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Side Effects of Opioids

Pain is a very common presentation to primary care clinics. It is often appropriate at some stage in management to prescribe opioid agonists. To prescribe rationally and responsibly, it is necessary to understand the most common side effects as well as those that are potentially very serious. For this review, it will be assumed that the decision to initiate opioid therapy was appropriate in the first place and that proper attention is paid to screening and monitoring for aberrant drug behaviors, which are beyond the scope of this review. Good management of side effects will improve patient safety as well as increase regimen efficacy and patient adherence

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.[1] 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. These side effects should not be dismissed as minor. Patients report a significant impact on quality of life, and these side effects can cause patients to be nonadherent to their analgesic regimen.[2,3] Unlike most other opioid side effects, tolerance does not generally develop to constipation.

Executive Summary

- Constipation is the most commonly reported side effect with opioid therapy. Tolerance does not generally develop. Most patients on chronic opioid therapy require prophylaxis. Failure to do so can result in patient non-adherence and decreased quality of life.
- Nausea is also common and another potential source of non-adherence.
- Respiratory depression is the most feared complication, being potentially life-threatening. Its prevalence is generally overestimated, but it makes sense to recognize the situations when it is most likely to occur. Other respiratory effects, such as central apnea, are more common and more likely to be of clinical importance to primary care providers.
- With increasing doses of opioids, the potential exists for neuroexcitatory toxicities. Failure to recognize these can lead to counterproductive dose increases. More serious forms of neuroexcitatory toxicity are potentially fatal.
- Urinary retention, pruritus, hallucinations, and sedation are less common but need to be addressed.

Prevalence estimates for constipation due to opioid use vary widely. They depend on the definitions used — some focus just on stool frequency, while others address subjective distress caused as well. 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%, but this included a range of 14-90%.[4]

Several classes of agents have been used in prophylaxis and treatment of opioid-induced constipation. Since constipation is such a common side effect, it is recommended that the default strategy is to start prophylaxis with any opioid prescription (in absence of contraindication) and then titrate. Patients should be asked about their premorbid bowel regimen. The goal for titration should be bowel movements at a similar frequency as premorbid normal, and also free of pain, straining to stool, or feeling of incomplete emptying. Avoid the error of attempting to induce daily bowel movements in all of your patients. If a patient's premorbid defecation frequency was every third day, then every third day is an entirely appropriate goal for bowel prophylaxis.

Choice of agent is driven more by expert opinion than it is by high-quality evidence. A recent systematic review attempted to answer the question,[5] but did not attempt any pooling of data as there are simply no large, well-powered randomized, controlled trials (RCTs) on the subject. An open-label RCT showed no difference in efficacy between senna and lactulose.[6] 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.[7] One additional study compared senna and lactulose vs magnesium hydroxide and mineral oil, once again with no differences in efficacy.[8] A useful general approach to management of opioid-induced constipation is summarized by Twycross in Table 1.[9]

Prophylaxis Options

This section will review various prophylaxis options, recommend for or against their use, and make dosing recommendations. Unless otherwise noted, all dosing recommendations are based on *Hospice and Palliative Care Formulary USA,* 2nd Edition.[9]

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.[10] Start prophylaxis when starting opioid therapy and titrate to effect. 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. Titrate upward to effect, with up to 12 tablets 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. Titrate in stages up to 20 mg 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.[11,12] It should not be administered as the sole agent for prophylaxis, although this mistake is commonly made 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. Treatment should be designed to achieve a bowel action every 1-3 days without straining. Below are steps to follow in determining treatment:

1. **Ask about the patient's current and premorbid bowel habits, including laxative use; note the date of the last bowel action.**
2. **Palpate for fecal masses in the line of the colon; examine the rectum digitally if the bowels have not been open for more than 3 days, if the patient reports rectal discomfort, or if the patient has diarrhea suggestive of fecal impaction with overflow.**
3. **For inpatients, keep a daily record of bowel actions.**
4. **Encourage fluids, specifically fruit juice and fruit.**
5. **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.**
6. **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.**
7. **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,[36] avoid the use of phosphate enemas, especially in elderly patients or those with any degree of renal impairment.**
8. **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.**
9. **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.**
10. **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.

primary care practice. 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 study with good design that was designed to test this hypothesis.[10] Very old studies suggested a robust effect,[13-15] but this effect has not been reconfirmed recently. In fact, more recent studies have called efficacy into question.[16-18] Of note, docusate should not be combined with mineral oil, as it enhances absorption and increases side effect potential.[19]

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).[20] 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,[21,22] 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 and is still used by some, likely out of clinical inertia. 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.[21,23]

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 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 GoLytely (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,[24] 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, considerably higher doses will be needed, with 136 g (8 × 17 g scoop/packet) as a common recommendation.

