Methylnaltrexone (Relistor®)
A novel treatment for opioid-induced constipation

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Objectives

1. Discuss the epidemiology and pathophysiology of opioid-induced constipation
2. Review the standard treatment modalities for opioid-induced constipation
3. Describe the novel mechanism of action of methylnaltrexone
4. Evaluate the evidence supporting the use of methylnaltrexone for opioid-induced constipation
5. Determine the place in therapy of methylnaltrexone for opioid-induced constipation
Opioid-Induced Constipation (OIC)

**Epidemiology**
- Constipation is the most common and debilitating adverse effect of opioid therapy
- OIC occurs in approximately 40% to 90% of patients who are chronically receiving opioids for pain
- The incidence of constipation is five times higher in opioid users than the general public (see Figure 1)
- Opioid users are two times more likely to have constipation resistant to laxative therapy
- Approximately one-third of opioid users will decrease or stop therapy to avoid constipation

![Figure 1. Epidemiology of Opioid-Induced Constipation](image)

**Opioid Analgesics**
- Opioid analgesics are commonly utilized for management of moderate to severe pain
  - Mechanism of action
    - Opioid receptor agonists alter perception of pain in the central nervous system (CNS)
    - Agonist binding decreases neuronal conduction and neurotransmitter release
  - Opioid receptors
    - Three are well characterized and their roles in analgesia are well known (see Table 1)
      - Mu (\(\mu\)), Kappa (\(\kappa\)), and Delta (\(\delta\))

**Table 1. Opioid Receptor Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Endogenous Agonist</th>
<th>Effect of Agonist Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta ((\delta))</td>
<td>Brain</td>
<td>Enkephalins</td>
<td>Analgesia, euphoria, and physical dependence</td>
</tr>
<tr>
<td>Kappa ((\kappa))</td>
<td>Brain, Spinal cord, GI tract</td>
<td>Dynorphins</td>
<td>Analgesia, sedation, miosis, decreased GI motility, dysphoria, diuresis, and psychomimetic effects</td>
</tr>
<tr>
<td>Mu ((\mu))</td>
<td>Brain, Spinal cord, GI tract</td>
<td>Endorphins</td>
<td>Analgesia, euphoria, respiratory depression, sedation, miosis, decreased GI motility, and physical dependence</td>
</tr>
</tbody>
</table>
**Pathophysiology**

- Mechanism is not fully understood (see Table 2)
  - Opioids bind to peripheral \( \mu \)-receptors located in the enteric nervous system (ENS) of the gastrointestinal (GI) tract
    - The ENS coordinates normal GI function and is composed of two plexuses (see Figure 2)
      - The myenteric plexus coordinates motor function
      - The submucosal plexus coordinates secretory and absorptive functions
  - Opioids augment GI function by three mechanisms within the ENS
    - Impaired motility
      - Decreased peristalsis (i.e. forward movement)
        - Inhibition of acetylcholine (Ach) release decreases longitudinal smooth muscle contractions
      - Increased segmental contraction (i.e. stasis)
        - Inhibition of vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) release increases circular smooth muscle tone
    - Decreased secretions
      - Inhibition of VIP and prostaglandin \( E_1 \) (PGE\(_1\)) release
      - Enhanced norepinephrine (NE) and serotonin (5-HT) release
    - Increased absorption
      - Intestinal stasis enhances passive absorption of water and electrolytes

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**The Brain in Your Gut**

The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

**Submucosal plexus**
Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

**Myenteric plexus**
Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

**Lumen**
No nerves actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.

Source: Dr. Michael D. Gershon, Columbia University


*Figure 2. The Enteric Nervous System*
Table 2. Mechanisms for Opioid-Induced Bowel Dysfunction\textsuperscript{1,4}

<table>
<thead>
<tr>
<th>Pharmacologic Action of Opioids</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased gastric motility and delayed emptying</td>
<td>Increased gastroesophageal reflux and anorexia</td>
</tr>
<tr>
<td>Inhibition of small intestine peristalsis</td>
<td>Delayed absorption of medications</td>
</tr>
<tr>
<td>Inhibition of large intestine peristalsis</td>
<td>Straining, bloating, and abdominal distention</td>
</tr>
<tr>
<td>Increased non-propulsive segmental contractions</td>
<td>Spasm, abdominal cramps, and pain</td>
</tr>
<tr>
<td>Constriction of Sphincter of Oddi</td>
<td>Biliary colic and epigastric discomfort</td>
</tr>
<tr>
<td>Increased anal sphincter tone</td>
<td>Incomplete evacuation</td>
</tr>
<tr>
<td>Diminished gastrointestinal secretions</td>
<td>Delayed digestion and hard, dry stool</td>
</tr>
<tr>
<td>Increased absorption of fluids from the bowel</td>
<td>Hard, dry stool</td>
</tr>
<tr>
<td>Decreased pyloric sphincter tone</td>
<td>Nausea/vomiting</td>
</tr>
</tbody>
</table>

Clinical Presentation\textsuperscript{1,3,4,6,9}

- **Characteristics**
  - Results from both acute and chronic opioid therapy
  - Unlike other adverse effects, tolerance will rarely develop
  - Most common dose-limiting adverse effect (may prevent adequate pain control)

- **Symptoms (see Figure 3)**
  - Hard/dry stools
  - Straining
  - Incomplete evacuation
  - Bloating
  - Abdominal distention

![Figure 3. Severity of Common Symptoms of Opioid-Induced Bowel Dysfunction\textsuperscript{2}](image)

- Severity of OIC is influenced by many factors
  - Agent (e.g. OIC appears to be worse with codeine than other agents)
  - Route (e.g. oral administration causes more OIC than parenteral)
  - Dose (e.g. opioids can inhibit GI transit even at sub-therapeutic doses)
  - Previous exposure (e.g. may predict patient-specific response)
  - Other concomitant causes of constipation (see Table 3)
Table 3. Non-Opioid Causes of Constipation\textsuperscript{1,10}

