PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

Gastrointestinal Symptoms: Part 1

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Titles and Affiliations

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Disclosures

Learning Objectives

- At the conclusion of this presentation the participant will be able to:
  - Define constipation, and opioid-induced constipation (OIC)
  - Describe methods to assess constipation, and specifically OIC
  - List mechanism of action, adverse effects, efficacy and cost effectiveness of common bowel regimens
  - Describe mechanism of action, adverse effects, efficacy and cost effectiveness of new bowel regimens
  - Assess and recommend a treatment for diarrhea

Prevalence of Constipation

- Constipation may be idiopathic or have functional causes
- Median prevalence of constipation:
  - Up to 27% of adults
  - Age 60-101 years the prevalence is almost 35%
  - Up to 50% of patients in a long-term care facility
  - 75%-87% of hospice patients require treatment for constipation
  - 2.5 million physician visits and 100,000 hospitalizations annually
  - $800 million/year spent on laxatives!
  - Can negatively impact quality of life

Higgins et al. *Am J Gastroenterol* 2004;99:750-759.
Vazquez et al. *Clin Interv Aging* 2015;10:919-930.

Hospice Prayer

Happy is the patient in the PM,
who has a BM in the AM

Definition and Incidence

- Constipation
  - Slow movement of feces through the large intestine
  - Results in hard, dry stool that may be difficult to expel
  - Means different things to different people
    - Stool infrequency
    - Incomplete evacuation of stool
    - Difficulty passing stools
    - May be accompanied by abdominal discomfort, bloating, distention, and pain

Rome IV Criteria

- Must have 3 months of symptoms
- Must have 2 or more of the following symptoms occurring more than 25% of defecations:
  - Straining
  - Hard stools
  - Incomplete evacuation
  - Anorectal obstruction or blockage
  - Use of manual maneuver for disimpaction
  - Less than 3 spontaneous bowel movements per week
- Loose stools are rare without laxatives
- It does meet the criteria for IBS
- The criteria are fulfilled with symptom onset 6 months prior to diagnosis

Hayat et al. *Cleve Clin J Med* 2017;84(5):397-408.

Opioid-Induced Constipation

- Opioids affect gastrointestinal (GI) motility and secretion via suppression of neural activity
  - Suppress forward peristalsis
  - Increase nonpropulsive segmental contractions
  - Raise anal sphincter tone and sphincter tone in both small and large intestines
- Opioids may vary in constipating severity
  - May be due to opioid dosage and potency
  - Experienced by 40%-90% opioid-requiring patients

Causes of Constipation

Category	Examples
Associated conditions	Chronic kidney disease, heart failure, chronic pain, bipolar disorder, schizophrenia, depression, IBS, inflammatory bowel disease, diverticulosis, Chagas disease
Metabolic causes	Hypokalemia, hypercalcemia, hypomagnesemia
Neurologic conditions	Parkinson's, cerebrovascular, dementia, spinal cord injury, sacral nerve pathology, lack of anal reflex, autonomic neuropathy, Hirschsprung's, malignancy impacting nerves, spinal ganglion tumors, neural plexus invasion
Motility abnormalities	Amyloidosis, scleroderma, immobility
Structural abnormalities	Pelvic floor dysfunction, fecal impaction, patulous anus, rectal prolapse, rectal intussusception, obstructing sigmoidocele, excessive perineal descent, malignancy related, mechanism obstruction, anal fissure
Endocrine conditions	Hypothyroidism, hyperparathyroidism, panhypopituitarism, diabetes mellitus
Medications	Antidepressants, antipsychotics, antispasmodics, antihistamines, anticonvulsants, antacids, sucralfate, sympathomimetics, opioids, antiemetics, ganglionic blockers, chemotherapy, vinca alkaloids, calcium supplements, iron, antihypertensives (CCB, diuretics)
Diet	Anorexia, dehydration, low fiber intake, excess alcohol/caffeine/dairy, foods high in fat or sugar

Agrawal, Shish. Constipation. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Laxative Options

