PAINWEEK®

Stop the (mu)sic, Management Of Opioid Induced Constipation

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Disclosure

- Nothing to disclose

Learning Objectives

- Recall the pathophysiology of opioid induced constipation
- Identify medications used in the management of opioid induced constipation
- Review the current guidelines for the management of opioid induced constipation

Physiology of the Colon

- Colonic motility is maintained though multiple systems
  - Neurological
    - Intrinsic system- Meissner's and Auerbach's plexus
    - Extrinsic system- sympathetic and parasympathetic systems
      - Sympathetic- thoracolumbar
        - Contracting of the anal sphincter
      - Parasympathetic- vagus nerve and sacral plexus
        - Causing peristalsis
  - Endocrine
  - Luminal factors

https://jnnp.bmj.com/content/74/1/13 accessed 2.6.2020

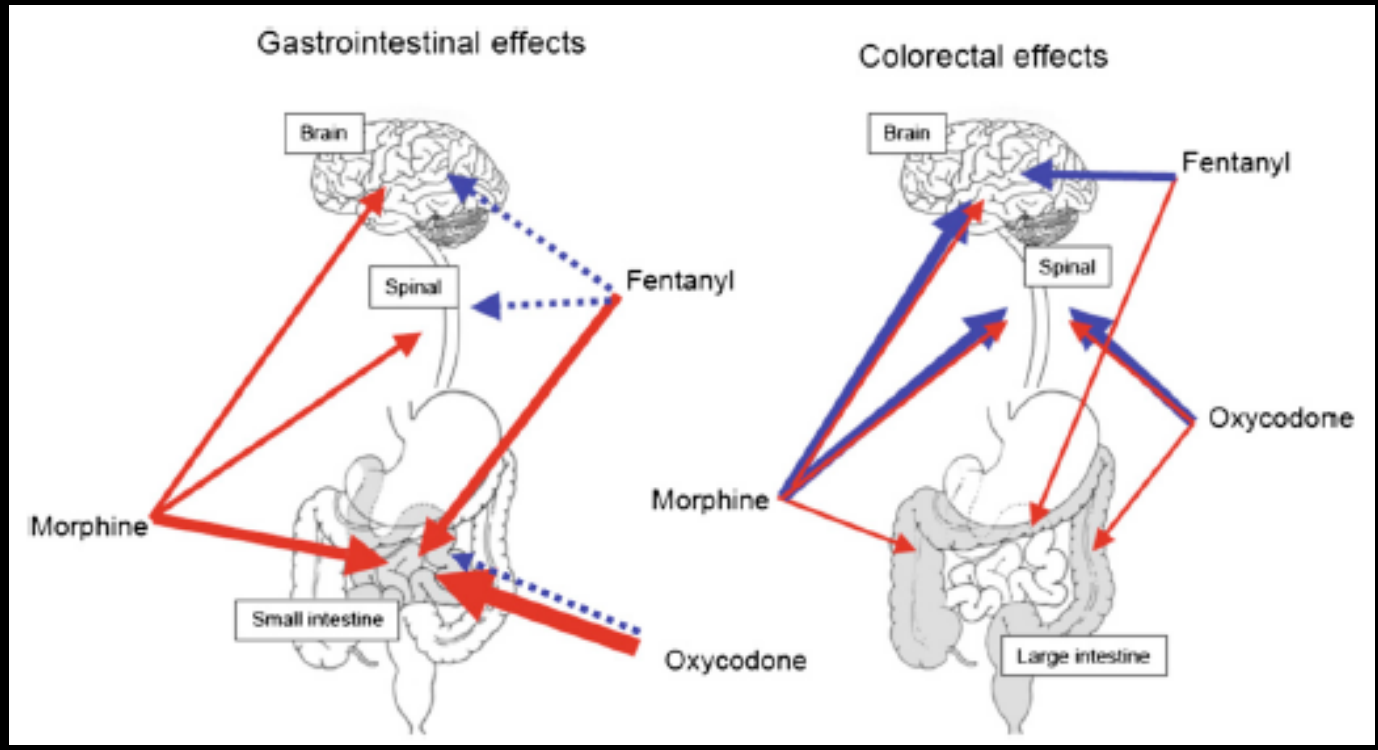
Opioid Induced Terminology

- Opioid induced constipation
- Activation of the m-opioid receptors in the small and large intestine
- Increase in colonic fluid absorption and stool desiccation
- Increase the minimum sensory threshold of the rectum
- Increase in anal sphincter tone
- Opioid induced bowel dysfunction
- Collection of the adverse effects of opioids on the GI system though agonism of the m-opioid receptors
  - Constipation
  - GERD
  - Nausea and vomiting
  - Bloating
  - Abdominal pain

Gastroenterology 2019; 156:218-226

Pathophysiology of OIC

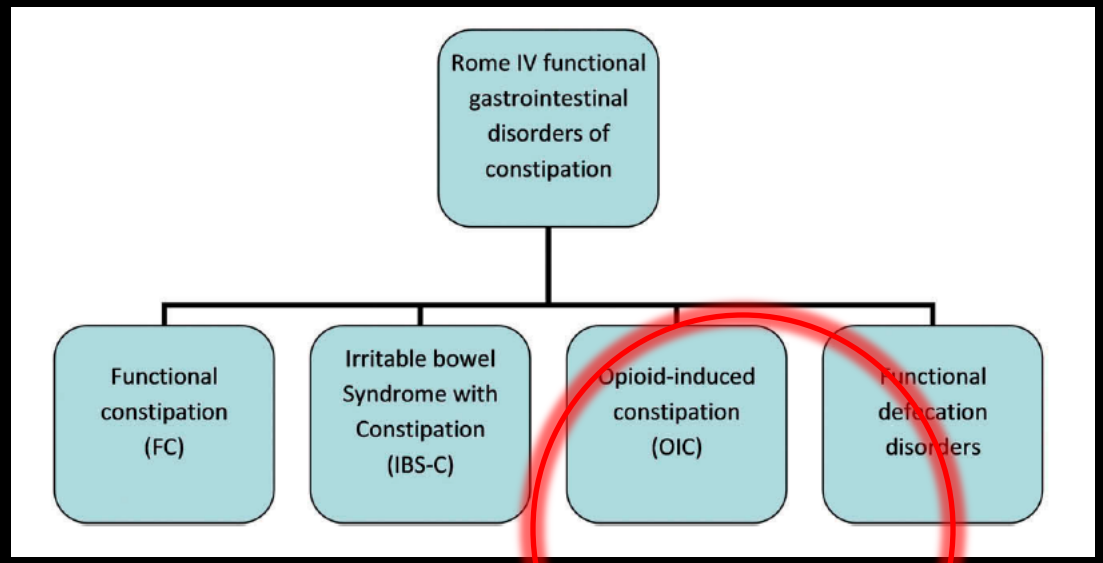
- Agonism of the μ-opioid receptors in the small intestine and proximal colon leading to reduced intestinal secretion and motility
- κ-opioid receptors in the stomach and small intestine exist but are not implicated in OIC



OIC = opioid-induced constipation

1. Aziz, A, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic Constipation. Expert Review of Gastroenterology & Hepatology 2020
2. Mori T, et al. Mechanisms That Underlie m-Opioid Receptor Agonist–Induced Constipation: Differential Involvement of m-Opioid Receptor Sites
and Responsible Regions. JPET 2013

