Objectives

- Summarize epidemiology of opioid-induced constipation (OIC)
- Understand opiates’ effects on the gastrointestinal system
- Introduce and evaluate pharmacologic agents used for the treatment of OIC
- Summarize drug properties and prescribing information

Opioid-Induced Constipation

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Chronic Pain and Opiate Use

- Chronic pain: >20% of US adults
- >90% receiving opiate prescriptions
- Opioid sales from 1990-2010:
  - Increased fourfold

Opioid-Induced Constipation

- Definition:
  - A change when initiating opioid therapy from baseline bowel habits (over 7 days) that is characterized by any of the following:
  - Reduced bowel movement frequency
  - Development/worsening of straining to pass bowel movements
  - Sense of incomplete rectal evacuation
  - Harder stool consistency
- Occurs in 40-80% of patients receiving chronic opioids
- Clinical Presentation: same as functional constipation (+concurrent opioid treatment)

Risk Factors:

- #1: long treatment duration
- Females
- Elderly

Sequelae:

- ↓ quality of life, work productivity, pain management efficacy
- Bowel obstruction, fecal impaction

Opioid-Induced Constipation

Receptor Activity in the GI Tract

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Mu (μ)</td>
<td>Supraspinal and spinal analgesia</td>
</tr>
<tr>
<td></td>
<td>Euphoria</td>
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<tr>
<td></td>
<td>Sedation</td>
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<tr>
<td></td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Respiratory/Depression</td>
</tr>
<tr>
<td></td>
<td>Addiction</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Supraspinal and spinal analgesia</td>
</tr>
<tr>
<td></td>
<td>Diuresis</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
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<tr>
<td></td>
<td>Dysphoria</td>
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<tr>
<td></td>
<td>Respiratory/Depression</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Less clearly established roles</td>
</tr>
<tr>
<td></td>
<td>Supraspinal and spinal analgesia</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular regulation</td>
</tr>
</tbody>
</table>
Pathophysiology

- 3 Main Mechanisms:
  - Slowed GI motility
  - Decreased secretion of fluids in the gut
  - Increased sphincter tone

Nonpharmacological Prevention and Treatment

- 1st Line
  - Recommendations:
    - Standard daily fluid and fiber intake
    - Moderate to intense physical activity
    - Tapering or withdrawal of opioids, or alternative pain management, if feasible
  - Education
    - Uninformed patients: interview study
      - 28% of patients with an opioid prescription remember being informed about risk of constipation
      - 13% of patients were prescribed laxatives or were instructed to request them

Pharmacological Prevention and Treatment: OTC

- 1st line pharmacologic choice
  - Recommendations:
    - Bisacodyl, polyethylene glycol, sennosides—similar efficacy seen in OIC

Consensus Recommendations

- 1st line: Prevention
  - Increased fluid and fiber intake
  - Exercise
  - OTC stool softeners, laxatives
  - Advantages: well-tolerated, cheap, readily available
  - Disadvantages: Per survey results, <50% achieve desired outcomes
- 2nd line: Prescription medications
  - Advantages: target the specific mechanism(s) of OIC
  - Disadvantages: expensive, less familiarity, higher risk of adverse effects

Naldemedine (SYMPROIC)

- Approved: 2017
- Mechanism of Action:
  - μ-opioid receptor antagonist
  - Peripherally selective
    - Naltrexone derivative
    - Additional side chain $\xrightarrow{\uparrow}$ molecular weight $\xrightarrow{\downarrow}$ BBB permeability
- Dosing:
  - 0.2mg once daily with or without food
Naldemedine (SYMPROIC)

Contraindications

- Known/suspected GI obstruction or at increased risk of recurrent obstruction
- Hypersensitivity to naldemedine

Warnings/Precautions

- GI perforation: use with caution in patients with known/suspected lesions in GI tract
- Opioid withdrawal: consider risk-benefit scenario in patients with altered BBB

Adverse Effects

- Abdominal pain
- Diarrhea
- Nausea

Drug Interactions

- Strong CYP3A4 inducers
  - ↓ naldemedine concentrations
- Moderate/strong CYP3A4 inhibitors
  - ↑ naldemedine concentrations
- Other opioid antagonists
  - Potential for additive effect; increased risk of opioid withdrawal
- P-gp inhibitors
  - Monitor for adverse reactions