<table>
<thead>
<tr>
<th>Metabolic Abnormalities</th>
<th>Morbidities</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Tumors</td>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td>Insufficient dietary fiber</td>
<td>Hemorrhoids</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Hypercalcemia/hyperkalemia</td>
<td>Hypothyroidism</td>
<td>Antiserotonergics</td>
</tr>
<tr>
<td>Reduced physical activity</td>
<td>Depression/Anger</td>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Neurological disorders</td>
<td>Calcium/iron supplements</td>
</tr>
</tbody>
</table>

**Diagnosis\textsuperscript{11}**
- Constipation that develops or worsens while on opioid therapy
- Rome III diagnostic criteria for constipation
  - Two or more of the following in the last three months with symptom onset in the previous six months:
    - Straining during at least 25% of defecations
    - Lumpy or hard stools in at least 25% of defecations
    - Sensation of incomplete evacuation for at least 25% of defecations
    - Sensation of anorectal obstruction/blockage for at least 25% of defecations
    - Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation)
    - Fewer than three defecations per week
    - Loose stools are rarely present without the use of laxatives
    - Insufficient criteria for irritable bowel syndrome (IBS)

**Complications\textsuperscript{1,3,4,6,9}**
- Increased discomfort
- Abdominal pain
- Bowel obstruction
- Bowel perforation
- Fecal impaction
- Post-operative ileus
- Hemorrhoids
- Anal fissure
- Spurious diarrhea
- Impaired drug absorption
- Increased hospital stay
- Increased healthcare costs
- Increased morbidity
- Exacerbated pain
- Analgesic underutilization
- Decreased quality of life (see Figure 4)

![Figure 4. Impact of OIC on Quality of Life and Satisfaction with Pain Treatment\textsuperscript{12}](image-url)
Standard Treatment Modalities

Non-Pharmacological Therapy

- Increase dietary fiber intake (avoid if at risk of bowel obstruction)
- Increase fluid intake as tolerated (avoid if patient is fluid restricted)
- Encourage mobility and ambulation
- Encourage daily bowel movements (BM) at the same time every day (preferably immediately after a meal)
- Non-pharmacological therapy is rarely sufficient to prevent or treat OIC

Laxative Therapy

- Recommended for prophylaxis and management of OIC
  - Endorsed by the National Comprehensive Cancer Network (NCCN)
  - Supported by expert opinion and anecdotal experience
- Goals of therapy
  - Increase peristalsis and fluid content of the stool
  - Achieve approximately one soft BM every one to two days
- Choice of agent (see Appendix I)
  - Combination of a stimulant and stool softener is considered first-line therapy
  - Osmotic agents and lubricants are recommended second-line
  - Enemas and suppositories should be reserved for third-line use or severe cases
  - Bulk-forming laxatives are generally least effective

Limitations of Therapy

- Poor treatment response (e.g. ineffective in approximately 50% of patients)
- Adverse effects (e.g. abdominal bloating or cramping)
- Increased pill burden (e.g. senna can require titration up to 12 tablets/day)
- Unpredictable time to laxation
- Caregiver burden (e.g. use of enemas and suppositories)

Alternative Therapies

- Acetylcholinesterase inhibitors (e.g. neostigmine)
- Serotonin agonists (e.g. cisapride, tegaserod)
- Dopamine antagonists (e.g. metoclopramide)
- Prostaglandin analogs (e.g. misoprostol)
- Chloride channel activator (e.g. lubiprostone)
- Opioid antagonists (e.g. naloxone)

Opioid Antagonists

- Non-selective μ-opioid receptor antagonists (e.g. naloxone, naltrexone)
  - When administered orally, despite low bioavailability, it can still readily cross the blood brain barrier
  - High doses are needed to reverse OIC, which also reverses analgesia
  - Results are highly unpredictable (i.e. intersubject variability in response)
- Peripherally-selective μ-opioid receptor antagonists (e.g. methylnaltrexone, Relistor®; alvimopan, Entereg®)
  - Developed to reverse OIC without reversing analgesia

Summary

- OIC is the most common and intolerable adverse effect of opioid therapy
- Local stimulation of peripheral μ-opioid receptors located in the ENS is the most well recognized mechanism by which opioids cause bowel dysfunction
- Opioid agonists can cause impaired motility, decreased secretion, and increased absorption in the bowel
- OIC may result in decreased quality of life, increased healthcare costs, and inadequate pain control
- Standard therapies, such as laxatives, can be unpredictable and may be ineffective for management of OIC
Methylnaltrexone (MNTX)

Mechanism of Action

- MNTX bromide is a selective μ-opioid receptor antagonist (see Figure 5)
  - Also antagonizes κ-opioid receptors, but to a much lesser extent
  - Has NO action on δ-opioid receptors
  - Lower binding affinity than naltrexone for opioid receptors
- Quaternary amine derivative of naltrexone
  - Formed by the addition of a methyl group to the tertiary amine naltrexone
  - Increases polarity and decreases lipid solubility, reducing CNS penetration
- Has restricted ability to cross the blood-brain barrier, so acts selectively on peripheral tissues
  - Reverses opioid-effects on GI tract without reversing central analgesic effects
  - No significant change in baseline pain scores and no symptoms of opioid withdrawal have been noted following the administration of subcutaneous MNTX in clinical trials

![Figure 5. Structure of Methylnaltrexone](image)

Addition of a methyl group to naltrexone creates a quaternary amine compound. The formation of the cation results in increased polarity and decreased lipid solubility.