Diagnosis



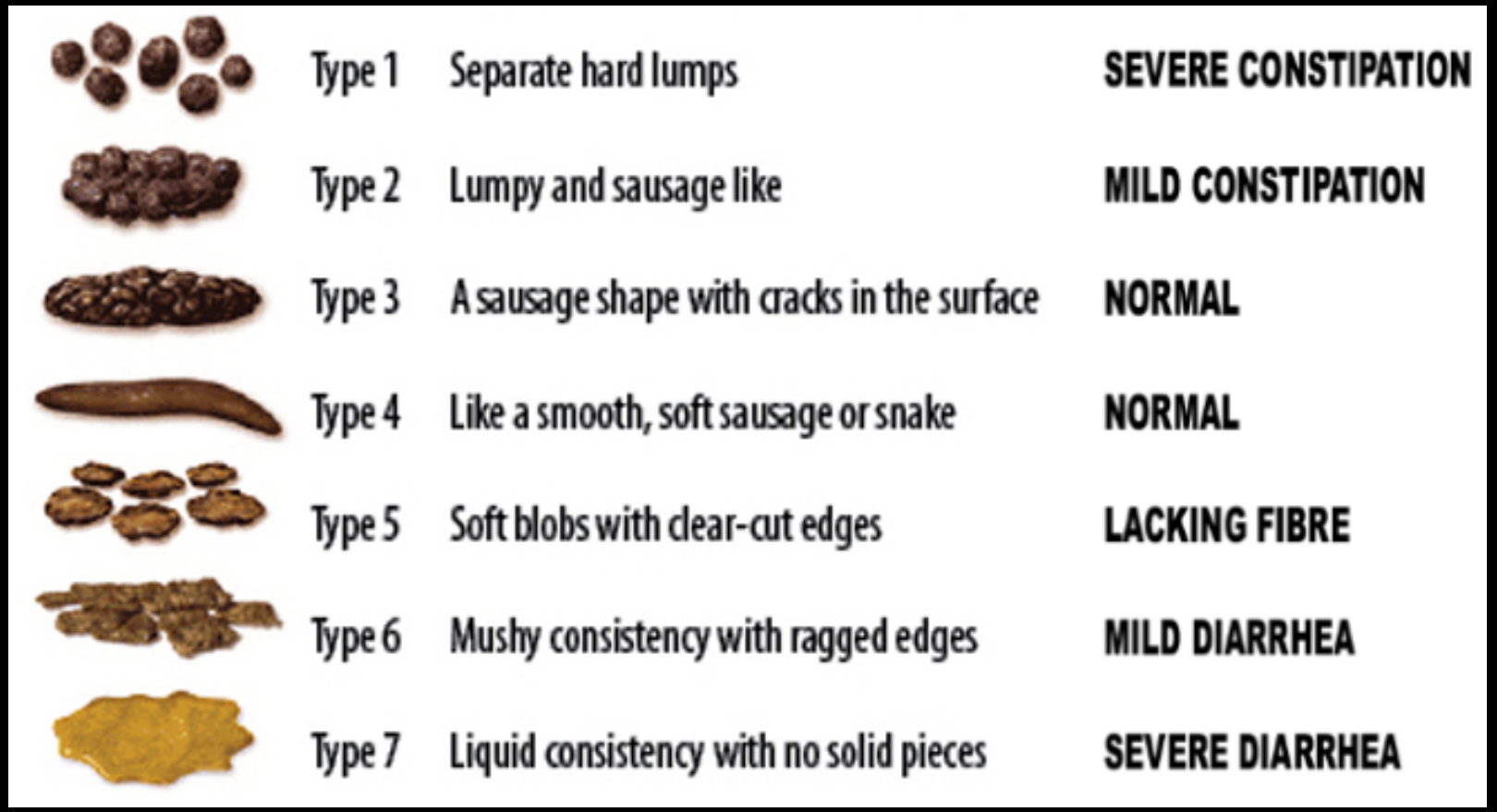
Aziz, A, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic Constipation. Expert Review of Gastroenterology & Hepatology 2020

Diagnosis, cont.

- Duration and nature of constipation
- Bristol stool form scale
- Other contributing factors
  - Neurological disorders
    - Parkinson's
  - Medications other than opioids
- Red flags for referral or further workup
  - Unintentional weight loss
  - Rectal bleeding
  - Inflammatory bowel disease
  - Family history of colorectal cancer

Aziz, A, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic Constipation. Expert Review of Gastroenterology & Hepatology 2020

Bristol Stool Form Scale



https://upload.wikimedia.org/wikipedia/commons/a/a7/BristolStoolChart_%28cropped%29.png accessed 2.10.20

Minimizing Medications Known to Cause Constipation, Other Than Opioids

- Anticholinergic agents
- Calcium channel blockers
- Tricyclic antidepressants
- Antacids (calcium and aluminum containing)
- Iron
- Anticonvulsants
- Antipsychotics
- Diuretics
- NSAIDs

https://www.healthline.com/health-news/drugs-have-problems-after-they-get-approved#1 accessed 3.4.2020

Non-pharmacologic

- Lifestyle modifications
  - –Increase fluid intake
    - •Only if the patient is dehydrated
  - –Increase in physical activity
    - •20 minutes daily (equivalent to 1 mile)
      - –Through anti-inflammatory and anti-oxidative mechanisms
- Dietary fiber
  - –Initiate at 3-4 grams of soluble fiber daily working up to 20-30 grams daily
    - •Psyllium fiber NOT bran fiber

Pharmacologic Management

- Non-PAMORA
  - –Standard laxatives
    - •Surfactants
    - •Osmotic agents
    - •Stimulants
    - •Lubricant
    - •Saline
  - –Pro-secretory agents
- PAMORA
  - –Alvimopan
  - –Methynaltrexone
  - –Nalmedine
  - –Naloxegol

PAMORA = peripherally acting mu-opioid receptor antagonist

Non-PAMORA

- Surfactants
  - Docusate
- Osmotic agents
  - Glycerin
  - Lactulose
  - Polyethylene glycol
  - Sorbitol
- Stimulants
  - Senna
  - Bisacodyl
- Lubricant
  - Mineral Oil
- Saline
  - Magnesium citrate/ hydroxide
  - Sodium phosphate
- Pro-secretory agents
  - Linaclotide
  - Lubriprostone
- Serotonin agonist
  - Prucalopride

PAMORA = peripherally acting mu-opioid receptor antagonist

Non-PAMORA, cont.

OTC Laxatives for Opioid-Induced Constipation

Laxative	Dosage	Onset of Action	Side Effects
Surfactants			
Docusate sodium	100 mg bid	24-72 h	Well tolerated
Docusate calcium	240 mg daily	24-72 h	Well tolerated
Stimulant Laxatives			
Bisacodyl	10-30 mg tab daily 10 mg suppository per rectum daily	6-10 h 15-60 min	Gastric irritation Rectal irritation
Senna	2-4 tabs (8.6 mg sennosides/tab) or 2 tabs (15 mg sennosides/tab) daily or divided bid	6-12 h	Melanosis coli

https://www.uspharmacist.com/article/opioidinduced-constipation-clinical-guidance-and-approved-therapies accessed 2.13.2020

Non-PAMORA, cont.