Laxative	Usual Adult Dose	Onset of Action	Side Effects
Bulk-Forming Laxatives			
Psyllium	Up to 1 tablespoon (~3.5 grams fiber) 3 times daily	12-72 hours	Impaction above strictures, fluid overload, gas and bloating
Methylcellulose	Up to 1 tablespoon (~2 grams fiber) or 4 caplets (500 mg fiber/caplet) 3 times daily	12-72 hours	
Polycarbophil	2-4 tabs (500 mg per tab) per day	24-48 hours	
Wheat dextrin	1-3 caplets (1 grams fiber/caplet) or 2 tsp (1.5 gram fiber/tsp) up to 3 times per day	24-48 hours	

Laxative Options

Laxative	Usual Adult Dose	Onset of Action	Side Effects
Surfactants (softeners)			
Docusate sodium	100 mg 2 times per day	24-72 hours	Well tolerated. Use lower dose if administered with another laxative. Contact dermatitis reported.
Docusate calcium	240 mg once daily	24-72 hours	
Stimulant Laxatives			
Bisacodyl	10-30 mg as enteric coated tabs once daily	6-10 hours	Gastric irritation
Bisacodyl	10 mg pr 1 time a day	15-60 minutes	Rectal irritation
Senna	2-4 tabs (8.6 mg sennosides/tab) or 1-2 tabs (15 mg sennosides/tab) as a single dose or divided twice daily	6-12 hours	Melanosis coli

Laxative Options

Laxative	Usual Adult Dose	Onset of Action	Side Effects
Osmotic Agents			
Polyethylene glycol	8.5 to 34 grams in 240 ml (8 oz) liquids	1-4 days	Nausea, bloating, cramping
Lactulose	10-20 grams (15-30 ml) qod (up to bid)	24-48 hours	Abdominal bloating, flatulence
Sorbitol	30 grams (120 mg of 25% solution) once daily	24-48 hours	Abdominal bloating, flatulence
Glycerin	One pr (2-3 grams) for 15 minutes once daily	15-60 minutes	Rectal irritation
Magnesium citrate	200 ml (11.6 grams) once daily	0.5-3 hours	Watery stools and urgency. Caution with renal insufficiency.
Magnesium hydroxide	5-15 ml as needed up to 4 times daily	0.5-6 hours	
Magnesium sulfate	1-2 tsp (5-10 grams) in 240 ml water once daily	0.5-3 hours	

Laxative Options

Laxative	Usual Adult Dose	Onset of Action	Side Effects
Enemas			
Docusate	283 mg docusate sodium, PEG and glycerin		
Sodium phosphate	7 g dibasic and 19 g monobasic sodium phosphate Adults – 118 ml; Children 2-12 years – 59 ml		
Bisacodyl	10 mg per 30 ml		
Mineral oil	Adults and children ≥ 12 years – 118 ml; Children 2-12 years – 59 ml		
Enemeez (Plus), others	Docusate, PEG, glycerin, benzocaine		

Docusate + Senna: Too Good To Be True?

- 2013 randomized, double-blind, placebo-controlled trial
- 74 patients randomized to receive either docusate and sennosides OR placebo and sennosides
- No significant between-group differences in stool frequency, volume, or consistency; or difficulty or completeness of evacuation.

Tarumi, Wilson, Szafran, Spooner. *J Pain Symptom Manage*. 2013;45(1):2-13.

Management of Opioid-Induced Constipation

- Prophylaxis!
- Encourage fluid intake and increase dietary fiber (within reason)
  - High fiber diet may worsen discomfort and constipation, especially fiber without fluid
- Physical activity (within reason)
- Osmotic agents, stimulant laxatives
- Newer agents

Laxative Options

Laxative	Usual Adult Dose	Onset of Action	Side Effects
Intestinal Secretogogues			
Lubiprostone	24 mg twice a day	Within 24 hours	Nausea
Linaclotide	145 ug daily	Take within 30 minutes before the first meal	Diarrhea
Plecanatide	3-6 mg daily		
Opioid Receptor Antagonists			
Methylnaltrexone	SQ: 8 mg (38-62 kg) or 12 mg (62-114 kg) or 0.15 mg/kg/dose (< 38 kg or > 114 kg) every other day	30-60 minutes	Abdominal pain, diarrhea, nausea, gas, headache. Avoid in patients with intestinal malignancy; contraindicated in bowel obstruction due to increased risk of perforation.
Naloxegol	12.5-25 mg daily		
Naldemedine	0.2 mg QD	Peaks in 0.75-2 hours	

Lubiprostone (Amitiza)

