Opioid Use in Palliative Care

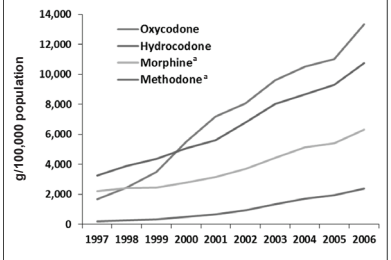
- Relief of pain is one of the core components of palliative care[1,2]
  - Up to 69% of patients with advanced cancer experience pain[3]
  - ~65% of patients dying from nonmalignant disease experience pain[4]
- Opioids are a mainstay of therapy for pain in palliative care[1,2]
  - Primarily used for moderate-to-severe pain[1,2]
  - Recommended for treatment of pain by World Health Organization[1]

1. World Health Organization. http://www.who.int/cancer/palliative/painladder/en/. Accessed February 8, 2016.
2. Swarm R, et al. NCCN adult cancer pain clinical practice guidelines in oncology 2011. http://nccn.org/professionals/physician_gls/default.asp. Accessed February 8, 2016.
3. van den Beuken-van Everdingen MHJ, et al. *Ann Oncol.* 2007;18:1437-1449.
4. Colvin L, et al. *BMJ.* 2006;332:1081-1083.

Opioid Use for Chronic Non-cancer Pain

- Opioids are increasingly prescribed to treat moderate-to-severe pain in patients with nonmalignant diseases[1,2]
- Common conditions treated with opioids include back pain, osteoarthritis, fibromyalgia, and headache[2]

Therapeutic Opioid Use in US (g/100,000 population)[1]



[a]For year 2000, data is not available, the average of 1999 and 2001 was taken.
Used with permission.

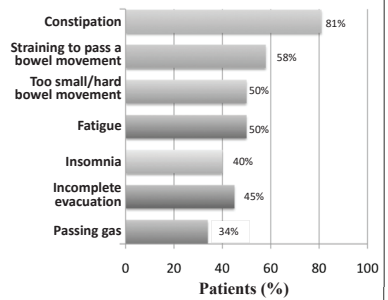
1. Manchikanti L, Singh A. *Pain Physician.* 2008;11(suppl):S63-S88.
2. Chou R, et al. *J Pain.* 2009;10:113-130.

Opioid-Induced Constipation

- Opioid-induced constipation (OIC) is one of the most common and troublesome adverse events (AEs) with opioid therapies[1-2]
  - Reported in 95% of patients with cancer pain and up to 80% of patients with nonmalignant pain[1,2]
- Tolerance to OIC rarely develops[2,3]
- Prevalence of constipation increased with duration of opioid treatment in patients with chronic, non-cancer pain[4]

PROBE, Patient Reports of Opioid-related Bothersome Effects.

Opioid-induced GI AEs That Patients With Chronic Pain Find Most Bothersome[2]*

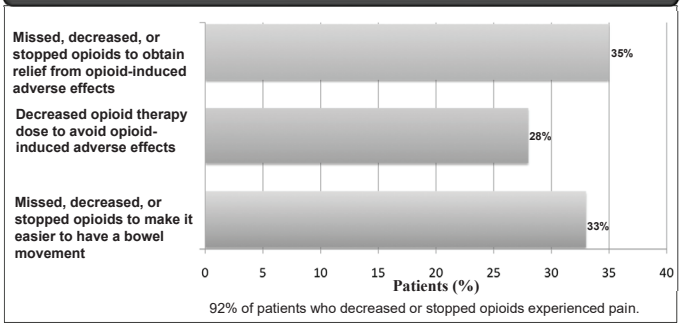


Data from PROBE 1 Survey. 4% of respondents suffered from cancer-related pain.
*AEs reported by ≥20% of patients.

1. Robinson CB, et al. *Clin J Oncol Nurs.* 2000;4:79-84.
2. Bell TJ, et al. *Pain Med.* 2009;10:35-42.
3. Panchal SJ, et al. *Int J Clin Pract.* 2007;61:1181-1187.
4. Tuteja AK, et al. *Neurogastroenterol Motil.* 2010;22:424-430.

OIC Can Compromise Pain Management in Patients with Chronic, Non-cancer Pain

Results From the PROBE 1 Survey*



92% of patients who decreased or stopped opioids experienced pain.

Bell TJ, et al. *Pain Med.* 2009;10:35-42.

*4% of survey respondents suffered from cancer-related pain.
PROBE=Patient Reports of Opioid-related Bothersome Effects.

