Un-bowel-ievable Constipation: Management of Opioid-Induced Bowel Dysfunction

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Meet the Speaker

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Disclosure

- Haleon Consumer Health—Pain Advisory Board, Symposium Speaker
- None of the planners for this activity have relevant financial relationships to disclose with ineligible companies.

Abbreviations

- AAPM: American Academy of Pain Medicine
- AGA: American Gastroenterological Association
- AE: Adverse Effect
- CI: Confidence Interval
- DB-RCT: Double blind, randomized controlled trial
- D/c'd: Discontinued
- ESMO: European Society for Medical Oncology
- MASCC: Multinational Association for Supportive Care in Cancer
- TDB: Transdermal Buprenorphine
- TDF: Transdermal Fentanyl
- OIBD: Opioid-Induced Bowel Dysfunction
- OIC: Opioid-Induced Constipation
- OINV: Opioid-Induced Nausea and Vomiting
- PO: oral
- PONV: Post-operative nausea and vomiting
- SBM: Spontaneous Bowel Movement
- SC: Subcutaneous
- QOD: Every other day

Objectives

1. Describe the burden of opioid-induced bowel dysfunction (OIBD) in patients with chronic non-cancer pain and cancer pain
2. Explain the pathophysiology of OIBD and opioid-induced constipation (OIC) and associated clinical features
3. Review clinical guidelines and clinical evidence for the management of OIC in cancer and non-cancer populations
4. Discuss the pharmacological tools in our OIC toolkit, including traditional laxatives, peripheral-acting mu opioid receptor antagonists (PAMORAs) and other therapies with novel mechanisms

Opioid Induced Bowel Dysfunction (OIBD)

Manifests with symptoms throughout the GI tract:

- **Constipation (OIC)**
- **Nausea/Vomiting (OINV)**
- Heartburn and acid reflux
- Postprandial epigastric distention
- Epigastric pain
- Sensation of low and/or incompletion digestion
- Bloating and/or flatulence
- Abdominal pain

De Giorgio et al. Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel. Adv Ther. 2021 Jul;38(7):3589-3621

Pain Medicine 2017; 18: 1837–1863

Gastroenterology 2019; 156: 218-226

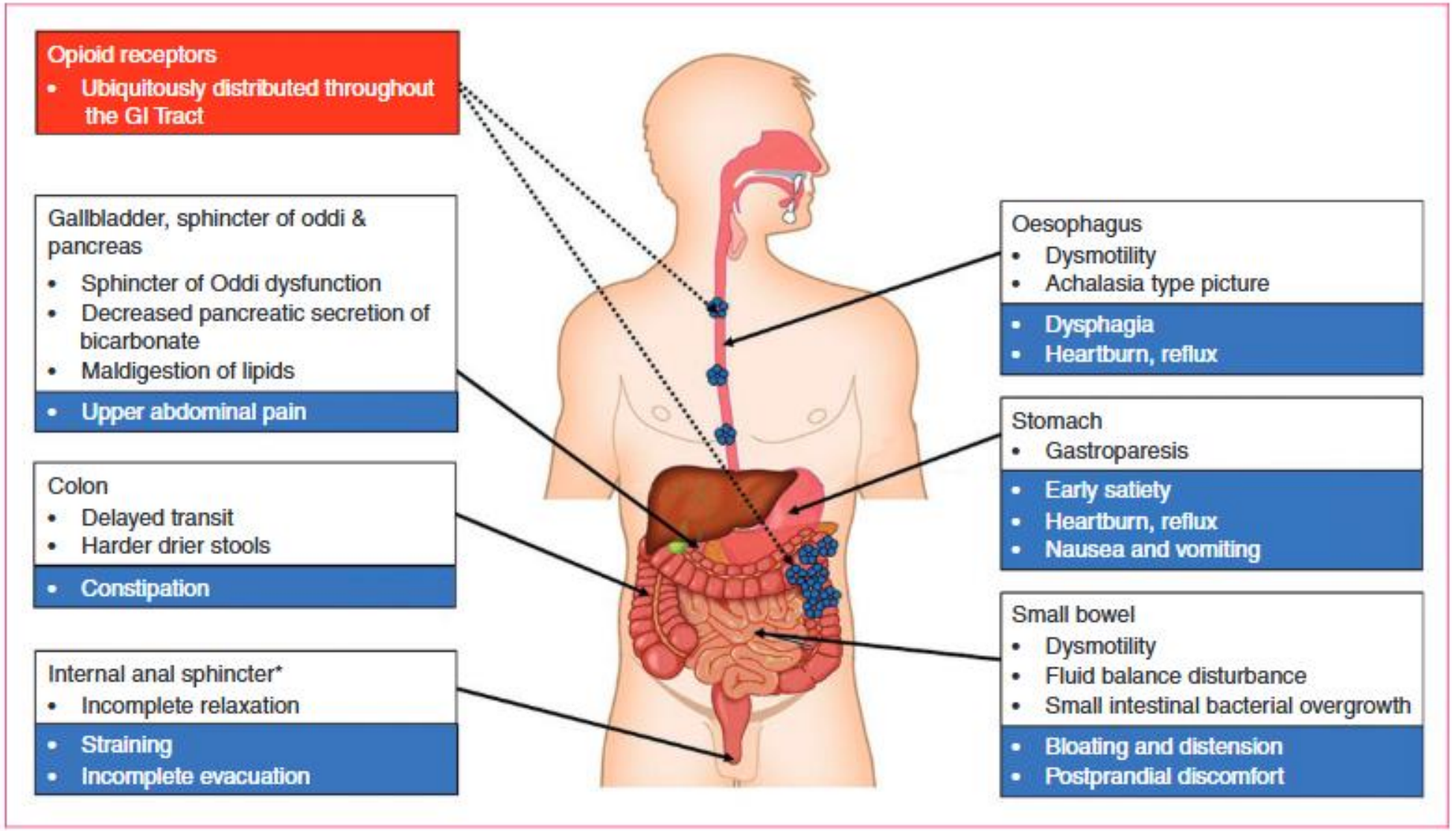
Curr Gastroenterol Rep. 2013 September ; 15(9): 344.

