Disclosures
• Dr. Foy is on the speakers bureau for AstraZeneca
• Dr. Herndon declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives
• Answer questions from patients and health care providers about the potential for constipation during opioid use.
• Discuss lifestyle modifications that may help prevent and manage constipation associated with opioid therapy.
• Compare current treatment options for the management of opioid-induced constipation.
• Evaluate patient cases and make clinical recommendations for patients with opioid-induced constipation.
• Describe patient education strategies that promote adherence to therapy to prevent and manage opioid-induced constipation.

The Price of Pain Relief: Opioid Induced Constipation
Maria Foy, PharmD, BCPS, CPE
Patient Care Coordinator, Palliative Care
Abington-Jefferson Health
Chris Herndon, PharmD, BCPS, CPE
Associate Professor
Southern Illinois University Edwardsville

Target Audience: Pharmacists
ACPE#:  0202-0000-16-056-L01-P
Activity Type: Application-based

Which of the following is the most commonly reported, troublesome side effect of opioids?

a) Constipation
b) Drowsiness
c) Nausea
d) Indigestion
The inhibition of the _____________ plexus is the most likely cause of opioid induced constipation.

a) Submucosal  
b) Myenteric  
c) Celiac  
d) Brachial

Which lifestyle change can help prevent constipation?

a) Eat primarily high fat foods  
b) Exercise  
c) Increase in intake of coffee  
d) Waiting until there is enough time to have a complete bowel movement

Which of the following is a peripherally acting mu opioid antagonist?

a) Lubiprostone  
b) Senna  
c) Polyethylene glycol  
d) Methylnaltrexone

Which of the following options should NOT be a part of an opioid induced constipation (OIC) bowel regimen?

a) Bisacodyl Suppository  
b) Docusate sodium  
c) Psyllium  
d) Sennasides  
e) Polyethylene glycol

Which opioid side effect is not associated with the development of tolerance?

a) Nausea  
b) Respiratory depression  
c) Constipation  
d) Sedation  
e) Confusion

What is Opioid Induced Constipation (OIC)?

• Cause of constipation differs from functional constipation  
  • Suggested definition  
    - Change in bowel habits after opioid therapy initiated  
      • Decrease in bowel movement (BM) frequency from baseline  
      • Increased straining during defecation  
      • Feeling of incomplete evacuation of stool  
      • Harder stools  
  • Opioids may worsen constipation in patients with a predisposition
Meet Caroline

52 year old female with persistent non-cancer pain due to osteogenesis imperfecta Type 1

PMHx: Osteogenesis Imperfecta, HTN, Depression

Meds: Fentanyl TTS 75mcg/hr Q72 hours, hydromorphone IR Q8H as needed, lisinopril 40mg QD, citalopram 40mg QD, senna plus docusate 2 tablets Q12, PEG 17gms QD, lubiprostone 24mcg Q12 hours

All: NKDA

SHx: Denies tobacco use, EtOH, recreational drug use

ROS: Unremarkable other than significant constipation. Last BM 5 days ago.

Vitals: 130/74 mmHg, HR 90, RR 16, Temp 98.6

Labs: All within normal limits, specifically Ca and Mg

Tests: Abdominal CT negative for diverticulitis

Etiologies of Constipation

- Bowel Dysfunction
- Medications
- Metabolic
- Structural
- Autonomic
- Diet

Prevalence of OIC, Opioid Regimen

Incidence versus Bothersomeness of Common Opioid Adverse Effects

- Symptom
- % patients reporting
- Bothersomeness Rank

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% patients reporting</th>
<th>Bothersomeness Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>Straining</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Small / hard bowel movement</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Incomplete evacuation</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>Passing gas</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Bloating</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Lower abdominal discomfort</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>

Opioid Induced Bowel Dysfunction

- Xerostoma
- Gastroesophageal reflux
- Retroperistalsis
- Bloating
- Abdominal pain
- Incomplete evacuation
- Opioid-induced constipation

The “Poop or No Poop” Game

- Each table will be one team
- One captain per table will control the buzzer
- Please turn your button on now
- The first team to press the button and answer the question correctly will get one point
- The team with the most points will get a nominally significant prize
Poop or No Poop Sample Question

Which MLB team won the World Series in 2015?

a) St. Louis Cardinals
b) Baltimore Orioles
c) Cincinnati Reds
d) Kansas City Royals
e) Oakland Athletics