- Mechanism of action
  - Chloride channel activator (ClC-2)
    - Promotes fluid secretion → increased motility
    - Bypasses the antisecretory action of opioids
- Indications
  - Chronic idiopathic constipation in adults
  - Opioid-induced constipation in adults with CNCP
    - 24 mcg orally twice daily
  - Irritable bowel syndrome with constipation in women ≥18 years old
    - 8 mcg orally twice daily

AMITIZA® package insert

Lubiprostone: Safety

- Contraindicated: known or suspected GI obstruction
- Precautions
  - Patients may experience dyspnea
  - Reduce dose in moderate (16 mcg bid) to severe (8 mcg bid) hepatic impairment
- Drug interactions
  - Not metabolized by cytochrome P450
  - Diphenylheptane opioids (eg, methadone) may reduce activation of CIC-2 in GI tract

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Lubiprostone: Efficacy and Cost

- 12-week study in patients receiving nonmethadone opioids with documented OIC at baseline (<3 SBM/week with ≥25% SBMs associated with: hard to very hard tool consistency, moderate to severe straining, sensation of incomplete evacuation
- Median weekly SBM frequency 1.5 for placebo;
  1-1.5 for lubiprostone baseline
- "Overall responders": ≥1 SBM improvement over baseline for all treatment weeks AND ≥3 SBMs/week reported for at least 9 of 12 weeks
- 27.1% lubiprostone vs 18.9% placebo (Study 1)
- Study 3: change in SBM by week 8; no sig difference
- NNT 13; lubiprostone 24 mcg by mouth twice daily ~ $350/month

AMITIZA® package insert

Lubiprostone: Adverse Effects

- Most common
  - Nausea (11%)
  - Diarrhea (8%)
  - Abd pain, flatulence (4%)
- Less common (<1%)
  - Fecal incontinence
  - Hypokalemia

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Linaclotide (Linzess)

- Mechanism of action
  - Guanylate cyclase-C (GC-C) agonist
  - Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of intestinal epithelium
  - Increase in intracellular/extracellular concentrations of cyclic guanosine monophosphate → stimulates secretion of chloride and bicarbonate into intestinal lumen → increased intestinal fluid and accelerated transit
- Indications
  - Irritable bowel syndrome with constipation
  - Chronic idiopathic constipation

Linaclotide: Safety

- Contraindications
  - Pediatric patients <6 years old
  - Known or suspected mechanical GI obstruction
- Precautions
  - Pediatric patients 6-17 years old
  - Development of diarrhea
- Drug Interactions
  - No drug-drug interaction studies conducted
    - Linaclotide and metabolite are not measurable in plasma
    - Does not interact with cytochrome P450
    - Not a substrate or inhibitor of efflux transporter P glycoprotein

Linaclotide: Cost

- Dose
  - IBS-C: 290 mcg orally once daily
  - CIC: 145 mcg orally once daily
  - Take on an empty stomach >30 minutes before first meal of the day
- Cost
  - 145 mcg or 290 mcg: 30 capsules = $350/month

Linaclotide: Adverse Effects

Adverse Reactions	Linaclotide 290 mcg (%)	Placebo (%)
Gastrointestinal		
Diarrhea	20	3
Abdominal pain	7	5
Flatulence	4	2
Abdominal distention	2	1
Infections and Infestations		
Viral gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

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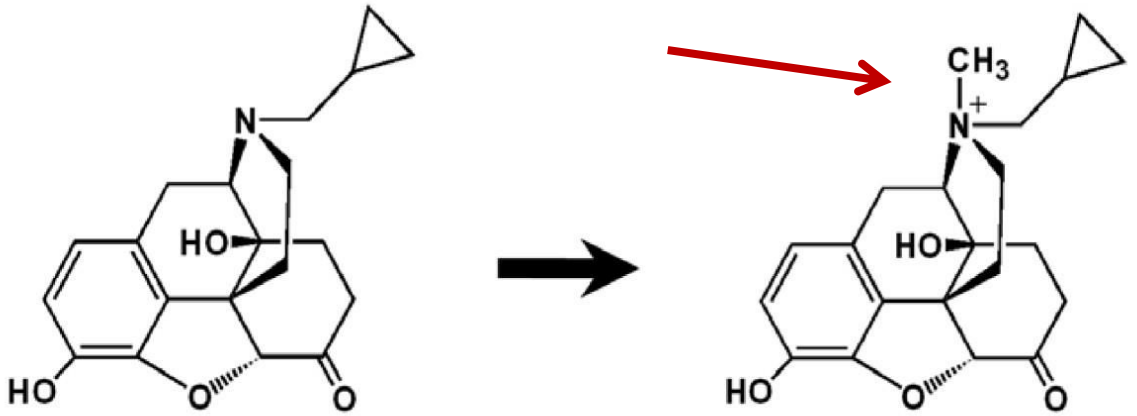
PAMORAs