OIBD: Many faces

- Patients on opioids with multiple symptoms but OIBD is not recognized

- Patients on opioid and aware of constipation and may be reluctant or reducing opioid use
- OIC is recognized

Opioid-induced effects on the Gastrointestinal (GI) System



Reproduced from Jan Tack, Bart Morlion, Tony O'Brien, et al . Pathophysiology and management of opioid-induced constipation: European expert consensus statement. United European Gastroenterology Journal 2019; 7(1): 7-20 with permission from John Wiley and Sons

Opioid Induced Constipation (OIC)

Opioid-Induced Constipation (OIC):

- Rome IV definition
- Consensus 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 evaluation,
  - or harder stool frequency.”

OIC prevalence:

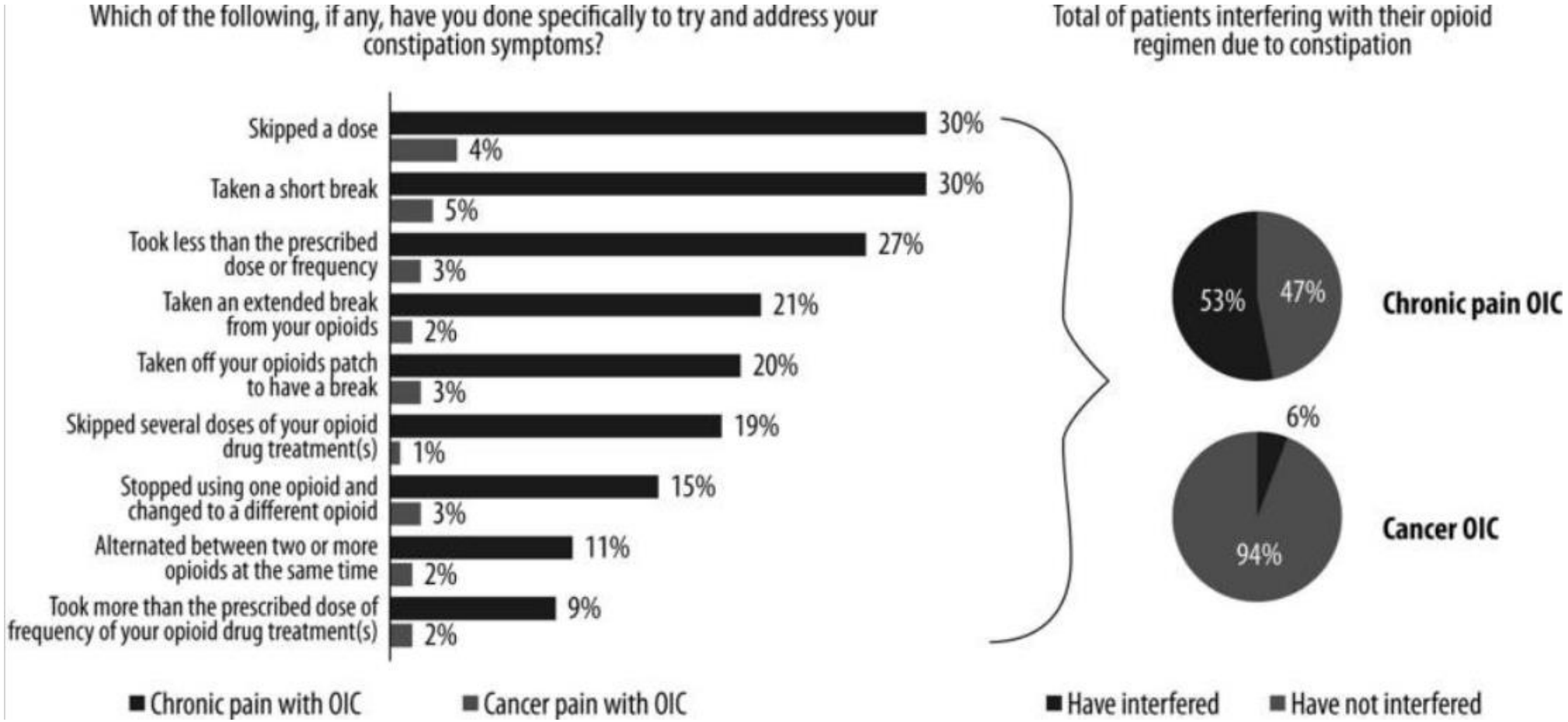
- Cancer and palliative care populations: 51-87%
- Chronic non-cancer pain: 41-57%

Pain Medicine 2017; 18: 1837–1863

Gastroenterology 2019; 156: 218-226

Curr Gastroenterol Rep. 2013 September ; 15(9): 344.

The impact of OIC on pain management



Pain Ther. 2021 Dec;10(2):1139-1153

Rates of OINV

- OINV within 72 hours after opioid administration
  - Nausea ~30-40%
  - Vomiting ~15-25%
- Not uncommon with initiation of opioid therapy or with dose titration
  - Generally, tolerance develops within 3-7 days (at the same opioid dose)

Chronic OINV?

MJA 1999; 170: 68-71

JPSM 1991; 6(6): 389-393
J Pain Symptom Manage. 1991;6(7):428-430

Weissman DE. Fast Fact: Opioids and Nausea, 2015;
https://www.mypcnow.org/fast-fact/opioids-and-nausea

Current Pharmaceutical Design 2012; 18: 6043-6052
J Am Assoc Nurse Pract 2017; 29: 704-710

Pain Medicine 2017; 18: 1837–1863

United European Gastroenterology Journal 2019; 7(1): 7-20

Chronic OINV

OINV ***may not*** always be a *short-lived* side effect:

- 3 year U.S. registry study of 233 patients on oxycodone CR (mean: 52.5 mg/day) for *non-cancer pain* (*Clin J Pain* 2007; 23: 287-299)
  - The most common adverse effects were constipation (15%) and nausea (12%)
  - Nausea greatest within the first 3 months
  - Small majority had persistence of nausea over years

- Prospective, open-labeled studies of outpatients with *cancer pain* on stable doses
  - 33% of patients on hydromorphone or morphine had nausea and emesis over 4-5 months (*Support Care Center* 2008; 16:999-1009)
  - 21% of patients taking transdermal buprenorphine, fentanyl, or controlled release hydromorphone had nausea/emesis despite long term therapy (*Eur J Pain* 2009: 13: 737-743)

Opioid-Induced Esophageal Dysfunction (OIED)?