Osmotic Agents			
Polyethylene glycol	17 g in 120-240 mL liquid once daily	1-4 days	Abdominal cramps, bloating, diarrhea, flatulence, nausea
Lactulose	10-20 g every other day up to bid	24-28 h	Abdominal cramps, distention, and distress; diarrhea, belching, flatulence, nausea, vomiting
Sorbitol	30-45 mL once daily	15-60 min	Abdominal distress, diarrhea, nausea, vomiting, xerostomia
Magnesium sulfate	2-4 level tsp granules dissolved in 8 oz water; may repeat in 6 h. Do not exceed 2 doses per day	0.5-3 h	Caution in renal insufficiency (magnesium toxicity). Abdominal pain, diarrhea, flatulence, nausea, vomiting
Magnesium citrate	195-300 mL once daily or in divided doses	0.5-3 h	Caution in renal insufficiency (magnesium toxicity). Abdominal pain, diarrhea, flatulence, nausea, vomiting
Glycerin	One suppository (1-2 g) per rectum once daily prn	15-30 min	Abdominal cramps; rectal pain, irritation, and cramping
Lubricants			
Mineral oil	5-45 mL in 24 h (max: 45 mL in 24 h)	Oral: 6-9 h Rectal: 2-15 min	Abdominal cramps, diarrhea, nausea, oily rectal leakage

https://www.uspharmacist.com/article/opioidinduced-constipation-clinical-guidance-and-approved-therapies accessed 2.13.2020

Non-PAMORA effectiveness in OIC

- Survey of chronic pain patients on opioids (twice a week minimum) found that despite being on a stimulant, hyperosmotic, bulk/ fiber or combination of laxative(s), at least five days per week, 81% still had constipation
- Survey of cancer pain patients on opioids found that 85.7% were constipated per their clinician's assessment, despite 84.7% being on non-PAMORA laxatives
- Survey of chronic pain patients on opioids found 63.5% had opioid-induced bowel dysfunction despite 89.5% of the population being on non-PAMORA laxatives

PAMORA = peripherally acting mu-opioid receptor antagonist
OIC = opioid induced constipation

Streicher & Bilsky. Peripherally Acting μ-Opioid Receptor Antagonists for the Treatment of Opioid-Related Side Effects: Mechanism of Action and Clinical Implications Journal of Pharmacy Practice 2018, Vol. 31(6) 658-669

PAMORA agents

FDA approved for use

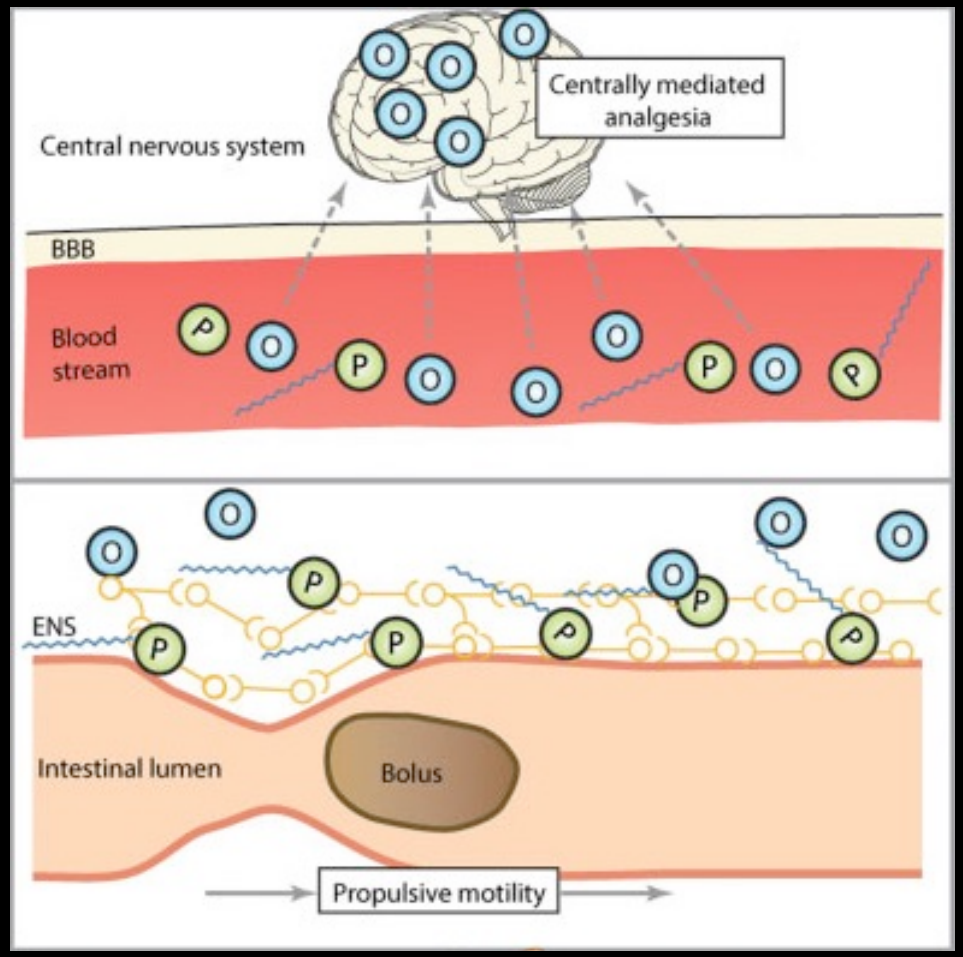
- Alvimopan
- MethylNaltrexone
- Nalmedine
- Naloxegol