Table 4. Recommended Dosing for Methylnaltrexone

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Injection Volume</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 38 kg</td>
<td>0.0075 mL/kg</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>38 – 61 kg</td>
<td>0.4 mL</td>
<td>8 mg</td>
</tr>
<tr>
<td>62 – 114 kg</td>
<td>0.6 mL</td>
<td>12 mg</td>
</tr>
<tr>
<td>&gt; 114 kg</td>
<td>0.0075 mL/kg</td>
<td>0.15 mg/kg</td>
</tr>
</tbody>
</table>

Indication

- The United States Food and Drug Administration (FDA) has approved MNTX for the treatment of OIC in patients with advanced illness who are receiving palliative care when response to laxative therapy is insufficient

Dosing/Administration (see Table 4)

- One dose every other day, as needed, but no more frequently than one dose in 24 hours
- Administered by subcutaneous (SQ) injection in the abdomen, thighs, or upper arms
- Dose reduction recommended in severe renal impairment (reduce dose by 50% if CrCl < 30mL/min)
- Not studied in patients with end-stage renal disease (dialysis-dependent)
- Not studied in severe hepatic impairment (Child-Pugh Class C)
Contraindication\textsuperscript{19}
- Known or suspected mechanical GI obstruction

Pharmacokinetics\textsuperscript{1,9,19}
- Absorption
  - Time to peak plasma concentration: \(\sim 0.5\) hours
  - Subcutaneous bioavailability: \(\sim 82\%\)
- Distribution
  - Volume of distribution: \(\sim 1.1\) L/kg
  - Plasma protein binding: \(\sim 15\%\)
- Metabolism
  - Conversion to methyl-6-naltrexol isomers (5%) and methylnaltrexone sulfate (1.3%)
  - Insignificant N-demethylation to naltrexone
  - Weak cytochrome P450 2D6 inhibitor (no clinically significant drug interactions)
- Excretion
  - 85% eliminated unchanged: \(\sim 50\%\) in the urine
  - Terminal elimination half-life: \(\sim 8\) hours

Adverse Effects\textsuperscript{19-20}
- Common
  - Abdominal pain, flatulence, nausea, dizziness, and diarrhea (see Table 5)
- Severe
  - GI perforation
    - Seven post-marketing case reports in patients with localized or diffuse reduction in structural integrity of the GI tract wall (e.g. cancer, peptic ulcer, Ogilvie’s syndrome)

Table 5. Adverse Effects of Methylnaltrexone\textsuperscript{19}

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MNTX, (n = 165)</th>
<th>Placebo, (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>47 (28.5%)</td>
<td>12 (9.8%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>22 (13.3%)</td>
<td>7 (5.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (11.5%)</td>
<td>6 (4.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (7.3%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (5.5%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>11 (6.7%)</td>
<td>8 (6.5%)</td>
</tr>
</tbody>
</table>

Summary
- MNTX is a peripherally-selective \(\mu\)-opioid receptor antagonist developed to target the mechanism of OIC
- Since MNTX does not cross the blood brain barrier, it does not reverse analgesia or induce opioid withdrawal
- MNTX is dosed based on weight, administered SQ, and not to be given more than once every 24 hours
- MNTX is FDA approved for short-term treatment of OIC in patients with advanced illness receiving palliative care when response to laxative therapy is insufficient
- Use of MNTX is contraindicated in cases of bowel obstruction
- The most common adverse effects of MNTX are abdominal pain, flatulence, nausea, dizziness, and diarrhea
**Clinical Trials**

**Opioid-Induced Constipation**
- Summarized below is one phase II and two phase III clinical trials that support the FDA approval of MNTX for treatment of OIC in patients with advanced illness (see Appendix II for additional clinical trials)

### Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study


<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, randomized, parallel-group, dose-ranging, phase II trial with 1 week double-blind phase followed by a 3 week open-label phase</th>
</tr>
</thead>
</table>
| Intervention | - MNTX 1, 5, 12.5, or 20 mg administered SQ every other day (days 1, 3, and 5)  
- Baseline laxatives were continued and rescue laxatives were permitted, but not 24 hours prior to day 1 study treatment and not within 4 hours after each double-blind dose |
| Subjects | **Inclusion Criteria:**  
- Adults ≥ 18 years  
- Advanced illness (e.g. metastatic cancer or AIDS) on palliative care  
- Stable opioid dose for ≥ 2 weeks  
- Stable laxative therapy for ≥ 4 days  
- Score of ≥ 3 on a 5-point scale for constipation-related distress (see Appendix III)  
- No BM in the last 2 days  
- Life expectancy of ≥ 4 weeks  
- Stable vital signs  

**Exclusion Criteria:**  
- History of GI obstruction  
- Other condition that could compromise drug action (e.g. acute abdomen or ostomy)  
- Active peritoneal cancer (e.g. ovarian cancer)  
- History of peritoneal catheter placement for chemotherapy or dialysis  
- New regimen or dose change in GI-motility altering agents (cholinergic, anticholinergics, chemotherapy) 3 weeks prior to study entry  
- Liver function tests > 3 times upper limit  
- Serum creatinine > 2 times upper limit  
- Platelet count < 50,000/mm³  
- Fever or unstable vital signs |
| Outcomes | **Primary:**  
Laxation response (BM) within 4 hours of the initial dose  

**Secondary:**  
Laxation within 4 hours of subsequent doses or 24 hours after each dose, time to laxation, BM/week, use of rescue laxatives, adverse effects, and subjective measures: constipation severity, constipation distress, difficulty passing stools, stool consistency, pain, opioid withdrawal (see Appendix III) |
| Statistics | Intention to treat  
Analysis of variance for continuous variables  
Pearson's Chi-square test for categorical variables  
Kaplan-Meier log-rank test for time to laxation |
| Results | **Baseline Characteristics:** (n = 33)  
- 1 mg (n = 10) vs. 5 mg (n = 7) vs. 12.5 mg (n = 10) vs. 20 mg (n = 6)  
- Mean age 61.1 years (range 20-87 years); mean body weight 63.8 kg (range 38.6-112.7 kg)  
- 45% male; 79% Caucasian; 85% with cancer as a primary diagnosis  
- Mean morphine equivalent dose 289.9 mg (median 180 mg, range 9-1,207 mg)  
- Mean of 2 BM/week; 88% using laxatives (73% stimulants, 33% softeners, 27% osmotics)  
- Groups were similar at baseline with no statistically significant differences between groups  