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).[25]

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.[26] 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. An additional concern for these agents is the possibility of causing hypermagnesemia 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. Offering this option in certain patients may increase chances of medication adherence. A recipe for a senna-fruit paste can be found online.[27] 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.[28] Caffeinated coffee can have a laxative effect, by stimulating colonic motor activity, increasing fluid secretion in the small intestine, and stimulating the gastrocolic reflex.[29-31] In patients who require only small doses of pharmacologic agents for bowel prophylaxis, it is reasonable to try them on only coffee and/or fruit and fruit juices if they are reluctant to continue pharmacologic methods.

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 due to any evidence. In absence of dehydration, there is no evidence that increased fluid intake alone is likely to be helpful.[32] 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.[33] 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.[34] 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.[35]

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. Typically, risk was associated with impaired baseline renal function, but a significant rise in serum phosphate was demonstrated in elderly patients with normal kidney function.[36] It appears that this risk extends to sodium phosphate enemas as well.[37] Calls have been made to remove them from over-the-counter availability.[38]

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 the approval 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

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.
For most primary care practitioners, until price decreases, this will only be a useful option for patients whose constipation is so severe that it entails hospitalization.

analgesia. It has been found to be effective in cases where conventional laxatives have failed.[39] It is comparatively expensive (a search at the time of writing showed $71 for a 12 mg vial or $500 for a kit with seven 12 mg vials). *See Table 2 for Dosing.*

Opioid rotation. If opioid-induced 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.[40,41] 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.[42] 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. Route of administration can affect rate and severity of constipation as well. It will not often be practical for a primary care population to switch to a non-oral route, but for morphine it appears that some routes are less constipating[43] (oral > subcutaneous ≥ intravenous ≥ transdermal ≥ epidural > intrathecal). The intrathecal route still induces some constipation. This confirms the phenomenon to be a combination of central and peripheral effects.

Nausea

Another common side effect of opioids is nausea. Unlike constipation, this side effect is often transient. Like constipation, it is frequently identified as a reason for treatment discontinuation. One systematic review found the incidence to be 21% in patients treated with opioids for chronic pain in a clinical trial setting.[44] Individual trials report incidence ranging between 10-50%.[45-48]

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.[48] Opioids can induce nausea from all four of these areas.[49]

Opioids cross the blood-brain barrier and directly stimulate the CTZ. This is due to mu and delta opioid receptors. The signaling to the vomiting center involves dopamine D2 and serotonin 5-HT3 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. Input to the vomiting center occurs via histamine H1 and cholinergic pathways. 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.[49]

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 prochloperazine 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. Most practitioners would prefer to use serotonin receptor antagonists rather than dopamine antagonists due to their more favorable side effect profile (and the stigma and regulatory issues associated with haloperidol). Domperidone has a better side effect profile than haloperidol, but is not currently available in the United States.

The vestibular apparatus theory would suggest H1 blockers may have a role in nausea, and some antiemetic treatment regimens have incorporated them.[50] Meclizine or promethazine could also be used, but initially they should be reserved for cases when there is a clear vertiginous component.

These recommendations are based largely on theoretical mechanisms and expert opinion. 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.[51] 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:[52]

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

The authors described studies that reported positive effects from levosulpiride (not approved in the United States), metoclopramide, and tropisetron, but felt that the total data were insufficient to make a recommendation.

Some studies showed no greater effect than placebo. This included a placebo-controlled study of either single-dose 24 mg ondansetron or 10 mg TID metoclopramide,[53] although this trial was stopped prematurely due to difficulties in patient recruitment.

