9:15 – 10:30 am

Achieving Balance: Practical Management Strategies for Opioid-Induced Constipation

SPEAKERS

Anthony J. Lembo, MD

James W. Atchison, DO

Darren M. Brenner, MD

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Anthony J. Lembo, MD: Consulting so the non-cme whatever language for: AstraZeneca; Ironwood Pharmaceuticals, Inc.; Salix Pharmaceuticals, Inc.; Valeant Pharmaceuticals.
- James W. Atchison, DO: Non-CME/CE services for Best Doctors Inc; The International School for Primary Education; PAREXEL International; and Pfizer, Inc.
- Darren M. Brenner, MD: Speakers' Bureau: Allergan, Inc.; AstraZeneca; Actavis; Ironwood Pharmaceuticals, Inc.; Procter & Gamble Co.; Salix Pharmaceuticals, Inc.; Advisory Board: Allergan, Inc.; AstraZeneca; Actavis; Ironwood Pharmaceuticals, Inc.; Procter & Gamble Co.; QOL Medical LLC; Salix Pharmaceuticals, Inc.

Presenter Disclosure Information

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Drug List

- Amitriptyline
- Axelopran
- Bisacodyl
- Denosumab
- Diltiazem
- Docusate calcium
- Docusate sodium
- Gabapentin ER
- Lactulose
- Lisinopril
- Loratadine
- Lubiprostone
- Metformin
- Methylcellulose
- Methylnaltrexone
- Naldemedine
- Naloxegol
- Naloxone
- Oxycodone
- Polyethylene glycol
- PR oxycodone and PR naloxone
- Psyllium
- Rosuvastatin
- Senna
- Transdermal fentanyl
- Elavil
- Investigational
- Dulcolax, Bisac-Evac, Correctol
- Prolia
- Dilt-cd, Cardizem
- Kaopectate
- Aqualax, Colace, Colace Micro-Enema
- Horizant
- Constulose, Kristalose
- Zestril, Prinivil
- Claritin
- Amitiza
- Glumetza, Glucophage, Fortamet, Riomet
- Citrucel
- Relistor
- Investigational
- Movantik
- Narcan
- Oxecta, OxyCONTIN, Oxyfast, Roxicodone
- Miralax
- Targin, Targiniq, Targinact
- Metamucil
- Crestor
- Senokot
- Duragesic

Educational Objectives

- Describe the effects of opioid receptor activation in the gastrointestinal tract
- Evaluate patients on chronic opioid therapy for bowel function and risk factors for OIC development
- Implement a prophylactic treatment plan to address OIC concurrent with the initiation of opioid therapy
- Compare the mechanisms of action and clinical profiles of current presciption medications for OIC
- Construct evidence-based treatment regimens for patients with OIC that reflect bowel symptoms, prior treatment response, and patient preferences
- Communicate with opioid-treated patients about treatment-emergent adverse events through open, patient-centered dialogue throughout the course of therapy

OIC, opioid-induced constipation.

Scientific Insights Into **OPIOID-INDUCED CONSTIPATION**

Anthony J. Lembo, MD

Associate Professor of Medicine
Director, GI Motility Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

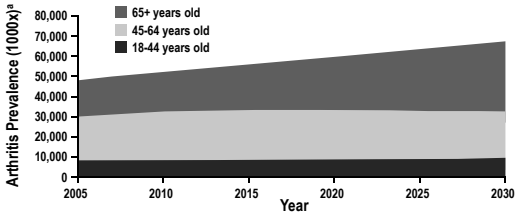
Scientific Insights Into Opioid-Induced Constipation
Key Points

- Opioid analgesics bind to opioid receptors throughout the CNS and PNS, including in the gastrointestinal tract
- Opioid receptor activation in the gastrointestinal tract modulates physiologic processes from the lower esophageal sphincter to rectum
- By antagonizing μ-opioid receptor activity, opioid antagonists reverse the effects of opioid analgesics
- Peripherally acting μ-opioid receptor antagonists are intended to block opioid receptor activation outside of the CNS
  - eg, the GI tract

CNS, central nervous system; PNS, peripheral nervous system.
Brennan MJ, et al. *J Multidiscip Health.* 2013;6:265-280; Leppert W. *Adv Ther.* 2010;27(10):714-730; De Schepper HU, et al. *Neurogastroenterol Motil.* 2004;16(4):383-394; Holzer P. *Eur Rev Med Pharmacol Sci.* 2008;12(suppl 1):119-127.