FDA NEWS RELEASE

FDA Requires Major Changes to Opioid Pain Medication Labeling to Emphasize Risks

Labeling change will affect all opioid pain medications and support more informed decision-making

For Immediate Release: July 31, 2025

5.x Risk of ~~Use in Patients with~~ Gastrointestinal ~~Conditions~~ Complications

[TRADENAME] is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The [drug] in [TRADENAME] may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including pancreatitis, for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate.

https://www.fda.gov/media/187944/download?attachment

https://www.fda.gov/news-events/press-announcements/fda-requires-major-changes-opioid-pain-medication-labeling-emphasize-risks

Dose Adjustment

1. For patients with OINV, opioid dose reduction (10-20% reduction) may be tried to reduce OINV while maintaining analgesia.
2. Dose reduction may not be appropriate for management of OIC for patients requiring daily opioid use.

<u>Supporting Principles:</u>

1. OINV appears to increase in a dose-dependent manner. This may be due to effects on the CTZ or GI tract.
2. The opioid dose that produces constipation may only be 25% of that required for adequate analgesia

Palliative Medicine 1999; 13: 159–160

JAMA.2007;298(10):1202

BMJ 1998;317 (7150):81

J Clin Oncol 2001; 19:2542-2554.

Curr Gastroenterol Rep. 2013 September ; 15(9): 344.

Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD006332.

Anesth Analg 2005; 101: 1343-1348

Anesth Analg 2020; 131: 411-448

Pharmacotherapy 2002; 22(2):240-250

Opioid Switching

- Opioid rotation may be considered in patients on stable opioid regimens experiencing OINV

- <u>Supporting Principles:</u>
  1. Given incomplete opioid cross-tolerance, opioid rotation may facilitate a lower dose of another opioid and potentially reduce incidence of OINV
  2. Specific opioids *may* be associated with a lower incidence of OINV
  3. The type of pure mu opioid agonist does not influence prevalence of OIC symptoms *

*Less OIC with tapentadol vs oxycodone

Pain Medicine 2017; 18: 1837–1863

Expert Opin. Pharmacother. 2010; 11(11):1787-1804

Pharmacotherapy 2002; 22(2):240-250

Can We Rank the Emetogenicity of Opioids?

- Theory: low opioid doses activate MOR in the CTZ but "high doses" may suppress emesis by a central mechanism in the vomiting center
  - Emetogenic potential of various opioids may then be inversely related to ***lipid solubility*** of the opioid
    - fentanyl's lipid solubility >> morphine

Retrospective Study of Mod-Severe Nausea 72 hours after Oral Opioid Initiation	Nausea in Cross-Over Randomized Controlled Trials(RCT)	Nausea/Vomiting in Open-label Trial of Outpatients with Cancer on Long Term Opioid Therapy	Nausea and Vomiting in RCT of Cancer Patients on Weak Opioids
• Morphine ≈ Codeine > Oxycodone > Buprenorphine	• Morphine > oxycodone • Oral morphine > IV morphine PCA • Oral morphine sustained release > transdermal fentanyl (TDF)*	• Oral morphine > oral hydromorphone • Oral hydromorphone CR > transdermal fentanyl > transdermal buprenorphine**	• Tramadol > Codeine > Hydrocodone

*constipation also better with TDF

**for vomiting only, no difference in nausea; in a network meta-analysis of cancer/non-cancer pain, significantly less nausea with TDB than TDF but similar rate of constipation

Clin Pharmacol Ther 1990; 47: 639-646

J Pain Symptom Manage 1997; 13(5): 254-261

Eur J Pain 2009: 13: 737-743

Curr Med Res Opin 2012, 28:5, 833-845

Opioid Switching in Cancer Patients with OINV: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
Morphine→Oxycodone (*weak recommendation*)	Morphine→Oxycodone or Hydromorphone (*weak recommendation*)
Tramadol→Codeine or Hydrocodone (*weak recommendation*)	Transdermal Fentanyl→Methadone (*weak recommendation*)
Morphine or oxycodone→methadone using three-day switch method (*weak recommendation*)	

Changing the Route of Administration

- Changing the route of opioid administration may partially alleviate symptoms of OINV or OIC

- <u>Supporting Principles:</u>
  1. Oral opioids theoretically may have a local effect on the GI tract, and therefore parenteral (intravenous or subcutaneous) or transdermal opioids may reduce symptoms of OINV*
  2. Due to first pass metabolism, oral morphine may produce greater plasma concentrations of metabolites (M6G) versus parenteral administration, which may contribute to OINV?
  3. Transdermal preparations of fentanyl and buprenorphine may be associated with lower incidence of OIC than oral opioids*

*Transdermal opioid will *still* reach the intestinal circulation and enteric nervous system to effect motility…but more uniform blood concentration with reduced peaks may be an advantage

Eur J Clin Pharmacol 1990; 38:121-124
Pain Medicine 2017; 18: 1837–1863

J Pain Symptom Manage 1997;14:157-167
Pharmacotherapy 2002; 22(2):240-250

Changing Route of Opioid Administration on OINV: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
No recommendations could be made based on available literature	Oral morphine→ SC morphine *(weak recommendation)*

Oral→ Subcutaneous (SC)

Palliat Med 1991; 5: 323-329: Prospective study of 164 patients with advanced cancer, changing from *oral morphine to intermittent (q4h) SC dosing reduced OINV*

Intermittent SC → Continuous SC

Pain 1989; 36: 169-176: Prospective controlled study of 36 inpatients with severe nausea or drowsiness on intermittent oral or subcutaneous (SC) morphine had *improvement in OINV with continuous subcutaneous morphine*

Oral → Transdermal

Eur J Pain 2009: 13: 737-743: Open-label trial of outpatients with cancer; *less emesis observed with transdermal products (buprenorphine and fentanyl) than controlled release oral hydromorphone*

Medications that Cause Nausea and Vomiting

Mechanism of N/V	Drug Class	
Stimulation of the CTZ	Acetylcholinesterase inhibitors Antibiotics *Chemotherapy* Dopaminergic Agents Digoxin	Nicotine Opioids Theophylline SSRIs/SNRIs
Gastric irritation and activation of vagal afferent nerves	Alcohol abuse Antibiotics Corticosteroids (also due to adrenal insufficiency)* Erythromycin Iron supplements	NSAIDs Potassium supplements Salicylates
Activation of 5-HT3 receptors on vagal afferent nerves	Antibiotics *Chemotherapy* SSRIs/SNRIs	
Gastric Stasis (may be cause of chronic nausea)	Anticholinergics Glucagon-like peptide (GLP)-1 agonists Opioids	

Curr Ther Res Clin Exp 2003; 64(4): 216–235.

