Guts & Glory: The Management of Nausea/Vomiting, Bowel Obstruction & Constipation in Palliative Care

Andrew C Knight, MD
Sault Ste Marie
April 10, 2015
Faculty/Presenter Disclosure: Slide 1

- **Faculty**: Andrew Knight, MD

- **Relationships with commercial interests:**
  - **Speakers Bureau/Honoraria**: Purdue Pharma
Disclosure of Commercial Support: Slide 2

- **Potential for conflict of interest:**
  - Andrew Knight, MD has previously received honoraria from Purdue Pharma whose product *oxycodone/naloxone controlled release tablet* is mentioned in this program.
Learning Objectives

• at the end of this presentation, participants will be better able to manage:
  – nausea & vomiting
  – bowel obstruction
  – constipation
Nausea & Vomiting
Neurophysiology

- cerebral cortex
- chemoreceptor trigger zone (CTZ)
- vestibular apparatus
- gastrointestinal tract
- vomiting centre
Neurophysiology of Nausea & Vomiting

Cerebral Cortex
- GABA, CB1

Chemoreceptor Trigger Zone
- D2, 5HT3, NK-1

Vomiting Centre
- H1, M1, 5HT2, NK-1

Gastrointestinal Tract
- D2, 5HT3, 5HT4

Vestibular Apparatus
- H1, M1

Adapted from G Fyles, 2008
Cerebral Cortex

• psychological, social & spiritual issues
• experience of “total pain”
• anxiety
• anticipatory nausea
• receptors:
  – γ-amino-butyric acid (GABA)
  – cannabinoid (CB1)
Cerebral Cortex

- benzodiazepines (lorazepam)

- cannabinoids:
  - nabilone (Cesamet®): 0.25, 0.5, 1mg capsules
  - dose: 1-2mg BID; max 6mg / 24h
  - *** caution in elderly

- Sativex® buccal spray: neuropathic central pain in MS
Intracranial Disease

- primary brain tumour
- metastatic disease
- leptomeningeal disease

- vasogenic edema, ↑ intracranial pressure
  → ? stimulation of vomiting centre (VC)
- steroids (dexamethasone)
- antihistamine (VC antagonist)
- radiation
Chemoreceptor Trigger Zone

- floor of 4\textsuperscript{th} ventricle (CSF & blood – poorly developed blood-brain barrier)
- toxins (ETOH)
- drug: opiates, SSRIs, digoxin, chemotherapy
- metabolic: renal failure, hypercalcemia
- infections: bacterial, viral
- receptors
  - dopamine (D2)
  - serotonin (5HT3)
  - neurokinin-1 (NK-1)
Vestibular Apparatus

- motion-induced nausea
- vertigo
- receptors:
  - histamine (H1)
  - muscarinic (M1)
Gastrointestinal Tract

- vagus nerve
- enterochromaffin cells
- chemoreceptors & mechanoreceptors
- malignant tumours
- bowel distension/ obstruction/ constipation
- radiation
- receptors:
  - dopamine (D2)
  - serotonin (5HT3 & 5HT4)
Vomiting Centre

- inter-related neuronal networks (medulla)
- final common pathway
- receptors:
  - histamine (H1)
  - muscarinic (M1)
  - serotonin (5HT2)
  - neurokinin-1 (NK-1)
## Anatomic Distribution of Receptors

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<tr>
<th>Receptor</th>
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(Modified from Twycross & Back, European Journal of Palliative Care, 1998; 5 (2), p 40.)
# Receptor Site Affinities of Selected Antiemetics

<table>
<thead>
<tr>
<th></th>
<th>Dopamine D2 antagonist</th>
<th>Histamine H1 antagonist</th>
<th>Acetylcholine (muscarinic) antagonist</th>
<th>5HT2 antagonist</th>
<th>5HT3 antagonist</th>
<th>5HT4 agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide (Maxeran®)</td>
<td>++</td>
<td>0</td>
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<tr>
<td>Domperidone (Motilium®)</td>
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<td>0</td>
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<td>Ondansetron (Zofran®)</td>
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<td>Hyoscine HydroBr (Scopolamine®)</td>
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<td>+++</td>
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<tr>
<td>Haloperidol (Haldol®)</td>
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<tr>
<td>Prochlorperazine (Stemetil®)</td>
<td>++</td>
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<td>0</td>
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<tr>
<td>Chlorpromazine (Largactil®)</td>
<td>++</td>
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<tr>
<td>Methotrimeprazine (Nozinan®)</td>
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“By the Ladder”

• Step 1: D2 antagonist

• Step 2: add 1st generation anti-histamine (H1, M1 & 5HT2)

• Step 3: add 5HT3 antagonist

• adjuvants: benzodiazepines, cannabinoids, steroids - add as indicated
D2 Antagonists

- metoclopramide* 10 - 20 mg po/ sq/ iv q6h
- domperidone* 10 mg po TID (↑QT Syndrome)
  (does NOT cross BBB but does act at CTZ)
- haloperidol: 0.5 – 2.5 mg po / iv / sq q8-12h
  *prokinetic agents
What About the Atypicals?