Pregnancy:

- May precipitate opioid withdrawal in fetus

Lactation:

- Discontinue drug or breastfeeding taking into consideration importance of drug to mother

Pediatrics:

- No clinical data

Hepatic Impairment:

- Avoid in severe (Child-Pugh Class C) impairment
- Safe in mild-moderate impairment: no dose adjustment

Compose-1 and COMPOSE-2 Trials

- Double-blind, randomized, placebo-controlled trials
- Patients with chronic non-cancer pain and OIC
- 12 week duration

- Primary endpoint: proportion of responders

Compose-3

- Extended treatment duration to 52 weeks
- Results:
  - Significant improvements in weekly bowel movement frequency compared to placebo at all time points measured (p ≤ 0.0001)

Compose-4 and 5

- Treatment with pain secondary to cancer
- Statistically significant results as well
Lubiprostone (AMITIZA)

• Mechanism: Chloride channel activator

Lubiprostone (AMITIZA)

• Indications
  1) treatment of chronic idiopathic constipation (CIC) in adults
  2) treatment of irritable bowel syndrome with constipation (IBS-C) in women ≥ 18 years old

• Clinical data: approval based on 6 clinical trials
  • Approved January 2006

Lubiprostone (AMITIZA) – Clinical Data

• Phase II trial (1)
  – 127 patients
  – Increase in bowel movements; no difference between once, twice, or thrice daily dosing

• Double Blind Trials (2)
  – 479 patients
  – Number of bowel movements, time to first bowel movement, and signs and symptoms of constipation decreased in treatment group

• Long-term safety studies (3)
  – 872 patients
  – Reduction in abdominal bloating and discomfort, and constipation severity over 6 to 12 months

Lubiprostone (AMITIZA)

• Dosing
  – CIC: 24 mcg by mouth BID with food and water
  – IBS-C: 8 mcg by mouth BID with food and water

• Dose adjustments
  – Renal: none
  – Hepatic
    • CIC: Child-Pugh B (16 mcg BID), Child-Pugh C (8 mcg BID)
    • IBS-C: Child-Pugh C (8 mcg once daily)
**Lubiprostone (AMITIZA)**

- **Contraindications**
  - Known or suspected mechanical gastrointestinal obstruction
- **Warning and precautions**
  - Do not prescribe for patients with severe diarrhea
  - Potential dyspnea 30 – 60 minutes after administration
- **Use in specific populations**
  - Pregnancy (C): may cause fetal harm
  - Nursing mothers: use caution

**Adverse reactions (≥ 4%)**

- CIC: nausea, diarrhea, headache
- IBS-C: nausea, diarrhea, abdominal pain

**Drug Interactions**

- Low likelihood based on in vitro studies
- No evidence of CYP effects

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**Naloxegol (MOVANTIK)**

- **Mechanism**: Mu-opioid receptor antagonist in the GI tract

**Indication**

- Treatment of opioid-induced constipation in adult patients with chronic non-cancer pain

**Clinical data**: approval based on KODIAC trials

- Approved September 2014
  - C-II status removed 2015
KODIAC trials

• 2 identical phase III, double-blind studies
  – Study 04: 652 participants
  – Study 05: 700 participants
• 12.5 or 25 mg naloxegol, or placebo
• Primary end-point: 12-week response rate

Results [vs placebo]
  – Study 04
    • response rate (25 mg), 44.4% vs 29.4%, p = 0.001; NNT = 6.7
    • response rate (12.5 mg), 40.8% vs 29.4%, p = 0.02; NNT = 8.8
  – Study 05
    • response rate (25 mg), 39.7% vs 29.3%, p = 0.01; NNT = 9.7
    • response rate (12.5 mg), 34.9% vs 29.3%, p = 0.20; NNT = 17.8

Methylnaltrexone (RELISTOR)

Naloxegol (MOVANTIK)

• Administration
  – Discontinue maintenance laxative therapy before initiating; may resume if still symptomatic after 3 days
• Dosing
  – 25 mg by mouth once daily on empty stomach around first meal of the day
• Dose adjustments
  – Renal adjustments: CrCl < 60 mL/min = 12.5 mg daily
  – Hepatic impairment: avoid in severe impairment