Rising Rates of Chronic Pain

- 100 million US adults currently affected by chronic pain
- Prevalence predicted to increase with aging population



[a]Projected prevalence of doctor-diagnosed arthritis in the US by age.
Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: The National Academies Press; 2011; Hootman JM, Helmick CG. *Arthritis Rheum.* 2006;54(1):226-229.

Opioid-Induced Constipation

- Constipation is most common adverse effect of prescription opioid analgesics[1,2]

Up to 1 in every 2 patients on opioid therapy will experience constipation symptoms[3]		1 in every 3 patients on opioid therapy does not discuss constipation symptoms with his or her clinician[4]		
Constipated	Not Constipated	Silently Suffering	Discusses Constipation	Discusses Constipation

Patients may not discuss constipation symptoms because they are embarrassed or worried that the opioid treatment will be reduced or discontinued.[4]

1. Chou R, et al. *J Pain.* 2009;10(2):113-130; 2. Moore RA, McQuay HJ. *Arthritis Res Ther.* 2005;7(5):R1046-R1051. 3. Cook SF, et al. *Aliment Pharmacol Ther.* 2008;27(12):1224-1232; 4. Coyne KS, et al. *Clinicoecon Outcomes Res.* 2014;6:269-281.

Opioid-Induced Constipation
Multidisciplinary Working Group Definition

A **change** when initiating opioid therapy from **baseline bowel habits** that is characterized by **any** of the following:

- Reduced bowel movement frequency
- Development or worsening of straining to pass bowel movements
- A sense of incomplete rectal evacuation
- Harder stool consistency

Camilleri M, et al. *Neurogastroenterol Motil.* 2014;26(10):1386-1395.

Constipation
What Does It Mean to Your Patient?

Infrequent Stools	**Straining**	**Incomplete Evacuation**
Pain	**Hard Stools**	**Bloating**

Lacy BE, et al. *Ther Adv Gastroenterol.* 2012;5(4):233-247; Coyne KS, et al. *Clinicoecon Outcomes Res.* 2014;6:269-281.

Development of OIC
Risk Factors

Patient Characteristics
- Female gender
- Advanced age

Drug Regimen
- Opioid type/ strength

Dietary Considerations
- Dehydration
- Nutritional deficits

Medical Issues
- Relative immobility
- Nausea/vomiting after starting opioids
- Mechanical obstruction
- Recent hospitalizations

Ahmedzai SH, Boland J. *BMJ Clin Evid* (Online). 2010;pii:2407; Clemens KE, Klaschik EK. *Ther Clin Risk Manag.* 2010;6:77-82; Wan Y CS, et al. Las Vegas, Nevada; 2013; Abstract 132.

Effect of OIC on Patient Functioning and Quality of Life (QoL)

Patients with OIC often

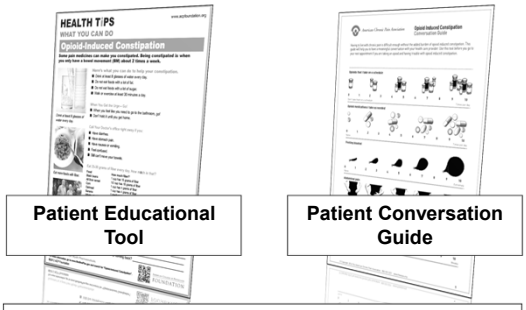
- Skip opioid doses to precipitate a bowel movement
- Suffer from inadequate pain control due to treatment nonadherence
- Experience reductions in QoL and activities of daily living
- Utilize more heath care resources; contributing to higher health care costs

Bell TJ, et al. *Pain Med.* 2009;10(1):35-42; Coyne KS, et al. *Clinicoecon Outcomes Res.* 2014;6:269-281; Gupta S, et al. *J Opioid Manag.* 2015;11(4):325-338; Harris JD. *Clin J Pain.* 2008;24(suppl 10):S8-S13; Wan Y, et al. *Am Health Drug Benefits.* 2015;8(2):93-102.