**Primary Outcome:** (see Table 6)  
- 11 of 23 (48%) patients receiving ≥ 5 mg experienced laxation within 4 hours vs. 1 mg dose; p = 0.05  
- There was a lack of dose response relationship across the 3 highest doses  
- Response continued throughout the open-label treatment phase at a rate of 49% to 63% |
Table 6. Patients (%) with Bowel Movements within 4 or 24 Hours After Double-Blind Dose

<table>
<thead>
<tr>
<th>MNTX Dose</th>
<th>1 mg</th>
<th>5 mg</th>
<th>12.5 mg</th>
<th>20 mg</th>
<th>≥ 5 mg combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Day</td>
<td>4-Hour Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1/10 (10%)</td>
<td>3/7 (43%)</td>
<td>6/10 (60%)</td>
<td>2/6 (33%)</td>
<td>11/23 (48%)</td>
</tr>
<tr>
<td>3</td>
<td>2/9 (22%)</td>
<td>4/6 (67%)</td>
<td>5/7 (71%)</td>
<td>2/4 (50%)</td>
<td>11/17 (65%)</td>
</tr>
<tr>
<td>5</td>
<td>0/7 (0%)</td>
<td>4/5 (80%)</td>
<td>4/7 (57%)</td>
<td>3/4 (75%)</td>
<td>11/16 (69%)</td>
</tr>
<tr>
<td>24-Hour Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5/10 (50%)</td>
<td>5/7 (71%)</td>
<td>7/10 (70%)</td>
<td>2/6 (33%)</td>
<td>14/23 (61%)</td>
</tr>
<tr>
<td>3</td>
<td>3/9 (33%)</td>
<td>4/6 (67%)</td>
<td>5/7 (71%)</td>
<td>3/4 (75%)</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>5</td>
<td>1/7 (14%)</td>
<td>4/5 (80%)</td>
<td>4/7 (57%)</td>
<td>3/4 (75%)</td>
<td>11/16 (69%)</td>
</tr>
</tbody>
</table>

Secondary Outcomes: (see Figure 6)
- Median time to laxation was > 48 hours for 1mg dose vs. 1.26 hours for all doses ≥ 5 mg; p = 0.0003
- Trends towards more BM/week, less rescue laxative use, improved stool consistency and difficulty passing stools, and decreased constipation severity and distress were observed for doses ≥ 5 mg
- No change in pain control, opioid-withdrawal symptoms, or patient satisfaction were observed

![Time to Laxation for All Double-Blind Doses (Kaplan-Meier)](image)

Adverse Effects:
- Most common adverse effects were abdominal pain 45%, flatulence 33%, and diarrhea 30%
- 2 patients discontinued MNTX during the study due to intolerable adverse effects
- 2 deaths occurred during the study and were both determined to be unrelated to study medication and consistent with underlying disease

Conclusions
MNTX administered SQ at a dose of ≥ 5 mg rapidly reverses OIC in ~50% of patients with advanced illness without reversing analgesia. No dose response relationship was observed for MNTX doses ≥ 5 mg.

Critique

Strengths:
- Multicenter, randomized, double blind design
- Intention to treat statistical analysis
- Some standardized assessment scales (e.g. Modified Himmelsbach Withdrawal Scale)
- Provides proof of concept

Limitations:
- Short duration and small sample size
- High drop-out rate (33%) during double-blind phase
- Some non-standardized assessment scales (e.g. constipation distress and stool consistency)
- Lack of control group
Methylnaltrexone for opioid-induced constipation in advanced illness

**Design**
- Multicenter, randomized, placebo-controlled, phase III trial with 2 week double-blind phase followed by a 3 month, open-label extension phase

**Intervention**
- MNTX 0.15 mg/kg or placebo administered SQ every other day for 2 weeks (could increase to 0.3 mg/kg if < 3 rescue-free laxations in first 8 days)
- Baseline laxatives and rescue laxatives (enemas/suppositories) were allowed, but could not be administered within 4 hours of the study drug

**Subjects**
- **Inclusion Criteria:**
  - Adults ≥ 18 years
  - Advanced illness (terminal/end-stage disease)
  - Stable opioid dose for ≥ 2 weeks
  - Stable laxative regimen for ≥ 3 days
  - OIC (< 3 BMs in the last week)
  - Life expectancy of ≥ 1 month
- **Exclusion Criteria:**
  - Constipation not primarily caused by opioids (as determined by investigator)
  - Mechanical GI obstruction
  - Fecal impaction
  - Indwelling peritoneal catheter
  - Clinically active diverticular disease
  - Acute surgical abdomen
  - Fecal ostomy

**Outcomes**
- **Primary:**
  - Rescue-free laxation within 4 hours after the first dose OR ≥ 2 of the first 4 doses
- **Secondary:**
  - ≥ 3 laxations per week, time to laxation, adverse effects, and subjective measures: global clinical impression of change (GCIC), pain, and opioid withdrawal (see Appendix III)

**Statistics**
- Intention to treat
- Chi-square test for categorical variables
- Alpha level of 0.05 for statistical significance
- Power 0.9 for a total of 130 patients with 65 in each group
- Post hoc logistic regression analysis to explore effects of baseline characteristics on results

**Results**
- **Baseline Characteristics:** (n = 134)
  - MNTX (n = 63) vs. placebo (n = 71)
  - Median age 71 years (range 34-98 years)
  - 44% male, 95% Caucasian; 59% with cancer as a primary diagnosis
  - Mean opioid dose of 378 mg/day (median 125 mg, range 9-10,160 mg)
  - Median of 2 laxatives (81% stimulants, 40% softeners, and 32% osmotics)
  - Groups were similar at baseline with no statistically significant differences between groups
- **Primary Outcome:** (see Figure 7)
  - Rescue free laxation within 4 hours after first dose (p < 0.001; NNT = 3)
  - Rescue free laxation within 4 hours after ≥ 2 doses (p < 0.001; NNT = 2)
  - Results remained significant after adjustment for baseline opioid dose, age, and diagnosis (p < 0.001)
  - Differences between study groups were significant for each of the 7 doses over 13 days (p < 0.005)