Poop or No Poop

Which of the following opioid dosing strategies has the highest risk of constipation?

a) around the clock dosing of opioid
b) as needed dosing of opioid
c) around the clock and as needed dosing of opioid
d) transdermal dosing of opioid

Pathophysiology of OIC

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Opioid Receptors and the Intestine

- Inhibition of distension-dependent peristaltic contractions
- Gastric emptying inhibition
- Gastrointestinal ion and fluid transport inhibition
- Increased pyloric resting muscle tone
- Elevation in resting anal sphincter pressure
- Decreased defecation response


Poop or No Poop

Which cooked vegetable has the highest dietary fiber content?

a) asparagus
b) cabbage
c) peas*
d) spinach
e) squash

Risk Factors for OIC

- Female gender
- Age > 70 years
- Concurrent aluminum antacids, antidepressants, and antihistamines
- Opioid dose
- Magnesium and calcium status
- Opioid type and route of administration


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Assessment Tools

- Bristol Scale
- Constipation Assessment Scale
- Bowel Function Index
- Patient Assessment of Constipation Symptoms

Caroline’s Bowel History

- Hard, ball-like stool (Bristol Scale Type 1)
- Last BM 5 days ago
- Trialed sodium phosphate (Fleets) enema without laxation
- Normal BM frequency every other day in the morning
- Describing cramping and abdominal pain

Bristol-type Stool Assessment Scale

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Separate hard lumps, similar to nuts</td>
</tr>
<tr>
<td>2</td>
<td>Lumpy, sausage-like pieces</td>
</tr>
<tr>
<td>3</td>
<td>Like sausage, but with cracks</td>
</tr>
<tr>
<td>4</td>
<td>Like a sausage or snake, but smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Soft blobs with definable edges</td>
</tr>
<tr>
<td>6</td>
<td>Fluffy, mushy pieces with ragged edges</td>
</tr>
<tr>
<td>7</td>
<td>Watery, no solid pieces</td>
</tr>
</tbody>
</table>

Bowel Function Index (BFI)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>INTENSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of defecation in the prior 7 days</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Feeling of incomplete bowel evacuation</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>Patient’s personal assessment of constipation</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

Constipation Assessment Scale

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patient Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distension or bloating</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Change in amount of gas passed rectally</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Less frequent bowel movements</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Oozing liquid stool</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Rectal fullness or pressure</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Rectal pain with bowel movement</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Small volume of stool</td>
<td>None / Some / Severe</td>
</tr>
<tr>
<td>Unable to pass stool</td>
<td>None / Some / Severe</td>
</tr>
</tbody>
</table>

Assessment

- Patient medical and medication history
- Physical exam
- Laboratory
  - Electrolyte abnormalities
  - Fluid status
- Testing
  - Abdominal CT
- Adherence
Current Therapeutic Approaches

- Behavioral health changes
- Medication Rotation
- Oral stool softeners and laxatives
- Enemas or suppositories
- Manual disimpaction/evacuation
- Propulsion agents
- Ion channel modulators
- Peripherally acting mu opioid receptor antagonists

Poop or No Poop

Which common drug is most likely to exhibit a side effect of constipation?

- a) metoprolol
- b) amlodipine
- c) sertraline
- d) aripiprazole
- e) metformin

Pharmacologic Treatment Options

- Bulk laxatives
- Osmotic laxatives
- Stimulant laxatives
- Chloride channel activators
- Peripherally acting mu opioid receptor antagonists (PAMORA)

Poop or No Poop

Which laxative / stool softener has the quickest onset of action?

- a) senna
- b) polyethylene glycol
- c) lactulose
- d) magnesium citrate
- e) bisacodyl

Bulk Forming Laxatives

- Mechanism
  - Increases stool bulk
  - Colonic distension
  - Stimulates peristalsis
- Commercially available
  - psyllium (Metamucil)
  - methylcellulose (CitruCel)
  - polycarbophil (FiberCon)
  - wheat dextrin (Benefiber)
- Inconsistent clinical evidence of utility
- Avoid in OIC due to risk of obstruction and lack of benefit

Poop or No Poop

The recommended daily intake of dietary fiber for a healthy adult is:

- a) 5-10 g/day
- b) 10-15 g/day
- c) 15-20 g/day
- d) 20-25 g/day
- e) 25-30 g/day
Stimulant Laxatives