Examples From Our Practices

Evaluating Bowel Habits in Patients on Chronic Opioid Therapy

Patient Resources



Patient Educational Tool

Patient Conversation Guide

www.**ExchangeCME**.com/**OICUpdates**

Opening the Conversation About Patient Bowel Patterns

Ask quantitative questions rather than open-ended or yes-or-no-style questions

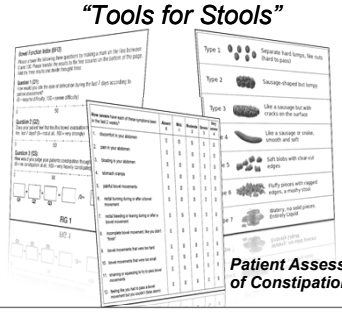
Instead of these	Ask these
"Are you having any problems moving your bowels?"	*"How many times do you have a bowel movement each week?"*
"Do you have any difficulties passing stool?"	*"Can you describe what your stool most commonly looks like?"*
"Are there any changes in your bowel habits that you would like to discuss?"	*"How have your bowel patterns changed since you started taking opioids?"*

Assessment of Bowel Habits

"Tools for Stools"

Bowel Function Index

Bristol Stool Form Scale



Patient Assessment of Constipation

www.**ExchangeCME**.com/**OICUpdates**

Rentz AM, et al. *J Med Econ.* 2009;12(4):371-383; Frank L, et al. *Scand J Gastroenterol.* 1999;34(9):870-887; Lewis SJ, Heaton KW. *Scand J Gastroenterol.* 1997;32(9):920-924.

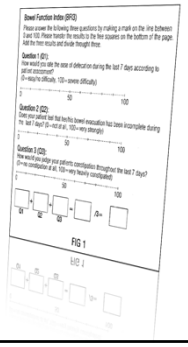
Bristol Stool Form Scale

Type 1		**Separate hard lumps, like nuts**
Type 2		**Sausage-like but lumpy**
Type 3		**Like a sausage but with cracks in the surface**
Type 4		**Like a sausage or snake, smooth and soft**
Type 5		**Soft blobs with clear-cut edges**
Type 6		**Fluffy pieces with ragged edges, a mushy stool**
Type 7		**Watery, no solid pieces**

Lewis SJ, Heaton KW. *Scand J Gastroenterol.* 1997;32(9):920-924.

Bowel Function Index (BFI)

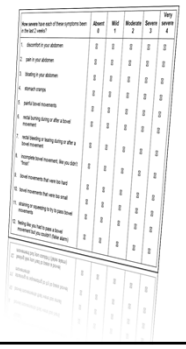
- Scored by numerical assessment scale (0-100, free from symptom to most severe symptom experienced) for prior 7 days
  - Ease of defecation
  - Feeling of incomplete evacuation
  - Personal judgment of constipation
- BFI score is the mean of the 3 component scores



Rentz AM, et al. *J Med Econ.* 2009;12(4):371-383.

Patient Assessment of Constipation (PAC-SYM)

- 12-item questionnaire of patient-reported symptoms over the 2 prior weeks, using 3 subscales
  - Bowel movements
  - Rectal symptoms
  - Abdominal symptoms
- Scored from no problems (score 0) to very severe symptoms (score 4)



Frank L, et al. *Scand J Gastroenterol.* 1999;34(9):870-887.

Which bowel assessment tool do you find most useful in practice?