![Figure 7. Laxation Response within 4 Hours and at 13 Days](image-url)
Secondary Outcomes: (see Figure 8)
- Median time to laxation was 6.3 hours for MNTX vs. > 48 hours for placebo (p < 0.001), and of those that responded, half responded within 30 minutes
- 3 or more rescue free laxations per week (MNTX 68% vs. placebo 45%; p = 0.009)
- At 0.3 mg/kg, laxation rates increased from 15% to 24% with MNTX vs. 8% to 7% with placebo
- Rescue-free laxation rates were 45% to 58% throughout the 3 month open-label phase (n = 89)
- MNTX improved stool consistency, difficulty with laxation, and constipation distress more than placebo
- The majority of MNTX patients (74%) considered bowel status improved while a majority of placebo patients (60%) considered it unchanged on the GCIC scale
- No change from baseline in pain scores or opioid-withdrawal scores was observed

Figure 8. Time to Laxation Response

Adverse Effects:
- Common adverse effects of MNTX were abdominal pain (17%), flatulence (13%), and nausea (11%)
- 10 (16%) MNTX-treated patients and 16 (23%) placebo-treated patients died during the study, but all events were determined to be unrelated to study medication and a result of underlying disease
- 4 (6%) of patients on MNTX and 5 (7%) on placebo discontinued the study due to adverse effects

Conclusions
MNTX 0.15 mg/kg SQ in addition to standard laxative therapy rapidly reverses OIC in ~50% of patients with advanced illness without reversing analgesia.

Critique
Strengths:
- Multicenter/multinational
- Randomized, double-blind design
- Intention to treat statistical analysis
- Some standardized assessment scales (e.g. Clinical Global Impression and Modified Himmelsbach Withdrawal Scale)

Limitations:
- Short treatment duration
- Laxative therapy may not have been optimized prior to study entry (not representative of laxative resistant populations)
- Some non-standardized assessment scales (e.g. constipation distress and stool consistency)
- Inherent conflict of interest (manufacturer sponsored, designed, and conducted trial)
**Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients.**


**Design**
- Multicenter (17 sites), single-dose, double-blind, randomized, placebo-controlled, phase III trial followed by a 28-day open-label phase and an elective 3-month open-label extension study

**Intervention**
- Single dose of MNTX 0.15 mg/kg or 0.3 mg/kg or placebo administered SQ (PRN every 24 hours during open-label phases)
- Baseline laxative regimens could be continued throughout the study, and rescue (PRN) laxatives were allowed at least 4 hours before or after the study drug

**Subjects**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults age ≥ 18 years</td>
<td>Non-opioid-induced constipation</td>
</tr>
<tr>
<td>Advanced illness</td>
<td>Bowel obstruction or fecal impaction</td>
</tr>
<tr>
<td>Stable opioid regimen for ≥ 3 days</td>
<td>Current peritoneal catheter for intraperitoneal chemotherapy or dialysis</td>
</tr>
<tr>
<td>Stable laxative regimen for ≥ 3 days</td>
<td>Active diverticular disease</td>
</tr>
<tr>
<td>No laxation within 48 hours</td>
<td>Acute surgical abdomen or fecal ostomy</td>
</tr>
<tr>
<td>Life expectancy 1-6 months</td>
<td>Previous treatment with MNTX, naltrexone, or naloxone for OIC</td>
</tr>
<tr>
<td>Stable vital signs</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**

**Primary:**
- Rescue-free laxation within 4 hours after administration of double-blind dose

**Secondary:**
- Rescue-free laxation within 24 hours after dosing, adverse effects, and subjective measures: GCIC, constipation distress, stool consistency, pain, and symptoms of opioid withdrawal (see Appendix III)

**Statistics**
- Intention to treat
- Cochran-Mantel-Haenszel and Chi-square test for 4-hour rescue free laxation response
- Logistic regression for correlation between laxation response and baseline opioid dose
- Kaplan-Meier graph for time to first laxation
- Alpha level of 0.05 for statistical significance
- Power calculation: 50 patients needed per group

**Results**

**Baseline Characteristics:** (n = 154)
- MNTX 0.15 mg/kg (n = 47), MNTX 0.3 mg/kg (n = 55), placebo (n = 52)
- Median age of 65.3 years (range 21-100 years); mean weight 67.6 kg (range 29-135 kg)
- 54.5% male; 82.5% Caucasian; 81.2% with cancer as a primary diagnosis
- Median opioid dose 186.5 mg/day (range 8-33,120 mg/day)
- Median of 2 laxatives (83% stimulants, 27% softeners, 56% osmotics)
- Groups were similar at baseline with no statistically significant differences between groups

**Primary Outcome:** (see Figure 9)
- Rescue-free laxation within 4 hours after study dose (p < 0.001; NNT = 2)
- Rescue-free laxation within 24 hours after study dose (p < 0.001; NNT = 2)
- Laxation response was not correlated to baseline oral morphine Equivalent opioid dose

**Figure 9. Rescue-Free Laxation Within 4 Hours and 24 Hours of a Double-Blind Dose**
**Secondary Outcomes** (see Figure 10):
- Median time to rescue-free laxation was 1.1 hours for MNTX 0.15 mg/kg, 0.8 hours for MNTX 0.3 mg/kg, and >24 hours for placebo ($p < 0.0001$)
- One-half of MNTX treated patients who responded within 4 hours, responded within 30 minutes
- 58% MNTX vs. 22% placebo treated patients reported improvement in GCIC
- 64% MNTX vs. 34% placebo treated patients reported an improvement in constipation distress
- No change in baseline pain scores or opioid withdrawal scores was observed
- No dose-response relationship was observed for MNTX 0.15 mg/kg vs. 0.3 mg/kg
- 147 patients entered the 28 day open-label phase, but only 27 entered the elective 3-month extension and mean individual laxation response within 4 hours of MNTX was 55.8% to 63.7% throughout