- Mechanism
  - Increasing colonic muscle contractions facilitates peristalsis
  - Reduces intraluminal water and electrolyte absorption
- Types of stimulant laxatives
  - Senna, bisacodyl most commonly used
  - Other options: cascara, aloe, castor oil
- Dosing
  - Senna: 2 tablets at bedtime or twice daily
  - Can titrate as tolerated to 8 tablets/day
  - Scheduled bisacodyl suppositories every 2-3 days in NPO patients

Osmotic Laxatives

- Pulls water into the colon, hydrating and softening stools
- Types of osmotic laxatives
  - Polyethylene glycol (PEG)
  - Carbohydrate laxatives (lactulose, sorbitol)
  - Phosphate, magnesium, or saline
- PEG studied for OIC use
  - Increase of softened stools seen in study of methadone induced constipation
  - As effective as other laxatives in chronic constipation
  - Initial dose: 17 g daily
- Lactulose studied for functional constipation
  - May be beneficial in concomitant liver disease
  - Initial dose: 30 ml daily

Adverse Effects of Laxatives

- Generally well tolerated
- Gastrointestinal side effects
  - Nausea/vomiting
  - Diarrhea
  - Abdominal pain
- Tolerance to laxatives with long term use
- Dysfunctional bowel syndrome may occur

Poop or No Poop

Which of the following therapies is not FDA indicated for opioid-induced constipation?

a) naloxegol
b) methylnaltrexone
c) alvimopan
d) lubiprostone

Chloride Channel Activators

- Mechanism
  - Works by increasing fluid secretion and gut motility
- Available agents
  - Lubiprostone
  - Linacotide
- Lubiprostone FDA approved for OIC in non-cancer pain
  - Efficacy lessened in trials including methadone
  - Linacotide currently being studied, not yet approved
- Dosing: 24 mcg twice daily
- Generally well tolerated
  - N/V, diarrhea, abdominal pain reported in studies
- Cost: Approximately $6/dose

Opioid Antagonists

- Naloxone primarily studied
  - Low dose oral naloxone
  - Equi-oral data in palliative care
- Oral bioavailability low
- Dose studied: 2-4 mcg three times a day
- Small number of patients enrolled
- Efficacy seen but reversal of analgesia occurred in up to 1/3 of patients
- Naloxone prolonged release (PR) added to oxycodone SR studied
  - Efficacious, but tolerability similar to placebo
  - Fixed dose studied, higher doses may cause withdrawal symptoms
- Naloxone monotherapy not recommended for OIC
**Peripherally Acting Mu Opioid Receptor Antagonists (PAMORA)**

- Designed to antagonize peripheral mu opioid receptors in the gut without reversing analgesia
  - Does not cross the blood brain barrier
  - Will not produce withdrawal symptoms
- Available agents
  - Methylnaltrexone (Relistor)
  - Naloxegol (Movantik)
  - Alvimopan (Entereg)

**Methylnaltrexone (Relistor)**

- Methyl group added to naltrexone allows blocking of opioid receptors in the gut without crossing the blood brain barrier
- Analgesia not affected
- Approved for OIC in both cancer and non-cancer opioid when other therapies have failed
- Dosing:
  - 8-12 mg subcutaneously (SC) every other day for advanced illness
  - In patients >114 kg, weight based dosing is recommended
  - 12 mg SC daily recommended for non-cancer pain
- Generally well tolerated
  - GI side effects most common adverse reaction seen in studies
- Cost: Approximately $55 per 12 mg dose

**Naloxegol (Movantik)**

- Polyethylene glycol group added to naloxone to prevent the naloxone from crossing the blood brain barrier
- First oral agent for treatment of OIC in non-cancer pain
- Dosing:
  - 25 mg po daily in the am on empty stomach
  - Reduce to 12.5 mg if 25 mg dose not tolerated
  - Reduce dose in renal impairment recommended (<60 ml/min)
- Substrate of CYP3A4 metabolism and P-glycoprotein
  - Contraindicated in moderate/strong CYP3A4 inhibitors and strong CYP3A4 inducers
  - GI side effects most common
- Cost: Approximately $10/dose

**Alvimopan (Entereg)**

- Potent peripheral mu receptor antagonist that blocks opioid receptors in the gut without crossing the blood brain barrier
- Indicated for prevention of post op ileus in colorectal and abdominal surgeries
- Initial studies showed inconsistent results for OIC treatment
- Recent meta-analysis of clinical trials (4) demonstrated potential efficacy of alvimopan for OIC
- Cardiovascular adverse events in early trials
  - Seen in patients with previous CV events or were high risk for CV adverse reactions
- Cost: Approximately $130 for 12 mg tablet
  - Lower doses studied for OIC