Peripherally-Acting Mu-Opioid Receptor Antagonists

- Methylnaltrexone
  - Mu-opioid receptor selective antagonist
  - Quaternary amine
- Naloxegol
  - Mu-opioid receptor antagonist
  - PEGylated derivative of naloxone



Naltrexone

Methylnaltrexone

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Methylnaltrexone (Relistor)

- OIC in CNCP: tablets and injection
  - Be within close proximity to toilet facilities once administered!
  - Discontinue laxatives prior to use, may use if no response to treatment after 72h
  - Inject 12mg SQ daily OR 450 mg by mouth once daily in the morning
- OIC in adults with advanced illness receiving palliative care who have not responded to laxative therapy – injection
  - Inject 1 dose SQ every other day prn
    - 8 mg for patients 38 kg-61.9 kg
    - 12 mg for patients 62 kg-114 kg
    - Patients <38 kg or >114 kg: 0.15 mg/kg

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Methylnaltrexone: Safety

- Creatinine clearance <60 ml/min:
  - CNCP: reduce oral dose to 150 mg po qd; 6 mg SQ daily
  - Advanced illness: 50% of full SQ dose
- Contraindicated in patients who may have gastrointestinal obstruction or those at high risk
- Warnings and precautions
  - GI perforation, severe or persistent diarrhea, opioid withdrawal

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Methylnaltrexone: Adverse Effects

Adverse Reaction	Tablets	Injection	Placebo
Abdominal pain	14%	29%	10%
Diarrhea	5%	6%	2%
Nausea		12%	5%
Dizziness		7%	2%

RELISTOR® package insert.

Methylnaltrexone – Clinical Efficacy

- OIC – CNCP (oral)
  - Defined as <3 SBM/week and ≥1 of the following:
    - Bristol Stool Form Scale of 1 or 2 for ≥25% of BMs, straining during ≥25% BMs or feeling of incomplete evaluation after at least 25% of BMs
  - Responder:
    - ≥3 SBM/week
    - An increase of ≥1 SBM/week over baseline, for ≥3 out of the first 4 weeks of the treatment period
  - Oral methylnaltrexone 52% responders (450 mg po qd) vs 38% placebo
  - NNT = 8

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Methylnaltrexone – Clinical Efficacy

- OIC – CNCP (SQ)
  - 4 weeks methylnaltrexone SQ therapy vs placebo
  - Constipation defined as ≥1 of the following:
    - Bristol Stool Form scale score of 1 or 2 for ≥25% BMs
    - Straining during ≥25% BMs
    - Sensation of incomplete evacuation after ≥25% of BMs
  - Responder: proportion of patients ≥3 SBMs per week x 4 weeks
  - Methylnaltrexone 12 mg SQ daily: 59% response
  - Placebo: 38% response

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Methylnaltrexone – Clinical Efficacy

- OIC – Advanced Illness (SQ)
  - Study 4
    - Methylnaltrexone 0.15 mg/kg SQ, 0.3 mg/kg SQ, placebo
    - In addition to usual laxative regimen
    - Endpoint: proportion of patients with rescue-free laxation within 4 hours of dose
    - Methylnaltrexone: 58%-62% patients; placebo: 14%

RELISTOR® package insert.