J Support Oncol 2013;11:8 –13

https://www.palliativedrugs.com/formulary/en/anti-emetics.html

Koch KL, Hasler WL, eds. Nausea and Vomiting: Diagnosis and Treatment. 2017.

Gastroenterology 2001; 120: 263-86





Medications that Contribute to Constipation

- Opioid Analgesics
- Serotonin (5HT-3) Antagonists (eg ondansetron)
- Cation-containing agents (iron, antacids, sucralfate)
- Diuretics
- Anticholinergic Agents
  - Antihistamines
  - Antispasmodics (all urinary antispasmodics except mirabegron, dicyclomine, cyclobenzaprine, orphenadrine)
  - Scopolamine, meclizine, promethazine
  - Antidepressant
    - Tricyclics (amitriptyline, nortriptyline, etc)
    - Paroxetine
  - Antipsychotics (olanzapine, quetiapine, etc)
- Antihypertensives (verapamil, diltiazem, clonidine)
- Anticonvulsants (carbamazepine, phenytoin)
- Antidiarrheal (loperamide, Pepto-Bismol)
- Cancer therapies
  - Chemotherapy: vinca alkaloids (eg vincristine)
  - ALK inhibitors (alectinib, crizotinib)
  - Antibody drug conjugates (adotrastuzumab emtansine, fam-trastuzumab deruxtecan)
  - Proteasome Inhibitors (bortezomib)
  - Immunomodulator (thalidomide, pomalidomide)
  - Monoclonal antibody (elotuzumab)
  - Others (temozolomide, entrectinib, futibatinib)

Annals of Oncology 29 (Supplement 4): iv111–iv125, 2018

Guideline Recommendations:		AAPM 2017	European Expert 2019	AGA 2019
		OIC, non-cancer		
Lifestyle	*Fiber*	Yes, standard intake	Yes, examine intake	Yes, if fiber-deficient diet
	Fluid	Yes, standard intake	Yes, examine intake	Yes, increase fluid intake
	Exercise	No recommendation	Yes, examine activity	Yes, moderate exercise
Opioid	*Switch opioid*	Yes, 1st line option: consider TDF, TDB, tapentadol, oxy/nalox	Yes, *last* line consider TDF or tapentadol	Yes, switch to TDF or oxycodone /naloxone ER
	Reduce opioid dose	"review dose of opioid"	Not discussed	"Minimum necessary dose"
Stimulant	*Senna, bisacodyl*	Yes, 1st line option	Yes, 1st line option/*consider prophylactic use*	Yes, 1st line option
Osmotic	*Polyethylene glycol*	Yes, 1st line option		Yes, 1st line option
Avoid	*Traditional laxative*	Lactulose and sorbitol	Lactulose	Bulking agent; fiber suppl
Novel	*PAMORA*	Yes, 1st line option: consider in cancer and non-cancer pain	Yes, 2nd line if OIC, 3rd line test treatment if mixed etiology	Yes, 3rd line strong for naldemedine, naloxegol; conditional for methylnaltrexone
	5HT4 Agonist	No, insufficient evidence	3rd line in combo with PAMORA; 4th line in combo with PAMORA if mixed etiology	No, insufficient evidence
	Chloride ion Secretagogues	No, insufficient evidence		No, insufficient evidence
Combo	*Two laxatives*	2nd line option	2nd line if mixed etiology	2nd line: favor 2 scheduled laxatives before PAMORA
	Laxative + PAMORA		Consider if PAMORA alone ineffective	No recommendation, data limited

Pain Medicine 2017; 18: 1837–1863 United European Gastroenterology Journal 2019; 7(1): 7-20 Gastroenterology 2019; 156: 218-226

Guideline Recommendations:		ESMO 2018	MASCC 2019
		Constipation in advanced cancer	
Lifestyle	*Fiber*	Avoid in older, non-ambulatory	No, limited role in cancer patients and OIC specifically
	Fluid	Yes, within patient limits (limited impact)	
	Exercise		
Opioid	*Switch opioid*	"review choice of opioid" Consider naloxone/opioid combination	Yes, may consider
	Reduce opioid dose	"reducing opioid dose is ineffective"	No, "does not improve OIC"
Stimulant	*Senna, bisacodyl*	Yes, 1st line option for *prophylactic use* with opioid	2nd line option (add or switch)
Osmotic	*Polyethylene glycol*		Yes, 1st line in advanced cancer (expert opinion); volume of fluid may limit use; *prophylactic use*
Avoid	*Traditional laxative*	Bulk laxatives, stool softner, mineral oil	Suppository/enema unless lack of response to other agents
Novel	*PAMORA*	Yes, in "unresolved OIC"	Yes, "always consider"
	5HT4 Agonist	Not discussed; no recommendation	Consider adding or switching to if inadequate response to PAMORA
	Chloride ion Secretagogues		
Combo	*Two laxatives*		
	Laxative + PAMORA		Not discussed

Annals of Oncology 29 (Supplement 4): iv111–iv125, 2018

Supportive Care in Cancer (2020) 28:23–33

Laxative Class	Examples	Onset of Action	Site of Action	Mechanism of Action	Precautions/Comments
Osmotic	Polyethylene Glycol	48 h	Small and large intestine	Produce an osmotic-directed influx of fluid intestine, increasing peristalsis and softening stool. Mainly osmotic action	17g daily (maximum 34 g daily)
	Magnesium citrate, magnesium hydroxide (Milk of Mag)	30 min to 3 h			Excessive doses can lead to hypermagnesemia Avoid /cautious use in renal impairment
	Lactulose	24-48 h	Colon		Fermented by microbiota within the colon and exacerbate gas, bloating and distension. Patients may also have intolerance to sweet taste and nausea
Stimulant	Senna	6-10 h	Colon	Prokinetic action in the colon by irritating sensory nerve endings; reduce colonic water absorption	Converted to active molecules by colonic bacteria Little evidence that routine use of stimulant laxatives is harmful to the colon
	Bisacodyl tablet	6-10 h	Colon		
	Bisacodyl supp	15-60 min			
Bulk-Forming	Psyllium (Metamucil) Methylcellulose (Citrucel)	12-24 h (up to 72 h)	Small and large intestine	Holds water in stool, leading to mechanical distention	Requires fluid volume and impact wanes over time; not recommended for OIC
Surfactant stool softeners	Docusate	24-72 h	Small and large intestine	Lower the surface tension of stool, allowing water and lipids to penetrate and soften stool	Little evidence to support use

