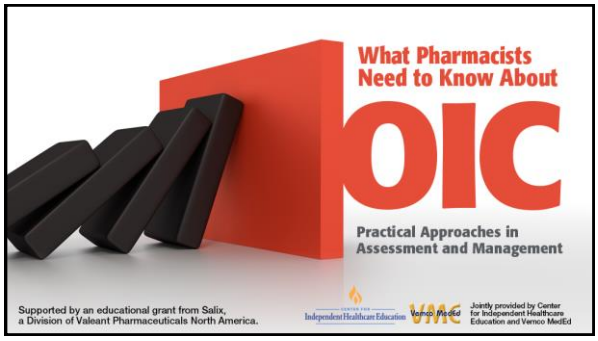

Activity Description

Target Audience

This continuing pharmacy education activity is planned to meet the needs of pharmacists in a variety of practice settings, including large and small healthcare systems, outpatient clinics, managed care organizations, long-term care facilities, community pharmacies, and academia. This program will target pharmacists who are involved in the management of patients who are taking opioid medications and may be at risk for OIC.

Learning Objectives

Those attending the program will be able at its conclusion to:

- Discuss the impact of opioid-induced constipation (OIC) on a patient's quality of life and overall well-being
- Utilize evidence-based approaches to prevent OIC among patients initiating or continuing opioid analgesic treatment for chronic pain
- Evaluate the use of newer, non-laxative pharmacotherapies in the management of OIC based on OIC severity and patient preferences

Faculty

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Pain and Palliative Care Specialist
Certified Pain Educator
Palliative Care Strategies
Seattle, WA

Opioid Analgesic Use in Chronic, Non-cancer Pain

Opioid Analgesics Are Often Prescribed for Patients With CNCP[1]

>240 million prescriptions were written for opioid analgesics in 2014[2]	**~20% of patients** presenting to a physician's office with non-cancer pain **receive a prescription for an opioid analgesic*[1]**	In a prospective, observational study, **up to 90% of patients** presenting at pain management centers **were already taking opioid medications[3]**

Although opioid analgesics can decrease pain and improve function, they are not always effective in treating all patients with CNCP and are associated with the risk of adverse effects.[4]

CNCP, chronic non-cancer pain

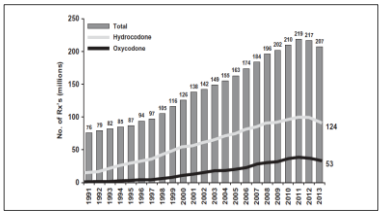
1. Dowell D, et al. *MMWR Recomm Rep.* 2016;65(No. RR-1):1-49.
2. Department of Health and Human Services Fact Sheet. https://www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf. Accessed on November 1, 2017.
3. Manchikanti L, et al. *Pain Physician.* 2004;7:431-437.
4. Chou R, et al. *J Pain.* 2009;10:147-159.

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/painladderlen/. Accessed November 1, 2017.
2. Swarm R, et al. NCCN adult cancer pain clinical practice guidelines in oncology 2011. http://nccn.org/professionals/physician_gls/default.asp. Accessed November 1, 2017.
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 Prescriptions in the US, 1991–2013



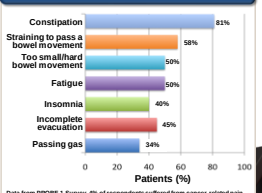
Opioid prescriptions dispensed by US retail pharmacies. IMS Health, National Prescription Audit, Years 1991–2013, Data Extracted 2014.

Diagram from: Gudin JA, Nalamachu SR. *Postgrad Med.* 2016;128:97-105.

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]

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



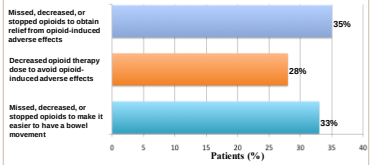
Data from PROBE 1 Survey. 4% of respondents suffered from cancer-related pain. [a]AEs reported by ≥25% of patients.

PROBE, Patient Reports of Opioid-related Bothersome Effects.

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.

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

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

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.*

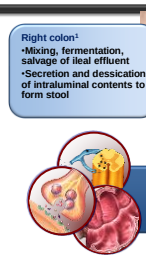
Bell T, et al. *J Opioid Manag*. 2009;5:137-144.

