritonavir (Norvir) greatly enhances the effects of opioids metabolized by the cytochrome P450 CYP3A isoform. Other agents with the same effect include fentanyl citrate, hyrodocodone, oxycodone, and methadone. FIGURE 3

Etiologies other than opioid effects should also be explored to explain the patient’s altered cognitive state. These include intracranial pathology, infections, and metabolic etiologies (e.g., hepatic dysfunction, renal dysfunction, hypo- and hypernatremia, hypercalcemia), and disseminated intravascular coagulation (DIC) (Figure 3 and Figure 4).

Management

While empiric opioid rotation may be appropriate for most patients, this strategy may expose the imminently dying to unnecessary undermedication. Even when a patient is already receiving opioids, the physician should thoroughly evaluate the patient’s status with regard to pain relief and opioid side effects. Laboratory tests should include blood cultures, a complete blood count, and an assessment of electrolytes, ammonia level, and pulse oximetry. FIGURE 4

Once the clinician is satisfied that the cognitive deficits are most likely to be opioid related (and the patient’s pain is well controlled), the around-the-clock dose can be reduced by 25% to 50%. Sequential trials of different opioids may be necessary if the patient’s pain is poorly controlled. One option is rotation to another opioid at 50% to 75% of the dose. If short-acting analgesics have been exhausted, rotation to methadone at 5% to 25% of the equianalgesic dose can be prescribed. However, a patient switched to methadone requires close monitoring because of the long half-life of the drug and the potential for drug accumulation and subsequent sedation. If these noninvasive measures are unsuccessful, a trial of an intraspinal opioid medication or a neurolytic procedure may be appropriate.

**Psychostimulants:** For patients who complain of excessive sedation in the setting of well-controlled pain, the addition of psychotropic medications may be beneficial. One useful approach entails the use of psychostimulants such as dextroamphetamine or methylphenidate at doses of 2.5 mg twice daily, with the dose titrated upward as tolerated toward the usual effective range of 10 mg twice daily. Possible side effects include anorexia, insomnia, anxiety, paranoia,
hypertension, and tachycardia. The cardiovascular side effects of the psychostimulants restrict their use in patients with decompensated ischemic heart disease and/or arrhythmias. Pemoline (Cylert), a third psychostimulant, can be absorbed across the buccal mucosa and is available in chewable formulations. The starting dose is 18.75 mg twice daily. This agent has relatively low sympathomimetic potential, but there have been reports of idiosyncratic fatal hepatotoxicity. For this reason, some physicians prefer not to prescribe the drug; others consider using it in patients with cardiac histories, hypertension, and impaired swallowing such as those with head and neck malignancies or cranial nerve palsies. Pemoline should not be administered to patients with known hepatic disease.

The use of psychostimulants in patients with cognitive deficits secondary to opioids may be appropriate, especially when the deficit is minor; however, the risk of agitation in more severe confusional states has not been evaluated. The efficacy of the psychostimulants compared with the serotonin-reuptake inhibitors and tricyclic antidepressants in the management of dysphoria secondary to opioids has not been studied.

In younger adults with prominent sedation and dysphoria, psychostimulants may be initiated unless the patient has preexisting comorbidities such as uncontrolled cardiac disease, hypertension, or moderate to severe delirium. In elderly patients, selective serotonin-reuptake inhibitors should be tried first. Young patients with prominent insomnia benefit from tricyclic antidepressants as a first-line therapy. In elderly patients, the anticholinergic side effects of tricyclic antidepressants may limit their use.

Antipsychotic Agents: Antipsychotic medications, such as haloperidol (Haldol), can be prescribed for patients who report confusion, delusional thoughts, or sensory distortions in the setting of opioid use. Low doses of haloperidol (0.5 mg at night and titrated to effect) can be helpful. Slow titration of these medications limits the potential for anticholinergic side effects. The newer antipsychotic medications such as risperidone (Risperdal) produce fewer anticholinergic side effects.

Myoclonus

Mild and infrequent multifocal myoclonus can occur with any of the opioids. The effect is dose related, and the mechanism is unclear. Pronounced myoclonus is extremely distressing to the patient. It occurs most frequently with meperidine, secondary to the accumulation of its neurotoxic metabolite, normeperidine. When the patient has preexisting renal and hepatic dysfunction, the oral administration of morphine is also associated with myoclonus.[37]

Management

After ruling out other potential etiologies of myoclonus (including electrolyte abnormalities), the patient should be treated with a benzodiazepine—clonazepam (Klonopin) is the most frequently used, or valproate. Clonazepam should be initiated at 0.5 mg at bedtime and increased by increments of 1 mg daily; if that dose is not effective, it should be increased to up to 2 mg four times daily. Sedation is the most commonly described side effect of this medication. Valproate should be started at 125 to 250 mg three times daily and increased to a maximum daily dose of 1,500 mg in three divided doses. That said, myoclonus can be symptomatic of opioid toxicity and is sufficient reason to switch to an alternate opioid.