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.

As one moves to more experimental approaches, the atypical antipsychotic risperidone (Risperdal) has D2 and 5-HT2 receptor antagonism and showed efficacy for refractory opioid-induced nausea in a 20-patient, pilot study in cancer patients.[54] 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.[55]

Additional options are available for inpatients. Low-dose naltrexone continuous infusion has been shown to reduce opioid-induced nausea (at a dose of 0.25 mcg/kg/hr)[56,57] and with an increased effect as dose increased to 1 mcg/kg/hr.[58]

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.[50] 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

This is the most feared side effect of opioid therapy. It is vastly overstated as a problem in appropriately dosed chronic opioid analgesic therapy. Pain itself is an antagonist to the respiratory depression effect of opioids.[59] When appropriately titrated to analgesia, opioids do not typically cause clinically significant respiratory depression in patients in pain.[60,61] These patients are not opioid naïve, they typically are using oral or transdermal formulations, and their doses have been titrated upward to analgesic effect.

This contrasts with some situations that do significantly increase the risk for opioid-induced respiratory depression. Patients who are opioid-naïve and receiving relatively high doses of (especially parenteral) opioids, as is seen in trauma or postoperative patients, have higher risk for respiratory depression. Also at risk are patients with combined benzodiazepine (or high doses of alcohol) and opioid prescriptions. The majority of opioid overdose deaths in the United States are associated with additional sedative/hypnotic agents, often benzodiazepines. A clinician should strongly consider whether either the benzodiazepine or the opioid can be substituted with another agent. Only with caution should both be given concomitantly.

Acute renal failure is a risk, especially when long-acting morphine is being used. 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. Initiation and titration of methadone should only be done by experienced clinicians or at minimum in collaboration with an experienced pharmacist or clinician.

A respiratory side effect that is more likely to be present in a primary care patient population is sleep-disordered breathing. Chronic opioid use has been associated with central sleep apnea and carbon dioxide retention.[62-65] The studies available so far are insufficiently representative to generalize upon. 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. There appears to be a dose-dependent relationship for methadone (but not necessarily other opioids).[64,65] This corresponds with the classically taught idea that tolerance to respiratory side effects develops concomitantly with tolerance to the opioid in general. If it is mediated by NMDA receptor, this explains why the weak NMDA receptor antagonist methadone seems to have a different respiratory side effect profile compared to other opioids. It is prudent to increase your vigilance regarding sleep-disordered breathing and potentially refer for polysomnography (especially in patients in whom you anticipate long-term opioid therapy). As central sleep apnea appears to be a more common side effect than obstructive sleep apnea, BiPAP rather than CPAP may be necessary.

Many clinicians are reluctant to use opioids in patients with severe chronic obstructive pulmonary disease (COPD).[66] Despite a dearth of evidence to support the view, previous editions of some guidelines have considered opioids to be contraindicated in COPD.[67] Newer guidelines from the American Thoracic Society[68] and the American College of Chest Physicians[69] have supported use of low-dose opioids for dyspnea. The literature supports both its efficacy[70,71] and its safety.[72]

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 better studied in rats, but data continue to accrue for humans. 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.[73-76] Inhibition of the NMDA receptor slows physiologic tolerance to opioids and is hypothesized to prevent opioid-induced hyperalgesia. Inhibition of glutamate transported increases the amount of glutamate available to the NMDA receptors and counteracts inhibition. This upregulation results in an unintended pro-nocioceptive effect.

Prevalence data are not currently available. In case reports and descriptive studies, OIH is more commonly described in patients with high opioid doses.[75] 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.[77,78] 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 where 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. Patients may choose to change providers,[76] especially if the process takes multiple visits.

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.[79] It is also possible to treat OIH with ketamine, currently the most potent legally available NMDA receptor antagonist. This would generally entail referral, as most generalists will consider this to be outside their scope.

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 — morphine, hydromorphone, and meperidine — are frequently cited morphine-3-glucuronide, hydromorphone-3-glucuronide, and normeperidine.[80-83] 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. For these patients, post-void residuals should be monitored, with catheterization if needed. Fentanyl causes less urinary retention,[84] 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%).[85,86] 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.[87] 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 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.[88] This needs to be a centrally acting antagonist, not the peripherally acting methylnaltrexone. 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. This reaction should be noted in the medical record, opioid rotation should be undertaken, and an antipsychotic should be used if the patient is a danger to themselves or others.