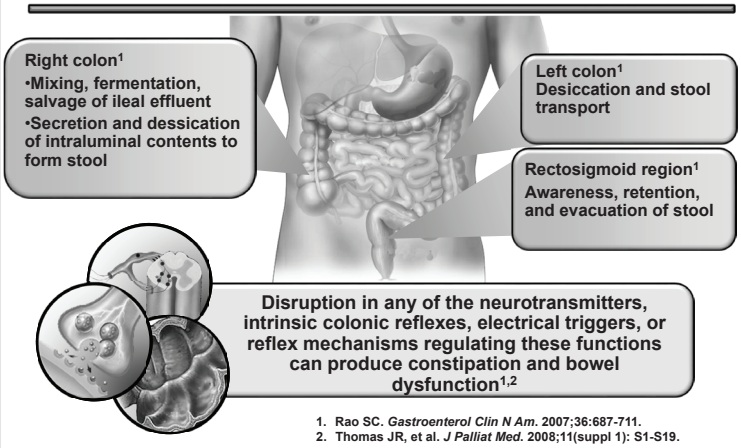
OIC Increases Use of Health Care Resources for Patients with Chronic, Non-cancer Pain

	Mean Number of Visits in Last 6 Months	
	OIC (n=359)	No OIC (n=2071)
Emergency room visits	0.5	0.5
Number of days hospitalized	1.6	1.6
Physician visits	13.5*	9.7
Alternative case visits	6.2*	4.4

Data from International Health and Wellness Survey 2004 from persons aged ≥18 years taking opioids for ≥6 months.
**P<.05.*

Bell T, et al. *J Opioid Manag.* 2009;5:137-144.

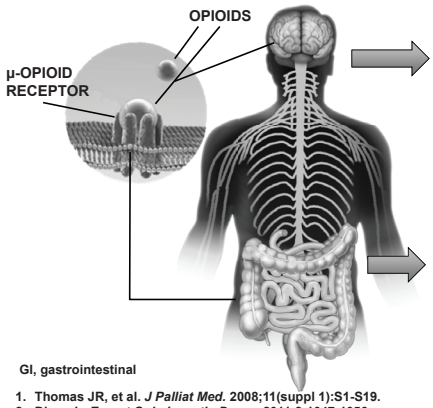
Normal Colorectal Functional Processes



Disruption in any of the neurotransmitters, intrinsic colonic reflexes, electrical triggers, or reflex mechanisms regulating these functions can produce constipation and bowel dysfunction[1,2]

1. Rao SC. *Gastroenterol Clin N Am.* 2007;36:687-711.
2. Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1): S1-S19.

Pathophysiology of OIC



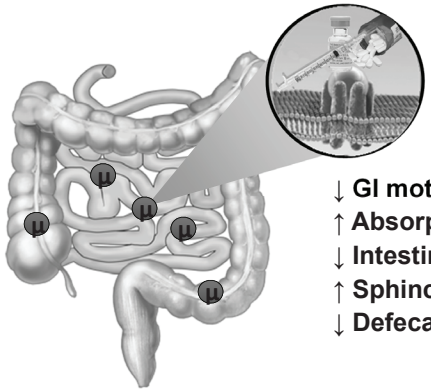
Opioids primarily exert analgesic effects via central μ-opioid receptors[1]

OIC is largely mediated by opioid actions on μ-opioid receptors in the GI tract[1-3]

GI, gastrointestinal

1. Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1):S1-S19.
2. Diego L. *Expert Opin Investig Drugs.* 2011;8:1047-1056.
3. Leppert W. *Adv Ther.* 2010;27:714-730.

Opioid Effects on the Gastrointestinal Tract

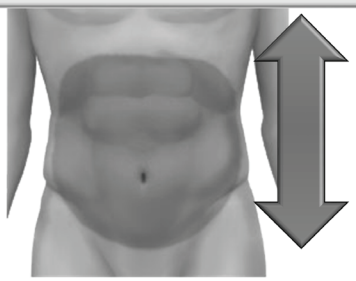


↓ GI motility
↑ Absorption of fluid from gut
↓ Intestinal secretion
↑ Sphincter tone
↓ Defecation reflex

1. Leppert W. *Adv Ther.* 2010;27:714-730.
2. Kurz A, Sessler DI. *Drugs.* 2003;63:649-671.

The Spectrum of Opioid-induced Bowel Dysfunction

Opioids Affect the Entire GI Tract[1,2]



- Reflux/heartburn
- Abdominal cramping
- Abdominal spasms
- Bloating
- Decreased appetite
- Nausea/vomiting
- Hard and dry stools
- Painful/incomplete defecation
- Constipation

1. Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1): S1-S19.
2. Kurz A, et al. *Drugs.* 2003;63:649-671.

Defining Constipation

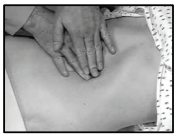
Daily ← 3 bowel movements → Weekly

- A wide range of bowel movement frequencies is considered normal[1]
- Definition of constipation depends on more than the daily number of bowel movements[1,2]
- Should address other symptoms such as passage of hard stools, excessive straining, and feeling of incomplete evacuation[1,2]

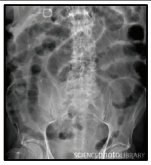
1. McMillan SC. *Cancer Control.* 2004;11(suppl 1):3-9.
2. Rao SSC. *Gastroenterol Clin North Am.* 2007;36:687-711.