![Figure 10. Kaplan-Meier Plots of Time to First Rescue-Free Laxation Within 4 Hours After a Double-Blind Dose](image)

**Adverse Effects:**
- Common adverse effects included abdominal pain 27.7% (MNTX 0.15 mg/kg) to 38% (MNTX 0.3 mg/kg) and flatulence 12.8% (MNTX 0.15 mg/kg) to 38.2% (MNTX 0.3 mg/kg)
- 3 patients experienced severe adverse effects: flushing, delirium, and severe diarrhea/dehydration
- 87 deaths occurred during the study's extension phase, and all but one were attributed to underlying disease and deemed unrelated to the study drug
- One 73 year old woman developed severe diarrhea resulting in dehydration and death with MNTX

**Conclusions**
MNTX 0.15 mg/kg rapidly reverses OIC in ~60% of patients with advanced illness without reversing analgesia. MNTX 0.3 mg/kg is NOT more efficacious but is associated with more adverse effects.

**Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized, double-blind design</td>
<td>Short treatment duration</td>
</tr>
<tr>
<td>Intention to treat statistical analysis</td>
<td>High drop-out rate during open-label phase (limits assessment of drug tolerability)</td>
</tr>
<tr>
<td>Some standardized assessment scales (e.g. Clinical Global Impression and Modified Himmelsbach Withdrawal Scale)</td>
<td>Inconsistent use of laxatives (unclear whether laxative therapy was optimized prior to study)</td>
</tr>
<tr>
<td>Some non-standardized assessment scales (e.g. constipation distress and stool consistency)</td>
<td></td>
</tr>
</tbody>
</table>
Post-Operative Ileus\textsuperscript{23-24}

- Results from a phase II clinical trial with MNTX demonstrated benefit\textsuperscript{25}
  - Design
    - Multicenter, randomized, double-blind, placebo-controlled study
    - 65 patients underwent segmental colectomy
    - MNTX 0.3 mg/kg intravenous ≤ 90 minutes after surgery and every 6 hours until GI recovery (first toleration of solid food or first BM) for up to 7 post-operative days
  - Results
    - Mean time to toleration of full liquids (MNTX 70 hours vs. placebo 100 hours, p = 0.05)
    - Mean time to first BM (MNTX 97 hours vs. placebo 120 hours, p = 0.01)
    - Mean time to hospital discharge (MNTX 119 hours vs. placebo 149 hours, p = 0.03)
    - Adverse effects were similar to those seen in other trials (e.g. abdominal pain, flatulence)
- Preliminary results from two separate phase III trials failed to validate benefit\textsuperscript{26-27}
  - Design
    - Multicenter, randomized, double-blind, placebo-controlled studies
    - Patients underwent segmental colectomy
    - Planned enrollment of ~500 patients in each trial
    - MNTX 12 or 24 mg IV every 6 hours until GI recovery for up to 10 days
  - Results
    - Preliminary results show MNTX was not superior to placebo at reducing the time to GI recovery (time to first BM or time to hospital discharge)

Cost-Effectiveness\textsuperscript{28-30}

- Average wholesale price (AWP)
  - Single-use vial (12 mg/0.6 mL) = $48/vial
  - Single-use prefilled syringe (12 mg/0.6 mL) = $336/7 syringe kit
- Increased cost of MNTX may be offset by the reduction in other constipation-related costs (direct and indirect)
  - Cost-benefit analysis based on a willingness-to-pay data estimated a hypothetical monthly cost savings of $87,574 for third-party payers with MNTX and laxatives compared to laxatives alone
  - Cost-effectiveness analysis estimated a cost per quality adjusted life years (QALY) of $54,101 with MNTX (authors suggest a threshold of $66,770 per QALY for cost-effectiveness)

Evidence-Based Conclusions

Efficacy

- MNTX is recommended for the treatment of OIC in patients with advanced illness on palliative care
  - In clinical trials of 321 patients with advanced illness and OIC, MNTX resulted in clinically significant improvement in rescue-free laxation and time to laxation
  - No changes in pain control or symptoms of opioid-withdrawal were observed
  - Approximately 50-60% of patients responded to MNTX within 4 hours of the first dose
  - Treatment failure may be attributable to non-opioid causes of constipation
  - Response does not seem to correlate with baseline opioid dose
- MNTX is recommended when response to laxative therapy is insufficient
  - Use of laxatives was inconsistent in clinical trials and not necessarily optimized prior to study entry
- MNTX has only been studied for short-durations, up to 4 months in clinical trials
  - Therefore, long-term use is currently not recommended

Safety

- The most common adverse effects of MNTX include abdominal pain and flatulence
  - > 10% of patients in clinical trials experienced these adverse effects
  - These effects were usually transient and resolved with a BM
- Only one serious adverse event related to MNTX occurred during clinical trials
  - However, rare cases of bowel perforation have occurred in post-marketing reports

Cost

- Cost-effectiveness of MNTX has not been clearly demonstrated; therefore, the cost of MNTX should always be considered in balance to the potential benefits before recommending therapy
### Appendix I