**The Bottom Line on Docusate**

- Facilitates the incorporation of water and fats into the stool allowing for softening
- Not recommended as monotherapy for OIC
  - “You just get the mush, not the push”
- Usually given in combination with a stimulant laxative
  - May be beneficial in patients who report hard stools
- Efficacy not demonstrated in OIC studies when compared to placebo
  - NOT NEEDED in every patient who is on opioids
  - NOT NEEDED in patients receiving PEG therapy for OIC

**Other Anecdotal Options**

- Prucalopride
  - Selective 5HT4 receptor agonist
  - Stimulates gut motility
  - Usual dose: 2-4 mg/day
- Misoprostol
- Colchicine

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**Additional Management Strategies**

- Healthy bowel habits
  - Eat consistent meals at consistent times daily
  - Smaller meals
  - Eat breakfast!
  - Increase non-caffeinated fluid intake
  - Try to "schedule" bowel movements
- Opioid dose decrease
- Opioid rotation
- Diary of bowel movements

**How to Rotate to Another Opioids**

- Assess your patients for comorbidities that affect choices
- Determine the correct dosing formulation
- Individualize dosage based on pain control on current opioid and/or adverse reactions
- Calculate current 24 hour opioid usage
- Decrease for incomplete cross tolerance
  - No correlation of tolerance between opioids
  - Dose is typically reduced by 25-75%
  - Decrease dose if pain controlled and switching to an alternative opioid
  - No dose reduction needed when switching to the **SAME** opioid
- Reassess, reassess, reassess

**Tips for OIC Prevention**

- Drink plenty of water
- Avoid high fat foods
- Avoid foods high in sugar
- Exercise
- **AND….**

IF YOU GET THAT FEELING, JUST GO!!!!
Holding it in can make it worse. Don’t wait until you get home.

**Fiber Content of Common Foods**

<table>
<thead>
<tr>
<th>FOOD</th>
<th>FIBER CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various beans</td>
<td>5-16 g per 1 cup</td>
</tr>
<tr>
<td>All bran cereal</td>
<td>10 g per ½ cup</td>
</tr>
<tr>
<td>Corn</td>
<td>4 g per 1 cup</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>4 g per 1 cup</td>
</tr>
<tr>
<td>Banana</td>
<td>3 g for medium size</td>
</tr>
<tr>
<td>Whole wheat bread</td>
<td>2 g</td>
</tr>
<tr>
<td>Quinoa</td>
<td>8 g per 1 cup</td>
</tr>
<tr>
<td>Various nuts</td>
<td>12-16 g per 1 cup</td>
</tr>
</tbody>
</table>

**Patient Education**

- Adequate fluid intake
- Maintain activity
- Dietary fiber intake
- Avoidance of bulk forming laxatives
- Avoidance of straining
**Patient Education Strategies**

- Areas of focus for education
  - How to avoid OIC
  - Information on appropriate prevention strategies utilizing medications
    - Stool softener not enough!
  - Titration information based on response
  - Re-evaluation of bowel regimen with opioid dose changes
  - Provide written education on the importance of constipation prevention
  - Develop a mechanism to ensure that EVERY patient on opioids receive information on constipation prevention

**Patient Resources**

- Patient Guide to Constipation Management
- Pharmacist letter
  - Lets get going: what helps for constipation
- Harvard Patient Education Center
- Individual PAMORA web sites

**Return to Caroline**

- Patient is requesting rotation to different analgesics despite favorable pain control
- She has trialed numerous commercially available treatment modalities
- Discussed with patient the pros and cons of either orally administered naloxone or misoprostol
- What wound up happening?

**Take Home**

- OIC is a significant barrier to effective pain control
- Aggressive anticipation, monitoring, and treatment greatly improves patient-related outcomes
- Discussing the bowel habits of a patient in pain is NOT taboo

**Which of the following is the most commonly reported, troublesome side effect of opioids?**

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b) Drowsiness  
c) Nausea  
d) Indigestion

**The inhibition of the _____________ plexus is the most likely cause of opioid induced constipation.**

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c) Psyllium  
d) Sennasides  
e) Polyethylene glycol

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