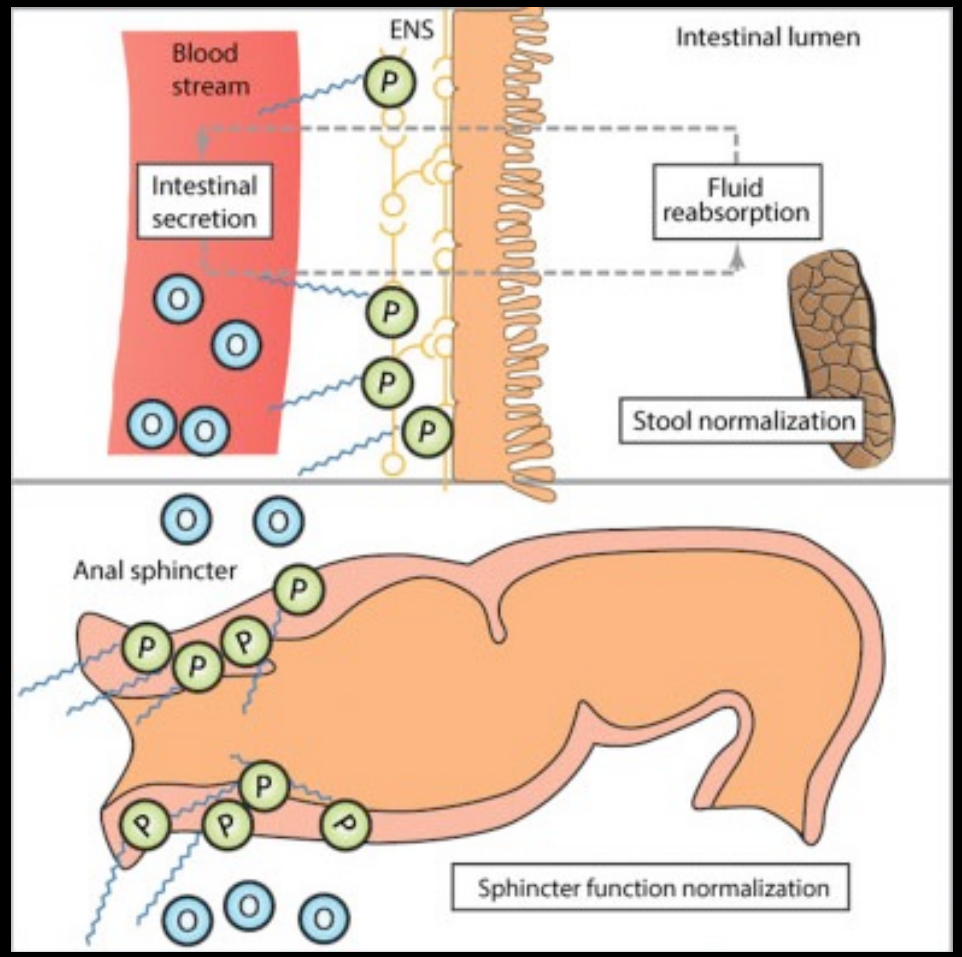
❖ Non-FDA approved agents

- ❖ Bevenopran
- ❖ Axelopran
- ❖ Naltrexamine derivative
- ❖ Naloxone

PAMORA = peripherally acting mu-opioid receptor antagonist

PAMORA Mechanism of Action





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Alvimopan

- Primarily used in the inpatient / surgical setting
  - –12 mg up to five hours prior to procedure then 12 mg twice daily starting on post operative day one until discharge
  - –MAX dose 180 mg over the entire treatment course (15 doses)
- Caution in severe renal or hepatic impairment
- Black box warning related to increased incidence of myocardial infarctions compared to placebo following long term (12 months) use
- REMS program medication
  - –Inpatient hospital use only and limited to 15 total doses

https://online.lexi.com/lco/action/doc/retrieve/docid/986/4067168 accessed 2.14.2020

MethylNaltrexone

Opioid induced constipation with advanced illness

- Dosing SubQ range based on weight
  - –<38 kg: 0.15 mg/kg (round dose up to nearest 0.1 mL)
  - –38 to <62 kg: 8 mg
  - –62 to 114 kg: 12 mg
  - –>114 kg: 0.15 mg/kg (round dose up to nearest 0.1 mL)

Opioid induced constipation for chronic non-cancer pain

- Fixed dosing
  - –12 mg SubQ once daily
  - –450 mg oral tab once daily
    - •On an empty stomach
- Discontinue all other laxatives prior to initiation of therapy

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1139899?cesid=4v7ah4WT9W4&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Drelistor%26t%3Dname%26va%3Drelistor accessed 2.14.2020

MethylNaltrexone, cont.

- Adjustments needed for renal or hepatic function
  - –Renal function less than 60 ml/min
    - •Decrease standard SubQ dose by one-half regardless of indication
    - •Decrease oral dose to 150 mg daily
  - –Moderate to severe hepatic dysfunction (Child-Pugh B or C)
    - •Decrease oral dose to 150 mg daily
  - –Severe hepatic dysfunction (Child-Pugh C)
    - •Decrease SubQ dosing by one-half regardless of indication

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1139899?cesid=4v7ah4WT9W4&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Drelistor%26t%3Dname%26va%3Drelistor accessed 2.14.2020

Methylnaltrexone for Reversal of Constipation Due to Chronic Methadone Use

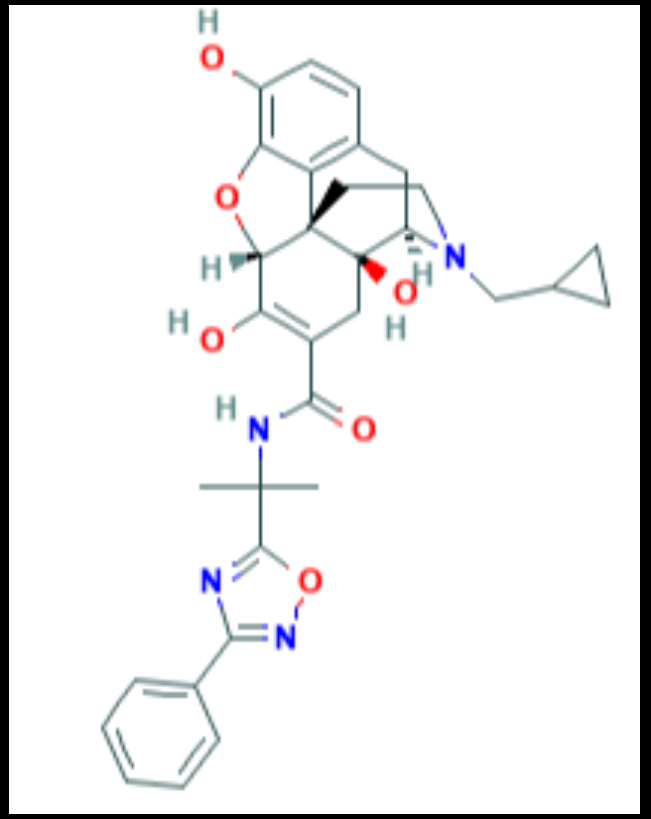
A Randomized Controlled Trial

- Double blind, placebo controlled using IV Methylnaltrexone in patients on methadone maintenance with constipation
  - Eleven subjects in each arm
    - Mean dose of Methylnaltrexone = 0.09 mg/kg on day one and 0.10 mg/kg on day two
- No laxation for the patients in the placebo group and all the patients in the treatment group experienced laxation
  - One active treatment patient only achieved laxation on day two, all others on day one and two
  - Mild to moderate cramping was reported in the treatment group
- No mention of opioid withdrawal in the treatment group

YuanCS, et. al. JAMA 2000; 283:367-72

Naldemedine

- 0.2 mg by mouth daily, discontinue if opioids are discontinued
- No dosage adjustment for renal or hepatic impairment
  - –Avoid in Child-Pugh class C
    - •Not studied in this population
- Caution with co-administration of CYP 3A and PGP inhibitors and inducers



https://pubchem.ncbi.nlm.nih.gov/compound/naldemedine#section=2D-Structure accessed 2.17.2020

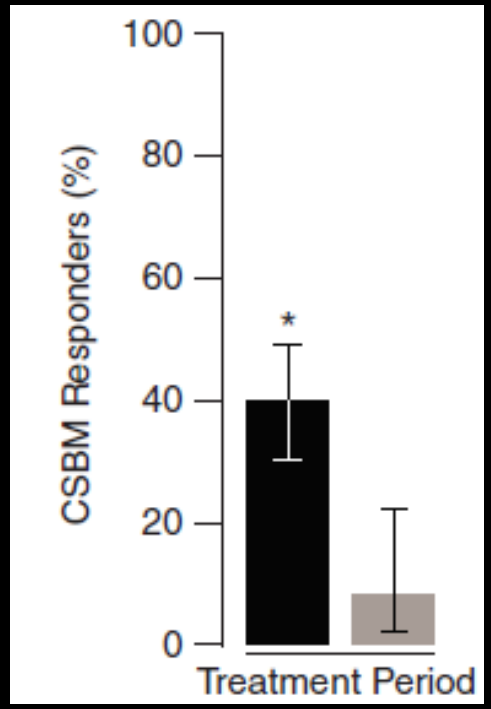
Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer

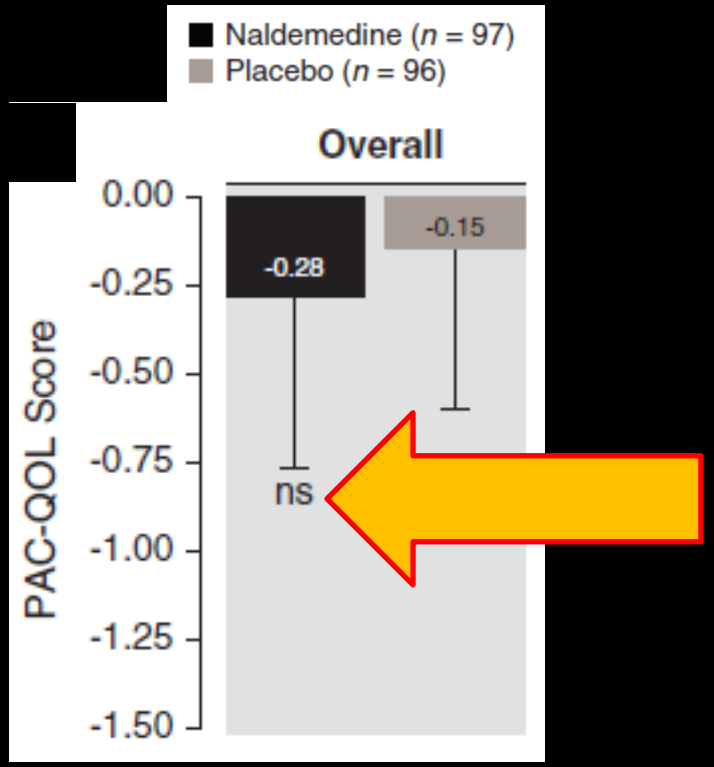
- Double blind, placebo controlled using oral naldemedine in patients with opioid induced constipation and a cancer diagnosis
  - 97 in the treatment arm and 96 in the placebo [COMPOSE-4]
  - GI cancers were the only cancer diagnoses excluded
- Compared spontaneous bowel movements at baseline and two weeks
  - Patient assessment of constipation- quality of life
- Baseline demographics similar
  - Daily opioid daily dose in treatment arm = 57.3 mg
  - Daily opioid daily dose in placebo arm = 69.5 mg

Annals of Oncology 29: 1461–1467, 2018 doi:10.1093/annonc/mdy118

Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer

- Results after two weeks
  - Complete SBM treatment group 40.2% v. placebo group 12.5% ($P < 0.001$)
  - No change in overall QOL
- No major adverse effects reported
- Funded by Shionogi Co.





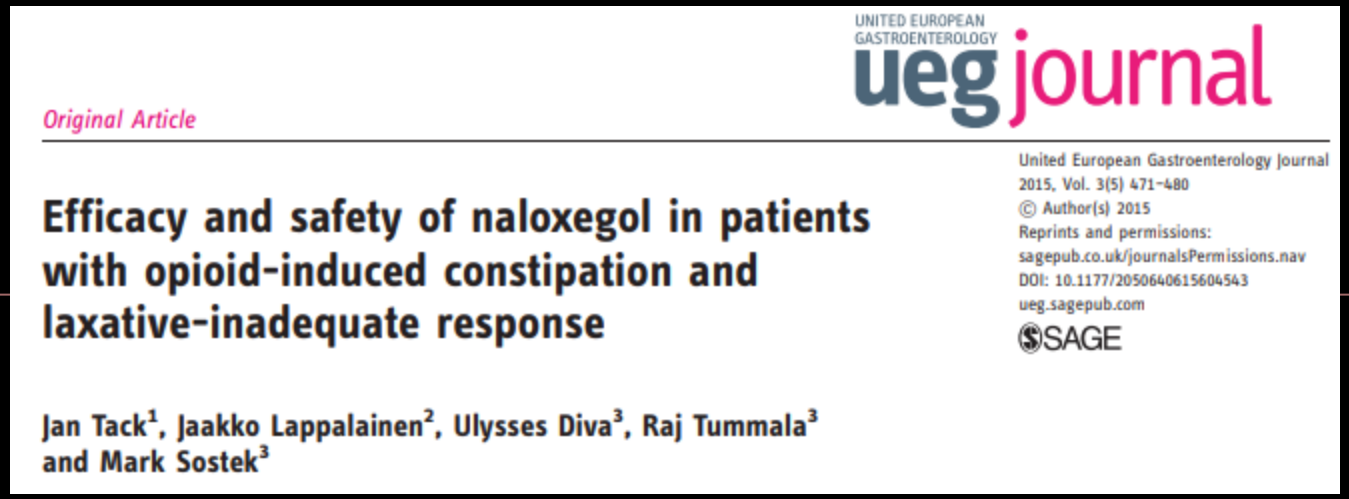
Annals of Oncology 29: 1461–1467, 2018

SBM = spontaneous bowel movement
QOL = quality of life

Naloxegol

- Discontinue all scheduled laxatives prior to initiation of therapy but may restart in three days after starting naloxegol
- 25 mg by mouth daily on an empty stomach
  - For excessive GI irritation, decrease dose to 12.5 mg by mouth daily
- Renal adjustment dosing
  - CrCl < 60 ml/min: 12.5 mg by mouth daily; if constipation symptoms persist may increase to 25 mg by mouth daily
- Hepatic adjustment dosing
  - Child-Pugh C: avoid use
- Drug interactions
  - Avoid co-administration with CYP 3A and PGP inhibitors and inducers

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5349444?cesid=99EM7kVigJM&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dnaloxegol%26t%3Dname%26va%3Dnaloxegol#doa accessed 2.18.2020



UNITED EUROPEAN GASTROENTEROLOGY ueg journal

Original Article

Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response

Jan Tack[1], Jaakko Lappalainen[2], Ulysses Diva[3], Raj Tummala[3] and Mark Sostek[3]

United European Gastroenterology Journal
2015, Vol. 3(5) 471–480

DOI: 10.1177/2050640615604543
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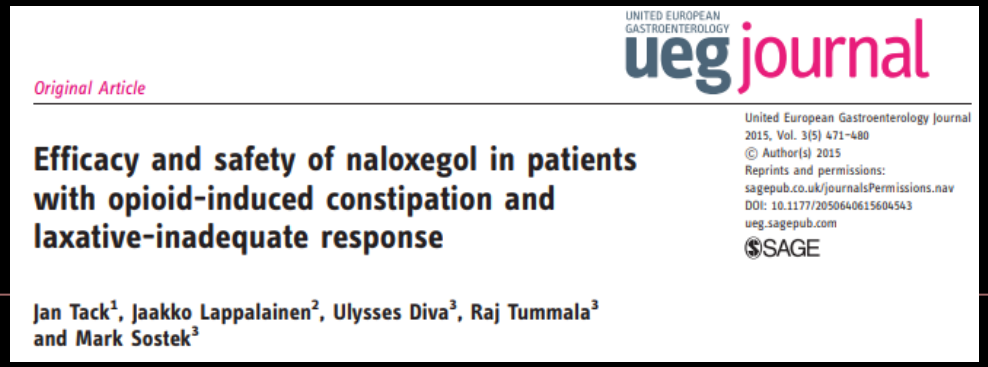
SAGE

- Pooled data from two double-blind, 12 week, placebo controlled trials compared to naloxegol 12.5 mg or 25 mg daily for outpatients [KODIAC-04 and 05]
- Patients were taking 30-1000 MEDD for non-cancer pain
- Response was defined as ≥ 3 SBM per week and for an increase by ≥ 1 SBM per week over baseline for ≥ 9 of 12 weeks and for ≥ 3 SBM over baseline the final 4 weeks
- Baseline characteristics were similar for all three groups in the pooled results

SBM = spontaneous bowel movements
MEDD = morphine equivalent daily dose
United European Gastroenterology Journal 2015, Vol. 3(5) 471–480