Patient-Provider Partnership

Educate

- **On the risks of developing OIC**
  - ~50% of patients on chronic opioid therapy
  - Increased likelihood if patients have risk factors

Discuss

- **Prophylactic treatment plan**
- **Bowel habits at *every* follow-up visit**
- **Results of bowel function evaluation**
- **Importance of adherence to opioid therapy and OIC management plan**

Coordinate

- **With other members of the health care team**

Prophylactic and Initial Management Options

Implementation of Prophylactic Treatment

- Guidelines on long-term opioid therapy recommend that all patients be advised on a prophylactic bowel regimen[1,2]
  - Adequate dietary fiber
  - Adequate water intake
  - Regular exercise
  - Laxatives?
- Patients who receive prophylactic laxative therapy are less likely to experience constipation[3,4]

1. Chou R, et al. *Pain*. 2009;10(2):113-130; 2. Department of Veterans Affairs/Department of Defense. http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf. Accessed September 1, 2015. 3. Myotoku M, et al. *J Palliat Med*. 2010;13(4):401-406; 4. Ishihara M, et al. *Clin J Pain*. 2012;28(5):373-381.

Commonly Used Laxatives to Treat Constipation

Type of Laxative	Specific Example
Stool Softener	Docusate sodium, docusate calcium
Stimulant	Senna, bisacodyl, castor oil
Osmotic	Polyethylene glycol, lactulose
Lubricant	Mineral oil
Bulking Agent	Psyllium, bran, methylcellulose

Ford AC, Suares NC. *Gut*. 2011;60(2):209-218; Lee YY. *Front Med (Lausanne)*. 2014;1-5; Pare P, Fedorak RN. *Can J Gastroenterol Hepatol*. 2014;28(10):549-557.

Practical Issues Related to Laxative Treatment

- Bulking agents and medicinal fiber, such as psyllium, should be avoided[1,2]
  - Efficacy data are lacking
  - May further harden the patient's stool
- Laxatives may have side effects[3,4]
  - Nausea, vomiting, diarrhea, abdominal pain – all of which usually dissipate after bowel movement
  - May increase the chance of poor adherence
- High dosages of laxatives and stimulants may be needed to improve bowel patterns[4]
  - May increase the chance of poor adherence

1. Pare P, Fedorak RN. *Can J Gastroenterol Hepatol*. 2014;28(10):549-557; 2. Yang J, et al. *World J Gastroenterol*. 2012;18(48):7378-7383; 3. Mueller-Lissner SA, Wald A. *BMJ Clin Evid*. 2010;2010. pii: 0413; 4. Sykes NP. *J Pain Symptom Manage*. 1996;11(6):363-369.

What prophylactic bowel regimen do you recommend for patients starting long-term opioid therapy?

Guidelines on Opioid Rotation

STEP 1	• **Calculate new opioid dose based on equianalgesic table** • **Identify "dose reduction window" 25% to 50% lower than equianalgesic dose (not for methadone or fentanyl)** – Switching to methadone: identify window 75% to 90% lower than equianalgesic dose – Switching to transdermal fentanyl: calculate dose conversions based on ratios included in the product information • **Choose smaller (25% of dose) or larger (50% of dose) reduction based on characteristics of regimen or patient** – Larger reductions for patients on high current opioid doses, non-Caucasians, and older or medically frail individuals
STEP 2	• **Reassess pain and other biopsychosocial characteristics to determine whether an additional 15% to 30% dose increase or decrease is needed** • **Repeatedly assess response and titrate new opioid to optimize outcomes**

Fine PG, et al. *J Pain Symptom Manage*. 2009;38(3):418-425.

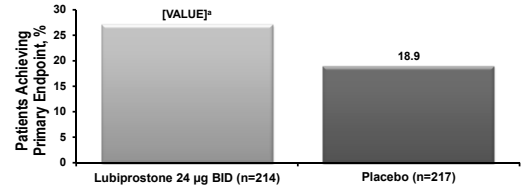
FDA-Approved Therapies for Opioid-Induced Constipation

Currently Approved Therapies

Agent	Lubiprostone	Methylnaltrexone	Naloxegol
Mechanism of Action	Chloride channel activator	Peripherally acting μ-opioid receptor antagonist (PAMORA)	
Mode of Administration	Oral	Subcutaneous	Oral
Recommended Dose	24 μg	12 mg/0.6 mL	25 mg/12.5 mg
Dosing Frequency	Twice daily	Once daily	Once daily
Clinical Considerations	• Take with food and water • May be used concomitantly for length of opioid treatment • May be less effective in patients taking methadone	• Discontinue laxative therapy prior to use • Need close proximity to toilet once administered • May be used concomitantly for length of opioid treatment • Monitor for signs of opioid withdrawal	• Discontinue laxative therapy prior to use • Take on an empty stomach and avoid grapefruit consumption • May be used concomitantly for length of opioid treatment • Monitor for signs of opioid withdrawal

Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed September 1, 2015.

