Making Management of Opioid-Induced Constipation 
a Smooth Move
Heidi Trautwein, RPh, PharmD, CGP, FASCP, Clinical Pharmacist, HospiScript

Constipation can be one of the most distressing symptoms for a hospice patient, and with approximately 50% of patients experiencing constipation, this symptom should not be overlooked.1 Have you noticed the multitude of prescription medications for opioid-induced constipation? Ever wonder what to use first? Let’s review opioid-induced constipation and explore the role of laxatives in hospice symptom management.

Constipation can contribute to delirium, abdominal pain and distension, and embarrassment. Frequent assessment of bowel function and use of preventive interventions is imperative for patients receiving hospice care. Assess the patient’s normal bowel habits and any complications of constipation such as agitation, anorexia, confusion, nausea, pain, and urinary dysfunction on admission and regularly throughout care.1,2 Patients with constipation may present with abdominal tenderness, bloating, flatulence, and the feeling of incomplete evacuation.1,2 In addition to discussing symptoms and normal bowel habits with a patient, a physical assessment including listening to bowel sounds, palpating the abdomen, and examining the rectal vault are also important assessment tools in managing constipation.1,2 The Bristol Stool Scale describes seven types of feces and is a tool for assessing intestinal transit time and changes in stool consistency.1 This scale can be used to assess severity of constipation.

Several factors contribute to constipation including dehydration, immobility, reduced food and fluid intake, and medications (Table 2).1 Opioids are likely the most prevalent medication-related cause of constipation in the hospice setting. To understand how to treat opioid-induced constipation (OIC), we must first understand how opioids cause constipation. Opioids provide analgesia through activation of the μ-opioid receptors in the central nervous system (CNS) which is comprised of the brain and spinal cord; however, they also exert their effects on peripheral μ-opioid receptors including those in the gastrointestinal (GI) tract. Activation of μ-opioid receptors in the GI tract reduces fluid secretion and increases water absorption from the colon resulting in hardened stool. Large intestine μ-opioid receptor activation also leads to reduced peristalsis of the bowel.1 Reduction in GI motility results in hardened stool in up to 90% of patients taking opioids.1

Prophylactic treatment for OIC should start at initiation of opioid therapy and continue throughout treatment with opioids. Fiber supplements such as psyllium (Metamucil®), polycarbophil (FiberCon®), methylcellulose (Citrucel®) are not recommended for use in patients with OIC. Avoid fiber supplements in OIC due to increased risk of fecal impaction. Other over-the-counter (OTC) medications for constipation are effective and the first step in managing symptoms.1 The least invasive route of administration (oral) is recommended however, if swallowing is impaired; bisacodyl rectal suppositories can be an effective alternative to oral stimulant laxatives. For a patient who desires a chewable product, chocolate sennoside tablets (Ex-Lax® Chocolate) may be useful in managing symptoms. Once stimulant laxatives are optimized, the addition of an osmotic laxative may be effective in managing symptoms. Osmotic laxatives cause water retention in the stool resulting in increased frequency of bowel movements. Of the osmotic laxatives, sorbitol is more cost effective than lactulose; however, patients may not find either of these palatable in higher doses. Polyethylene glycol 3350 (Miralax®) is a flavorless osmotic laxative, that is mixed in 4-8 ounces of juice, tea or other fluids of patient preference.6 The fluid

<table>
<thead>
<tr>
<th>Table 1: Bristol Stool Scale3</th>
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<tbody>
<tr>
<td><strong>STOOL TYPE</strong></td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>7</td>
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</table>

* Type 1 and 2 may indicate constipation

Continued on page 2
volume required for use of polyethylene glycol may be difficult for patients to manage.

When stimulant and osmotic laxatives have been optimized without sufficient results, medications for refractory constipation should be considered. Table 3 lists the available prescription-only laxative medications. Methylnaltrexone (Relistor®) and naloxegol (Movantik®) are peripherally-acting µ-opioid receptor antagonists (PAMORA) that may be effective if first line agents have been exhausted.7,8 PAMORA drugs work by blocking the activation of the µ-opioid receptors in the gastrointestinal tract while preserving the activation of µ-opioid receptors in the CNS, maintaining analgesia.7,7 Consideration of goals of care and current swallowing status is important in determining which µ-opioid receptor antagonist to choose. Methylnaltrexone is given subcutaneously; while naloxegol’s oral formulation may be desirable for some. Both methylnaltrexone and naloxegol have an onset of action of under 2 hours.8,9 Both methylnaltrexone and naloxegol are contraindicated in patients with known or suspected bowel obstruction or for those with an increased risk of recurrent obstruction.8 Neither will be effective if the patient is not taking opioids.