Contraindications
  – Known or suspected GI obstruction and increased recurrent obstruction risk
  – Concomitant use with strong CYP3A4 inhibitors

Warning/Precautions
  – GI perforation: consider the overall risk-benefit in patients with known or suspected GI tract lesions. Monitor for abdominal pain or other symptoms
  – Opioid withdrawal: consider overall risk-benefit in patients with disruptions to the BBB. Monitor for symptoms of opioid withdrawal

Adverse reactions
  – Most common (≥ 3%): abdominal pain, diarrhea, N/V, flatulence, headache

Drug Interactions:
  – Moderate or strong CYP3A4 inhibitors
  – Other opioid antagonists

Use in specific populations
  – Pregnancy (C): may precipitate opioid withdrawal in fetus
  – Nursing mothers: discontinue drug or nursing

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Use in specific populations
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Methylnaltrexone (REListor)

- **Indication**
  - Treatment of opioid induced constipation

- **Mechanism of Action**
  - Selective antagonist of opioid binding at the mu-opioid receptor
  - Limited ability to cross blood brain barrier

Methylnaltrexone (REListor)

- **Clinical Data**
  - 2 randomized, double-blind, placebo-controlled studies
  - Patients with advanced illness and life expectancy of < 6 months
  - Primary endpoints: proportion of patients with rescue-free laxation within 4 hours of double-blind dose of study medication
    - Statistically significant with p<0.0001

Methylnaltrexone (REListor)

- **Dosing**

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Injection Volume</th>
<th>Dose (SQ every other day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 38</td>
<td>Multiply weight by 0.0075 and round up volume to nearest 0.1 mL</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>38 – 61.9</td>
<td>0.4 mL</td>
<td>8 mg</td>
</tr>
<tr>
<td>62 – 114</td>
<td>0.6 mL</td>
<td>12 mg</td>
</tr>
<tr>
<td>&gt;114</td>
<td>Multiply weight by 0.0075 and round up volume to nearest 0.1 mL</td>
<td>0.15 mg/kg</td>
</tr>
</tbody>
</table>

Methylnaltrexone (REListor)

- **Contraindications**
  - Known or suspected mechanical gastrointestinal obstruction

- **Warnings and Precautions**
  - Severe or persistent diarrhea
  - Rare cases of GI perforation reported in advanced illness patients

Methylnaltrexone (REListor)

- **Special Populations**
  - Pregnancy
    - Studied in pregnant rats, rated category B, use only if clearly needed
  - Lactation
    - Excreted in breast milk of rats, use caution
  - Pediatric
    - Safety and efficacy have not been established

Methylnaltrexone (REListor)

- **Adverse Reactions**
  - Abdominal pain, flatulence, nausea, dizziness, diarrhea, hyperhidrosis

- **Drug Interactions**
  - CYP2D6 inhibitor in vitro but not in vivo
**Alvimopan (ENTEREG)**

- **Indication**
  - Partial bowel resection surgery to accelerate the time to upper and lower GI recovery
  - NOT for opioid induced constipation

- **Mechanism of Action**
  - Selective antagonist of mu-opioid receptor peripherally

**Clinical Data**
- 6 multicenter, randomized, double-blind, parallel-group, placebo-controlled studies
- Primary endpoint: time to achieve resolution of postoperative ileus
  - In all 6 studies, accelerated time to recovery of gastrointestinal function

**Dosing**
- 12 mg PO x1 prior to surgery, then 12 mg PO BID beginning day after surgery for up to 7 days
  - First dose 30 min – 5 hours prior to surgery
  - Max: 15 doses

**Contraindications**
- Warnings and Precautions
  - Potential risk of myocardial infarction with long-term use
  - EASE Program

**Special Populations**
- Pregnancy
  - Category B
  - No fetal harm observed in animals
- Lactation
  - Detected in rat milk, use caution
  - Pediatrics
  - Safety and efficacy is not established
Alvimopan (ENTEREG)

• Adverse Reactions
  – Dyspepsia (> 1.5%)
  – Increased incidence of myocardial infarction

• Drug Interactions
  – Opioids: may decrease opioid efficacy and precipitate opioid withdrawal

References


Conclusions

• Non-pharmacologic vs. Pharmacologic treatment

• Which agent is best?
  – Lack of head-to-head trials comparing agents
  – Physician preferences
  – Cost