Methylnaltrexone – Clinical Efficacy

- OIC – Advanced Illness (SQ)
  - Study 5
    - Methylnaltrexone SQ 0.15 mg/kg every other day for 2 weeks (could increase to 0.3 mg/kg in second week) vs placebo
  - Endpoint: proportion of patients with a rescue-free laxation within 4 hours of first dose, and proportion of patients with a rescue-free laxation within 4 hours after ≥2 of the first 4 doses
  - Outcomes: within 4 hours of first dose; methylnaltrexone 48% vs 16%
  - After second of 4 doses; methylnaltrexone 52% vs placebo 9%

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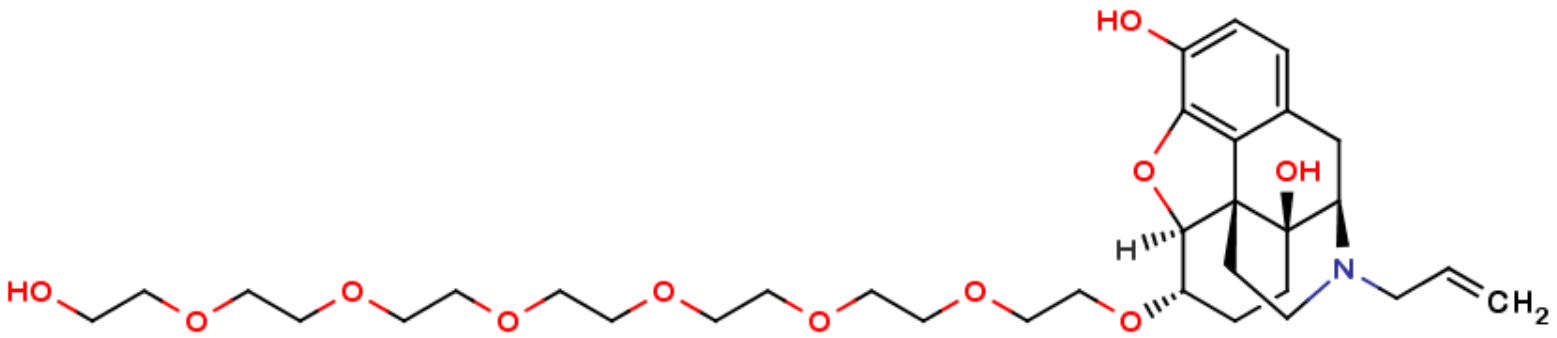
Methylnaltrexone: Cost

- SQ methylnaltrexone 12 mg daily
  - CNCP: NNT = 4
  - Advanced Illness: NNT = 2-3
  - Methylnaltrexone 12mg SQ daily
  - $120 per dose
- Cost for oral methylnaltrexone – ??

Michna, Blonsky, Schulman, et al. *J Pain*. 2011;12(5):554-562.

Naloxegol

- OIC in adults with CNCP
  - 25 mg po QAM on an empty stomach
    (may reduce to 12.5 mg or with CLcr <60ml/min)
  - Discontinue laxatives prior to use, may use if no response to treatment after 72 h



Polyethylene glycol derivative of naloxone; PEG moiety reduces BBB permeability

MOVANTIK® package insert.

Naloxegol

- Contraindications
  - Gastrointestinal obstruction or those at high risk
  - Concomitant use of strong CYP3A4 inhibitors (clarithromycin, ketoconazole)
- Precautions/warnings
  - Opioid withdrawal, severe abdominal pain/diarrhea, GI perforation, moderate-strong 3A4 inducers or inhibitors
- Drug interactions
  - Avoid concurrent use of moderate CYP3A4 inhibitors; grapefruit juice (13x fold increase!)
- Adverse effects
  - Abdominal pain, nausea, diarrhea, headache, back pain

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Naloxegol Clinical Efficacy

- Study 1 and 2
  - Constipation defined as <3 SBM/week on average with ≥25% of SBMs associated with ≥1 of the following: straining, hard or lumpy stools, sensation of incomplete evacuation
  - Primary endpoint – ≥3 SBMs/week and a change from baseline of ≥1 SBM per week for ≥9 of the 12 study weeks and 3 out of the last 4 weeks
  - Time to first postdose SBM

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Naloxegol Clinical Efficacy

	Placebo	12.5 mg	25 mg
Study 1: % patients responding	29%	41%*	44%*
Study 2: % patients responding	29%	35%	40%*

- Median times to first postdose SBM in Study 1:
  - 25 mg – 6 hours
  - 12.5 mg – 20 hours
  - Placebo – 36 hours
- Median times to first postdose SBM in Study 2 were:
  - 25 mg – 12 hours
  - Placebo – 37 hours

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Naloxegol Adverse Effects and Cost

Adverse Reaction	25 mg qd	12.5 mg qd	Placebo
Abdominal pain	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%

- NNT in clinical trials 7-10 (about 8)
  - Naloxegol 25mg po QAM
  - $300.00 per 30 tablets

MOVANTIK® package insert.