Normal Colorectal Functional Processes

Right colon[1]
- Mixing, fermentation, salvage of ileal effluent
- Secretion and dessication of intraluminal contents to form stool

Left colon[1]
Desiccation and stool transport

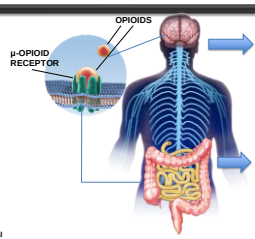
Rectosigmoid region[1]
Awareness, retention, and evacuation of stool



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



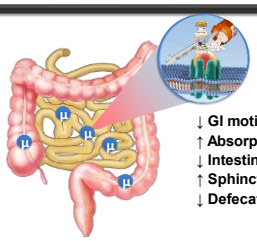
Opioids primarily exert analgesic effects via central μ-opioid receptors[1]

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

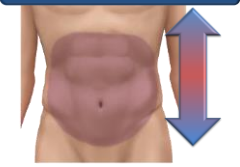


- ↓ GI motility
- ↑ Absorption of fluid from gut
- ↓ Intestinal secretion
- ↑ Sphincter tone
- ↓ Defecation reflex

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

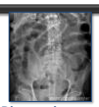
- A wide range of bowel movement frequencies is considered normal[1]
- Definition of constipation depends on more than the daily number of bowel movements[1,2]
- Should address other symptoms such as passage of hard stools, excessive straining, and feeling of incomplete evacuation[1,2]

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]

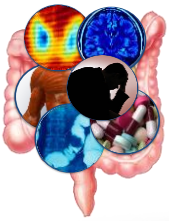
1. Peppin JF. *Practical Pain Management*. 2012 Apr:59-65.
2. Rao SSC. *Gastroenterol Clin N Am*. 2007;36:687-711.

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. Candiotti 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 1: OIC in a Patient with Chronic, Non-cancer Pain

- A 62-year-old female patient recently seen by her PCP for chronic unremitting joint pain.
- Patient has suffered with chronic OA for over 10 years, utilizing acetaminophen, NSAIDS, and a variety of both regularly scheduled and PRN opioid medications.
- Patient presents prescriptions for hydrocodone ER 40 mg QD and hydrocodone/acetaminophen 5/325 mg PRN.

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. Something else
6. Combination of 2 & 3

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.

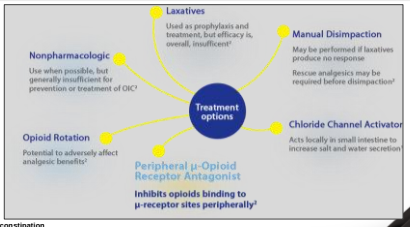
OIC Counseling Pearls

- Even low-to-moderate doses of opioid 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 easily treated 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 (1–2 small BM per week)
  - Feeling bloated or full
  - Not feeling that bowels completely empty
  - Straining
- Consider other causes of constipation
- Consider targeted 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.

Goal for OIC….RELIEF!

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

Laxative class	Examples of Agents	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[2]
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.

How Effective are OTC-type Laxatives?

The analysis of a multinational longitudinal study of 493 patients with chronic, non-cancer pain and clinician-identified, patient-confirmed OIC found that at baseline:

60% of patients reported using ≥1 OTC laxative to manage their OIC in the previous 2 weeks

71% reported little to no benefit from constipation treatments* §

*Constipation treatments included OTC laxatives (stool softeners, osmotics, stimulants, salines, and rectal options), prescription laxatives, and behavioral therapies (fiber supplements, increased fluids and exercise, and dietary changes).

§ 29% of patients in the study reported "much benefit" from constipation treatments

Coyne KS, et al. *Clinicoecon Outcomes Res*. 2014;6:269-281.

What do Patients Think about OTC Laxatives?

>50% of patients who use OTC laxatives are dissatisfied with treatment due to lack of efficacy (range: 58% for stimulant laxatives to 84% for osmotic laxatives)*

*Prospective longitudinal study conducted in the United States, Canada, Germany, and the United Kingdom assessed the burden of OIC in 489 patients with non-cancer pain

LoCasale RJ, et al. *J Manag Care Spec Pharm*. 2016;22:246-253.