Assessment of OIC

Patient interview[1-3]
- **Bowel habit**
- **Activity level**
- **Medical history**
- **Drug history**
- **Cancer history**



Physical exam[1-3]
- **Abdominal**
- **Neurologic**
- **Anorectal**



Diagnostic imaging[2,3]
- **R/O obstruction**

Signs That May Indicate Insufficient Laxative Response[3,4]
- **Hard stools**
- **Infrequent stools (<3 per week)**
- **Excessive straining**
- **Sense of incomplete evacuation**
- **Excessive time spent on toilet**
- **Unsuccessful defecation**

R/O, rule out

1. McMillan SC. *Cancer Control.* 2004;11(suppl 1):1-9.
2. Leppert W. *Adv Ther.* 2010;27:714-730.
3. Rao SSC. *Gastroenterol Clin N Am.* 2007;36:687-711.
4. Lembo A, Camilleri M. *N Engl J Med.* 2003;349:1360-1368.

The Patient History: Asking the Right Questions

- **Previous bowel pattern prior to starting opioids[1,2]**
- **Current pattern while taking opioids[1,2]**
  - **Stool frequency, consistency, and size**
  - **Degree of straining during defection**
  - **History of ignoring call to stool**

- **Fiber intake[1]**
- **Fluid intake[1]**
- **Number and timing of meals (particularly breakfast because colonic motility increases 2–3 times after waking and after a meal)[1]**

- **Laxative use (frequency and types)[1,2]**
- **Other medications (anticholinergics, calcium channel antagonists, iron supplements, calcium supplements)[1,2]**

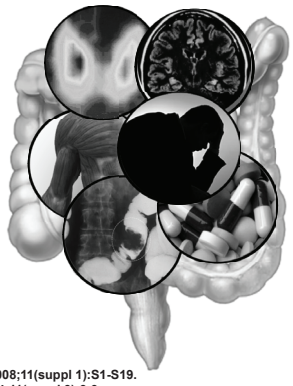
1. Peppin JF. *Practical Pain Management.* 2012 Apr:59-65.
2. Rao SSC. *Gastroenterol Clin N Am.* 2007;36:687-711.

Differential Diagnosis of OIC: Secondary Causes of Constipation

Endocrine/metabolic
Diabetes mellitus
Hypercalcemia
Hyperparathyroidism
Hypothyroidism
Uremia

Myopathic
Amyloidosis
Myotonic dystrophy
Scleroderma

Mechanical/structural
Anal dyssynergia
Anal fissures, strictures, hemorrhoids
Inflammatory bowel disorder
Obstructive colonic lesions



Neurologic diseases
Autonomic neuropathy
Cerebrovascular disease
Multiple sclerosis
Parkinson's disease
Spinal cord injury, tumors

Psychological
Anxiety
Depression
Somatization

Medications
Antacids
Anticholinergic agents
Calcium channel blockers
Clonidine
Iron
Levodopa
Nonsteroidal anti-inflammatory drugs

Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1):S1-S19.
McMillan SC. *Cancer Control.* 2004;11(suppl 3):3-9.

OIC – Issues for Patients

- Feared by many patients as much as the symptom of pain[1]
- Patients may refuse higher doses of opioid or may discontinue opioid therapy because of GI effects of opioid analgesics[2]
- Patients with OIC have more opioid-related adverse events[3]
- Can lead to a vicious cycle in which patients take more opioids to relieve pain associated with constipation, which exacerbates OIC[4]

1. Clemens KE, Klaschik E. *Ther Clin Risk Manag.* 2010;6:77-82.
2. Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1):S1-S19.
3. Candrilli SD, et al. *J Pain Palliat Care Pharmacother.* 2009;23:231-241.
4. Fallon M, O'Neill B. *BMJ.* 1997;315:1293-1296.

Practice Case – OIC in a Patient with Chronic Non-cancer Pain

- A 75-year-old female patient recently discharged from the hospital for left total hip replacement surgery
- Prior to hospitalization, patient had suffered with chronic osteoarthritis pain for over 10 years, utilizing a variety of both regularly scheduled and PRN opioid medications
- Patient presents a prescription for hydrocodone-acetaminophen 1–2 tablets PO PRN for pain

Audience Question

Is this patient at risk for becoming constipated?

1. Yes
2. No
3. Maybe

Audience Question

Which laxative(s) would you recommend for this patient?

1. High-fiber diet/bulking agents
2. Stool softener (e.g., docusate)
3. Stimulant laxative (e.g., senna)
4. Miralax® or generic equivalent
5. Combination of above

OIC Counseling Pearls

- Patients are reluctant to discuss constipation with their physician.
  - Fear of pain medication being reduced
  - Accept OIC as an unmanageable side effect
  - Already tried (and failed) multiple laxatives
- The pharmacist is often the last chance to provide a proactive recommendation for treating OIC.

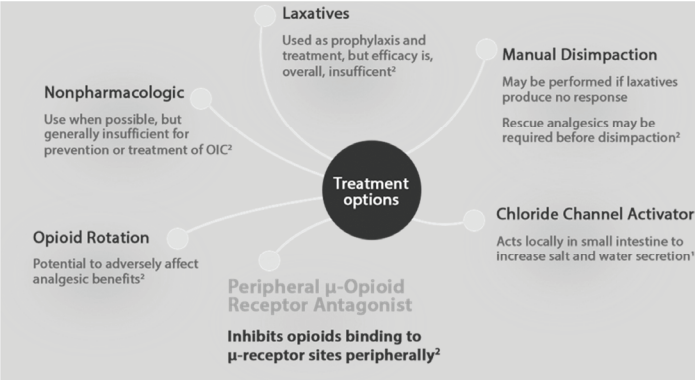
OIC Counseling Pearls

- Even very low doses of pain medications can lead to opioid-induced constipation.
- Better to prevent constipation than to react to it after the patient has become impacted with stool.
- Constipation from opioids can be prevented and does not have to affect patient's life or pain regimen.
- High-fiber diet alone will not be helpful and may be harmful.