Self-Assessment!

- Which of the following bowel preparations acts by blocking the mu opioid receptor in the gut to prevent constipation?
  A. Senna
  B. Magnesium sulfate
  C. Methylnaltrexone
  D. Linaclotide

Self-Assessment!

- Which of the following bowel preparations acts by blocking the mu opioid receptor in the gut to prevent constipation?
  A. Senna
  B. Magnesium sulfate
  C. Methylnaltrexone
  D. Linaclotide

Switching Gears…Diarrhea!

- Diarrhea is less common than constipation in the palliative care population
  - Occurs in 7%-10% hospice patients
  - Up to 50%-80% of patients on certain chemotherapies
- Can cause dehydration, electrolyte imbalance, malnutrition
  - Can compromise wound healing and immune function
  - Hypokalemia, metabolic acidosis, altered pharmacokinetics of medications
- Defined as loose stools with increased frequency
  - >3 loose stools in 24 hours
  - Water content >75%
  - Increased stool weight of >200 g

Causes of diarrhea

Category	Examples
Motility	Obstructive tumors, hyperthyroidism, diabetic autonomic neuropathy, irritable bowel syndrome, postvagotomy diarrhea, celiac plexus blockade
Osmotic	Pancreatic insufficiency, hypoalbuminemia, celiac disease, lactase insufficiency, small intestine bacterial overgrowth, dietary, nonabsorbable sugars, phosphate products, magnesium products, tube feeds, chemotherapy reactions (eg, 5-FU), radiation therapy
Inflammatory	Infection, invasive bacteria, ulcerative colitis, Crohn's radiation therapy, craft vs host, chemotherapy
Secretory	Infection, viral, noninvasive bacteria, protozoal, HIV, ulcerative colitis, microscope colitis, chemotherapy reactions, neuroendocrine tumors, VIPomas, gastrinomas, carcinoid
Medications	Laxatives, antibiotics, antiretrovirals, magnesium-containing antacids, metformin, levothyroxine, statins, metoclopramide, NSAIDs, myophenolate, proton pump inhibitors, cholinesterase inhibitors, chemotherapy (5-FU, irinotecan, capecitabine, docetaxel), targeted therapy (erlotinib, gefitinib, sorafenib, sunitinib, imatinib, bortezomib), immunotherapy (ipilimumab, nivolumab)

Agrawal, Shish. Constipation. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Assessment and Treatment of Diarrhea

- Complete history; consider patient's self-reported history of bowel movements
- Physical exam, abdominal exam
- Lab tests if secondary causes suspected
- General supportive care
  - Mild acute symptoms – rehydration is main focus; oral route preferred
  - Start with clear liquids; avoid dairy
  - Rule out *C. difficile*; consider probiotics

Symptomatic Management of Diarrhea

- Opioid agonists
  - Loperamide: duration 8-16 hours; start at 4 mg, then 2 mg after each loose stool
  - (max 16 mg per day)
    - Reduces peristalsis in the colon, decreases secretion in the GI tract, increases anal sphincter tone
  - Diphenoxylate: less effective; crosses blood-brain barrier
- Somatostatin medications (eg, octreotide): 100-200 ug tid SQ
- Specific etiologies
  - Antibiotics as appropriate
  - Cholestyramine (ileal resection and chologenic diarrhea)
  - Pancreatic enzymes
  - Serotonin antagonists (methysergide, cyproheptadine)
- Other therapies: PG inhibitors, bismuth subsalicylate

Agrawal, Shish. Constipation. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

Conclusions

- Both constipation and diarrhea can be a cause of distress for palliative care patients
- Constipation may be related to nausea, delirium, urinary obstruction, anorexia
- Consider etiology in choosing therapeutic intervention
- Consider opioid-induced constipation specifically
- Loperamide is a first-line agent for diarrhea
- Octreotide may be useful for more severe diarrhea

Agrawal, Shish. Constipation. In: Bruera et al. *Textbook of Palliative Medicine and Supportive Care*, 2021.

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Gastrointestinal Symptoms – Part 1

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