Respiratory Depression

Morphine-like agonists can act on respiratory centers in the brain stem to produce dose-dependent respiratory depression to the point of apnea. Opioid agonists depress the pontine and medullary centers involved in regulating the rhythmicity of breathing. Therapeutic doses may depress respiratory rate, minute volume, and tidal exchange. The resulting increase in Paco₂, however, stimulates central chemoreceptors, leading to a compensatory increase in the respiratory rate and allowing maintenance of Pao₂ in most patients.[48,49] Individual opioids are thought to cause an equivalent amount of respiratory depression at equianalgesic doses.[50,51] Patients with advanced cardiopulmonary disease, particularly those with type 2 chronic obstructive pulmonary disease (COPD) are most at risk, as are those with hepatic and renal dysfunction.[37]

Opioid-associated respiratory depression usually occurs in opioid-naive patients who are exposed to an opioid medication for the first time. It is accompanied by other signs of CNS depression, including sedation and confusion. Fortunately, tolerance to this side effect usually develops rapidly, allowing the use of opioids in the setting of chronic cancer pain.
The appearance of respiratory depression in a patient who is opioid tolerant and on a stable dose of an opioid medication should suggest alternative etiologies. This situation should prompt a careful review of the patient’s medications, particularly the recent addition of benzodiazepines. The patient should be examined for pneumonia, other infections, metabolic disturbance, and pulmonary embolus. Clinically significant respiratory depression secondary to opioids is usually accompanied by other symptoms of CNS depression. Respiratory distress along with tachypnea suggests a non-opioid-related etiology.

There are case reports involving respiratory depression after neuroablative procedures, insertion of intraspinal delivery systems, and chemoembolization. Therefore, when a decline in the need for an opioid is anticipated, long-acting formulations should not be administered.

Management

As with other side effects, clarification of the goals of care is essential for the appropriate management of respiratory depression. Fear of respiratory depression is a frequently cited concern among medical and nursing staff when initiating opioid therapy or when increasing opioid drugs rapidly to control pain in a debilitated patient at the end of life.

Prevention may be achieved with appropriate routes of administration, equianalgesic dosing, and titration of the dose in response to severity of pain. Clinicians are encouraged to familiarize themselves with a few opioid drugs and to avoid using cocktails of multiple opioid medications.[52] Optimal use of opioid medications is facilitated by clinician awareness of the half-life of a medication and the potential for disparities between the overall half-life of a medication and its analgesic half-life.

Use of naloxone is best avoided, but a decision to administer it commits the clinician to ensuring adequate monitoring of a recurrence of pain as well as the patient’s vital signs (including respiratory rate, every 15 minutes until the individual is alert and maintains alertness). Naloxone’s onset of action is 1 to 3 minutes, but its duration of action is only 45 minutes. If a patient is receiving a long-acting medication (eg, methadone or levorphanol) or a long-acting formulation of a medication (transdermal fentanyl, controlled-release morphine [MS Contin, Kadian], or controlled-release oxycodone [Oxycontin]), careful monitoring is necessary because repeated naloxone boluses or a naloxone infusion may be required.

Prior to the administration of naloxone, transdermal delivery systems should be removed. In the comatose patient, airways should be protected with endotracheal intubation, if necessary. Naloxone may precipitate aspiration (by causing increased oropharyngeal secretions), bronchospasm, and, in rare instances, pulmonary edema. The patient may develop hypertension or hypotension, ventricular fibrillation, nausea, vomiting, sweating, and tachycardia. Thus, naloxone should be administered with caution in patients with cardiac disease. Naloxone may also precipitate seizures, particularly in patients receiving meperidine, due to the unopposed neuroexcitatory effects of its active metabolite, normeperidine.

Naloxone is not indicated in the somnolent but rousable patient. Basal infusions of opioids should be delayed in such patients until they are more alert. Patients should be stimulated frequently and observed closely. Naloxone is indicated for the patient with respiratory depression, ie, with a respiratory rate less than 8 breaths per minute, hypercapnia by arterial blood gases or capnometry, hypoxia on pulse oximetry, or progressive obtundation. A 0.4-mg dose of naloxone diluted to 0.04 mg/mL should be administered intravenously over 15 seconds and repeated every 1 to 3 minutes as necessary.

For respiratory arrest, undiluted naloxone can be given by IV push followed by a repeat bolus every 1 to 3 minutes as necessary. Pediatric patients should receive diluted naloxone. Patients receiving long-acting opioid formulations can be given a continuous infusion of naloxone at 2 mg/500 mL or 4 µg/mL, which should be titrated to respiratory rate, not the level of consciousness.

Opioid-tolerant patients are extremely sensitive to naloxone, and their respiratory depression will frequently reverse with a 0.04-mg dose of naloxone, whereas a 0.4-mg dose administered undiluted may precipitate systemic withdrawal as well as exacerbation of severe pain. A change in mental status or respiratory rate that is apparently in response to a dose of naloxone does not rule out the need to perform a work-up for other etiologies. Once the patient’s level of alertness improves, he or she should be maintained on 25% to 50% of the previous equianalgesic dose to prevent the development of narcotic withdrawal.

Conclusions
The prevalence of opioid-related side effects is associated with advanced disease, chronic liver and renal disease, and polypharmacy.[17] Clinicians need to be educated on how to prevent side effects secondary to inappropriate selection of opioids, route of administration, dose escalation, and lack of knowledge about equianalgesic dosing.[11]

Knowledge of appropriate management strategies is necessary to prevent premature discontinuation of opioid medications secondary to misdiagnosing symptoms as being opioid related or dose limiting. More clinical research must be conducted in this area to determine if the prevalence of opioid-related side effects is drug or route specific. Future research may lead to the development of opioids that have specific mu-receptor subtype agonism. Finally, management strategies, which should be appropriate for the accepted goals of the patient, also need to be investigated in comparative studies.

References:


