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## Side Effects of Opioids

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*More than 40% of ED visits are related to pain.<sup>1</sup> The Joint Commission has made the assessment and treatment of pain in the ED one of its standards.<sup>2</sup> The use of opioid medications has been increasing in both adults and children.<sup>3-5</sup> In 2009 there were more than 200 million prescriptions for opioid medications, with enough medication dispensed to supply every adult in the United States with the equivalent of 5 mg of hydrocodone every four hours for one month.<sup>4,6</sup>*

*Along with the increase in opioid use has come an increase in misuse and in adverse events. Much has been written and discussed about the problem of drug abuse and overdose. This monograph will not further discuss this topic. It is estimated that in 2009 there were 4.6 million ED visits for drug-related events — 50% of these were for drugs taken as prescribed. Our focus in this article will be the prevention and treatment of the side effects of opioid use.*

— Sandra M. Schneider, MD, Editor

## Constipation

Constipation is the most common side effect of opioids. The gastrointestinal tract is innervated by the enteric nervous system, with mu, kappa, and delta receptors. The mu-opioid receptors in the submucosal plexus are mainly responsible for constipating effects.<sup>7</sup> During times of stress, bodies synthesize endogenous opioids, which suppress intestinal motility. Exogenous opioids also bind to these enteric receptors, inhibiting neurotransmitter release. This decreases peristalsis and mucosal secretions (as well as pancreatic and biliary secretions). Stool remains in the intestines longer, increasing fluid reabsorption and leading to hard stools. There is also a degree of centrally mediated effect, as spinally administered opioids also decrease gastric emptying and increase transit time. Subsequently, patients strain to stool and sometimes have painful defecation. If they have incomplete emptying or avoid stooling due to pain, the situation only worsens. Cramping and bloating often occur.<sup>8,9</sup> Unlike most other opioid side effects, tolerance does not generally develop to constipation.

Prevalence estimates for constipation due to opioid use vary widely. They depend on the definitions used. They also vary based on whether assessments are made by chart review or by patient survey (with the latter revealing higher numbers). A meta-analysis showed pooled prevalence of 41%, with a range of 14-90%.<sup>10</sup>

Several classes of agents have been used in prophylaxis and treatment of opioid-induced constipation. Since constipation is such a common side effect, providers should consider starting prophylaxis with any opioid prescription (in absence of contraindication).

## EXECUTIVE SUMMARY

- One of the most frequent side effects of opioids is constipation. Unlike other side effects, this does not decrease with long-term treatment. Consider initiating laxative treatment when prescribing opioids for opioid-naïve patients.
- Severe constipation and impaction require more aggressive treatment. Avoid sodium phosphate (Fleets) enemas in the elderly, particularly those with renal failure. Consider the use of methylnaltrexone.
- Naloxone is available in injectable and nasal forms. Increasingly it is available without a prescription for home use. Many providers now prescribe or recommend naloxone for home use when prescribing opioids.
- Some patients will develop a hyperalgesia to opioids. Increasing doses of opioids will not be effective or will lead to increased pain. Such patients may be difficult to manage, as the most effective treatment is a decrease in medication. Switching to an alternative medication may be beneficial.

Choice of agent is driven more by opinion than it is by high-quality evidence. A recent systematic review<sup>11</sup> found no large, well-powered randomized, controlled trials (RCTs) on the effectiveness of laxative agents. An open-label RCT showed no difference in efficacy between senna and lactulose.<sup>12</sup> A crossover RCT (in younger patients on methadone maintenance therapy, which often involves higher doses than those used in analgesia) showed no differences between lactulose and polyethylene glycol, with both being superior to placebo.<sup>13</sup> One additional study compared senna and lactulose vs. magnesium hydroxide and mineral oil, once again with no differences in efficacy.<sup>14</sup> A useful general approach to management of opioid-induced constipation is summarized by Twycross in Table 1.<sup>15</sup>

### Prophylaxis Options

Unless otherwise noted, all dosing recommendations are based on *Hospice and Palliative Care Formulary USA*, 2nd Edition.<sup>15</sup>

**Stimulant Laxatives.** Typically considered to be first-line prophylaxis for constipation, stimulant laxatives frequently are combined with the stool softener docusate, based on the argument that this will decrease the likelihood of abdominal pain, although the evidence for significant effect from docusate is scant.<sup>16</sup> The most common limiting side effect is intestinal colic, which is dose dependent.

**Senna.** This is a mixture of naturally occurring plant glycosides (known as sennosides A and B). It passes unchanged through the small intestine and then is hydrolyzed by bacterial gut

flora in the large intestine to an active metabolite. Systemic absorption is very small. The metabolite has a direct effect on both submucosal and deep myenteric plexus, causing motor and secretory effects. Differences in gut flora may explain patient variability in response. A typical starting dose for opioid prophylaxis is two tablets orally twice daily. Up to 12 tablets can be taken daily divided into three doses. The most common limiting side effect is intestinal colic.

**Bisacodyl.** Laxative effects are similar to senna, but bisacodyl is hydrolyzed by endogenous intestinal enzymes and functions in both the small and large intestines. Start with 10 mg orally at bedtime. Up to 20 mg can be taken orally three times daily. It can also be given by suppository.

#### **Stool Softener: Docusate (Colace).**

Docusate is a surface-wetting agent, with little effect on gastrointestinal transit. It lowers surface tension, allows fat and water to penetrate feces, and stimulates fluid secretion in the intestines.<sup>17,18</sup> It should not be administered as the sole agent for prophylaxis. Docusate is frequently combined with a stimulant laxative on the theory that it would decrease the likelihood of abdominal pain and cramping. This assumption was not supported by a recent study.<sup>16</sup> Very old studies suggested a robust effect,<sup>19-21</sup> but more recent studies have called efficacy into question.<sup>22-24</sup> Of note, docusate should not be combined with mineral oil, as it enhances absorption and increases side effect potential.<sup>25</sup>

**Bulk-forming Agents (Fiber).** When combined with adequate fluid intake and physical activity, bulk-forming agents such as methylcellulose, psyllium

husk, or sterculia have weak evidence for improving constipation symptoms. The American College of Gastroenterology Chronic Constipation Task Force concluded that psyllium increases stool frequency in patients with chronic constipation (in a recommendation not specifically geared toward opioid-induced constipation).<sup>26</sup> The task force found that insufficient data existed to recommend calcium polycarbophil, methylcellulose, or bran. Symptom improvement may take as long as 2-3 months. These agents should not be routinely recommended for opioid-induced constipation,<sup>27,28</sup> as they can actually exacerbate the constipation and even lead to obstruction, especially in the elderly and debilitated. If used, they should be limited to younger, ambulatory patients who can maintain good fluid intake.

**Lubricant.** Mineral oil (liquid paraffin) was used extensively in the past. There is no good evidence that it is effective. It interferes with absorption of lipid-soluble vitamins. It has a serious risk for lipoid pneumonia, especially in patients who are at risk for aspiration. Risk is increased if used concomitantly with docusate. There is no role for its use in prophylaxis or treatment of opioid-induced constipation.<sup>27,29</sup>

**Osmotic Laxatives.** These are typically considered second-line agents after the stimulant laxatives.

**Lactulose.** Lactulose is a synthetic combination of galactose and fructose that is unabsorbed by the small intestine. It drives a large amount of fluid into the large intestine. There it is fermented, increasing acidity. This stimulates peristalsis and discourages proliferation of ammonia-producing organisms (thus explaining its use in

## Table 1: General Approach to Managing Opioid-induced Constipation

All opioids cause constipation to varying degrees. Morphine is more constipating than methadone or fentanyl. Below are steps to follow in determining treatment:

- Ask about the patient's current and premorbid bowel habits, including laxative use.
- Encourage fluids, specifically fruit juice, and fruit.
- When prescribing an opioid, prescribe 50 mg docusate sodium and 8.6 mg senna, 2 tablets twice a day. Note: Consider a patient's existing laxative regimen, rather than changing automatically to docusate sodium/senna.
- Adjust the dose every 2-3 days as needed, up to 4 tablets three times a day, for a total daily dose of 600 mg docusate sodium and 103 mg senna.
- During dose titration and subsequently: If more than 3 days have passed since last bowel action, give suppositories, e.g., 10 mg bisacodyl and 4 g glycerin, or a micro-enema. Based on case reports of severe metabolic disturbances,<sup>36</sup> avoid the use of phosphate enemas, especially in elderly patients or those with any degree of renal impairment.
- If the maximum dose of docusate sodium/senna is ineffective, halve the dose and add 20 mL lactulose twice daily or 1 sachet polyethylene glycol each morning and titrate as necessary.
- Alternately, switch to an osmotic laxative, e.g., 20-40 mL lactulose 2-3 times per day or 1-3 sachets polyethylene glycol each morning.
- Lactulose or polyethylene glycol may be preferable in patients with a history of colic with colonic stimulants (senna, bisacodyl).

Adapted from: Twycross R, Wilcock W. *Hospice and Palliative Care Formulary USA*. 2nd ed. Nottingham, UK: palliativedrugs.com Ltd. 2008; 24.

hepatic encephalopathy). It is not significantly bioavailable and can be used without issue in diabetics. It can cause intestinal colic. Some patients do not tolerate the intensely sweet taste. A starting dose of 15 mL can be used and then titrated to effect. It can also be used as a rescue medication in cases where prevention failed. As long as there are no signs of obstruction, one can prescribe 30 mL every 4 hours until bowel movement as a rescue.

**Polyethylene Glycol 3350 (Miralax).** This is becoming a more popular prophylactic, especially since becoming over-the-counter and generic. It is the main active ingredient in the colonoscopy bowel preparation GoLytyl (which has additional electrolytes). It

has an osmotic effect in the intestines, increasing stool volume and therefore causing laxation. It is not significantly bioavailable, thus does not cause electrolyte disturbance. Side effects are rare and relatively benign. It is typically better tolerated than lactulose,<sup>30</sup> and thus is the osmotic laxative of choice in many centers. As a prophylactic, it can be started at 17 g once daily and titrated as needed (up to three times daily). When used as a rescue medication for impaction, higher doses are used, 136 g (8 × 17 g scoop/packet).

**Sorbitol.** This is less commonly used, but can be given as 30 mL at bedtime. It also is effective as an enema of 120 mL in a 25% solution (with a much faster onset of action).<sup>31</sup>

**Magnesium Salts.** Magnesium hydroxide (Milk of Magnesia) and magnesium sulfate (Epsom salts) are available over the counter and have both been used as osmotic agents for treating constipation. They should be considered third- or fourth-line agents, typically to be used if abdominal colic limits other choices. The effect is mainly osmotic, although some have theorized a role for cholecystokinin release.<sup>32</sup> Magnesium hydroxide is typically given as a 30 mL dose at bedtime. Magnesium sulfate is a more potent laxative. It is available in bulk as crystals and is inexpensive. Dosing is 4-10 g dissolved in warm water, typically before breakfast. However, it is generally poorly tolerated for prophylaxis, as it is difficult to titrate effectively, tending to cause sudden, liquid stools. Thus, its use is probably best reserved for rescue. Hypermagnesemia may occur in patients with renal impairment.

**“Natural” Alternatives.** Some patients have a distinct preference for remedies that they consider to be more natural. Anecdotally, a mixture of senna tea and stewed fruits is helpful for some patients. A recipe for a senna-fruit paste can be found online.<sup>33</sup> Castor oil and cascara sagrada are sometimes offered as “natural” options. They function as stimulant (irritant) laxatives, but are of limited utility due to high rate of cramping pain at therapeutic doses.<sup>34</sup> Caffeinated coffee can have a laxative effect, by stimulating colonic motor activity, increasing fluid secretion in the small intestine, and stimulating the gastrocolic reflex.<sup>35-37</sup>

**Other Non-pharmacologic Strategies.** Strategies that may be effective in mild constipation that is not opioid-induced are not likely to be sufficient to prevent opioid-induced constipation. It is reasonable to encourage, to the extent possible, increased physical activity and adequate fluid intake. But this is as much due to the benign nature of these interventions (and potential general benefit) as any evidence. In absence of dehydration, there is no evidence that increased fluid intake alone is likely to be helpful.<sup>38</sup> Timed voiding may prevent progression to obstipation.

**Rescue Interventions.** Patients frequently need additional treatments for constipation even if on oral laxatives.

Up to one-third of patients in palliative settings need additional treatments.<sup>39</sup> In addition to those medications listed for rescue above, one can use enemas, suppositories, or subcutaneous injections.

**Glycerin Suppository.** Glycerin draws fluid into the rectum, which has a softening and lubricating effect.

**Bisacodyl Suppository.** This works locally by direct contact with rectal mucosa. It requires metabolism by intestinal flora, and thus needs at least 30 minutes to have a pharmacologic effect. It is not significantly absorbed.<sup>40</sup> Any effect prior to 30 minutes is likely due to ano-rectal stimulation.

**Enemas.** Tapwater or soapsud enemas are frequently used. Little data can be marshalled with regard to their efficacy. Some risk could be postulated for fluid shifts in large-volume tapwater enemas. Docusate sodium is frequently given by enema (DocuSol), with 283 mg per unit in a mini-enema. Osmotic enemas containing sodium phosphate (Fleets) are effective but potentially dangerous.<sup>41</sup> In one case series, 11 elderly patients developed severe hyperphosphatemia (levels 5.3–45.0 mg/dL), hypocalcemia (2.0–8.7 mg/dL), and renal failure, with 5 deaths.<sup>42</sup>

In 2006, the FDA issued a warning about acute kidney injury risk for oral sodium phosphate, which led to the products being withdrawn from the over-the-counter market and obtaining a black box warning as a prescription.<sup>43</sup> Calls have been made to remove them from over-the-counter availability.<sup>44</sup>

**Methylnaltrexone (Relistor).** Methylnaltrexone is a quaternary derivative of naltrexone and a peripherally selective mu-opioid antagonist. It is a subcutaneous injection that was FDA approved in 2008 for use in palliative care patients with advanced illness who had ongoing opioid-induced constipation despite treatment with standard laxative therapies. In trials, half the patients had a bowel movement within 4 hours of injection. It does not cross the blood-brain barrier, and thus can antagonize peripheral effects of opioids without reversing central analgesia. It has been found to be effective in cases where conventional laxatives have failed.<sup>45</sup> (See Table 2 for dosing.)

**Opioid Rotation.** If opioid-induced

## Table 2: Dosing for Methylnaltrexone

Dosing per manufacturer suggestions is weight-based:

- 38-62 kg = 8 mg every other day.
- 62-114 kg = 12 mg every other day.
- Outside of these ranges, 0.15 mg/kg is recommended.
- Halve the dose in severe renal insufficiency (CrCl < 30). Titrate to efficacy, but no more than once daily.

constipation cannot be adequately managed with any of the above strategies, it is reasonable to attempt a rotation to a different opioid. Cross-tolerance is incomplete and there is genetic variability in receptor subtypes from individual to individual. For most opioid side effects, a rotation to a different drug may allow analgesia while maintaining tolerability. Codeine is by expert opinion considered to be the most constipating opioid. There is some evidence that fentanyl is less likely than morphine to cause constipation.<sup>46,47</sup> This is theorized to be due to the fact that fentanyl is much more lipid-soluble than morphine and spends less time in the systemic circulation. The anecdotal experience of many clinicians suggests that methadone is less constipating could be due to similar reasoning. At least one study did not demonstrate any difference between fentanyl and morphine or oxycodone.<sup>48</sup> However, this study was in a hospice population and was observational rather than interventional. In this population, a fentanyl patch typically only would be used in patients who had renal insufficiency or who were unable to tolerate oral medications. Thus, they were not a matched population compared to those on other agents.

## Nausea

Another common side effect of opioids is nausea. Unlike constipation, this side effect is often transient. One systematic review found the incidence to be 21% in patients treated with opioids for chronic pain in a clinical trial setting.<sup>49</sup> Individual trials report incidence ranging between 10–50%.<sup>50-53</sup>

There are multiple mechanisms by which opioids induce nausea. The vomiting center receives input from four major areas: chemoreceptor trigger zone

(CTZ), vagus nerve and gastrointestinal tract, vestibular apparatus, and cerebral cortex.<sup>53</sup> Opioids can induce nausea from all four of these areas.<sup>54</sup>

Opioids cross the blood-brain barrier and directly stimulate the CTZ. This is due to mu and delta opioid receptors. Tolerance develops with repetitive stimulus.

Opioids inhibit gut motility, which can cause distention and increased emptying time. This leads to stimulation of visceral chemo- and mechano-receptors, inducing nausea.

Opioids also appear to stimulate the vestibular apparatus, although this is still theoretical. Mu-, kappa-, and delta-opioid receptors are present in the inner ear. This manifests in patients who experience new-onset vertigo after starting opioids.

The cerebral cortex is responsible for anticipatory nausea. Although this is more commonly seen in chemotherapy, it is postulated to occur with opioids.<sup>54</sup>

Management of nausea can be tailored to the specific areas likely to be causing the trouble. If the nausea is thought to be related to constipation, then obviously this must be treated. If there still appears to be an additional gastric stasis element, then metoclopramide (Reglan) 10 mg Q6H (5 mg if renal insufficiency) can be used.

Other ways to treat CTZ stimulation are targeting the receptors that communicate with the vomiting center. Dopamine antagonists such as prochlorperazine or haloperidol can be used. Metoclopramide also has dopamine receptor inhibition, so may work on the gut as well as the CTZ. Serotonin receptor antagonists such as ondansetron are also effective.

The vestibular apparatus theory would suggest H1 blockers may have a role in

nausea, and some antiemetic treatment regimens have incorporated them.<sup>55</sup> Meclizine or promethazine could also be used, but initially they should be reserved for cases in which there is a clear vertiginous component.

There is a general lack of controlled trial data on opioid-induced nausea, and the data that do exist are equivocal. One systematic review displayed a wide variation in antiemetic efficacy.<sup>56</sup> A more recent systematic review and recommendations from the European Palliative Care Research collaborative considered several issues, but only felt confident in issuing three (weak, level C) guidelines:<sup>57</sup>

1. Weak recommendation for switching from morphine to an alternative opioid, such as oxycodone or hydromorphone, in patients with nausea;
2. Weak recommendation for switching from fentanyl to methadone in patients with nausea;
3. Weak recommendation for the use of the subcutaneous route for morphine as an alternative to oral morphine.

Opioid rotation makes sense as a potential strategy if tolerance does not develop and the above strategies are ineffective or not tolerated. Morphine appears to be more emetogenic than oxycodone or hydromorphone.

The atypical antipsychotic risperidone (Risperdal) has D2 and 5-HT<sub>2</sub> receptor antagonism and showed efficacy for refractory opioid-induced nausea in a 20-patient, pilot study in cancer patients.<sup>58</sup> Similarly, the atypical antipsychotic olanzapine (Zyprexa) was studied in refractory nausea at 2.5, 5, and 10 mg doses, as well as placebo, with appropriate washout periods. Fifteen patients were investigated, with significant decrease in nausea at all three doses and a dose response effect noted.<sup>59</sup>

Low-dose naltrexone continuous infusion has been shown to reduce opioid-induced nausea (at a dose of 0.25 mcg/kg/hr)<sup>60,61</sup> and with an increased effect as dose increased to 1 mcg/kg/hr.<sup>62</sup>

One group showed efficacy of an antiemetic cocktail of 10 mg metoclopramide, 25 mg diphenhydramine, and 4 mg dexamethasone combined in saline and given intravenously every 6 hours.<sup>55</sup> This pilot study was not blinded

or controlled, but showed 57 out of 63 patients with improvement in symptoms. The etiology of the nausea was frequently thought to be multifactorial, not just opioid-induced.

## Respiratory Depression

Most emergency providers are all too familiar with the respiratory depression seen with opioids. Opiate-naïve patients and those who use/abuse alcohol with their medications are at highest risk. Naloxone is a proven safe and effective antidote for opioid respiratory depression and hypotension. Aside from acute withdrawal, even large doses have few if any side effects. It is currently available in injectable and nasal formulations.

More than 19 states and 200 communities have programs that supply naloxone to patients who abuse opioids. Because so many patients, and their “friends,” overdose on prescription medications, many providers now prescribe naloxone as a rescue measure to high-risk patients. Because naloxone has a high safety profile, many pharmacies now dispense the drug without a prescription, and there has been increased demand for it to be available over the counter.

Patients with increased intracranial pressure from either head injury or mass may hyperventilate, reducing carbon dioxide and potentially lowering intracranial pressure. Respiratory depression from opioids could theoretically increase carbon dioxide and increase intracranial pressure. Studies in head-injured patients with intracranial pressure monitors have not been consistent; however, there is some suggestion that an increase in intracranial pressure may occur with opioid administration.<sup>63</sup>

Patients with renal failure may be at higher risk of respiratory depression. Renally excreted metabolites build up to much higher serum levels than normal. This functions similarly to a large (inappropriate) dose increase, which leads to sedation then respiratory depression.

Finally, methadone has increased risk for respiratory depression. Part of the reason for lower risk of respiratory depression in general in patients on chronic opioid therapy is that a physiologic tolerance develops. Methadone, via NMDA receptor antagonism, does

not have this same level of physiologic tolerance. While this a useful characteristic in terms of not needing to dose escalate for efficacy as often in methadone, it does not afford the same degree of protection against respiratory depression. The half-life of the drug is much higher, and it is dual peaking. If a patient takes the medication again when the initial short-acting analgesia peak wears off, the drug can build up in fat stores. The American Pain Society no longer recommends use of methadone as an as-needed pain medication due to increased mortality. Methadone has a non-linear dosing curve. It inhibits its own metabolism. Thus, dose increases cannot be made the same way one would in a typical opioid with linear dosing and shorter half-life.

Chronic opioid use has been associated with central sleep apnea and carbon dioxide retention.<sup>64-67</sup> It seems fair to conclude that sleep-disordered breathing is increased in chronic opioid use, but the incidence and clinical importance are yet to be established.

Many clinicians are reluctant to use opioids in patients with severe chronic obstructive pulmonary disease (COPD).<sup>68</sup> Despite a dearth of evidence to support the view, previous editions of some guidelines have considered opioids to be contraindicated in COPD.<sup>69</sup> Newer guidelines from the American Thoracic Society<sup>70</sup> and the American College of Chest Physicians<sup>71</sup> have supported use of low-dose opioids for dyspnea. The literature supports both its efficacy<sup>72,73</sup> and its safety.<sup>74</sup>

## Neuroexcitatory Toxicities

**Opioid-induced hyperalgesia (OIH).** There is a rare but important phenomenon in some patients prescribed opioids whereby a paradoxical response occurs and they become more sensitive to certain types of stimuli. This is hypothesized to be due to a compensatory upregulation of pathways that are actually pronociceptive. Neuroplastic changes occur in both the peripheral and central nervous systems. The current level of understanding is still incomplete, and there are undoubtedly multiple mechanisms at work. The central glutaminergic system, especially the NMDA receptor, is the most commonly

hypothesized component.<sup>75-78</sup> Inhibition of the NMDA receptor slows physiologic tolerance to opioids and is hypothesized to prevent opioid-induced hyperalgesia. Inhibition of glutamate transport increases the amount of glutamate available to the NMDA receptors and counteracts inhibition. This upregulation results in an unintended pro-nociceptive effect.

Prevalence data are not currently available. In case reports and descriptive studies, OIH is more commonly described in patients with high opioid doses.<sup>77</sup> Despite the fact that methadone has weak NMDA receptor antagonism (and thus can be used as a strategy for treating OIH), OIH has been demonstrated with high-dose methadone as used in maintenance programs for addiction.<sup>79,80</sup> These high doses are sometimes used in difficult-to-manage chronic pain cases as well.

It is important to distinguish between OIH and tolerance. Physiologic tolerance is an expected consequence of chronic opioid treatment. In a patient with tolerance, a dose increase should still result in an increase in analgesic effect. Clinicians should suspect OIH when a dose increase seems to have no effect on pain or even seems to result in increased pain. OIH should also be considered in cases in which a patient on opioid therapy develops diffuse pain that is not associated with the original pain being treated. Allodynia is the perception of pain with stimuli that would not normally be painful. OIH can induce diffuse allodynia.

Treatment strategies for OIH include dose reduction, opioid rotation, and NMDA receptor antagonism.

Opioid dose reduction is done empirically rather than by any particular formula. A dose-reduction strategy may prove troublesome in practice. It may be difficult to achieve patient buy-in.

Opioid rotation may be a sounder general approach. Due to incomplete cross-tolerance, a patient on chronic opioid therapy can often decrease dose by 25-50% of equianalgesic calculations with a switch to a different opioid. This switch and reduction by itself may be sufficient to resolve the OIH. Methadone has appeal as an agent to rotate to, as it has weak NMDA

receptor antagonism. Its pharmacology is complex, and opioid-related side effects and deaths are disproportionately high with its use, so it is best initiated and titrated only by (or in collaboration with) experienced practitioners or pharmacists. A strategy of halving the current opioid dose and adding a low dose of methadone has been reportedly successful.<sup>81</sup> It is also possible to treat OIH with ketamine, currently the most potent legally available NMDA receptor antagonist.

**Myoclonus.** Patients can develop myoclonus as part of an OIH picture or separately. The uncontrollable muscle twitching usually occurs in the extremities and may be subtle at first. With continued opioid use, especially if dose is increased, the twitching can increase in frequency and distribution. Without intervention, this can escalate to delirium and seizure. If hyperalgesia is part of the clinical picture, a clinician may worsen the problem with a dose increase in attempt to treat the increasing pain, thus exacerbating the toxicity. Certain metabolites of morphine, hydromorphone, and meperidine — morphine-3-glucuronide, hydromorphone-3-glucuronide, and normeperidine — are frequently cited.<sup>82-85</sup> Strategy for dealing with this side effect is the same as for OIH, namely dose reduction and opioid rotation. As an acute treatment, benzodiazepines can be considered.

## Other Side Effects

The side effects mentioned so far represent the most common as well as the most potentially dangerous. Several other side effects occur with opioids, and can be common in subsets of the population. A few of these will be briefly considered.

**Urinary retention.** This side effect is typically transient. It is important to ensure that an adequate bowel regimen is in place, as constipation can lead to urinary retention via external obstruction. For most patients, this side effect will abate within a few days to a week. Men with benign prostatic hyperplasia may find this an ongoing problem, however. Fentanyl causes less urinary retention,<sup>86</sup> and rotation to a transdermal patch is appropriate if feasible.

**Pruritus.** Like most opioid side effects, this is often transient. It is much more common in spinal opioids (up to 90%) rather than in oral (< 1%).<sup>87,88</sup> Topical emollient cream is a reasonably benign intervention. Although antihistamines are frequently used, evidence suggests that this phenomenon (when associated with systemic opioids) is often not mast-cell histamine mediated.<sup>89</sup> In these cases, a histamine antagonist will not help with the itching, although a patient may still report feeling better due to anxiolytic or sedating effects. Pruritus seems to be more common in patients who intermittently require intravenous opioids for cyclically painful conditions, such as sickle cell pain crises. Although histamine antagonists are frequently used in these patients, it may be out of clinical inertia rather than efficacy. Oral rather than intravenous forms should be used if possible, as intravenous formulations have no inherent advantage in pruritus for patients who can tolerate oral, and intravenous is associated with euphoria and perhaps addiction. Alternative approaches center around the fact that most of these cases are a central phenomenon rather than peripheral mast-cell response. Ondansetron has been used at 8 mg orally twice a day (initial dose can be given intravenously). Also effective is concomitant low-dose opioid antagonist.<sup>90</sup> This needs to be a centrally acting antagonist, not the peripherally acting methyl naltrexone. Intravenous naloxone 0.25-2.4 mcg/kg/hr and oral naltrexone 9 mg (6 mg was less effective and 3 mg did not work) have been successful. Both ondansetron and opioid antagonists have the additional benefit of preventing/treating opioid-induced nausea as well.

**Confusion.** During the first few days of opioid therapy, patients may experience some cloudy thinking. They should be warned about this possibility, which tends to resolve within the first few days. Hallucinations also can be a side effect, and should be treated differently than mild confusion. Patients are unlikely to develop tolerance.

**Sedation.** A feeling of sedation is very common on initiation of opioid therapy. Some of this effect may be due to analgesia allowing a patient to catch

up on a sleep deficit caused by pain. This is usually transient. Patients should be advised that the feeling is likely to go away within 3-7 days. If sedation persists, then dose reduction or opioid rotation should be considered. In palliative care settings, low-dose methylphenidate is sometimes given to combat sedation, but this would rarely be appropriate in an ED setting.

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- A. an 80-year-old woman on short-acting morphine for severe knee osteoarthritis, who has been on a stable dose for > 6 months
- B. a 20-year-old man with no significant past medical history or medication use, who had a serious automobile accident, and is placed on continuous intravenous hydromorphone
- C. a 60-year-old woman who takes the combination of morphine and gabapentin for her diabetic peripheral neuropathy
- D. a 58-year-old man with end-stage COPD who takes 2.5 mg oral morphine every 4 hours as needed for dyspnea

2. Which of the following opioid side effects is most likely to be persistent?
  - A. constipation
  - B. nausea
  - C. sedation
  - D. confusion
3. Which of the following prophylaxis options is likely to exacerbate rather than alleviate constipation in a debilitated patient with prostate cancer and bony metastasis?
  - A. lactulose
  - B. methylcellulose
  - C. senna
  - D. methylnaltrexone

## CME Questions

1. Which patient is most likely to experience clinically significant respiratory depression?

## EMERGENCY MEDICINE REPORTS

### CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

4. Which of the following is most likely to fail as a single agent for prophylaxis of opioid-induced constipation?
  - A. lactulose
  - B. senna
  - C. docusate
  - D. polyethylene glycol
5. A patient has been experiencing nausea since starting on an opioid a week ago. He was started on senna at the same time as his opioid and is not experiencing any constipation. Along with the nausea, he is experiencing flatulence, epigastric fullness, and hiccups. Which of the following agents is the best choice to treat his nausea?
  - A. metoclopramide
  - B. ondansetron
  - C. meclizine
  - D. diphenhydramine
6. A 28-year-old woman is taking short-acting oxycodone after breaking her leg in a skiing accident. She sustained no head trauma with this accident. Since starting the opioid,

she is experiencing nausea when she stands up or walks quickly. She also gets a sensation of the room spinning at these times. She had no prior history of vertigo. Which of the following would be the most appropriate next step in management of this patient?

- A. Epley's otolith repositioning maneuvers
- B. head CT without contrast
- C. addition of meclizine
- D. addition of paroxetine

7. Sodium phosphate enemas have been reported to cause significant side effects in elderly patients, particularly those with renal failure. These side effects may include all of the following *except*:
  - A. hyperphosphatemia
  - B. hypocalcemia
  - C. hypokalemia
  - D. metabolic acidosis
8. A patient with chronic pancreatitis complains of increasing pain. You note that he has been in the ED several times in the past 2 months

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and his use of opioids has been increasing dramatically. The best course of action is:

- A. Refuse to give him any further opioids, as he is likely diverting his medication.
  - B. Refer him to a pain treatment center for possible opioid-induced hyperalgesia.
  - C. Increase his dose and frequency of the same opioid.
  - D. Maintain the same daily opioid dose, but take it in smaller quantities more frequently.
9. A patient recently started on opioids after back surgery presents with constipation for the past 7 days. Rectal exam shows some hard stool in the rectum, and he is disimpacted. Which of the following is an option for treatment in the ED?
- A. methylnaloxone
  - B. docusate
  - C. increase fluids and fruit consumption
  - D. over-the-counter fiber supplements

10. Which of the following statements about naloxone is *not true*?
- A. Naloxone has a high safety profile.
  - B. Naloxone can only be legally used by healthcare providers.
  - C. Naloxone comes in an injectable and nasal formulation.
  - D. Some pharmacies provide naloxone without a prescription.

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## Side Effects of Opioids

### General Approach to Managing Opioid-induced Constipation

All opioids cause constipation to varying degrees. Morphine is more constipating than methadone or fentanyl. Below are steps to follow in determining treatment:

- Ask about the patient's current and premorbid bowel habits, including laxative use.
- Encourage fluids, specifically fruit juice, and fruit.
- When prescribing an opioid, prescribe 50 mg docusate sodium and 8.6 mg senna, 2 tablets twice a day. Note: Consider a patient's existing laxative regimen, rather than changing automatically to docusate sodium/senna.
- Adjust the dose every 2-3 days as needed, up to 4 tablets three times a day, for a total daily dose of 600 mg docusate sodium and 103 mg senna.
- During dose titration and subsequently: If more than 3 days have passed since last bowel action, give suppositories, e.g., 10 mg bisacodyl and 4 g glycerin, or a micro-enema. Based on case reports of severe metabolic disturbances,<sup>36</sup> avoid the use of phosphate enemas, especially in elderly patients or those with any degree of renal impairment.
- If the maximum dose of docusate sodium/senna is ineffective, halve the dose and add 20 mL lactulose twice daily or 1 sachet polyethylene glycol each morning and titrate as necessary.
- Alternately, switch to an osmotic laxative, e.g., 20-40 mL lactulose 2-3 times per day or 1-3 sachets polyethylene glycol each morning.
- Lactulose or polyethylene glycol may be preferable in patients with a history of colic with colonic stimulants (senna, bisacodyl).

Adapted from: Twycross R, Wilcock W. *Hospice and Palliative Care Formulary USA*. 2nd ed. Nottingham, UK: palliativedrugs.com Ltd. 2008; 24.

### Dosing for Methylnaltrexone

Dosing per manufacturer suggestions is weight-based:

- 38-62 kg = 8 mg every other day.
- 62-114 kg = 12 mg every other day.
- Outside of these ranges, 0.15 mg/kg is recommended.
- Halve the dose in severe renal insufficiency (CrCl < 30). Titrate to efficacy, but no more than once daily.