OIC Counseling Pearls

- Watch for early signs of constipation becoming worse:
  - Infrequent stools
  - Feeling bloated or full
  - Not feeling that bowels completely empty
  - Straining
- Consider other causes of constipation
- Consider non-traditional medication options for constipation caused by opioid pain medications

There Are No Consensus-Based Guidelines for the Management of OIC[1]



OIC=opioid-induced constipation.

1. Thomas JR, et al. *J Palliat Med.* 2008;11(suppl 1):S1-S19.
2. McCarberg BH. *Postgraduate Med.* 2013;125(4):7-17.

Traditional Laxatives Used for Prevention and Treatment of OIC[1-3]

Laxative class	Agent	Time to efficacy/Limitation
Bulking agents	Dietary fiber Bran Psyllium Methylcellulose Calcium polycarbophil	• 1–3 days • Fiber may not be appropriate in palliative care[1,2]
Surfactant laxatives/Stool softeners	Docusate	• 1–3 days • Water required for ingestion of capsules
Stimulant laxatives	Senna Bisacodyl	• 6–12 hours • Water required for ingestion of capsules
Osmotic agents	Lactulose	• 1–2 days • Sweet taste may be intolerable[3]
Saline laxatives	Magnesium hydroxide Magnesium citrate Magnesium sulfate	• 1–6 hours • Magnesium hydroxide should be used as last resort[3]
Macrogols	Polyethylene glycol	• 1–4 days

OIC, opioid-induced constipation

1. Librach SL, et al. *J Pain Symptom Manage.* 2010;40:761-773. 2. Larkin PJ, et al. *Palliat Med.* 2008;22:796-807.
3. Economou. In: Ferrell and Coyle, eds. *Oxford Textbook of Palliative Nursing.* 3rd ed. 2010:269-290.

Laxative Mechanisms of Action

Laxative class	Mechanism of action[1-3]
Bulking agents	↑ Fecal bulk and luminal fluid retention ↑ Colonic transit time
Surfactant laxatives /Stool softeners	↑ Water and electrolyte secretion in jejunum and colon ↓ Water and electrolyte reabsorption in small and large intestines ↑ Peristalsis at high doses
Stimulant laxatives	↑ Gut motility by stimulation of peristalsis ↓ Water absorption from gut by altering intestinal mucosal permeability
Osmotic agents	↑ Water in intestinal lumen ↑ Fecal weight ↑ Peristalsis by mechanical distention
Saline laxatives	↑ Water secretion in intestine ↑ Peristalsis
Macrogols	↑ Stool water content and stool volume Trigger direct colonic propulsion and defecation

1. Librach SL, et al. *J Pain Symptom Manage.* 2010;40:761-773. 2. Larkin PJ, et al. *Palliat Med.* 2008;22:796-807.
3. Economou. In: Ferrell and Coyle, eds. *Oxford Textbook of Palliative Nursing.* 3rd ed. 2010:269-290.

Insufficient Response to Standard Laxative Therapy Marked by Symptoms of Chronic Constipation

Signs That May Indicate Insufficient Response
• Hard stools • Infrequent stools (<3 per week) • Excessive straining • Sense of incomplete evacuation • Excessive time spent on toilet • Unsuccessful defecation

OIC, opioid-induced constipation

Lembo A, Camilleri M. *N Engl J Med.* 2003;349:1360-1368.

Newer FDA-approved Alternatives to Treat OIC

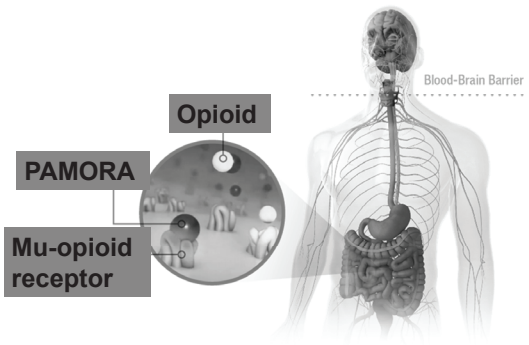
- Targeting the mu-opioid receptor
  - PAMORAs
    - Methylnaltrexone
    - Naloxegol
- Type 2 chloride channel activator
  - Lubiprostone
    - Available in oral formulation
    - Methadone use can interfere with efficacy

PAMORAs

- Peripherally Acting Mu Opioid Receptor Antagonists
- Two FDA-approved products in the U.S. market
  - Methylnaltrexone (Relistor®)
  - Naloxegol (Movantik™)
- Contraindicated for patients with bowel obstruction or at risk for obstruction

Relistor® (methylnaltrexone bromide) is manufactured by Salix Pharmaceuticals, Inc., Raleigh, NC.
Movantik™ (naloxegol) is a trademark of the AstraZeneca Group of companies, Wilmington, DE.