Lubiprostone
Chloride Channel Activator



12-week, double-blind, randomized, placebo-controlled, phase 3 clinical trial

Primary Endpoint: Overall SBM response rate (≥1 SBM/week improvement over baseline for all 12 weeks and ≥3 SBM/week for ≥9 out of the 12 treatment weeks)

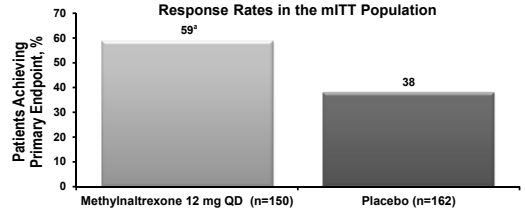
BID, twice daily; SBM, spontaneous bowel movement.
SBM, defined as a BM with no laxative use within prior 24 hours.
[a]P=0.03 vs placebo. N=431 patients with chronic noncancer pain who were treated with non-methadone opioids.
Jamal MM, et al. *Am J Gastroenterol.* 2015;110(5):725-732.

Lubiprostone
12-Week Safety Data

TEAE, No. (%) of Patients	Placebo BID (n=212)	Lubiprostone 24 μg BID (n=212)	*P* value
≥1 TEAE[a]	**105 (49.5)**	**117 (55.2)**	**0.285**
Gastrointestinal disorders	41 (19.3)	59 (27.8)	0.051
• Diarrhea	8 (3.8)	24 (11.3)	
• Nausea	10 (4.7)	21 (9.9)	
• Vomiting	11 (5.2)	9 (4.2)	
• Abdominal pain	0	15 (7.1)	
≥1 Treatment-related AE[b]	**32 (15.1)**	**62 (29.2)**	**<0.001**
Gastrointestinal disorders	22 (10.4)	49 (23.1)	<0.001
• Diarrhea	3 (1.4)	21 (9.9)	
• Nausea	6 (2.8)	18 (8.5)	
• Abdominal pain	0	12 (5.7)	
• Flatulence	5 (2.4)	6 (2.8)	
• Vomiting	3 (1.4)	6 (2.8)	

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]TEAEs observed in ≥5% of patients in either treatment group. [b]Treatment-related AEs observed in ≥2% of either treatment group.
Jamal MM, et al. *Am J Gastroenterol.* 2015;110(5):725-732.

Methylnaltrexone
Peripherally Acting μ-Opioid Receptor Antagonist



4-week, double-blind, randomized, placebo-controlled, phase 3 clinical trial

Primary Endpoint: % patients with ≥3 SBMs per week, during 4-week period

[a]P<0.001 vs placebo; QD, once daily. N=312 patients with chronic noncancer pain.
mITT, modified intent-to-treat population, included all randomized patients who received ≥1 dose of double-blind study medication.
Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed September 1, 2015.

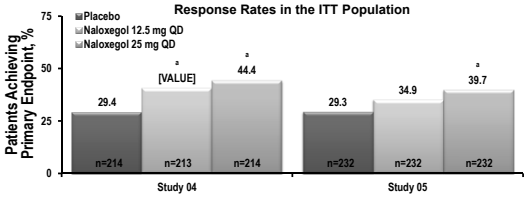
Methylnaltrexone
4-Week Safety Data

Adverse Event	Methylnaltrexone 12 mg QD (n=150), %	Placebo (n=162), %
Adverse events occurring in ≥1% of patients receiving methylnaltrexone and at an incidence greater than placebo		
• 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 leading to treatment discontinuation		
• Any adverse event	7%	3%

Safety data from 48-week, open-label, uncontrolled study (N=1034) were consistent with 4-week results.

Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed September 1, 2015.

Naloxegol
Peripherally Acting μ-Opioid Receptor Antagonist



Two 12-week, double-blind, randomized, placebo-controlled, phase 3 clinical trials

Primary Endpoint: 12-week response rate (≥3 SBM/week and increase over baseline of ≥1 SBM for ≥9 of 12 weeks and ≥3 of the final 4 weeks)

SBM, defined as a BM with no laxative use within prior 24 hours.
[a]P<0.05 vs placebo in each study; N=652 patients with noncancer pain, Study 04; N=700 patients with noncancer pain, Study 05.
ITT, intent-to-treat.
Chey WD, et al. *N Engl J Med.* 2014;370(25):2387-2396.

Naloxegol
12-Week Safety Data

Adverse event, n (%)[1]	Study 04			Study 05		
	Naloxegol 25 mg (n=214)	Naloxegol 12.5 mg (n=211)	Placebo (n=213)	Naloxegol 25 mg (n=232)	Naloxegol 12.5 mg (n=230)	Placebo (n=231)
Any AE[a]	**131 (62.2)**	**104 (49.3)**	**100 (46.9)**	**160 (69.0)**	**137 (59.6)**	**136 (58.9)**
AE leading to discontinuation	22 (10.3)	9 (4.3)	12 (5.6)	24 (10.3)	12 (5.2)	12 (5.2)
Serious AE	7 (3.3)	11 (5.2)	11 (5.2)	8 (3.4)	14 (6.1)	12 (5.2)
AEs in ≥5% of any treatment arm[b]						
Abdominal pain	27 (12.6)	18 (8.5)	7 (3.3)	44 (19.0)	25 (10.9)	18 (7.8)
Diarrhea	20 (9.3)	7 (3.3)	9 (4.2)	21 (9.1)	18 (7.8)	10 (4.3)
Nausea	16 (7.5)	15 (7.1)	10 (4.7)	20 (8.6)	14 (6.1)	10 (4.3)
Flatulence	12 (5.6)	9 (4.3)	4 (1.9)	14 (6.0)	4 (1.7)	7 (3.0)
Upper abdominal pain	11 (5.1)	3 (1.4)	4 (1.9)	6 (2.6)	5 (2.2)	3 (1.3)
Vomiting	6 (2.8)	3 (1.4)	7 (3.3)	14 (6.0)	7 (3.0)	6 (2.6)

Safety data from 52-week, open-label, parallel-group phase 3 study (N=804) with patients randomized 2:1 to either naloxegol 25 mg/day or usual care were similar to 12-week results.[2]

[a]Occurring during either the treatment or posttreatment follow-up period. [b]Occurring during the treatment period.

1. Chey WD, et al. *N Engl J Med.* 2014;370(25):2387-2396; 2. Webster L, et al. *Aliment Pharmacol Ther.* 2014;40(7):771-779.

Emerging μ-Opioid Receptor Antagonists for Treatment of OIC

Agent[1]	Mode of Administration	Mechanism of Action	Current Stage
Naldemedine	Oral	Peripherally selective μ-opioid receptor antagonist	Phase 3
Axelopran	Oral	Peripherally selective μ-opioid receptor antagonist	Phase 2, completed

The opioid agonist/antagonist combination of prolonged-release oxycodone and naloxone was shown to reduce OIC in a 3-week, open-label phase 3b study.[2]

1. www.clinicaltrials.gov Information updated as of September 1, 2015.
2. van Dongen VC, et al. *Int J Clin Pract.* 2014;68(11):1364-1375.

How do you incorporate patient preference into the selection of pharmacologic therapy for the treatment of OIC?

Conclusions

- OIC is common in patients on long-term opioid therapy
- Prophylactic treatment regimens can reduce risk of constipation
- Routine bowel function assessment is imperative
- Multimodal laxative therapy can be effective in some patients
- Approved pharmacologic therapies include
  - Oral and injectable peripherally acting μ-opioid receptor antagonists
  - Chloride channel activator