- 2\textsuperscript{nd} generation neuroleptics
- reduced incidence of EPS, etc
- olanzapine (Zyprexa\textregistered, ZyprexaZydis\textregistered)
- multiple publications support role as anti-emetic

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Contents of above table extracted from Clinical Handbook of Psychotropic Drugs, 16\textsuperscript{th} Edition, 2006; p 108
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Methotrimeprazine data from [Clinical Handbook of Psychotropic Drugs, 16th Edition, 2006; p 108.](https://example.com)
Olanzapine

- dosing:
  2.5 – 5 mg po / sl / sq OD or BID

- Zyprexa®: 2.5, 5, 7.5, 10, 15, 20 mg tabs
- ZyprexaZydis®: 5, 10, 15, 20 mg oral disintegrating tabs
- ZyprexaIntraMuscular®: 10 mg / 5 ml single dose vial
Methotrimeprazine:

• **Dosing:**
  
  5 - 10 mg po or 6.25 – 12.5 mg sq q8h
  
  (↑to max 25 mg / dose)

• **Nozinan®:**

  25 mg / ml  1 ml amps
  
  5, 25, 50 mg tabs
Further Reading


• Fraser Health – Hospice Palliative Care Program – Symptom Guidelines – Nausea & Vomiting


• https://www.cancercare.on.ca/toolbox/symptools/
  → Nausea & Vomiting algorithm, pocket guide & guide-to-practice
Bowel Obstruction
Bowel Obstruction

- often prior event
- most common: colorectal, ovary
- clinical:
  - ↑ belching / ↓ flatus
  - emesis: bilious vs. feculent
  - abdomen often distended & tympanitic
  - ± bowel sounds
  - incomplete vs complete
  - opiate / narcotic bowel syndrome
Bowel Obstruction

- surgical options often limited
- focal vs diffuse metastatic disease
- life expectancy
- setting of care (home vs hospital)
- conservative approach often favoured
Bowel Obstruction

- NO anti-emetic may be effective
- NG tube – often best option
- increased secretion in setting of SBO
- SBO may curtail substantial absorption distal to level of obstruction
Bowel Obstruction – The Vicious Cycle

- Fluid Accumulation & Vomiting
- Increased Gut Secretions
- Gut Dilatation

James L Hallenbeck, Palliative Care Perspectives, 2003 (On-line version)
NG Tube

- often temporary measure
- vents fluid load proximal to obstruction, reducing vomiting stimulus
- often settles nausea
- NG fluid replacement not necessary
- oral fluids not precluded at EOL
Steroids

- reduce peri-tumoural edema
- potential benefit in metastatic disease involving both solid & hollow viscera
- benefit usually seen in first 5 days in steroid naïve patients, if not then stop
- dexamethasone (Decadron®) 4-8mg OD sq
- useful anti-emetic & analgesic adjuvant
Octreotide (Sandostatin®)

- somatostatin analogue
- reduction of blood flow to gut
- role in UGI bleeding & secretory diarrhea
- ↓ secretions → potential benefit in bowel obstruction when secretions ↑
- 100 – 200 mcg q8-12h sq
- funding through PCFA
Anticholinergics

• hyoscine butylbromide (Buscopan®)
• 10-20mg q4h sq
• reduction of secretions (octreotide more effective) & peristalsis
Bowel Obstruction

• if nausea persists, consider trial of appropriate anti-emetic

Reference:
• [http://www.fraserhealth.ca/media/13FHSymptomGuidelinesMalignantBowelObstruction.pdf](http://www.fraserhealth.ca/media/13FHSymptomGuidelinesMalignantBowelObstruction.pdf)
Constipation
Constipation - defined

**Rome III**

**Must Include ≥2 of the following**:§

- Straining*
- Lumpy or hard stools*
- Sensation of incomplete evacuation*
- Sensation of anorectal obstruction/blockage*
- Manual manoeuvres to facilitate defecation*
  - Digital evacuation, support of pelvic floor
- <3 defecations per week

Loose stools are rarely present without the use of laxatives; insufficient criteria for IBS