Lubiprostone ( Amitiza® ) is a chloride channel activator that recently received FDA-approval for OIC in patients with chronic noncancer pain. Lubiprostone acts by enhancing intestinal fluid secretion and motility.5 Results from clinical trials studying lubiprostone have been somewhat inconsistent. Improvement in constipation in the trials was measured as an increase of at least 1 spontaneous bowel movement over baseline.9 Patients tend to report higher incidence of nausea with the higher dose of lubiprostone needed for OIC.6 If patients cannot tolerate the 24mcg twice daily dose, the 8mcg dose is not likely to be effective for OIC and therapy should be changed. When evaluating improvement in OIC related symptoms or quality of life, at least one study found no significant difference between senna and lubiprostone.10

Finally, Vaseline® balls may be effective if a high impaction is suspected. Vaseline® balls are pea-sized balls of petrolatum that are rolled in confectioner sugar, or any preferred flavored powder, and swallowed whole.11 Because docusate is a surfactant that can emulsify mineral oil or petrolatum, discontinue all docusate containing preparations prior to use due to the risk of systemic absorption and toxicity.12 Oral mineral oil is not recommended due to high risk of aspiration and aspiration pneumonia.11

Opioid-induced constipation is a distressing symptom frequently experienced by hospice patients. Assessing the patient at initiation of therapy and throughout the course of treatment is imperative in early detection and treatment. Stimulant laxatives plus stool softeners remain the gold standard of treatment and doses should be maximized before adding second line therapies or other adjuvants. Newer agents, such as µ-opioid receptor antagonists, should be reserved for the management of refractory constipation.

Table 2: Medications Causing Constipation8

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Anticholinergics</th>
<th>Antiepileptics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Opioids</td>
<td>• Tricyclic antidepressants</td>
<td>• Phenytoin</td>
</tr>
<tr>
<td>• NSAIDs</td>
<td>• Antihistamines</td>
<td>• Carbamazepine</td>
</tr>
</tbody>
</table>

Table 3: Prescription Medications for Constipation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Route</th>
<th>Formulation</th>
<th>Clinical Considerations</th>
<th>AWP/Day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose (Chronulac®)</td>
<td>30mL Daily</td>
<td>PRN</td>
<td>Oral solution: 10g/15 mL</td>
<td>• More costly than stimulants with no improved efficacy</td>
<td>$2.30</td>
</tr>
<tr>
<td>Methylnaltrexone (Relistor®)</td>
<td>12mg Daily</td>
<td>PRN</td>
<td>Injection: 8mg/0.4mL, 12mg/0.6mL</td>
<td>• Indicated for second line treatment of OIC, after oral stimulant laxatives and suppositories have failed</td>
<td></td>
</tr>
<tr>
<td>Naloxegol (Movantik®)</td>
<td>25mg QAM on empty stomach</td>
<td>Tablets: 12.5mg, 25mg</td>
<td></td>
<td></td>
<td>$86.50</td>
</tr>
<tr>
<td>Lubiprostone (Amitiza®)</td>
<td>24mg BID</td>
<td>PO</td>
<td>Capsules: 8mcg, 24mcg</td>
<td></td>
<td>$12.00</td>
</tr>
<tr>
<td>Linaclootide (Linizens®)</td>
<td>145mcg Daily</td>
<td>PO</td>
<td>Capsules: 145mcg, 290mcg</td>
<td></td>
<td>$11.10</td>
</tr>
</tbody>
</table>

* AWP=average wholesale price per day based on initial dosage listed.