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 ambulatory outpatient primary care setting.

References

1. De Schepper HU, et al. Opioids and the gut: Pharmacology and current clinical experience. *Neurogastroenterol Motil* 2004;16:383-394.
2. Choi YS, Billings JA. Opioid antagonists: A review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage* 2002;24:71-90.
3. Fallon M. Constipation in cancer patients: Prevalence, pathogenesis and cost-related issues. *Eur J Pain* 1999;3(Suppl 1):3-7.
4. Kalso E, et al. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004;112:372-380.
5. Ruston T, et al. Efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid-induced constipation: A systematic review. *Can Oncol Nurs J* 2013;23:236-246.
6. Agra Y, et al. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *J Pain Symptom Manage* 1998;15:1-7.
7. Freedman MD, et al. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial. *J Clin Pharmacol* 1997;37:904-907.
8. Sykes N. A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. 1991. Unpublished data.
9. Twycross R, Wilcock W. *Hospice and Palliative Care Formulary USA*. 2nd ed. Nottingham, UK: palliativedrugs.com Ltd. 2008; 24.
10. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med* 2008;11:575-581.
11. Donowitz M, Binder HJ. Effect of dioctyl sodium sulfosuccinate on colonic fluid and electrolyte movement. *Gastroenterology* 1975;69:941-950.
12. Moriarty KJ, et al. Studies on the mechanism of action of dioctyl sodium sulphosuccinate in the human jejunum. *Gut* 1985;26:1008-1013.
13. Cass L, Frederik W. Use of dioctyl sodium sulfosuccinate (aerosol O.T.) for severe constipation. *JAMA* 1956;158:261-263.
14. Harris R. Constipation in geriatrics; management with dioctyl sodium sulfosuccinate. *Am J Dig Dis* 1957;2:487-492.
15. Hyland C, Foran J. Dioctyl sodium sulphosuccinate as a laxative in the elderly. *Practitioner* 1968;200:698-699.
16. Chapman RW, et al. Effect of oral dioctyl sodium sulfosuccinate on