PAMORAs: Overall Mechanism of Action



Practice Case – OIC in a Patient with Chronic Non-cancer Pain

- A 45-year-old male with severe low back pain has been taking methadone every 8 hours on a chronic basis for several months.
  - Additionally, using PRN oxycodone, of which in the last month, usage appears to have doubled.
- He was initially prescribed docusate and senna to manage constipation.
- Despite treatment with these laxatives and increasing the dose to TID, the patient continues to experience infrequent stools that are hard and difficult to pass.
- He also complains that he spends excessive time on the toilet and frequently feels that he has failed to completely evacuate his stools.

Audience Question

Should this patient be classified as constipated?

1. Yes
2. No
3. Maybe

Audience Question

Which next steps are most appropriate for this patient?

1. Change the long-acting opioid to oxycodone
2. Further increase the dose of senna and docusate
3. Change regimen to lubriprostone
4. Change regimen to a PAMORA
5. Make no changes, constipation is expected

OIC Counseling Pearls

- All opioids can be constipating
  - Mu receptor activity leads to constipation
- Patients do not build up a tolerance to the constipating effects of opioids
- OIC can cause significant abdominal pain leading to increased dosing of PRN pain medications by the patient.
  - Not best practice to use opioids for the management of abdominal pain caused by constipation.

OIC Counseling Pearls

- Constipation is often a constellation and progression of symptoms.

  PREVENTION IS KEY TO PREVENTING SEVERE COMPLICATIONS.
- Higher dosages of ineffective traditional laxatives typically do not improve the overall management of OIC.
- Consider newer FDA-approved alternatives for OIC

Practice Case – OIC in a Cancer Patient

- A 53-year-old male with advanced lung cancer with bone metastases receiving palliative care has been an inpatient for over a week.
- He has been receiving morphine and fentanyl for severe pain.
- The patient now complains of abdominal pain and the medical chart indicates no bowel movement for several days.
- Malignant causes for the pain and bowel obstruction have been ruled out.
- The medical team determines the patient has OIC.

Audience Question

Which next steps are most appropriate for this patient?

1. Call the enema team
2. Advance dose of current laxatives and continue to monitor the patient
3. Add in a macrogol
4. Change regimen to a PAMORA
5. Manually disimpact the patient

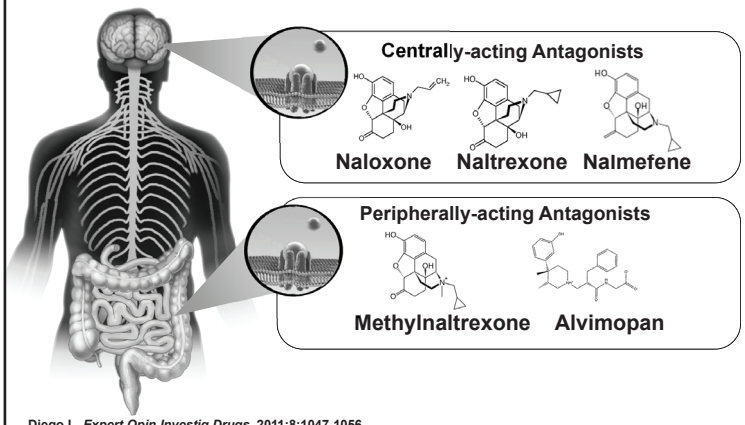
OIC Counseling Pearls

- Constipation in this patient is a serious health issue and could lead to serious morbidity if not dealt with rapidly.
- OIC in this patient appears to be resistant to the current regimen of traditional laxatives and an alternative approach should be explored.
- Inappropriate strategies for OIC may contribute to extending the length of hospital stay for patients.

OIC Counseling Pearls

- Enemas and disimpaction are time-consuming, humiliating, painful and costly; and will most likely not improve the patient in the short- or long-term.
- Consider a PAMORA to rapidly treat OIC in hospitalized patients or patients in the ED setting.
- Upon discharge, continue the outpatient use of the PAMORA as long as the patient continues on opioid therapy.
  - Many patients with OIC are effectively treated in the hospital with a PAMORA, then discharged on a traditional (and ineffective) laxative that may lead to a costly re-admission to the ED or the hospital

μ-Opioid Receptor Antagonists



Diego L. *Expert Opin Investig Drugs.* 2011;8:1047-1056.

Oral Naloxone for OIC

- Low (2%) systemic bioavailability due to extensive first-pass effect[1,2]
  - Oral administration of the IV formulation results in local action on opioid receptors in GI tract
- Clinical use limited by narrow therapeutic index[1-3]
  - Doses that reverse OIC often cause reversal of analgesia or symptoms of opioid withdrawal (e.g., yawning, sweating, shivering)[1-3]

IV, intravenous

1. Camilleri M. *Am J Gastroenterol.* 2011;106:835-842.
2. Diego L. *Expert Opin Investig Drugs.* 2011;8:1047-1056.
3. Liu M, Wittbrodt E. *J Pain Symptom Manage.* 2002;23:48-53.

