Gastrointestinal Symptoms in Hospice: Managing Nausea, Vomiting and Constipation

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Objectives

- The learner will be able to:
- Describe the pathophysiology of nausea, vomiting and constipation in hospice patients.
- Analyze potential etiologies of nausea and vomiting based on clinical assessment.
- Evaluate the choice of antiemetic regimens based on presumed symptom etiology and current evidence.
- Understand the rationale for use of a standardized constipation protocol in patients on opioid therapy

Nausea and Vomiting

Definitions

- Nausea: subjective
  - uncomfortable sensation, often precedes vomiting
- Vomiting: objective
  - rapid, forceful, retrograde evacuation of stomach contents

Nausea is common

- 40-60% of patients with advanced cancer experience nausea
- Nausea or N/V affects physical activities, social and emotional functioning, ability to eat and drink
- Persistent nausea has a significantly greater impact than vomiting on overall functioning
- Distressing, overwhelming, all consuming

How to Approach the Problem

- Assess nausea and vomiting
- Elements of the history can help you determine the cause of nausea
- Knowing the cause can lead to a targeted therapy

Case

- Ms R is a 66 year old woman with advanced ovarian cancer with ascites who complains of nausea, vomiting and abdominal pain.

What else do we need to know?

Assessment

- History
- Physical Exam
- Laboratory Studies
- Diagnostic Tests

Nausea/Vomiting History

- Timing
  - Onset
  - Duration
  - Frequency
- Severity
  - Numerical rating scale, VAS, Verbal description
- Triggers
  - And Relieving Factors
- Type and Quantity of vomitus

Nausea/Vomiting History

- Is it related to eating
  →gastroparesis/obstruction
- Is vomiting intermittent, relieved by vomiting
  →gastroparesis
- Is patient constipated
- Are there secretions, cough, throat pain
- Is it positional or related to movement
  - With vertigo →brainstem/vestibular
  - Without vertigo →mesenteric traction
- Is it anticipatory
  →anxiety
- Is it related to medications
  →toxins
- Bilious, or food
  → gastroparesis/obstruction

Nausea/Vomiting History, continued…

- Morning nausea, vomiting, cognitive changes, neurologic deficits, refractory to antiemetics
  → posterior fossa, increased intracranial pressure
- Polyuria, polydipsia
  →hyperglycemia, hypercalcemia, pituitary, Addison's crisis
- Myoclonus, cognitive changes
  →opioids, uremia, hyponatremia
- Reflux, hiccups, early satiety and headaches
  →not useful

Assessment

- **N**ausea
  - Intensity (0 – 10), onset, duration, description
- **A**ggravating factors
  - Eating/drinking related stimuli, medications, time of day
- Q**U**ality of life disruption
- **S**ymptoms associated with N/V
  - Constipation/diarrhea, dizziness, fatigue, pain, diaphoresis, anxiety/depression
- **E**metic episodes per 24 hours
- **A**lleviating factors
  - Distraction, rest, eating, medication (What kind? How much? How often?)

Ms. R

- She complains of constant nausea all day
- Nausea is worse after eating
- It is not related to position
- She vomits soon after eating and the sight of food now makes her nauseated
- She feels like the food gets "stuck" and like she is always full

History

- Underlying illness and course
- Treatment history
- Current medications
- Comorbid conditions

History of Illness

- She has not received any chemotherapy, radiation or surgery
- She is currently taking MS Contin 30 bid for pain in addition to MS IR 5-10 mg q 3 hours
- She is taking zofran around the clock. She is also taking docusate.
- Her last BM was over four days ago

Physical Exam

- General: signs of dehydration, hypotension, tachycardia
- Papilledema
- Oropharynx: secretions, mucositis (candida, herpetic)
- Abdomen: distention, bowel sounds, pain, organomegaly, ascites
- Rectal: rule out impacted stool
- Neurologic: rectal tone, focal neurologic deficits

Physical Exam

- She is a very thin, cachectic woman, lying in bed
- Oropharynx is dry
- She is not coughing and there are no secretions. No thrush.
- She has large ascites.
- Her abdomen is diffusely tender.
- Bowel sounds are very quiet
- Rectal exam with soft stool.