intake-output studies of human small and large intestine. *Gastroenterology* 1985;89:489-493.
17. Castle SC, et al. Constipation prevention: Empiric use of stool softeners questioned. *Geriatrics* 1991;46:84-86.
18. Hurdon V, et al. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *J Pain Symptom Manage* 2000;19:130-136.
19. Godfrey H. Dangers of dioctyl sodium sulfosuccinate in mixtures. *JAMA* 1971;215:643.
20. Brandt LJ, et al. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol* 2005;100(Suppl 1):S1–S21.
21. McKay SL, et al. Management of constipation. Iowa City, IA: University of Iowa Gerontological Nursing Interventions Research Center, Research Translation and Dissemination Core. 2009: 51.
22. Panchal SJ, et al. Opioid-induced bowel dysfunction: Prevalence, pathophysiology and burden. *Int J Clin Pract* 2007;61:1181-1187.
23. Ahmedzai S, Boland J. Constipation in people prescribed opioids. *Clin Evid* (Online) 2010:2407.
24. Attar A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut* 1999;44:226-230.
25. Avila JG. Pharmacologic treatment of constipation in cancer patients. *Cancer Control* 2004;11(3 Suppl):10-18.
26. Harvey RF, Read AE. Mode of action of the saline purgatives. *Am Heart J* 1975;89:810-812.
27. Yakima Valley Fruit Paste. Available at: www.cancerlynx.com/fruitpaste.html. Accessed Feb. 5, 2014.
28. Sykes N, et al. *Handbook of Opioid Bowel Syndrome.* Opioid bowel dysfunction in acute and chronic non-malignant pain. Binghamton, NY: The Haworth Medical Press. 2005: 116.
29. Wald A, et al. Effect of caffeine on the human small intestine. *Gastroenterology* 1976;71:738-742.
30. Brown SR, et al. Effect of coffee on distal colon function. *Gut* 1990;31:450-453.
31. Rao SS, et al. Is coffee a colonic stimulant? *Eur J Gastroenterol Hepatol* 1998;10:113-118.
32. Müller-Lissner SA, et al. Myths and misconceptions about chronic constipation. *Am J Gastroenterol* 2005;100:232-242.
33. Twycross RG, Harcourt JMV. The use of laxatives at a palliative care centre. *Palliative Med* 1991;5:27-33.
34. Flig E, at al. Is bisacodyl absorbed at all from suppositories in man? *Int J Pharm* 2000;196: 11-20.
35. Goldman M. Hazards of phosphate enemas. *Gastroenterology Today* 1993;3:16-17.
36. Gumurdulu Y, et al. Age as a predictor of hyperphosphatemia after oral phosphosoda administration for colon preparation. *J Gastroenterol Hepatol* 2004;19:68-72.
37. Ori Y, et al. Fatalities and severe metabolic disorders associated with the use of sodium phosphate enemas: a single center's experience. *Arch Intern Med* 2012;172:263-265. doi: 10.1001/archinternmed.2011.694.
38. E Widera. Geripal. The dangers of fleet enemas. Available at: www.geripal.org/2012/02/dangers-of-fleet-enemas.html. Accessed Feb. 6, 2014.
39. Candy B, et al. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev* 2011 Jan 19;(1):CD003448. doi: 10.1002/14651858.CD003448.pub3.
40. Clark AJ, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Curr Med Res Opin* 2004;20:1419-1428.
41. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy, and quality of life. *J Pain Symptom Manage* 1997;13:254-261.
42. Weschules DJ, et al. Toward evidence-based prescribing at end of life: A comparative analysis of sustained-release morphine, oxycodone, and transdermal fentanyl, with pain, constipation, and caregiver interaction outcomes in hospice patients. *Pain Med* 2006;7:320-329.
43. Sykes N, et al. *Handbook of Opioid Bowel Syndrome.* Opioid bowel dysfunction in acute and chronic non-malignant pain. Binghamton, NY: The Haworth Medical Press. 2005: 105.
44. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005;7:R1046-R1051.
45. Cherny NI. Opioid analgesics: Comparative features and prescribing guidelines. *Drugs* 1996;51:713-737.
46. Chou R, et al. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. *J Pain Symptom Manage* 2003;26:1026-1048.
47. Villars P, et al. Differences in the prevalence and severity of side effects based on type of analgesic prescription in patients with chronic cancer pain. *J Pain Symptom Manage* 2007;33:67-77.
48. Porreca F, Ossipov MH. Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: Mechanisms, implications, and management options. *Pain Med* 2009;10:654-662.
49. Herndon CM, et al. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy* 2002;22:240-250.
50. Kumar G, et al. Efficacy of a scheduled IV cocktail of antiemetics for the palliation of nausea and vomiting in a hospice population. *Am J Palliat Care* 2008;25:184-189.
51. McNicol E, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. *J Pain* 2003;4:231-256.
52. Laugsand EA, et al. Management of opioid-induced nausea and vomiting in cancer patients: Systematic review and evidence-based recommendations. *Palliat Med* 2011;25:442-453.
53. Hardy J, et al. A double-blind, randomised, parallel group, multinational, multicentre study comparing a single dose of ondansetron 24 mg p.o. with placebo and metoclopramide 10 mg t.d.s. p.o. in the treatment of opioid-induced nausea and emesis in cancer patients. *Support Care Cancer* 2002;10:231-236.
54. Okamoto Y, et al. A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients. *J Pain Symptom Manage* 2007;34:217-222.
55. Passik SD, et al. A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. *J Pain Symptom Manage* 2002;23:526-532.
56. Gan TJ, et al. Opioid-sparing effects of a low-dose infusion of naloxone