REFERENCES:
Clinical Case Study: Opioid-Induced Constipation

Molly Sinert, RPh, PharmD, Clinical Pharmacist, HospiScript

Patient: SD, male, age 71
Hospice Diagnosis: Lung cancer, with metastases to bone
Chief Complaint: Severe constipation
Functional Status: Palliative Performance Scale (PPS) 40%
Past Medical History: Benign Prostatic Hyperplasia (BPH), hypertension, anemia

History of Present Illness: SD resides in a nursing home. He has gone 6 days without a bowel movement. He received doses of PRN milk of magnesia, followed by PRN bisacodyl (Dulcolax®) suppository 2 days ago. Manual disimpaction today was unsuccessful. SD has reduced oral intake of foods and fluids, but has been compliant with all routine medications, including his bowel regimen, linacotide (Linzess®) and senna (Senokot®). The nursing home physician has discontinued linacotide and senna with new orders for methylnaltrexone (Relistor®) 12mg subcutaneous daily until the patient has a bowel movement, then start lubiprostone (Amitiza®) 24mcg PO BID for opioid-induced constipation.

Allergies: Penicillin (hives)

Current Medications:
- Acetaminophen (Tylenol®) 325mg 1 tablet PO q4h prn mild pain or fever
- Acetaminophen/Codeine (Tylenol #3®) 300-360mg 1 tablet PO q6h prn moderate pain
- Hydrochlorothiazide, and acetaminophen/codeine.
- Morphine ER (MS Contin®) 15mg tablet PO q12h
- Naproxen (Naprosyn®) 250mg tablet PO q8h ATC
- Senna (Senokot®) 5mg tablet PO BID
- Milk of magnesia 400mg/5mL, take 30mL PO daily prn constipation
- Linsoprin (Zestril®) 5mg tablet PO daily
- Tamsulosin (Flomax®) 0.4mg capsule PO daily
- Ferrous sulfate is associated with constipation, dark stools, and GI upset, and does not offer palliative benefit making it easy to discontinue without sacrificing comfort.

Pharmacist consultation with the nurse revealed the following:
- Patient is mainly bed bound and has no trouble swallowing pills
- BP 136/78 mmHg, pulse 86; no signs of edema
- Bowel sounds hypoactive
- Disimpaction was unsuccessful, as RN was only able to "scrape off" some stool
- Patient denies nausea/vomiting, but states his belly feels full and that is why he does not eat or drink as much
- There is recent evidence of dehydration (skin is dry and pulse is higher than normal)
- Pain has increased "all over", so the patient started using more PRN acetaminophen/codeine 2 weeks ago; prior to that he required only one dose a week on average
- Linacotide was started 3 weeks ago, because the patient has had ongoing trouble with constipation
- Patient has been on Senna 1 tablet PO BID since he started Morphine ER (before hospice admission)
- Patient refuses enema due to past use resulting in residual diarrhea; type of enema unknown

Medication points of discussion:
- Review all potential causes of constipation, including medications for this patient.
- Evaluate risk vs benefit of medications that may be contributing to constipation to guide decision-making about the need to continue these medications.
- Although opioids cause constipation, most patients continue opioid therapy for pain and dyspnea management:
  - In order to provide analgesic effects, codeine requires metabolism to morphine. Some patients may have reduced ability to metabolize codeine, impairing efficacy but still exposing them to side effects like constipation.
  - Optimizing adjuvant analgesics may reduce total opioid intake, thus reducing risk of constipation. Oral corticosteroids can help manage pain related to the patient’s bone metastases. Ferrous sulfate is associated with constipation, dark stools, and GI upset, and does not offer palliative benefit making it easy to discontinue without sacrificing comfort.
- Blood pressure, edema, and hydration status should be regularly assessed, with prompt discontinuation of diuretics when clinically indicated (i.e. hypotensive, no edema present, dehydration).
- Immobility and dehydration can lead to fecal impaction and bowel obstruction, especially in elderly patients.
- Patient has denied nausea and vomiting; there was no mention of new or significant abdominal pain or cramping, therefore low suspicion of bowel obstruction.
- Fecal impaction is likely high in the rectum or in the colon based on difficulty reaching stool for manual disimpaction.
- High impactions can be treated with Vaseline® balls.
- Vaseline® balls are frozen pea-sized balls of white petrolatum coated with a powder for taste (cocoa powder, fruit juice powder, powdered sugar). They function to lubricate the lower GI passageway and soften the stool.
- Discontinue docusate-containing products during therapy with Vaseline® balls.
- Although methylnaltrexone and lubiprostone are approved to treat opioid induced constipation, they are not first-line options.
- Stimulant laxatives can overcome reduced intestinal motility caused by opioids, and the addition of a stool softener can make it easier for stool to pass.
- Senna (stimulant) and docusate (stool softener) is the preferred first-line regimen to manage opioid-induced constipation.
- Consider osmotic laxatives if additional therapy is needed once senna and docusate are optimized. Sorbitol is more cost effective than lactulose although palatability may be difficult with either sorbitol or lactulose.
- Reserve methylnaltrexone or lubiprostone as second-line therapy if the patient has not responded to preferred treatments and all causal factors have been addressed.