**Commonly Prescribed Laxatives**<sup>1,2,3</sup>

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
<th>Mechanism</th>
<th>Onset of Action</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming</td>
<td>• Psyllium (Metamucil&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Increases stool bulk</td>
<td>12 – 72 hours</td>
<td>• Flatulence</td>
<td>Take with 8oz of water</td>
</tr>
<tr>
<td></td>
<td>• Methylcellulose (Citrucel&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Increases intraluminal fluid retention in bowel</td>
<td></td>
<td>• Bloating</td>
<td>Avoid in patients with esophageal strictures or bowel obstruction</td>
</tr>
<tr>
<td></td>
<td>• Calcium polycarbophil (FiberCon&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td>• Intestinal blockage</td>
<td>Cost ~$8-30/month</td>
</tr>
<tr>
<td></td>
<td>• Dietary fiber/Bran</td>
<td></td>
<td></td>
<td>• Choking if not taken with enough fluid</td>
<td></td>
</tr>
<tr>
<td>Stool Softeners/Emollients</td>
<td>• Docusate sodium (Colace&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Increases absorption of water in stool</td>
<td>24 – 48 hours</td>
<td>• Well tolerated</td>
<td>Ineffective if fluid intake is inadequate</td>
</tr>
<tr>
<td></td>
<td>• Docusate calcium (Kaopectate Stool Softener&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Lubricates and softens fecal mass</td>
<td></td>
<td>• Liquid formulation burns if taken by mouth</td>
<td>Rarely effective if administered alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost ~$6-8/month</td>
</tr>
<tr>
<td>Stimulants/Irritants</td>
<td>• Bisacodyl (Dulcolax&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Alters intestinal mucosal permeability</td>
<td>6 – 12 hours</td>
<td>• Electrolyte imbalance</td>
<td>Caution with chronic use (risk of cathartic colon)</td>
</tr>
<tr>
<td></td>
<td>• Sennosides (Senokot&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Stimulates ENS</td>
<td></td>
<td>• Diarrhea/incontinence</td>
<td>Cost ~$12-32/month</td>
</tr>
<tr>
<td>Osmotic Agents</td>
<td>• Lactulose (Chronulac&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Increases intraluminal fluid retention in bowel</td>
<td>24 – 48 hours</td>
<td>• Electrolyte imbalance</td>
<td>Lactulose is preferred in hepatic failure</td>
</tr>
<tr>
<td></td>
<td>• Polyethylene glycol (Miralax&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td>(&lt; 2 hours for large doses used for bowel cleansing prior to GI procedures)</td>
<td>• Flatulence</td>
<td>Avoid sodium phosphate in kidney disease and heart failure</td>
</tr>
<tr>
<td></td>
<td>• Sodium phosphate (Fleet&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td>• Abdominal cramps</td>
<td>Cost ~$7-73/month</td>
</tr>
<tr>
<td></td>
<td>• Milk of magnesia (MOM)</td>
<td></td>
<td></td>
<td>• Bloating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Magnesium citrate</td>
<td></td>
<td></td>
<td>• Dehydration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sorbitol 70%</td>
<td></td>
<td></td>
<td>• Diarrhea/incontinence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubricants</td>
<td>• Mineral oil</td>
<td>Lubricates colon to facilitate transit</td>
<td>6 – 8 hours</td>
<td>• Aspiration pneumonia</td>
<td>Generally, not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Malabsorption of fat soluble vitamins</td>
<td>Cost ~$4-8/month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Dehydration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Diarrhea/incontinence</td>
<td></td>
</tr>
<tr>
<td>Rectal Interventions</td>
<td>• Tap water/Soap Suds enema</td>
<td>Reflex evacuation due to colonic distention</td>
<td>5 – 15 minutes</td>
<td>• Dehydration</td>
<td>Reserve for severe cases or when rapid onset is indicated</td>
</tr>
<tr>
<td></td>
<td>• Phosphate enema (Fleet&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Mechanical lavage</td>
<td></td>
<td>• Electrolyte imbalance</td>
<td>Cost ~$9-36/month</td>
</tr>
<tr>
<td></td>
<td>• Glycerin suppository</td>
<td>Rectal irritation</td>
<td></td>
<td>• Mechanical trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bisacodyl suppository</td>
<td></td>
<td></td>
<td>• Incontinence</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix II

### Summary of Phase I Clinical Trials for Methylnaltrexone

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design, Subjects</th>
<th>Interventions</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Yuan et al. (1996)⁵²       | Randomized, 12 healthy volunteers | Intravenous                      | 1 hour sessions separated by at least 7 days | • Oral-cecal transit time (H₂ Breath Test)  
  Morphine significantly increased oral-cecal transit time from baseline of 104.6 ± 31.1 min (mean ± SD) to 163.3 ± 39.8 min (p<0.01). MNTX + morphine significantly decreased transit time to 106.3 ± 39.8 min (p < 0.01) compared to morphine alone.  
• Perception of pain (Cold-Pressor Test)  
  The effect of MNTX on pain intensity rating compared with morphine alone was not statistically significant (p = 0.78). |
| Murphy et al. (1997)³³     | Randomized, 11 healthy volunteers | Intravenous                      | Sessions separated by at least 7 days | • Rate of gastric emptying (electrical bioimpedance technique)  
  The average time to empty half of the stomach contents after administration of placebo was 5.5 ± 1.9 min versus morphine 21 ± 9.0 min (p < 0.03). MNTX reversed morphine-induced delay in gastric emptying to 7.4 ± 3.0 min (p < 0.04).  
• Rate of gastric emptying (acetaminophen absorption test)  
  Maximum serum acetaminophen level and the area under the curve from 0 to 90 min after morphine administration was significantly decreased from those values observed after administration of placebo (p < 0.01) or morphine + MNTX (p < 0.05). |
| Yuan et al. (1997)²⁴       | Randomized, 14 healthy volunteers | Oral                             | 7 hour sessions separated by at least 7 days | • Oral-cecal transit time (H₂ Breath Test)  
  The delay in oral-cecal transit time induced by IV morphine was effectively prevented by oral MNTX in all but one subject. Morphine significantly increased oral-cecal transit time to 158.5 ± 50.2 min (mean ± SD) from baseline (placebo + placebo) 114.6 ± 37.0 min (p < 0.001). MNTX + morphine showed no increase in transit time (110.4 ± 45.0 min), effectively preventing morphine-induced delay in oral-cecal transit time (p < 0.005 compared to placebo + morphine). |
| Yuan et al. (2002)³⁵       | Randomized, 12 healthy volunteers | Subcutaneous                     | 7 hour sessions separated by at least 7 days | • Oral-cecal transit time  
  Morphine increased oral-cecal transit time from baseline 85± 20.5 min to 155 ± 27.9 min (p < 0.01) in the MNTX 0.1 mg/kg group. MNTX 0.1 mg/kg prevented morphine-induced delay in oral-cecal transit time (110 ± 41 min). In the 0.3 mg/kg group, morphine increased oral-cecal transit time to 140 ± 58.2 min from baseline 98 ± 49.1 min (p < 0.01) and MNTX + morphine 108 ± 59.6 min (p < 0.05).  
• Subjective effects  
  MNTX + morphine significantly reduced subjective morphine effects, such as nausea, itching, flushing, and stimulation (p<0.01). |
## Appendix II (continued)