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- Laxative-inadequate responder group SBMs were higher in the naloxegol 12.5 mg (95% CI: 1.106-1.797; p = 0.005) and 25 mg (95% CI: 1.253-2.001; p < 0.001) group versus placebo
- Flatulence, upper abdominal pain and hyperhidrosis were reported more frequently in the 25 mg treatment group compared to the 12.5 mg or placebo groups

	SBMs/wk at baseline			
	0 to <1[a]	1 to <2[a]	2 to <3[a]	Total
Patients with an increase of ≥3 SBMs/wk, *n/N* (%)				
Placebo	21/76 (27.6)	25/88 (28.4)	18/71 (25.4)	65/239 (27.2)
Naloxegol 12.5 mg	41/74 (55.4)	28/80 (35.0)	24/77 (31.2)	94/240 (39.2)
Naloxegol 25 mg	47/88 (53.4)	54/90 (60.0)	30/58 (51.7)	131/241 (54.4)

SBM = spontaneous bowel movements

United European Gastroenterology Journal 2015, Vol. 3(5) 471–480

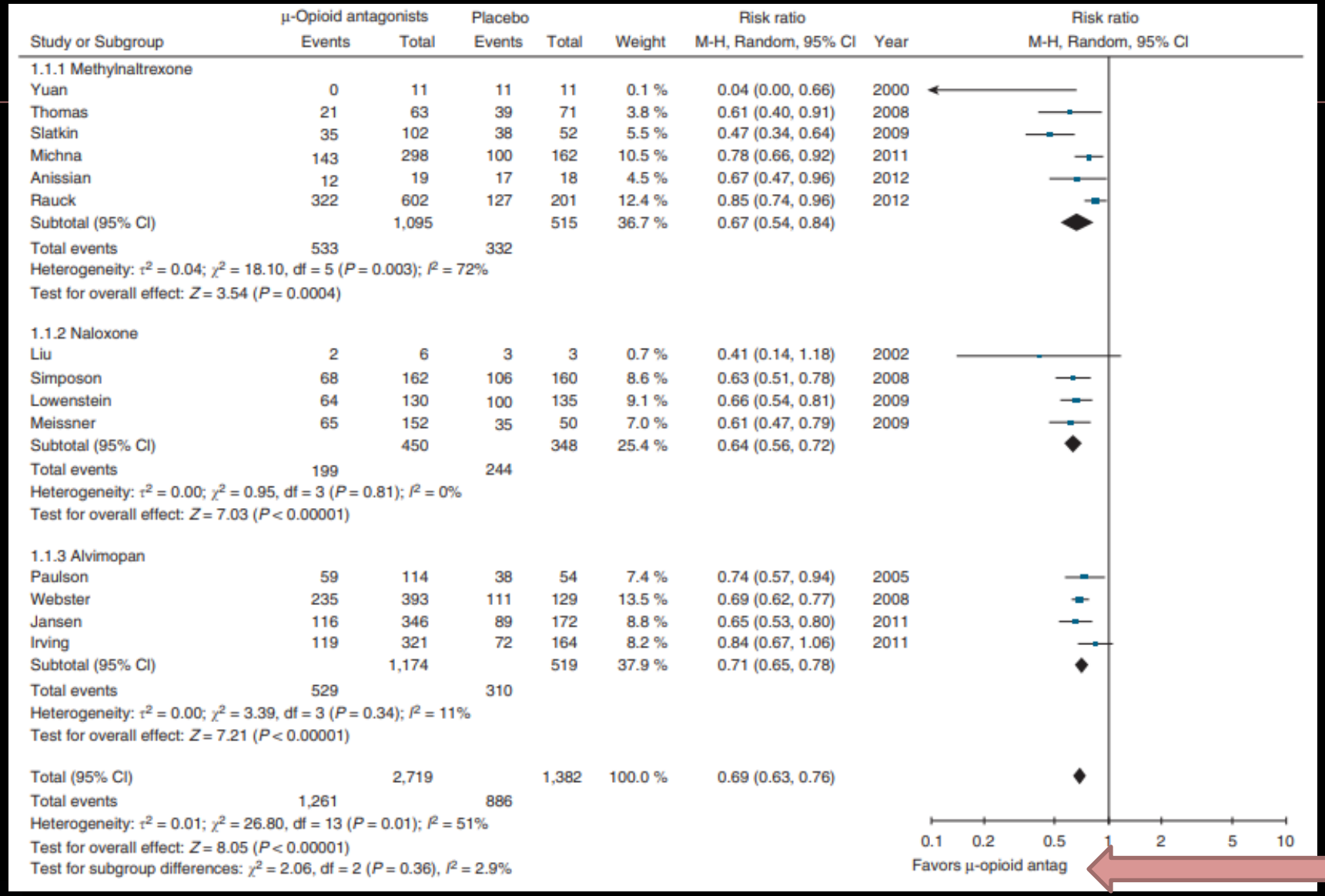
PAMORA Meta Analysis

- Primary outcome compared efficacy of active treatments to placebo for opioid induced constipation
- Secondary outcomes reviewed active treatments for adverse events
- Twenty-seven articles reviewed
  - Included PAMORAs and pro-secretory agents
    - Naloxone*, methylnaltrexone, naldemedine, alvimopan and naloxegol
    - Lubiprostone and prucalopride

*NOT FDA APPROVED FOR TREATMENT OF OPIOID INDUCED CONSTIPATION

Luthra, P, Burr, NE orcid.org/0000-0003-1988-2982, Brenner, DM et al. (2019) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut, 68 (3). pp. 434-444. ISSN 0017-5749

PAMORA meta analysis, cont.



Study or Subgroup	μ-Opioid antagonists Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
1.1.1 Methylnaltrexone							
Yuan	0	11	11	11	0.1 %	0.04 (0.00, 0.66)	2000
Thomas	21	63	39	71	3.8 %	0.61 (0.40, 0.91)	2008
Slatkin	35	102	38	52	5.5 %	0.47 (0.34, 0.64)	2009
Michna	143	298	100	162	10.5 %	0.78 (0.66, 0.92)	2011
Anissian	12	19	17	18	4.5 %	0.67 (0.47, 0.96)	2012
Rauck	322	602	127	201	12.4 %	0.85 (0.74, 0.96)	2012
Subtotal (95% CI)		1,095		515	36.7 %	0.67 (0.54, 0.84)	
Total events	533		332				
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 18.10$, df = 5 ($P = 0.003$); $I^2 = 72\%$							
Test for overall effect: $Z = 3.54$ ($P = 0.0004$)							
1.1.2 Naloxone							
Liu	2	6	3	3	0.7 %	0.41 (0.14, 1.18)	2002
Simposon	68	162	106	160	8.6 %	0.63 (0.51, 0.78)	2008
Lowenstein	64	130	100	135	9.1 %	0.66 (0.54, 0.81)	2009
Meissner	65	152	35	50	7.0 %	0.61 (0.47, 0.79)	2009
Subtotal (95% CI)		450		348	25.4 %	0.64 (0.56, 0.72)	
Total events	199		244				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.95$, df = 3 ($P = 0.81$); $I^2 = 0\%$							
Test for overall effect: $Z = 7.03$ ($P < 0.00001$)							
1.1.3 Alvimopan							
Paulson	59	114	38	54	7.4 %	0.74 (0.57, 0.94)	2005
Webster	235	393	111	129	13.5 %	0.69 (0.62, 0.77)	2008
Jansen	116	346	89	172	8.8 %	0.65 (0.53, 0.80)	2011
Irving	119	321	72	164	8.2 %	0.84 (0.67, 1.06)	2011
Subtotal (95% CI)		1,174		519	37.9 %	0.71 (0.65, 0.78)	
Total events	529		310				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.39$, df = 3 ($P = 0.34$); $I^2 = 11\%$							
Test for overall effect: $Z = 7.21$ ($P < 0.00001$)							
Total (95% CI)		2,719		1,382	100.0 %	0.69 (0.63, 0.76)	
Total events	1,261		886				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 26.80$, df = 13 ($P = 0.01$); $I^2 = 51\%$							
Test for overall effect: $Z = 8.05$ ($P < 0.00001$)							
Test for subgroup differences: $\chi^2 = 2.06$, df = 2 ($P = 0.36$), $I^2 = 2.9\%$							

Luthra, P, Burr, NE orcid.org/0000-0003-1988-2982, Brenner, DM et al. (2019) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut, 68 (3). pp. 434-444. ISSN 0017-5749

PAMORA meta analysis, cont.