in patient-administered morphine sulfate. *Anesthesiology* 1997;87:1075-1081.
57. Maxwell LG, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. *Anesth Analg* 2005;100:953-958.
58. Monitto CL, et al. The optimal dose of prophylactic intravenous naloxone in ameliorating opioid-induced side effects in children receiving intravenous patient-controlled analgesia morphine for moderate to severe pain: A dose finding study. *Anesth Analg* 2011;113:834-842. doi: 10.1213/ANE.0b013e31822c9a44. Epub 2011 Sep 2.
59. Borgbjerg FM, et al. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: A controlled study in human volunteers. *Pain* 1996;64:123-128.
60. Sykes NP. Morphine kills the pain, not the patient. *Lancet* 2007;369:1325-1326.
61. Estfan B, et al. Respiratory function during parenteral opioid titration for cancer pain. *Palliat Med* 2007;21:81-86.
62. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am* 2010;94:435-446.
63. Walker JM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med* 2007;3:455-461.
64. Webster LR, et al. Sleep-disordered breathing and chronic opioid therapy. *Pain Med* 2008;9:425-432.
65. Wang D, et al. Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005;128:1348-1356.
66. Young J, et al. Using opioids to treat dyspnea in advanced COPD: Attitudes and experiences of family physicians and respiratory therapists. *Can Fam Physician* 2012;58:e401-407.
67. Rabe KF, et al. Global strategy for the diagnosis, management, and preven-tion of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.
68. Lanken PN, et al. An official American Thoracic Society clinical policy statement: Palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008;177:912-927.
69. Mahler DA, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest* 2010;137:674-691.
70. Jennings AL, et al. A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002;57:939-944.
71. Abernethy AP, et al. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003;327:523-528.
72. Ekstrom MP, et al. Safety of benzodiazepines and opioids in very severe respiratory disease: National prospective study. *BMJ* 2014;348:g445.
73. Lee M, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011;14:145-161.
74. Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 2006;104:570-587.
75. Chu LF, et al. Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. *Clin J Pain* 2008;24:479-496.
76. Silverman SM. Opioid induced hyperalgesia: Clinical implications for the pain practitioner. *Pain Physician* 2009;12:679-684.
77. Compton P, et al. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. *Drug Alcohol Depend* 2001;63:139-146.
78. Doverty M, et al. Hyperalgesic responses in methadone maintenance patients. *Pain* 2001;90:91-96.
79. Vorobeychik Y, et al. Improved opioid analgesic effect following opioid dose reduction. *Pain Med* 2008; 9:724-727.
80. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998;74:5-9.
81. Smith MT. Neuroexcitatory effects of morphine and hydromorphone: Evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol* 2000;27:524-528.
82. Wright AW, et al. Hydromorphone-3-glucuronide, a more potent neuroexcitant than its structural analogue morphine-3-glucuronide. *Life Sci* 2001;69:409-420.
83. Simopoulos TT, et al. Use of meperidine in patient-controlled analgesia and the development of normeperidine toxic reactions. *Arch Surg* 2002;137:84-88.
84. Tassinari D, et al. Transdermal fentanyl as a front-line approach to moderate-severe pain: A meta-analysis of randomized clinical trials. *J Palliat Care* 2009;25:172-180.
85. Ballantyne JC, et al. The incidence of pruritus after epidural morphine. *Anaesthesia* 1989;43:806-807.
86. Ballantyne JC, et al. Itching after epidural and spinal opiates. *Pain* 1988;33:149-160.
87. Twycross R, et al. Itch: Scratching more than the surface. *QJM* 2003;96:7-26.
88. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: A quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001;18:346-357.

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

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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CME Questions

1. Which patient is most likely to experience clinically significant respiratory depression?
   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
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 nausea, 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 78-year-old man with known mild benign prosthetic hyperplasia is started on an opioid after a hip replacement. At his subacute rehabilitation facility, seven days post-procedure, he is still noted to have urinary retention. Post void residuals are elevated. The best approach to dealing with this situation is:
   a. reassurance, as this problem is likely transient and unlikely to be clinically serious in the short term.
   b. intermittent catheterization and rotation to a different opioid.
   c. addition of a tricyclic antidepressant, such as amitriptyline.
   D addition of a alpha-blocker, such as tamsulosin.
7. 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. The opioid is helping with her pain, she is already taking acetaminophen, and you do not feel a non-opioid alternative would currently be sufficient. 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

In Future Issues: Obesity

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