Peripheral Acting Mu-Opioid Receptor Antagonist (PAMORA)

- Do not enter the CNS
  - Avoid in conditions that compromise the blood-brain barrier?
    - Primary brain malignancies
    - CNS metastases
    - Advanced Alzheimer's
- Block mu-opioid receptors in the gut, restoring the function of the enteric nervous system
  - Antagonism of mu-receptors reverse the effect of opioids on the esophagus and stomach, increases gut motility in the intestine, and reduces effect of opioids on sphincter function
  - The onset action of PAMORAs is ≤ 1 week for all
  - Response to PAMORA *may* be affected by dose and previous response to laxatives
    - Greater response with higher opioid doses and in "laxative refractory"

Clinical Gastroenterology and Hepatology 2018;16:1569–1584

Pain Medicine 2017; 18: 1837–1863

Gastroenterology 2019; 156: 218-226

Clin J Pain 2019;35:174–188

Curr. Treat. Options in Oncol. (2021) 22: 26

Peripheral Acting Mu-Opioid Receptor Antagonist (PAMORA)

- **Contraindicated in known or suspected GI obstruction and in patients at risk for recurrent obstruction**
- **<u>Caution in patients with impaired integrity of the GI tract wall:</u>**
  - **Diverticular disease**
  - **Infiltrative GI tract malignancies**
  - **Peritoneal malignancies**
  - **Ischemic colitis**
  - **Recent GI surgery**
  - **Ogilvie syndrome**
  - **Peptic ulcer disease**
  - **Crohn's disease**
  - **Concurrent treatment with bevacizumab**
- <u>Cardiovascular safety signal with alvimopan (use for post-op ileus) is not specific to PAMORA class</u>

Common Adverse Effects:

- Nausea
- Diarrhea
- Abdominal Pain
- Distention
- Flatulence

Clinical Gastroenterology and Hepatology 2018;16:1569–1584

Gastroenterology 2019; 156: 218-226

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Clin J Pain 2019;35:174–188

Drug	MOA	FDA-approved Indication	Dosing	Take on empty stomach?	Renal Dosing	Hepatic Dosing	Metabolism	NNT*
Methyl-naltrexone (Relistor)	Quaternary ammonium derivative of naltrexone	OIC, advanced illness	Every other day as needed (max 1 dose/24 hours): <38 kg: 0.15 mg/kg SC 38 to <62 kg: 8mg SC 62 to 114 kg: 12 mg SC > 114 kg: 0.15 mg/kg SC	n/a	Yes	Yes	CYP2D6 (minor)	**3.4**
		OIC, non-cancer pain	12 mg SC daily 450 mg po daily	Yes, 30 min before 1st meal				
Naldemedine (Symproic)	Structurally related to naltrexone		0.2 mg po daily	Without regard to food	No	Avoid use (Severe impair-ment)	CYP3A4** (major)	**5**
Naloxegol (Movantik)	Pegylated naloxone		25 mg po daily in the morning; reduce to 12.5 mg if intolerance develops	Yes, 1 hour before 1st meal	Yes (12.5 mg daily but increase to 25 mg if well-tolerated)		CYP3A4** (major)	**7**
Lubiprostone (Amitiza)	Chloride Channel Secretagogue		24 mcg po twice daily	With food	No	Yes	n/a	**15**

*Risk of failure to respond vs placebo
**Contraindicated with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin); avoid with moderate inhibitors (diltiazem, verapamil, erythromycin, etc) and inducers (carbamazepine, St. John's wort, etc)*

Clin J Pain 2019;35:174–188
Clinical Gastroenterology and Hepatology 2018;16:1569–1584

Methylnaltrexone

Route	Dose	Indication	Evidence	Outcome Measure	Efficacy	NNT	Safety Concerns
SC	1 dose QOD <38 kg or >114 kg: 0.15 mg/kg SC 38 to <62 kg: 8 mg SC 62 to 114 kg: 12 mg SC	Advanced Illness	Meta-analysis of 2 RCTs (Slatkin 2009, Thomas 2008)	**Short term laxation** with 0.15-0.3mg/kg x 1 or 0.15 mg/kg QOD x 2 weeks	**SBM within 4 hours** *48% to 62%* vs 13% to 15% placebo group OR 6.95 (95% CI 3.83-12.61) **Time to laxation:** Single dose: median 1.1 hours Multiple-dose: median 6.3 hours **SBM within 24 hours** 52% to 68% vs 8% to 27% in placebo RR 2.97, 95% CI 2.13 to 4.13)	**3 (within 24 hours) 95% CI 2-3**	No difference in opioid withdrawal or analgesia AE vs placebo: SC RR 1.17 (95% CI 1.05 to 1.30) Abdominal pain, flatulence, nausea, and vomiting PO: AE similar to placebo
	12 mg SC daily	Chronic non-cancer pain	Meta-analysis 2 RCTs (Thomas 2008; Bull 2015)	**Medium term laxation** 0.15 mg/kg QOD x 2 weeks or weight-based (8-12 mg) x 2 weeks	**SBM within 2 weeks** RR 8.15 (95% CI 4.76 to 13.95)	**2 95% CI 2-2**	
PO	450 mg PO daily		1 DB-RCT (Rauck 2016)	**Short to medium laxation** 150, 300, or **450 mg/day** x r 4 weeks, then PRN x additional 8 weeks	**SBM within 4 hours with first dose** *450 mg (23.5%)* vs 8% placebo p< 0.0001) **SBM within 4 hours at 4 hours** 26.2% of doses vs 19.2% with placebo (P ≤ 0.05)	**6.7** **14.2**	

Pain Practice 2017; 17(6): 820–828
Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD003448. DOI: 10.1002/14651858.CD003448.pub3
Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD006332.

Counseling Points for SC Methylnaltrexone

- Be within close proximity to toilet facilities once administered.
- For subcutaneous use only.
- Inject in upper arm, abdomen or thigh. Rotate injection sites.