Methylnaltrexone

- Quaternary salt of naltrexone (positively charged)
  - Positive charge minimizes/eliminates penetration across the BBB
- Indicated for OIC in patients with advanced illness who are receiving palliative care AND for the treatment of OIC in adult patients with chronic non-cancer pain.
- Currently available for subcutaneous administration
  - An oral formulation is under review by the FDA

BBB, blood-brain barrier

1. Diego L. *Expert Opin Investig Drugs.* 2011;8:1047-1056.
2. Camilleri M. *Am J Gastroenterol.* 2011;106:835-842.

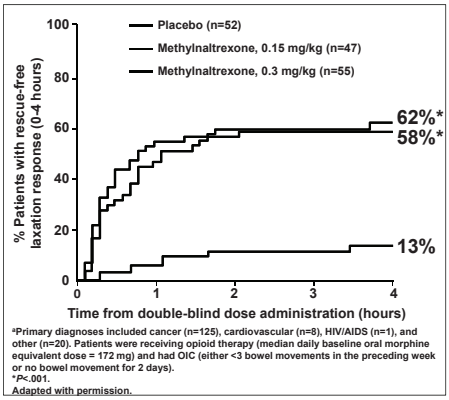
Methylnaltrexone SQ for OIC

Study	Patient description	Results
Advanced Illness: 1. Single dose a. 0.15 mg/kg SQ x 1 vs. placebo, then open label prn 2. Multi-dose a. 0.15 mg/kg SQ QOD vs. placebo for 2 weeks, then open label for 3.5 months	1. N = 232 2. Age 21 – 100 3. Current laxatives continued 4. Avg oral MS equivalent dose 172 mg/day 5. <3 BMs in prior week	Study 1: • 62% with BM in <4 hrs compared to 14% placebo • Approx. 50% of responders had BM in <30 minutes Study 2: • 48% with BM in <4 hrs compared to 15% placebo • Approx. 50% of responders had BM in <30 minutes
Chronic Non-cancer pain: 12 mg fixed dose SQ QD versus placebo for 4 weeks, then open label for 8 weeks	1. N = 312 2. Age 25 – 83 3. Current laxatives Dc'd 4. Avg oral MS equivalent dose 161 mg/day 5. Avg 1.1 SBM per week	• 59% ≥3 SBM per week compared to 38% placebo • Under four hours to first SBM: • 33% methylnaltrexone • 10% placebo

Slatkin N, et al. *J Support Oncol.* 2009;7:39-46.
Michna E, et al. *J Pain.* 2011;12:554-62.
Thomas J, et al. *N Engl J Med.* 2008;358:2332-2343.

SBM = spontaneous bowel movement

Single-Dose Methylnaltrexone for OIC in Patients With Advanced Illness[a]

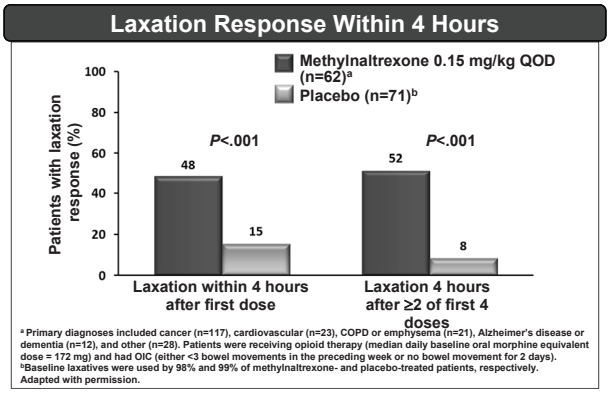


[a]Primary diagnoses included cancer (n=125), cardiovascular (n=8), HIV/AIDS (n=1), and other (n=20). Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg) and had OIC (either <3 bowel movements in the preceding week or no bowel movement for 2 days).
*P<.001.
Adapted with permission.

No difference in baseline pain or opioid withdrawal scores were noted between treatment groups

Slatkin N, et al. *J Support Oncol.* 2009;7:39-46.

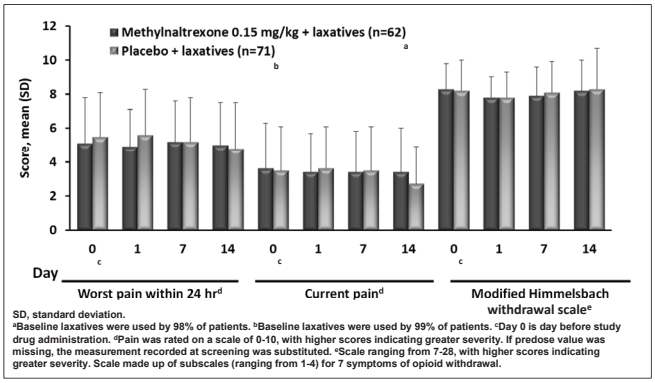
Repeated Dosing of Methylnaltrexone for OIC in Patients With Advanced Illness*



[a] Primary diagnoses included cancer (n=117), cardiovascular (n=23), COPD or emphysema (n=21), Alzheimer's disease or dementia (n=12), and other (n=28). Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg) and had OIC (either <3 bowel movements in the preceding week or no bowel movement for 2 days).
[b]Baseline laxatives were used by 98% and 99% of methylnaltrexone- and placebo-treated patients, respectively.
Adapted with permission.