### Summary of Phase II Clinical Trials for Methylnaltrexone

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Subjects</th>
<th>Interventions</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Yuan et al. (1999) | Randomized, single-blind, placebo-controlled, crossover trial | 4 adults with methadone-induced constipation | **Intravenous**                  | 8 days   | - Laxation response  
All subjects showed no response to placebo injection and demonstrated immediate positive laxation to MNTX. Two of the four subjects received 0.05-0.15 mg/kg instead of the study dose of 0.45 mg/kg. Stool frequency increased in all four subjects from an average 1.5 stools/week to 1.5 stools/day with MNTX.  
- Adverse effects  
Subjects reported mild abdominal cramping after injections, but no symptoms of opioid withdrawal. |
| Yuan et al. (2000) | Randomized, single-blind, placebo-controlled, crossover trial | 12 adults with methadone-induced constipation | **Oral**                        | 2 days   | - Laxation response  
Mean time to laxation with oral MNTX was 18, 12.3, and 5.2 hours, respectively, for doses 0.3, 1.0, and 3.0 mg/kg (p = 0.04 for dose-response effect).  
- Plasma concentrations  
Plasma drug levels were low or undetectable after administration of oral MNTX, suggesting a direct local action of MNTX on the gut.  
- Adverse effects  
Most patients reported mild abdominal cramping similar to a defecation sensation. |
| Yuan et al. (2000) | Randomized, double-blind, placebo-controlled, parallel trial | 22 adults with chronic, methadone-induced constipation | **Intravenous**                  | 2 days   | - Oral-cecal transit time (H₂ Breath Test)  
Baseline oral-cecal transit times for MNTX and placebo-treated groups were 132.3 and 126.8 min on average, respectively. The average change in the MNTX group was -77.7 ± 37.2 min, significantly greater than for placebo group (-1.4 ± 12 min), p < 0.01.  
- Immediate laxation response (during or within 1 min after infusion)  
None of placebo treated patients showed laxation response, but all 11 MNTX treated patients responded (p < 0.01). Most subjects (>90%) had soft to loose stools in large quantities. 100% of patients reported satisfaction with MNTX laxation response.  
- Opioid withdrawal  
No opioid withdrawal symptoms were observed in any subjects.  
- Adverse effects  
Mild-moderate abdominal cramping similar to a defecation sensation reported by all subjects during or immediately after study drug administration. |
| Thomas et al. (2003) | Randomized, double-blind, dose-finding trial | 15 hospice patients with OIC unrelieved by laxatives | **Subcutaneous**                  | 3 days   | - Bowel Movements  
MNTX produced a dose-related response with up to 70% laxation response within 4 hours at a dose of 12.5 mg SQ.  
- Symptoms of opioid withdrawal  
No symptoms of opioid withdrawal or increased pain were observed.  
- Adverse effects  
Most common adverse effects were abdominal cramping (42.9%) and flatulence (21.4%), which were both transient. |
Appendix III

Rating Scales Utilized in Clinical Trials with Methylnaltrexone

<table>
<thead>
<tr>
<th>Score</th>
<th>Global Clinical Impression of Change</th>
<th>Stool Consistency</th>
<th>Constipation Severity</th>
<th>Constipation Distress</th>
<th>Difficulty Passing Stool</th>
<th>Pain Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very much improved</td>
<td>Very hard</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Much improved</td>
<td>Hard</td>
<td>Mild</td>
<td>A little bit</td>
<td>Slight</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Minimally improved</td>
<td>Slightly hard</td>
<td>Moderate</td>
<td>Somewhat</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>No change</td>
<td>Firm</td>
<td>Severe</td>
<td>Quite a bit</td>
<td>Considerable</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>Minimally worse</td>
<td>Soft/formed</td>
<td>Very severe</td>
<td>Very much</td>
<td>Great</td>
<td>Excruciating</td>
</tr>
<tr>
<td>6</td>
<td>Much worse</td>
<td>Watery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very much worse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified Himmelsbach Scale for Opioid Withdrawal

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Least Severe</th>
<th>Severity Rating</th>
<th>Most Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yawning</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Perspiration</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Piloerection</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score = ______ (Out of 28)

Appendix IV

Abbreviations

5-HT  Serotonin                             LFTs  Liver function tests
Ach   Acetylcholine                         mg    Milligrams
BBB   Blood brain barrier                  mL    Milliliter
BID   Twice daily                          MNTX  Methylnaltrexone
BM    Bowel movement                       NCCN  National Comprehensive Cancer Network
BRBPR Bright red blood per rectum         NE    Norepinephrine
CNS   Central nervous system               NNT   Number needed to treat
CrCl  Creatinine clearance                 NO    Nitric oxide
ED    Emergency department                 OIC   Opioid-induced constipation
ENS   Enteric nervous system               PCA   Patient controlled analgesia
FDA   Food and Drug Administration         PGE<sub>1</sub> Prostaglandin E<sub>1</sub>
GCIC  Global Clinical Impression of Change PRN   As needed
GI    Gastrointestinal                     RCT   Randomized controlled trial
gm    Grams                                QALY  Quality adjusted life years
IV    Intravenous                          SQ    Subcutaneous
kg    Kilogram                             ULN   Upper limit of normal
L     Liter                                VIP   Vasoactive intestinal polypeptide
References