Methylnaltrexone {package insert]

Clin J Pain 2019;35:174–188

Oral PAMORAs

Drug	Study	Primary Endpoint	Result (% of Patients)			Median Time to Laxation	SBM within 24 hours	SBM within 72 hours
			Drug	Placebo	Statistically Significant?			
Naldemedine	Compose -1 Compose-2	≥ 3 SBM per week for 9 of 12 weeks	47.6%-52.5%	33.6%-34.6%	Yes	n/a	n/a	n/a
Naloxegol 12.5mg	KODIAC-04 KODIAC-05		40%	29%	Yes	20 h	58%	~75%
Naloxegol 25 mg			40-44%	29%	Yes	6-12h	61-70%	~90%

Movantik [Package Insert]

Lancet Gastroenterol Hepatol. 2017 Aug;2(8):555-564

N Engl J Med. 2014 Jun 19;370(25):2387-96

Clin J Pain 2019;35:174–188

Counseling Points for Oral PAMORA

- Educate on difference between PAMORA and traditional laxative
- Do not stop taking the PAMORA after have bowel movement
- Majority of patients have a response within 24 hours
- A fair trial is **3-**7 days
- Monitor for “over-response”: diarrhea, abdominal distress (cramping, pain)
  - Discontinue if severe symptoms, particularly severe, persistent, or worsening (concern for GI perforation)
  - Reduce dose if mild symptoms (naloxegol 12.5 mg)
  - Symptoms general occur within a few days of initiation
- Administration in regard to meals
- Advise patients to tell their healthcare provider when they start or stop taking any concomitant medications (naloxegol and naldemedine)

Clin J Pain 2019;35:174–188

Movantik {package insert]

Laxative + PAMORA?

Prescribing Information:

- Discontinue maintenance laxative therapy before starting PAMORA
- May resume laxatives if patients have OIC symptoms after taking PAMORA for 3 days

Clinical Practice:

- Continue laxative with PAMORA initiation if constipation multifactorial

OR

- Reduce laxative with PAMORA initiation

OR

- Stop laxative with PAMORA initiation

Curr. Treat. Options in Oncol. (2021) 22: 26

McPherson ML. Demystifying opioid conversion calculations. 2nd ed. Bethesda, MD: American Society for Health-System Pharmacists, Inc; 2018.

Transdermal Analgesics: Quick Comparison

Transdermal Opioid	Acute Pain	Chronic Pain	Opioid Naïve Dosing	Opioid Tolerant Dosing*	Max Dosing	Patch Change	Lag Time to Benefit	Phase I Metabolism	Active Metabolite
Fentanyl	✗	✓	✗	✓	✗	Every 72 hours	12-24 hours	✓	✗
Buprenorphine	✗	✓	✓	✓	✓	Weekly	72 hours	✓	✗

* ***For transdermal fentanyl***, patients must be taking the following **daily** for **1 week or longer, the equivalent of 60 mg of oral morphine/day**

* ***For transdermal buprenorphine***, patients using **>80mg of morphine equivalents** are **NOT** candidates for this formulation

Buprenorphine

Partial mu-opioid receptor agonist	• Potent analgesia • Dose-related ceiling effect on respiratory depression and euphoria ⬇ Risk opioid overdose (risk increases when combined with alcohol, benzodiazepines, other central nervous system depressants [CNS]) ⬇ Addiction, tolerance, withdrawal ⬇ Constipation, immune suppression, hypogonadism ⬇ Depression, suicidal ideation, dysphoria, anxiety
Kappa-opioid receptor antagonist	⬇ Depression, suicidal ideation, dysphoria, anxiety, hostility ⬇ Sedation, hyperalgesia, immune suppression, addiction, tolerance
Delta-opioid receptor antagonist	• Anti-opioid effects, myocardial protection ⬇ Constipation, respiratory depression
Reduced affinity for orphan-like receptor 1 (ORL-1)	• Increased spinal analgesia ⬇ Supraspinal analgesia, opioid rewarding effects, tolerance
Blocks monoamine reuptake	• Not associated with serotonin syndrome

https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/IB_1497_Provider_BupChronicPain.pdf

Buprenorphine

- Available parenteral (for acute pain), transdermal or buccal (for chronic pain) and sublingual (for opioid use disorder)
  - **Transdermal buprenorphine (Butrans)**
  - Buccal film (Belbuca)
- Advantages of buprenorphine for pain:
  - Potentially less adverse effects (nausea/vomiting, constipation, cognitive impairment, respiratory depression, immunosuppression, hypogonadism)
  - Better safety profile in elderly, renal impairment, and dialysis
  - Patch is worn for 7 days
  - Buccal film is long acting and dosed once or twice daily

Clin Ther. 2013;35:1669–1689

McPherson ML. Demystifying opioid conversion calculations. 2nd ed. Bethesda, MD: American Society for Health-System Pharmacists, Inc; 2018.

https://www.mypcnow.org/fast-fact/low-dose-buprenorphine-patch-for-pain/

Transdermal buprenorphine (Butrans) CIII

- Indicated for the treatment of moderate to severe chronic pain
  - Efficacy in cancer and non-cancer chronic pain, including osteoarthritis pain and chronic low back pain
- Dosage forms: 5, 7.5, 10, 15, 20mcg/hour transdermal patch
  - Maximum dose is 20 mcg/hr
  - Dosing should follow the manufacturer recommendations
- Rotate sites every 7 days
- IR opioids indicated in the first 72 hours of titration (time to steady state)
  - The patch should not be increased before 3 days; should wait a full week

Clin Ther. 2013;35:1669–1689

McPherson ML. Demystifying opioid conversion calculations. 2nd ed. Bethesda, MD: American Society for Health-System Pharmacists, Inc; 2018.

McPherson ML. Demystifying opioid conversion calculations. 2nd ed. Bethesda, MD: American Society for Health-System Pharmacists, Inc; 2018.

<u>Use of Transdermal Buprenorphine as the First Opioid Analgesic</u>
(opioid-naive patients): Initiate treatment with a 5 mcg/hour patch.

<u>Conversion from Other Opioids to Transdermal Buprenorphine:</u>
Discontinue all other around-the-clock opioid drugs when therapy is initiated.

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
Recommended BUTRANS Starting Dose	**5 mcg/hour**	**10 mcg/hour**

BUTRANS™ (buprenorphine) transdermal patch [package insert]. 2019

Prior Total Daily Dose of Opioid Between 30 mg to 80 mg of Oral Morphine Equivalents per Day: Taper the patient's current around-the-clock opioids for up to 7 days to no more than 30 mg of morphine or equivalent per day before beginning treatment. ***(because potential to cause withdrawal)*** Then initiate treatment with 10 mcg/hour patch at the next dosing

***Prior Total Daily Dose of Opioid Greater than 80 mg of Oral Morphine Equivalents per Day*:** The 20 mcg/hour patch may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic.