Thomas J, et al. *N Engl J Med.* 2008;358:2332-2343.

Effect of Methylnaltrexone on Central Analgesia and Opioid Withdrawal



SD, standard deviation.
[a]Baseline laxatives were used by 98% of patients. [b]Baseline laxatives were used by 99% of patients. [c]Day 0 is day before study drug administration. [d]Pain was rated on a scale of 0-10, with higher scores indicating greater severity. If predose value was missing, the measurement recorded at screening was substituted. [e]Scale ranging from 7-28, with higher scores indicating greater severity. Scale made up of subscales (ranging from 1-4) for 7 symptoms of opioid withdrawal.

Thomas J, et al. *N Engl J Med.* 2008;358:2332-2343.

Methylnaltrexone AEs in Controlled Trials in Advanced Illness Patients

Adverse Event	Methylnaltrexone 0.075, 0.15, 0.30 mg/kg (n=165)	Placebo (n=123)
Abdominal pain	29%	10%
Flatulence	13%	6%
Nausea	12%	5%
Dizziness	7%	2%
Diarrhea	6%	2%

Relistor© [package insert]. Raleigh, NC: Salix Pharmaceuticals, Inc.; 2014.

Adverse Reactions During Double-Blind Phase Opioid-Induced Constipation in Adult Patients With Chronic Non-Cancer Pain

Adverse Event*	Methylnaltrexone 12 mg QD (n=150)	Placebo (n=162)
Abdominal pain	21%	6%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot flush	3%	2%
Tremor	1%	<1%
Chills	1%	0%

*Adverse events occurring in ≥1% of patients and more frequently in the treatment group than the placebo group.

Michna E, et al. *J Pain.* 2011;12:554-62.

Methylnaltrexone Dosing for OIC

- Advanced Illness: Usual schedule is one dose every other day as needed, but not more frequently than a 24-hour period

Methylnaltrexone Dosing in Advanced Illness Patients

Patient Weight		Injection Volume	Dose
lb	kg		
<84	<38	Calculated[a]	0.15 mg/kg
84 to <136	38 to <62	0.4 mL	8 mg
136 to 251	62 to 114	0.6 mL	12 mg
>251	>114	Calculated[a]	0.15 mg/kg

- For patients with chronic non-cancer pain, the dose is 12 mg SQ QD.
- Dose should be reduced by half in patients with severe renal impairment (CrCl <30 mL/min)

[a]Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL
Relistor® [package insert]. Raleigh, NC: Salix Pharmaceuticals, Inc.; 2014.

Naloxegol

- PEGylated derivative of naloxone
  - Reduced passive permeability to CNS compared with naloxone:
    - Substrate for the P-glycoprotein transporter (P-gp)
    - Presence of the PEG moiety
- Approved for treatment of adult patients with OIC due to chronic non-cancer pain
- Oral formulation 12.5 mg, 25 mg
- Drug-interactions:
  - Contraindication: Strong CYP 3A4 inhibitors
  - Warnings: Moderate CYP 3A4 inhibitors

Movantik® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2014.

Naloxegol Oral for OIC

Study	Patient description
Chronic Non-cancer pain: 12.5 mg oral vs. 25 mg oral vs. placebo QD for 12 weeks	1. N = 1352 (+1497 safety) 2. Mean age 52 y 3. Current laxatives Dc'd 4. Avg oral MS equivalent dose 140 mg/day 5. Avg 1.4 SBM per week

MS, morphine sulfate; SBM, spontaneous bowel movement

Chey WD, et al. *N Engl J Med.* 2014;370:2387-96.

Naloxegol (oral) for OIC: Study Design – Chronic Non-cancer Pain

Laxative use within 2 weeks prior to enrollment	65.7%	77.6%	70.6%	67.2%	71.6%	74.6%
Baseline mean number of SBMs per week	1.4	1.3	1.4	1.6	1.3	1.5

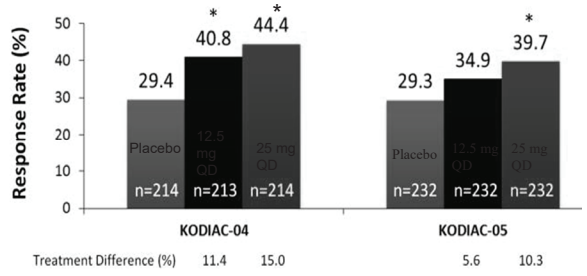
Primary Efficacy Endpoint[1]

More Bowel Movements ≥3 SBMs/week and ≥1 SBM/week over baseline + **Over a Period of Time** ≥9 of the 12 weeks and ≥3 of the last 4 weeks = **RESPONSE** (Primary Endpoint)

[1]Primary efficacy endpoint was response rate during 12-week treatment period and response was defined as ≥3 SBMs per week and an increase of ≥1 SBMs over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks

Chey WD, et al. *N Engl J Med.* 2014;370:2387-96.