Pinto Sanchez et al, *Can J Gastroenterol* 2011 25(Suppl B) 11B-15B
Common Causes of Constipation

• Lifestyle, demographic & environmental factors
  – nutritional (low fibre diet, decreased food & fluid intake)
  – physical barriers (reduced mobility, generalized weakness)
  – ignoring urge to defecate
  – advanced age

CCO’s Symptom Management Guides-to-Practice: Bowel Care, 2012
Common Causes of Constipation

- Lifestyle, demographic & environmental factors
  - physical surroundings
  - lack of privacy (visual, auditory, olfactory)
  - use of bed pan / commode
  - caregiver apathy / burnout
  - limited resources
Common Causes of Constipation

• Disease effects
  – mechanical (bowel obstruction, pelvic mass)
  – endocrine & metabolic (hypothyroidism, hypercalcemia, hypokalemic, dehydration)
  – neuromuscular (spinal cord compression, sacral nerve infiltration, myopathy, diabetic autonomic neuropathy)
  – depression, pain, dyspnea, sedation
Common Causes of Constipation

• Related to treatment
  – chemotherapy (vincristine)

• Comorbid conditions
  – IBS
  – painful anorectal conditions
Common Causes of Constipation

• Drugs
  – opioids
  – any drug with anticholinergic effects (antispasmodics, antidepressants, antihistamines, phenothiazines)
  – 5HT3 antagonists
  – iron, calcium

CCO’s Symptom Management Guides-to-Practice: Bowel Care, 2012
**Constipation Symptoms in Adults with Cancer**

**Screening and Assessment** (Screen for constipation at each visit)

**Assessment using Acronym O, P, Q, R, S, T, U and V** (adapted from Fraser Health)

<table>
<thead>
<tr>
<th>Onset</th>
<th>When did the constipation start? How often are you constipated? How often do your bowels move?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoking / Palliating</td>
<td>What makes it better? What makes it worse (e.g., medications, cancer treatments, diet changes, changes in amount of food or fluid eaten, decreased ability to walk or move around)?</td>
</tr>
<tr>
<td>Quality</td>
<td>How would you describe your stools (e.g., colour, hardness or softness, odor, amount)? Is there blood or mucus with the stool? (Assessment tools: Vicarious Bowel Performance Scale and the Bristol Stool Chart)</td>
</tr>
<tr>
<td>Related Symptoms</td>
<td>Is there any discomfort associated with the constipation? Where do you feel this discomfort? Can you describe it? Any abdominal bloating? Do you have lots of gas? Do you feel like your rectum is not empty after a bowel movement? Do you have hemorrhoids? Do you have pain in your anal area? Do you have any drainage from your rectum when you are not having a bowel movement? Do you have any other symptoms (e.g., nausea, vomiting, loss of appetite, urinary symptoms such as leaking urine accidentally or trouble emptying your bladder)?</td>
</tr>
<tr>
<td>Severity</td>
<td>When was your last bowel movement? How often do you feel the urge to pass stool? Do you need to strain a lot with each bowel movement?</td>
</tr>
<tr>
<td>Treatment</td>
<td>What are you doing to manage your bowels? How effective is this? Do you have any side effects from the medications or treatment you use for your bowels? What have you tried? What tests have been done for the constipation?</td>
</tr>
<tr>
<td>Understanding / impact on You</td>
<td>How does the constipation affect your life? How bothered are you by it?</td>
</tr>
<tr>
<td>Values</td>
<td>What are your normal bowel habits? What does the constipation mean to you? Has it affected you and your family or caregiver?</td>
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- Physical assessment should include vital signs, functional ability, hydration status, cognitive status, abdominal exam, rectal exam and neurological exam if a spinal cord or cauda equina lesion is suspected.
- Consider abdominal x-rays if bowel obstruction or severe stool loading of the colon is suspected.

**Interventions for all patients, as appropriate**

- Identifying the underlying etiology of constipation is essential in determining the interventions required.
- Consider performance status, fluid intake, diet, physical activity and lifestyle when managing constipation.
- It is not necessary to have a bowel movement every day. As long as stools are soft and easy to pass, every two days is generally adequate.
- Avoid excessive straining.

**Non-Pharmacological Interventions**

**PPS Stable, Transitional and End of Life (30-100%)**

- **Fluid Intake**
  - Encourage fluid intake (1500-2000 ml per day)
  - Encourage sips throughout the day.
  - Minimize caffeine and alcohol intake.