Laboratory Tests

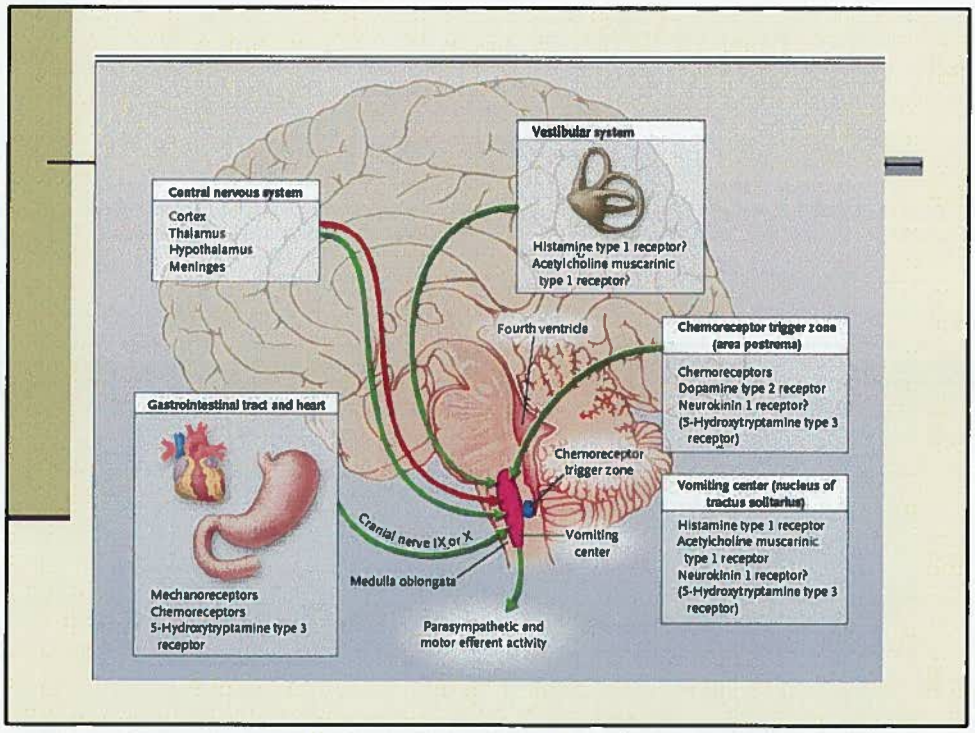
- Creatinine, urea
- Calcium
- Sodium
- Liver function tests
- Bicarbonate/acid base status

Imaging Studies

- Head CT for intracranial mass
- Gastric emptying study for gastroparesis
- CT abdomen for peritoneal carcinomatosis, peritoneal mass, obstruction

Causes of Nausea and Vomiting

- Signals originate in the:
  - Gastrointestinal tract
  - Inner ear
  - Cerebral Cortex
  - Chemoreceptor Trigger Zone
  - Vomiting Center
- Messages all terminate in CTZ and vomiting center
- To treat nausea effectively need to determine where the signal originated



Causes of nausea and vomiting

- Gut: visceral disturbance stimulating vagal pathways and causing serotonin release
  - Constipation
  - Radiation
  - Surgery
  - Ulcer/GERD
  - Esophagitis
  - Ascites
  - Hepatomegly
  - Obstruction
  - Cough
  - Carcinomatosis
  - Irritating medications: chemo/nsaids

Causes of Nausea and Vomiting

- Toxins: stimulate the chemoreceptor trigger zone via dompamine, serotonin, substance P (ligand for neurokinase-1 receptors)
  - Hypercalcemia
  - Uremia
  - Opioids
  - Chemotherapy
  - anesthetics

Opioid associated nausea is multifactorial

- Opioids act on CTZ via dopamine
- Opioids release histamine in the brain that acts on vomiting center
- Opioids cause slowed bowel motility
- Opioids cause constipation

Causes of Nausea and Vomiting

- Central Nervous System-activates CTZ and vomiting center
  - Increased intracranial pressure
  - Direct effect of mass

Causes of Nausea and Vomiting

- Vestibular: activate vomiting center (via cholinergic muscarinic receptors)
  - Motion sickness
  - Opioids, aspirin
  - Local tumors (rare)

Causes of Nausea and Vomiting

- Psychological
  - Emotional factors stimulate the emetic receptors of the brain
  - Fear
  - Anxiety
  - Anticipatory nausea

What Causes Nausea?