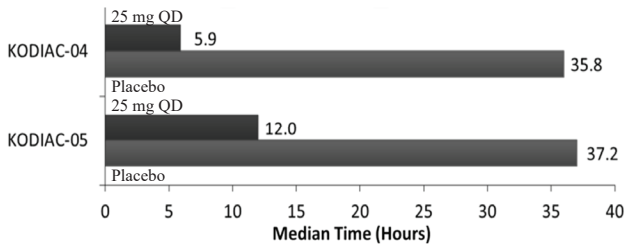
Naloxegol (oral) for OIC: Response Rates – Chronic Non-cancer Pain



* = statistically significant compared to placebo

Chey WD, et al. *N Engl J Med.* 2014;370:2387-96.

Naloxegol (oral) for OIC: Time to First Post-dose BM



Chey WD, et al. *N Engl J Med.* 2014;370:2387-96.

Adverse Reactions with Naloxegol in Patients with OIC who have Chronic non-Cancer pain

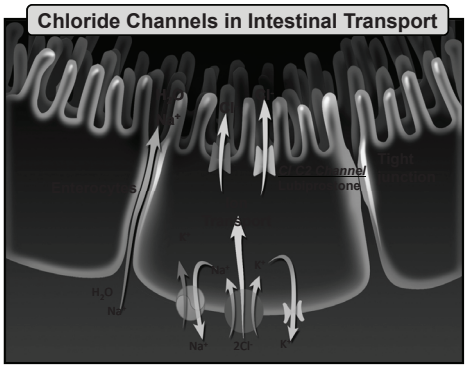
Adverse reactions in KODIAC-04 and KODIAC-05, which occurred in ≥3% of patients receiving naloxegol 25 mg, and at an incidence greater than placebo

Adverse Event*	Placebo (n=444)	Naloxegol 25 mg (n=446)
Abdominal pain	7%	21%
Diarrhea	5%	9%
Nausea	5%	8%
Flatulence	3%	6%
Vomiting	4%	5%
Headache	3%	4%
Hyperhidrosis	<1%	3%

Chey WD, et al. *N Engl J Med*. 2014;370:2387-96.

Lubiprostone

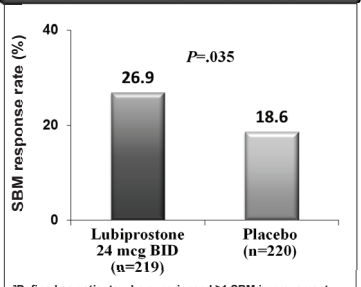
- Lubiprostone is a chloride channel activator that induces intestinal secretion
- FDA-approved for chronic idiopathic constipation, IBS-C in women and OIC for patients with chronic non-cancer pain
- Available in oral formulation



IBS-C, constipation-predominant irritable bowel syndrome.
Adapted from Rome Foundation, Inc. Computer-Based Learning Program for Functional GI Disorders [CD-ROM]; 2009. http://www.romecriteria.org/pdfs/AllSlides_Pictures.pdf. Accessed February 9, 2016.
Wong BS, Camilleri M. *Expert Opin Pharmacother*. 2011;12:983-990.

Lubiprostone for Non-Methadone OIC in Chronic, Noncancer Pain: Results of 12-Week Controlled Trial

SBM Responder Rate[a]



[a]Defined as patients who experienced ≥1 SBM improvement over baseline SBM frequency for all treatment weeks for which observed data were available, and full response (≥3 SBMs per week) for ≥9 of the 12 treatment weeks.

Jamal MM, et al. *Gastroenterology*. 2012;142(5 Suppl 1):S144-5.

Most Common (>5%) Treatment-Related AEs

Adverse Events	Lubiprostone (n=219) %	Placebo (n=220) %
Diarrhea	9.6	1.4
Nausea	8.2	2.7
Abdominal pain	5.5	0

Investigational Therapies for OIC

Drug	Description	Development Phase		
		1	2	3
Prucalopride[1]	5-HT_4 agonist			
Naldemedine[3]	Peripheral μ-opioid receptor antagonist			
Linaclotide	Guanylate cyclase-C agonist			
TD-1211[1,2]	Peripheral μ-opioid receptor antagonist			

1. Camilleri M. *Am J Gastroenterol*. 2011;106:835-842.
2. Diego L. *Expert Opin Investig Drugs*. 2011;8:1047-1056.
3. Nelson AD. *Ther Adv Gastroenterol* 2015;8:206-220

Conclusions

- OIC is an increasingly common problem for patients with chronic pain that can compromise patient quality of life and pain management and increase costs to the health care system.
- Traditional laxatives have been a mainstay of therapy for prevention and management of OIC
  - Usefulness may be limited by poor efficacy and side effects
- Peripheral μ-opioid receptor antagonists (PAMORAs) improve OIC without reversing analgesia
  - Methylnaltrexone SQ FDA-approved for treatment of OIC in patients with chronic non-cancer pain, and in patients with advanced illness.
    - Oral formulation to be reviewed at April FDA meeting
  - Naloxegol oral approved for the treatment of OIC in patients with chronic non-cancer pain.
- Studies suggest some benefit of lubiprostone in OIC
  - Methadone use can decrease effectiveness