- **Physical Activity**
  - Tailor exercise to patient’s physical ability, condition and preference to optimize adherence.
  - Frequency, intensity and duration of exercise should be based on the patient’s tolerance.
  - PPS 60% and above: walking is recommended (15-20 min once or twice per day at 30-60 min daily, 3-5 times per week).
  - For PPS 30-50% exercises such as low trunk rotation and single leg lifts, for up to 15 to 20 minutes per day, are encouraged, if able.

- **Personal Considerations**
  - Provide privacy during toileting.
  - Attempts at defeeting should be made 30 to 60 minutes following ingestion of a meal, to take advantage of the gastrocolic reflex.

**PPS Stable and Transitional (40-100%)**

- **Diet**
  - The following dietary recommendations are not applicable if bowel obstruction is suspected.
  - Gradually increase dietary fibre once patient has consistent fluid intake of at least 1500 ml per 24 hrs.
  - Aim for at least 25 g of dietary fibre per day by:
    - Choosing 7-10 servings per day of whole fruits and vegetables, instead of juices.
    - Choosing 5-8 servings of grain products per day, selecting 100% whole grain breads and high fibre cereals (>4 grams per serving)
  - Including plant proteins daily as part of the 2-3 servings of meats and alternatires.
  - Consult with dietitian for specific nutritional advice regarding fibre intake.

- **Personal Considerations**
  - Walking to the toilet, if possible, is recommended.
  - If walking is difficult, use a bedside commode.
  - Assuring the squat position on the toilet can facilitate the defeeting process.
  - Sitting with feet on a stool may help with defeeting.

**PPS End of Life (10-30%)**

- Raising the head of the bed may facilitate the defeeting process.
- Simulate the squat position by placing the patient in the left-lateral decubitus position, bending the knees and moving the legs toward the abdomen.

**PPS End of Life (10-20%)**

- For patients with PPS 10-20%, consider the burdens and benefits of regular bowel care, using good clinical judgment when making recommendations.
**Constipation in Adults with Cancer: Care Map**

**Pharmacological Interventions**

- The recommendations below are based on low level evidence and consensus due to limited available research.
- Consider etiology of constipation, patient’s preferences, patient’s recent bowel function and response to previous treatments to guide appropriate selection and sequence of pharmacologic treatments.
- Ask whether the patient is using non-traditional or alternative therapies for bowel management to be aware of what they are using and to consider potential drug interactions and toxicities.
- Many oral laxatives, suppositories and enemas share common side effects, including cramping, flatulence, nausea and diarrhea, which can be reduced with dose adjustments. Generally avoid laxatives if bowel obstruction is suspected.

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**Recommended first line agents**

- Oral colonic stimulant (senna or bisacodyl)
- Oral colonic osmotic (lactulose or polyethylene glycol)

**Recommended second line agents**

- Suppositories (glycerin or bisacodyl)
- Enemas (phosphate enema)

**Recommended third line agents**

- Picosulfate sodium-magnesium oxide-citrnic acid
- Methylnaltrexone (if the patient is taking regular opioids).

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**Fecal Impaction**

- If stool is impacted in the rectum, use a glycerin suppository to soften the stool, followed 1 hr later by digital disimpaction, if necessary (after pretreatment with analgesic and sedative), and/or a phosphate enema.
- If stool is higher in the left colon, use an oil retention enema, followed by a large volume enema at least 1 hour later.

**Colostomy Patients**

- A patient with a very proximal colostomy may not benefit from colonic laxatives.
- There is no role for suppositories since they cannot be retained in a colostomy.
- Enemas may be useful for patients with a descending or sigmoid colostomy.

**Paraplegic Patients**

- Oral laxatives may be needed to move stool to the rectum.
- Assist with emptying the rectum using one or more of the following: suppository, enema, digital emptying.

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**Initial 3 Day Trial of methylnaltrexone**

If no bowel movement for 48 hours, give methylnaltrexone subcutaneously - 8 mg if 35-62 kg or 12 mg if 62-114 kg

Methylnaltrexone is considered effective if a bowel movement occurs within 4 hours after injection.

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The same dose can be repeated every 24 hours for 2 days, if necessary, if a bowel movement does not subsequently occur spontaneously.

Methylnaltrexone is unlikely to work for this patient at this time. No further doses should be given.

The same dose can be offered in the future if no bowel movement occurs for 48 hrs. Doses should not be given more frequently than 48 hrs apart.

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For full references and more information please refer to CCO’s *Symptom Management Guide-to-Practice* document.