Pharmacist and case manager agreed on the following plan to discuss with the attending physician:

1) Discontinue linacotide as per patient's attending physician.
2) Discontinue medications contributing to constipation: ferrous sulfate, hydrochlorothiazide, and acetaminophen/codeine.
3) Non-pharmacological management:
   a) Encourage oral hydration and/or foods with high water content as tolerated (e.g., fruits, soups, yogurt).
   b) Encourage low-impact "exercise" as tolerated in bed or chair, or abdominal massage.

4) Acute impaction (recommend the following in place of methylnaltrexone):
   a) Increase plain senna to 2 tablets PO BID, then increase by 1 tablet per dose every day there is no bowel movement (maximum 4 tablets PO BID).
   b) Initiate Vaseline® balls 3-6 balls swallowed whole daily until a bowel movement occurs.

5) Chronic prevention (recommend the following in place of lubiprostone):
   a) Once patient has the first bowel movement, discontinue plain senna and Vaseline® balls.
   b) Initiate senna-docusate 2 tablets PO BID, may titrate gradually up to 4 tablets PO BID if necessary.
   c) If senna-docusate is not effective alone to prevent opioid-induced constipation, add sorbitol 15mL PO daily and titrate as necessary.

6) Pain management:
   a) Replace acetaminophen/codeine with morphine immediate release (20mg/mL) 5mg PO/SL q4h prn pain or dyspnea.
   b) Replace naproxen with dexamethasone 4mg PO QAM to improve pain and breathing, and reduce overall opioid needs.

REFERENCES:
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Hospice Item Set (HIS): NQF 1617 Patients Treated with an Opioid who are Given a Bowel Regimen

Opioids are commonly used for management of moderate to severe pain; constipation is a common opioid adverse effect. Clinical studies demonstrate that opioid-related constipation is a significant problem in adults of all ages using opioids for cancer-related pain or chronic non-cancer pain.1 Severe constipation may cause patients to access hospital emergency departments even in the last 6 months of life.2 Tolerance to the constipating effects of opioids is not developed; therefore, preventive laxative therapy is necessary for most patients.1 Additionally, patients in hospice care frequently have limited mobility and dehydration, further contributing to the risk of constipation.

Centers for Medicare & Medicaid Services (CMS) and the National Quality Forum (NQF), as well as other patient advocacy organizations, consider effective symptom management to be a hallmark of quality hospice care. Hospices are now required to report data for patient admissions for 7 quality measures, also known as the Hospice Item Set (HIS). These include measures on screening and assessment of pain and dyspnea, preferences for life sustaining treatment, discussion of religious/spiritual concerns, and patients treated with opioids who are prescribed a bowel regimen. The quality measure concerning opioids and bowel regimens (NQF 1617) describes the percentage of adult hospice patients treated with an opioid that are offered or prescribed a bowel regimen.3,4 To meet this quality measure, when opioids are initiated, orders for a bowel regimen should be in place unless there is documentation in the patient’s chart that a bowel regimen is not needed. CMS has clarified that comfort care kits including opioids, delivered to the patient’s home, are considered “on standby” and not initiated until the hospice begins using the opioid. CMS has not yet determined what the benchmark percentage indicator will be for NQF 1617. Based on patient medication profiles, just over 77% of patients cared for by Hospiscare partners have both an opioid and a laxative in place. We recommend incorporating the HospiRxMonitor™ report, “Opioids No Laxatives” into your patient discussions during your interdisciplinary group meetings. Contact your account manager for assistance in accessing HospiRxMonitor™.

For more information on HIS requirements, please visit the “Hospice Item Set (HIS)” portion of the CMS Hospice Quality Reporting Program website at http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment- Instruments/Hospice-Quality-Reporting/.

REFERENCES:
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