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

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

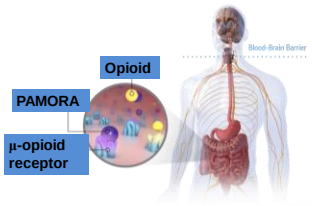
Newer FDA-approved Alternatives to Treat OIC

- Targeting the μ-opioid receptor
  - PAMORAs
    - Methylnaltrexone (oral and SQ)
    - Naloxegol (oral)
    - Naldemedine (oral)
- Type 2 chloride channel activator
  - Lubiprostone
    - Available in oral formulation
    - Methadone use can interfere with efficacy

PAMORAs

- **P**eripherally **A**cting **M**u **O**pioid **R**eceptor **A**ntagonists
- Three FDA-approved products in the U.S. market
  - Methylnaltrexone (Relistor®)
  - Naloxegol (Movantik®)
  - Naldemedine (Symproic®)
- Contraindicated for patients with bowel obstruction or at risk for obstruction

PAMORAs: Overall Mechanism of Action



Practice Case 2: 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 fentanyl transdermal
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.
- Straining to have a bowel movement can exacerbate low back pain, leading to an increased use of PRN opioids.
- OIC itself can often 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 3: 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 an oral PAMORA
5. Change regimen to a SQ PAMORA
6. Manually disimpact the patient

OIC Counseling Pearls

- Constipation in cancer and palliative care patients is a serious health issue and can lead to serious morbidity if not dealt with rapidly.
- OIC is often resistant to regimens that include only 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.
  - SQ may be a preferred route initially in hospitalized patients
- Upon discharge, continue the outpatient use of the PAMORA as long as the patient continues on opioid therapy.
  - Patients with OIC may be effectively treated in the hospital with a PAMORA, then discharged on a traditional (and ineffective) laxative that may lead to a costly re-admission for OIC to the ED or the hospital

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, Wiltbrodt 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 as oral tablets and as an injectable for subcutaneous administration

BBB, blood-brain barrier

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

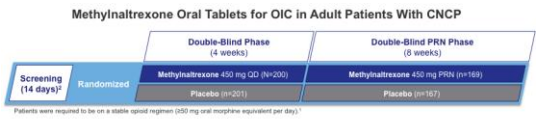
Methylnaltrexone SQ for OIC

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 yr 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 yr 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

SBM, spontaneous bowel movement

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.

Methylnaltrexone Oral for OIC in Patients with Chronic Non-cancer Pain: Study Design



- **Responder Endpoint:** Proportion of patients with ≥3 spontaneous bowel movements (SBMs)* per week, with an increase of ≥1 SBM/week over baseline, for ≥3 of the first 4 weeks of the treatment period[1]
- **Primary Endpoint:** Mean percentage of dosing days that resulted in SBM within 4 hours of dosing during weeks 1-4[2]
- **Secondary Endpoint:** Mean percentage of dosing days that resulted in SBM within 4, 6, or 8 hours of dosing over the entire 12-week study period[2]

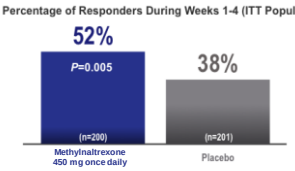
Rauck R, et al. *Pain Pract*. 2017;17:820-8.

Methylnaltrexone Oral for OIC: Patient Characteristics

Parameter	Methylnaltrexone 450 mg QD (n=200)	Placebo
Age, Mean(SD), y	51.4 (10.50)	52.6 (10.33)
Male:Female, %	36:64	35:65
White race, %	86	83
Opioid dose, oral morphine equivalent, median (range), mg/d	155.55 (27.0-1272.0)	132.00 (42.6-1077.3)
Weekly rescue-free BMs, mean (SD)	1.37 (0.789)	1.49 (1.045)

Rauck R, et al. *Pain Pract*. 2017;17:820-8.

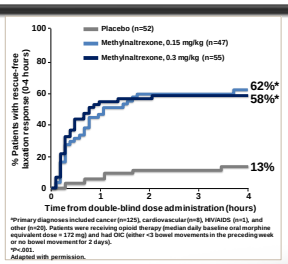
Methylnaltrexone Oral for OIC: Results



Responder Endpoint: Proportion of patients with ≥3 spontaneous bowel movements (SBMs) per week, with an increase of ≥1 SBM/week over baseline, for ≥3 of the first 4 weeks of the treatment period

Rauck R, et al. *Pain Pract.* 2017;17:820-8.