Table 2. League Table of Results for Failure to Achieve an Average of ≥3 BMs per Week with an Increase of ≥1 BM per Week Over Baseline or an Average of ≥3 BMs per Week.

Naloxone									
0.97 (0.75; 1.25)	**Naldemedine**								
0.96 (0.73; 1.27)	0.99 (0.80; 1.24)	**Alvimopan**							
0.88 (0.64; 1.21)	0.91 (0.69; 1.19)	0.91 (0.68; 1.23)	**Methylnaltrexone SC**						
0.87 (0.62; 1.22)	0.90 (0.68; 1.20)	0.91 (0.66; 1.23)	0.99 (0.70; 1.41)	**Prucalopride**					
0.83 (0.60; 1.16)	0.86 (0.64; 1.15)	0.86 (0.63; 1.17)	0.95 (0.67; 1.34)	0.95 (0.66; 1.37)	**Bevenopran**				
0.76 (0.58; 1.01)	0.79 (0.63; 0.99)	0.79 (0.62; 1.02)	0.87 (0.65; 1.17)	0.88 (0.64; 1.19)	0.92 (0.68; 1.25)	**Naloxegol**			
0.71 (0.51; 0.99)	0.74 (0.56; 0.97)	0.74 (0.55; 1.00)	0.81 (0.58; 1.14)	0.82 (0.57; 1.16)	0.86 (0.60; 1.22)	0.93 (0.69; 1.26)	**Methylnaltrexone**		
0.71 (0.55; 0.92)	0.73 (0.60; 0.90)	0.74 (0.58; 0.93)	0.81 (0.61; 1.07)	0.81 (0.60; 1.10)	0.85 (0.63; 1.15)	0.93 (0.74; 1.17)	1.00 (0.75; 1.33)	**Lubiprostone**	
0.65 (0.52; 0.80)	0.67 (0.59; 0.77)	0.67 (0.57; 0.80)	0.74 (0.58; 0.94)	0.74 (0.58; 0.96)	0.78 (0.61; 1.01)	0.85 (0.71; 1.01)	0.91 (0.71; 1.17)	0.92 (0.79; 1.07)	**Placebo**

Luthra, P, Burr, NE orcid.org/0000-0003-1988-2982, Brenner, DM et al. (2019) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut, 68 (3). pp. 434-444. ISSN 0017-5749

Gastroenterology 2019;156:218–226

AGA SECTION

American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation

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Recommendations

1. In patients with OIC, the AGA recommends use of laxatives as first-line agents. *Strong recommendation, moderate-quality evidence*
2. In patients with laxative refractory OIC, the AGA recommends naldemedine over no treatment. *Strong recommendation, high-quality evidence*
3. In patients with laxative refractory OIC, the AGA recommends naloxegol over no treatment. *Strong recommendation, moderate-quality evidence*

Gastroenterology 2019; 156:218-226
OIC = Opioid induced constipation

Recommendations

4. In patients with laxative refractory OIC, the AGA suggests methylnaltrexone over no treatment. **Conditional recommendation, low-quality evidence**
5. In patients with OIC, the AGA makes no recommendation for the use of lubiprostone. No recommendation, evidence gap
6. In patients with OIC, the AGA makes no recommendation for the use of prucalopride. No recommendation, evidence gap

Gastroenterology 2019; 156:218-226
OIC = Opioid induced constipation

AGA Guideline Deep Dive

- Laxatives is a broad category with many different sub-classes
- The recommendation for laxatives was an aggregate of the group compared to placebo
  - –No head to head laxative trials reviewed
  - –Low overall cost and few safety concerns associated with over-the-counter laxatives was considered by the reviewers
- Combination laxative therapy is favored for laxative-refractory OIC as well as scheduled use of laxatives
- A bowel function index may be used on patients not experiencing relief from the above

Gastroenterology 2019; 156:218-226
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Bowel Function Index

Item	Question	Scale
1	During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100?	0 = easy or no difficulty 100 = severe difficulty
2	During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100?	0 = not at all 100 = very strong
3	During the last 7 days, how would you rate your constipation on a scale from 0 to 100?	0 = not at all 100 = very strong
Total score		**Mean of 3 scores**

Scores > 30 indicate clinically significant constipation and would benefit from an escalation in therapy, per trial data

Clinical practice validation of this scoring data are lacking at this time

Gastroenterology 2019; 156:218-226

AGA guidelines laxatives table

Class/type	Examples	Mechanism of action
Traditional laxatives		
Osmotic	PEG, lactulose, magnesium citrate, magnesium hydroxide	Draw water into intestine to hydrate and soften stool
Stimulant	Bisacodyl, sodium picosulfate, senna	Irritate sensory nerve endings to stimulate colonic motility and reduce colonic water absorption
Detergent/surfactant stool softeners	Docusate	Allow water and lipids to penetrate the stool to hydrate and soften fecal material
Lubricant	Mineral oil	Lubricate the lining of the gut to facilitate defecation
PAMORAs	Naldemedine Naloxegol Methylnatrexone	Block μ-opioid receptors in the gut, thereby effectively restoring the function of the enteric nervous system
Intestinal secretagogues	Lubiprostone	Act on chloride channels or guanylate cyclase receptors in enterocytes to stimulate fluid secretion into the intestinal lumen
Selective 5-HT agonists	Prucalopride	Activate 5-HT4 receptor, leading to increased colonic motility and accelerated transit

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AGA Guideline Deep Dive, cont.

- Naldemedine data came from four randomized controlled trials with over 2400 patients in total
  - –Three times weekly SBM; 52% naldemedine, 35% placebo
    - •Risk Ratio for SBM 1.51; 95% CI: 1.32-1.72
  - –Adverse drug events (ADE) were more common in the naldemedine treated patients and included infection, abdominal pain, diarrhea, flatulence, nausea and back pain
    - •Risk Ratio for ADEs 1.44; 95% CI: 1.03-2.03

Gastroenterology 2019; 156:218-226
SBM = spontaneous bowel movement

AGA Guideline Deep Dive, cont.

- Naloxegol data came from two randomized controlled trials
  - –Three times weekly SBM; 41.9% naloxegol, 29.4% placebo
    - •Risk Ratio for SBM 1.43; 95% CI: 1.19-1.71
  - –Adverse drug events (ADE) were more common in the naldemedine treated patients and included upper abdominal pain, diarrhea, headache, nausea and flatulence
    - •Risk Ratio for ADEs 2.33; 95% CI: 1.62-3.35

Gastroenterology 2019; 156:218-226
SBM = spontaneous bowel movement

AGA Guideline Deep Dive, cont.