Morphine equivalent dose (MME)

Buprenorphine: oral MME (mg)/day

- 1 mg buccal: 50 mg MME
- 1 mg parenteral: 100 mg MME
- 1 mg sublingual: 30 mg MME
- 1 mg transdermal: 100 mg MME
  - 5 mcg/hr = 12 mg MME
  - 7.5 mcg/hr = 18 mg MME
  - 10 mcg/hr = 24 mg MME
  - 15 mcg/hr 36 mg MME
  - 20 mcg/hr = 48 mg MME

Support Care Cancer 2024:32(8):542



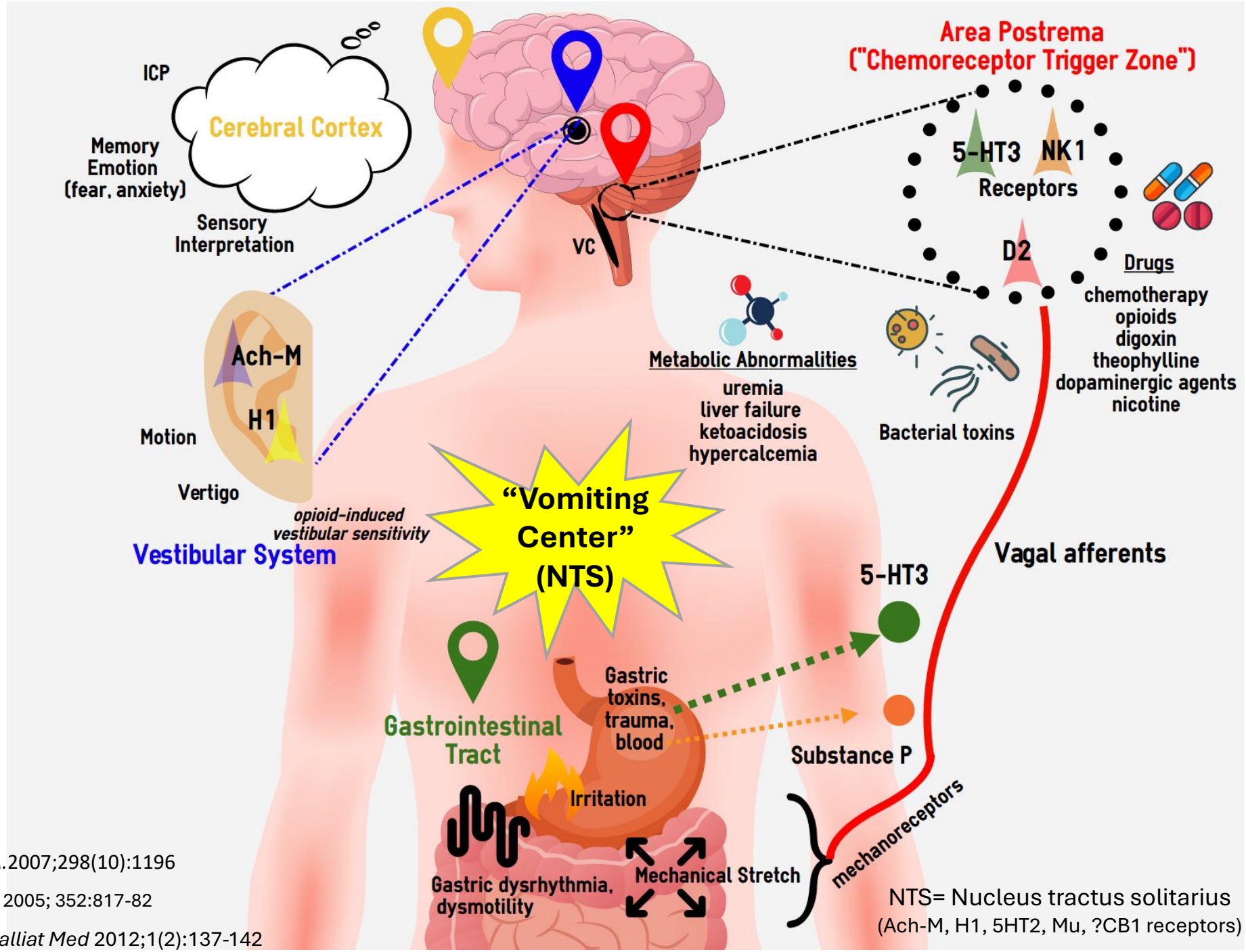


Use of Antiemetics

- Treatment of OINV or prophylaxis should be based on knowledge of neural pathways for OINV and other possible etiologies of nausea and vomiting.

- <u>Supporting Principles:</u>
    1. Limited randomized controlled studies exist to guide antiemetic selection. Dopamine D2 receptor may be most important target for OINV for acute OINV whereas abnormal GI motility/constipation may be the target for chronic OINV.
    2. Prophylaxis may be considered in patients with a history of OINV or in patients with significant risk factors for OINV.
        1. Risk factors (i.e. such as in PONV) and history of OINV may guide decision to use antiemetic prophylaxis.
        2. Match duration of prophylaxis to suspected duration of OINV (2-3 days after opioid initiation or titration)

J Pain Symptom Manage 1997;14:157-167 *Eur J Clin Pharmacol* 1990; 38:121-124 *Pharmacotherapy* 2002; 22(2):240-250



JAMA.2007;298(10):1196

NEJM 2005; 352:817-82

Ann Palliat Med 2012;1(2):137-142

NTS= Nucleus tractus solitarius
(Ach-M, H1, 5HT2, Mu, ?CB1 receptors)

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	*Possible Source of OINV*	*Drug Action Needed*	*Antiemetic Selection*
OINV with opioid initiation or dose increases **(*Acute OINV*)**	Direct stimulation of the CTZ with rising opioid levels (chemical source)	D2 blockade in the CTZ (preferentially)	*Butyrophenones* (Haloperidol) *Phenothiazines* (Prochlorperazine, Promethazine) *Atypical Antipsychotics* (Olanzapine, Risperidone) *Prokinetic Agents* (metoclopramide)*
		5HT3 blockade in the CTZ (in refractory cases or PONV prevention)	*Serotonin antagonists* (ondansetron, dolasetron, granisetron, palonesteron)

* At higher doses?