**Disclaimer**: Care has been taken in the preparation of the information contained in this Algorithm document. Nonetheless, anyone seeking to apply or consult the guidance for practice document is expected to use independent clinical judgment and skills in the context of individual clinical circumstances or seek out the supervision of a qualified specialist clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.
Non-Pharmacologic Treatments

• CCO Bowel Care SMG stratifies interventions according to PPS ranges: stable, transitional & end-of-life
• performance status must be considered in management of constipation
• as PS diminishes, some interventions become less appropriate & are no longer indicated

CCO’s Symptom Management Guides-to-Practice: Bowel Care, 2012
Non-Pharmacologic Treatments

- general education
- fluid intake
- diet
- exercise / physical activity
- personal considerations
Pharmacologic Treatments

• 1\textsuperscript{st} line
  – oral colonic stimulant (sennosides, bisacodyl) &/or
  – oral colonic osmotic (lactulose, PEG)

• 2\textsuperscript{nd} line
  – suppositories (glycerine, bisacodyl) or
  – enemas (phosphate)

• 3\textsuperscript{rd} line (rescue)
  – picosulfate sodium-magnesium oxide-citric acid or
  – methylnaltrexone (if regular opioid dosing)

• (NB: docusate (Colace®) is NOT mentioned!)

CCO’s Symptom Management Guides-to-Practice: Bowel Care, 2012
Opioid-Induced Constipation (OIC)
Opioid Bowel Dysfunction (OBD)

Opioid receptors are widely distributed in the central & peripheral nervous system, smooth muscle of the gut

• Opioids can affect the entire gut
  – dry mouth
  – gastroparesis
  – nausea, vomiting
  – GERD
  – abdominal cramping, bloating and spasm
  – constipation (OIC)

Constipation is the most frequently reported ongoing symptom of OBD

OIC = Opioid-Induced Constipation

Thomas et al, J Palliative Med 2008 11(Suppl 1) S1-S19
Prevalence of OIC

90%
• Of patients taking opioids may develop constipation

50%
• Frequency of opioid-induced constipation in nonmalignant pain patients

27%
• Of patients self-reported constipation within the past 3 months and approximately one-third of these patients visited a physician for it

OIC prevalence is 2-3 times higher than the average population

Undertreatment of OIC

- ~50% of elderly patients dispensed an opioid were concomitantly dispensed a laxative.
- Of subjects who required a laxative, only 46% of opioid-treated patients reported achieving desired treatment results >50% of the time (control subjects, 84%).

Williams R et al., 2008; Pappagallo M, 2001
Strategies to Address OIC

Nonpharmacologic  Pharmacologic
methylnaltrexone (Relistor®) for OIC

- approved for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient
- contraindicated in known or suspected bowel obstruction or acute surgical abdomen
- caution in known or suspected GI lesions in advanced illness where patients may be at increased risk of GI perforation if they have conditions associated with localized or diffuse reduction of structural integrity in the GI wall

Figure 1. PROPOSED Initial 3-Day Trial of methylnaltrexone

If there has been no bowel movement for 48 hours, give methylnaltrexone 0.15 mg/kg subcutaneously on the first day (use 8 mg if 38-62 kg or 12 mg if 62-114 kg). Methylnaltrexone is considered effective if a bowel movement occurs within 4 hours after injection.

- **Effective**
  - The same dose can be offered in the future if no bowel movement occurs for 48 hours. Doses should not be given more frequently than 48 hours apart.
  - Effective
  - NOT Effective
  - On the next day, repeat the same dose subcutaneously, if a bowel movement has not subsequently occurred spontaneously.
  - Effective
  - NOT Effective
  - On the third day, repeat the same dose subcutaneously, if a bowel movement has not subsequently occurred spontaneously.
  - Effective
  - NOT Effective
  - Methylnaltrexone is unlikely to work for this patient at this time. No further doses should be given.

CCO’s Symptom Management Guides-to-Practice: Bowel Care
Oral Naloxone for OIC

• antagonist of all opiate receptors
• acts locally on $\mu$ receptors in the gut, counteracting opioid-induced constipation
• undergoes extensive first-pass metabolism in the liver, with <3% bioavailability*

  • doses of oral CR naloxone in approved† oxycodone/naloxone controlled release tablets** (as CR naloxone 20 mg po q12h) do not lead to reversal of analgesia
  • *high doses of orally-administered intravenous immediate-release (iv IR) naloxone†† may lead to reversal of analgesia from opioid (>12 mg orally of iv IR formulation)

†Approved indication: The oxycodone component is indicated for the relief of moderate to severe pain in adults who require continuous around the clock opioid analgesia for several days or more. The naloxone component is indicated for the relief of OIC.

††Off-label usage.
• Reference:

https://www.cancercare.on.ca/toolbox/symptools/

→ Bowel Care algorithms
    pocket guide
guide-to-practice
Questions?