- Methylnaltrexone data came from five randomized controlled trials
  - –Three times weekly SBM was evaluated in three of the five total trials
    - •Risk Ratio for SBM 1.43; 95% CI: 1.21 to 1.68
  - –Adverse drug events were not statistically significant compared to placebo
  - –The reviewers marked this as low quality evidence based on indirectness, inconsistency and imprecision across several outcomes

Gastroenterology 2019; 156:218-226
SBM = spontaneous bowel movement

AGA Guideline Deep Dive, cont.

- Secretagogue
  - –Lubiprostone data were pooled from three randomized controlled trials
    - •Three times weekly SBM; 38% lubiprostone, 32.7% placebo
      - –Risk Ratio for SBM 1.15; 95% CI: 0.97-1.37
  - –Limited, consistent evidence exists regarding the use of lubiprostone in opioid induced constipation

Gastroenterology 2019; 156:218-226
SBM = spontaneous bowel movement

AGA Guideline Deep Dive, cont.

- Serotonin agonists
  - –Prucalopride data were from a single randomized controlled trial
    - •Response to treatment; 58.3% prucalopride, 41.6 % placebo
      - –Risk Ratio of SBM 1.36; 95% CI: 1.08-1.70
    - •Adverse drug events were not statistically significant
    - •The study was terminated by the manufacturer prior to completion

Gastroenterology 2019; 156:218-226
SBM = spontaneous bowel movement

Pain Medicine 2017; 18: 1837–1863
doi: 10.1093/pm/pnw255

OXFORD

GENERAL SECTION

Review Article

Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline

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Company, and Mundipharma International. No competing interests.

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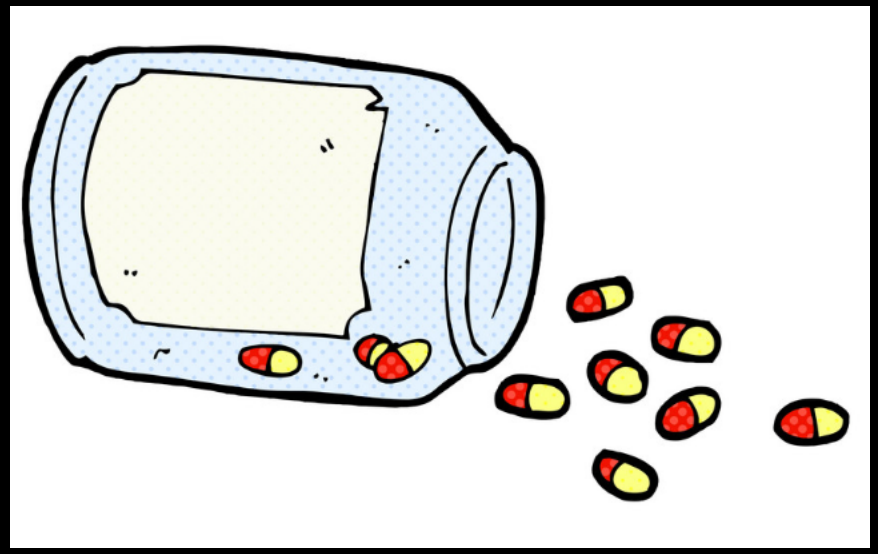
Pharmacological Prevention and Treatment of OIC/ OIBD

- The choice of a laxative to treat OIC/OIBD depends on the perceived efficacy and the preference of the patient; indirect evidence favors bisacodyl, sodium picosulfate, polyethelene glycol, and sennosides as first choice
- Sugars and sugar alcohols such as lactulose, lactose, and sorbitol should not be used to prevent or treat OIC
  - Bloating and abdominal distension
- Patients with nausea secondary to opioid treatment should be offered dopamine antagonists

Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255
OIC = Opioid induced constipation
OIBD = Opioid induced bowel dysfunction

Pharmacological Prevention and Treatment of OIC/ OIBD, cont.

- Treatment of OIC with non-PAMORA, new laxatives (prucalopride, lubiprostone) may be promising; however, there are insufficient data to warrant such treatments in OIC patients
- Gastro-esophageal reflux symptoms as part of OIBD should be treated like primary reflux disease



Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255
OIC = Opioid induced constipation
OIBD = Opioid induced bowel dysfunction

https://www.vectorstock.com/royalty-free-vector/comic-cartoon-jar-of-pills-vector-6801969 accessed 3.3.2020

PAMORAs

- Peripherally acting μ-opioid receptor antagonists (PAMORAs) effectively reduce OIC
  - –Sixteen randomized controlled trials reviewing the currently approved four PAMORAs
- In patients with chronic cancer or non-cancer pain, prolonged-release naloxone/oxycodone combination effectively reduces OIC while maintaining equal analgesia to prolonged-release oxycodone alone
- Methylnaltrexone injections can effectively relieve OIC in patients with postoperative cancer and non-cancer chronic pain

Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255
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Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255

PAMORAs, cont.

- Alvimopan is approved in the United States for use in hospitalized patients for preventing or decreasing the course of postoperative ileus after bowel resection; long-term safety studies indicated that it may possibly increase the risk of cardiovascular events; there is some evidence that alvimopan reduces OIC in subjects with chronic opioid intake
- Both laxatives and opioid antagonists for OIC have benefits on quality of life

Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255
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Pain Medicine 2017; 18: 1837–1863 doi: 10.1093/pm/pnw255

Show Me the Money

- Non-PAMORA < PAMORA regarding efficacy and cost in management of opioid induced constipation
  - –Polyethylene glycol 3350 average price $22.69 v. Naloxegol average price $451.68 for a month supply
  - –The branded non-PAMORA agents are also closer in cost to the PAMORA agents
    - •Lubiprostone average price $484.00 for a month supply
- Keep in mind financial assistance programs, coupons and samples may be of use especially when initiating therapy

https://www.goodrx.com accessed 3.3.2020
PAMORA = peripherally acting mu opioid antagonist

Patient Case

BB is a 72 year old male with severe osteoarthritis on morphine ER and IR (MEDD = 90 mg) presenting to the office with continued difficulties with bowel movements. Bristol scale type 2 (mild constipation) with no other GI symptoms. He has not tried other laxatives as there are “too many to try and figure out which to use”. Other pertinent home medications include

- Amitriptyline and hydrochlorothiazide

What are some options for BB?

MEDD = morphine equivalent daily dose

Patient Case, cont.

1. Any medications other than opioids that could be implicated?

- Amitriptyline and hydrochlorothiazide

2. Could this be OIC or OIBD?

- OIC since the GI symptoms are primarily constipation and do not include nausea, abdominal pain or GERD

3. What laxatives could be considered?

- Non-PAMORA agents as first line, scheduled treatment

Patient Case, cont.

BB discussed with his PCP and the amitriptyline and hydrochlorothiazide were changed to other agents and he started on scheduled sennosides with docusate. His Bristol stool scale remains at a type 2 despite those changes three weeks ago.

1. What should be considered next?

- A peripherally acting opioid receptor antagonist (PAMORA) agent

Patient Case, cont.

2. Which ones would be most appropriate?

- Naldemedine or naloxegol
  - –Both are AGA-OIC guideline strong recommendations, moderate quality of evidence
- Naldemedine could be started in conjunction with the non-PAMORA laxatives
- Naloxegol would necessitate discontinuation or the non-PAMORA agents

Conclusions

- Determining opioid induced bowel dysfunction from opioid induced constipation is crucial to correct treatment plans
- Medications used to manage opioid induced constipation have made advances
- Data now support the use of peripherally acting opioid antagonists in the management of opioid induced constipation compared to traditional laxatives