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

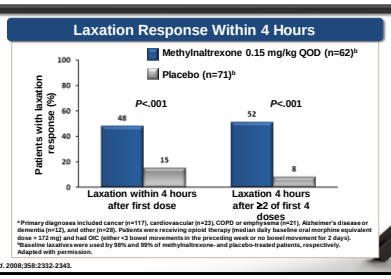


[a]Primary diagnoses included cancer (n=125), cardiovascular (n=8), HIV/AIDS (n=1), and other (n=20). Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg) and had OIC (either <3 bowel movements in the preceding week or no bowel movement for 2 days).
*P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

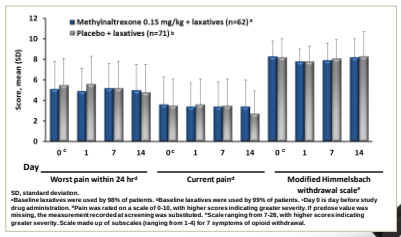
Repeated Dosing of Methylnaltrexone for OIC in Patients With Advanced Illness[a]



[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.
[b]Baseline laxatives were used by 98% of patients. [a]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%

Slatkin N, et al. *J Support Oncol.* 2009;7:39-46.
Thomas J, et al. *N Engl J Med.* 2008;358:2332-2343.

Adverse Reactions During Double-Blind Phase OIC in Adult Patients With Chronic Non-cancer Pain

Adverse Event*	Methylnaltrexone 12 mg QD SQ (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 Oral: Adverse Reactions

Adverse Reactions Occurring in ≥2% of Patients Receiving Methylnaltrexone Tablets and at an Incidence Greater than Placebo

Adverse Reaction	Methylnaltrexone 450 mg QD (n=200)	Placebo (n=201)
Abdominal pain *	14%	10%
Diarrhea	5%	2%
Headache	4%	3%
Abdominal distension	4%	2%
Vomiting	3%	2%
Hyperhidrosis	3%	1%
Anxiety	2%	1%
Muscle spasms	2%	1%
Rhinorrhea	2%	1%
Chills	2%	0%

*Includes abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, and abdominal tenderness.

Rauck R, et al. *Pain Pract.* 2017;17:820-8.

Methylnaltrexone SQ 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 SQ 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 any patient 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® (methylnaltrexone bromide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC. January 2017.

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, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation
- Oral formulation: 12.5 mg, 25 mg
- Drug-interactions:
  - Contraindication: Strong CYP 3A4 inhibitors
  - Warnings: Moderate CYP 3A4 inhibitors
    - Reduce dose by 50%

Movantik® (naloxegol) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; August 2017.

Naloxegol Oral for OIC

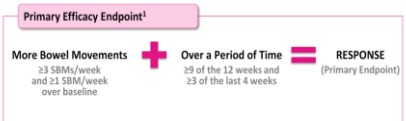
Study	Patient description
Chronic Non-cancer pain: 12.5 mg oral vs. 25 mg oral vs. placebo QD for 12 weeks	1. N = 1352 (+1497 safety) 2. Mean age 52 years 3. Current laxatives discontinued 4. Average oral MS equivalent dose 140 mg/day 5. Average 1.4 SBM per week

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

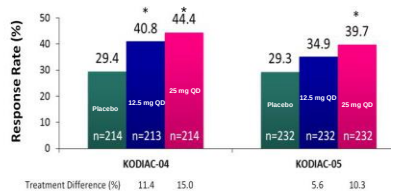
Laxative use within 2 weeks prior to enrollment	65.7%	77.6%	70.6%	67.2%	71.6%	74.6%
Baseline mean number of SBMs per week	1.4	1.3	1.4	1.6	1.3	1.5



[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.

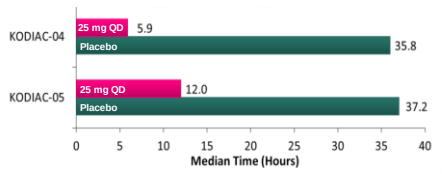
Naloxegol (oral) for OIC: Response Rates – Chronic, Non-cancer Pain



*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.