Pharmacotherapy 2002; 22(2):240-250
European Journal of Pharmacology 2014; 722: 67-78
Current Pharmaceutical Design 2012; 18: 6043-6052

Antiemetic	Dose (lower end for older adults)	Receptor Affinities (lower number= tighter binding)				Side Effects
		D2	5HT3	H1	Ach-M	
Prokinetics						
Metoclopramide	5-10 mg PO/IV/SC QID	++ (270)	+ (319)	- (1100)	- (10000)	Restlessness, drowsy, involuntary movement
Phenothiazines						
Promethazine	12.5-25 mg PO/ 25 mg PR q6h	++ (240)	- (-)	++++ (3)	+++ (21)	Sedation, anticholinergic SE, orthostasis
Prochlorperazine	2.5-10 mg IV/PO, 25 mg PR 3-4 x/day	+++ (15)	- (-)	++ (100)	+ (2100)	Sedation, orthostasis, involuntary movement
Atypical Antipsychotic						
Olanzapine	2.5-10 mg PO at bedtime	+++ (30)	++ (57)	+++ (7)	++ (76)	Sedation, orthostasis, anticholinergic & metabolic SE, ↑appetite
Butyrophenones						
Haloperidol	0.5-2 mg TID SC/IV = ½ PO	**++++ (4.2)**	- (-)	- (1600)	- (10000)	EPS, ↑QTc, ↑ mortality in dementia patients

NCCN Guideline Version 2.2021. Palliative Care. NCCN.org

Lancet 1982; 1 (8273): 658-659

JAMA.2007;298(10):1202

https://kidbdev.med.unc.edu/databases/pdsp.php

Palliative Care Perspectives,2003.

Clinical Inter in Aging 2011: 6: 249

Drugs 1992; 43 (3):295-315

Antiemetic	Dose (lower end for older adults)	Receptor Affinities (lower number= tighter binding)				Side effects
		D2	5HT3	H1	Ach-M	
5-HT3 Antagonists						
Ondansetron	4-8 mg PO/IV q6-8 h	- (-)	++++ (4)	- (10000)	- (10000)	Constipation, headache, ↑QTc
Agents for Vestibular Source						
Scopolamine	1.5 mg TD q 72h	- (10000)	- (-)	- (10000)	++++ (0.8)	Anticholinergic SE, delirium
Diphenhydramine	25-50 mg PO/IV/SC q 6h	- (10000)	- (-)	+++ (17)	++ (120)	Anticholinergic SE, delirium
Steroids						
Dexamethasone	2-4 mg PO/IV QAM-BID (↑ if ↑ ICP or brain mets)	- (-)	- (-)	- (-)	- (-)	Insomnia, anxiety, dyspepsia, ↑BG/BP, edema, appetite
Cannabinoids						
Dronabinol	2.5 mg PO BID (max 20 mg/d)	- (-)	- (-)	- (-)	- (-)	Dysphoria, hallucinations, delirium drowsiness

JAMA.2007;298(10):1196-1207
Palliative Care. NCCN.org
https://kidbdev.med.unc.edu/databases/pdsp.php
Tucker et al. *Managing Nonpain Symptoms*. AAHPM: Glenview, IL; 2012
Drugs 1992; 43 (3):295-315

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	*Possible Source of OINV*	*Drug Action Needed*	*Antiemetic Selection*
OINV stimulated by motion or rapid head movement, or dehydration May complain of poor balance, vertigo/dizziness, or ear ringing *(Acute OINV when opioids initiated or when patients are ambulating)*	Direct stimulation of the vestibular apparatus (vestibular source)	H1 blockade in the vestibular apparatus or vomiting center	*1st generation antihistamines* (Diphenhydramine, Meclizine, Hydroxyzine) *Antiemetics with activity vs* H1 (Promethazine, Olanzapine)
		Ach-M blockade in the vestibular apparatus or vomiting center	*Anticholinergics* (Scopolamine, Meclizine)

Pain Medicine 2009; 10(4): 654-662 *J Pain Symptom Manage* 1991; 6: 389-393
Hallenbeck, JL. *Palliative Care Perspectives. NY, NY:* Oxford Press, 2003. *Pharmacotherapy* 2002; 22(2):240-250 *Current Pharmaceutical Design* 2012; 18: 6043-6052

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	Possible Source of OINV (gastrointestinal source)	Drug Action Needed	Antiemetic Selection
Chronic nausea ~ 2 weeks or more of stable opioid doses	Opioid-induced gastroparesis and small bowel dysmotility	Regulation of upper bowel dysmotility; 5HT4 stimulation of GI tract	*Prokinetic Agent* (Metoclopramide)
Post-prandial bloating, early satiety, or small volume emesis 45 min-1 hour after a meal (suggestive of gastric stasis/delayed gastric emptying)	Gut distention with luminal contents leading to release of serotonin from mucosal enterochromaffin cells	5HT3 blockade in GI tract	*Serotonin antagonists* (ondansetron, *metoclopramide)*
	Opioid related effects on the colon, small bowel, and internal anal sphincter	Peristalsis-induction	*Stimulant Laxatives* (Senna, Bisacodyl) *Osmotic Laxatives* (polyethylene glycol)
Constipation, hard or dry stools		Peripheral mu opioid receptor antagonism	PAMORAs

Pain Medicine 2009; 10(4): 654-662 *J Pain Symptom Manage* 1991; 6: 389-393
Hallenbeck, JL. *Palliative Care Perspectives. NY, NY:* Oxford Press, 2003. *Pharmacotherapy* 2002; 22(2):240-250 *Current Pharmaceutical Design* 2012; 18: 6043-6052

Antiemetic Selection for OINV: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
"None of these studies provided sufficient evidence to formulate any recommendations."	"Current evidence is too limited to give evidence-based recommendations for the use of antiemetics for opioid-induced nausea or vomiting in cancer patients." "Recommendations must…be based upon knowledge about etiologies for nausea/vomiting and expert opinion."





Conclusion

- OIBD can have detrimental consequences, including suboptimal pain management, functional decline, and reduced quality of life
- Recognition and proper management of drug-induced side effects is important to reduce secondary burdens of opioid therapy