Naldemedine Clinical Trials

- Two replicate, 12-week, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2)
  - No other laxatives used
  - Patients with OIC and chronic non-cancer pain
- Patients receiving a stable opioid morphine equivalent daily dose of at least 30 mg for at least 4 weeks before enrollment and self-reported OIC were eligible for clinical trial participation.

Hale M, et al. *Lancet Gastroenterol Hepatol*. 2017;2:555-64.

Naldemedine Oral Clinical Outcomes

Clinical Trial	Treatment Arm: Proportion of Responders, % (95% CI)		Difference of Proportions	
	Naldemedine (N=549)	Placebo (N=546)	% (95% CI)	*p-value*
Study V9231	47.6 (41.6, 53.7)	34.6 (28.9, 40.5)	13.0 (4.8, 21.3)	*0.0020*
Study V9232	52.5 (46.5, 58.6)	33.6 (28.0, 39.5)	18.9 (10.8, 27.0)	*<0.0001*

A responder was defined as a patient who had at least 3 SBMs per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 weeks and 3 out of the last 4 weeks in Studies 1 and 2.

Hale M, et al. *Lancet Gastroenterol Hepatol*. 2017;2:555-64.

Naldemedine Oral Adverse Reactions Summary

Common Adverse Reactions* in Patients with OIC and Chronic Non-Cancer Pain (12-week data from Studies 1 and 2)

Adverse reaction	Naldemedine 0.2 mg QD N = 542	Placebo N = 546
Abdominal pain**	8%	2%
Diarrhea	7%	2%
Nausea	4%	2%
Gastroenteritis	2%	1%

*Adverse reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo

**Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain.

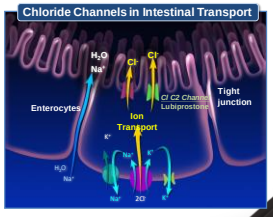
Hale M, et al. *Lancet Gastroenterol Hepatol*. 2017;2:555-64.

PAMORAs: Drug Interactions

- Some PAMORAs have clinically-significant drug interactions
  - **Methylnaltrexone** – no clinically significant drug interactions with CYP
  - **Naloxegol** – contraindicated in patients receiving strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin).
    - Dose reduction by 50% in patients receiving moderate CYP3A4 inhibitors (e.g., erythromycin, diltiazem, verapamil)
  - **Naldemedine** –
    - Strong CYP3A inducers (e.g., rifampin): Decreased naldemedine concentrations; avoid concomitant use.
    - Moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A4 inhibitors: Increased naldemedine concentrations; monitor for adverse reactions;
    - P-gp inhibitors (e.g., cyclosporine): Monitor for adverse reactions
- ALL: Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use

Lubiprostone

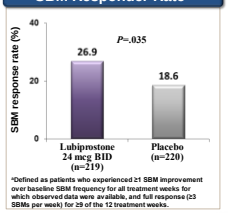
- Lubiprostone is NOT a PAMORA.
- MOA: a chloride channel activator that induces intestinal secretion
- FDA-approved for chronic idiopathic constipation, IBS-C in women and OIC for patients with chronic non-cancer pain
- Available in oral formulation



IBS-C, constipation-predominant irritable bowel syndrome
Adapted from Rome Foundation, Inc. http://www.theromefoundation.com. Accessed November 1, 2017.
Wong BS, Camilleri M. *Expert Opin Pharmacother*. 2011;12:983-990.

Lubiprostone for Non-Methadone OIC in Chronic, Non-cancer 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.

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

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

Investigational Therapies for OIC

Drug	Description	Development Phase 1	2	3
Prucalopride[1]	5-HT_4 agonist			
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
  - No placebo-controlled trials suggesting benefit in patients with OIC

Conclusions *(continued)*

- Peripheral μ-opioid receptor antagonists (PAMORAs) improve OIC without reversing central analgesia
  - Methylnaltrexone SQ FDA-approved for treatment of OIC in adult patients with chronic non-cancer pain, and in patients with advanced illness.
  - Methylnaltrexone oral tablets FDA-approved for treatment of OIC in adult patients with chronic non-cancer pain.
  - Naloxegol oral FDA-approved for the treatment of OIC in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.
  - Naldemedine oral tablets FDA-approved for the treatment of OIC in adult patients with chronic non-cancer pain.