- **V**-vertigo/vestibular
- **O**-obstipation/constipation
- **M**-motility dysfunction
- **I**-inflammation of the gut
  (surgery/infection/carcinomatosis)
- **T**-toxins (chemotherapy, opioids, uremia, hypercalcemia)
- **I**-intracranial (direct irritation by tumor or increased pressure)
- **N**- nerves—anxiety, anticipatory
- **G**-glossopharyngeal, mouth, oropharynx

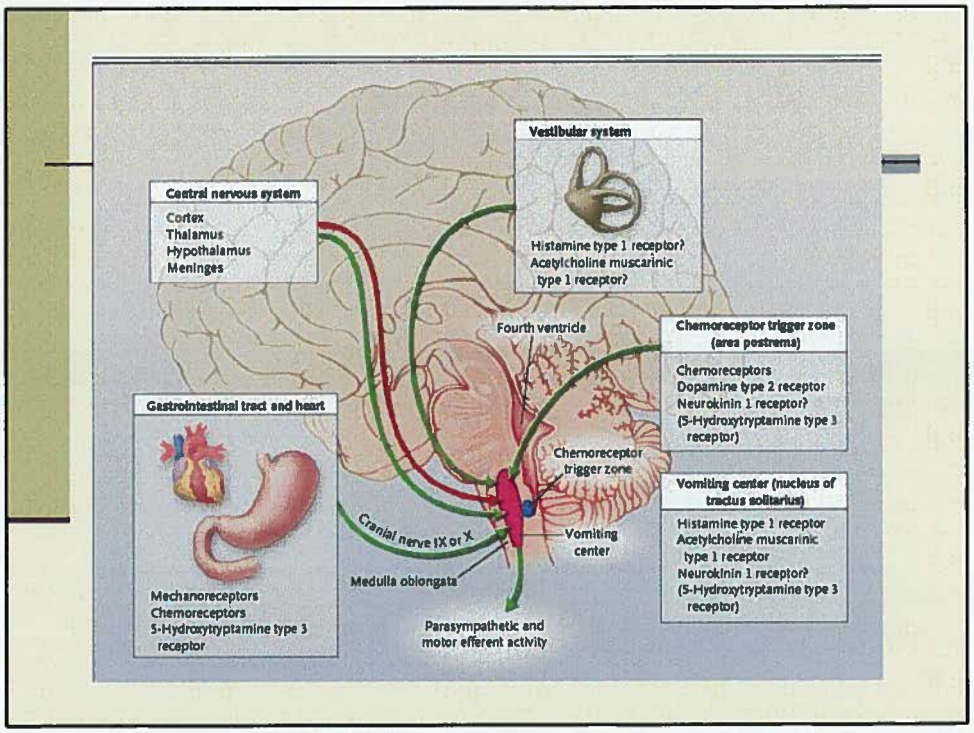
Causes of Nausea and Vomiting

- Etiology is evident in 75%
- Etiology is obscure in 25%
- Single cause 77%
- At least 2 different etiologies in 23%
- 50% reversible

Neurotransmittors are activated that communicate nausea to the brain

- Dopamine
- Histamine
- Acetylcholine
- Serotonin
- Substance P

Different Neurotransmittors are associated with different pathways



What is Causing Nausea and Vomiting in Ms. R?

- Multifactorial:
  - Gastroparesis: from opioids and her disease (symptoms of fullness and food getting stuck)
  - Dysmotility from opioids and peritoneal disease
  - Opioid induced nausea
  - Constipation from opioids, disease and zofran

Steps to choosing a specific antiemetic

- Based on etiology
  - Pattern of nausea and vomiting
  - Relevant physical findings
  - Identify likely neurotransmitters involved
- Select most potent antagonist for that receptor
- Select a route that will ensure medication will reach site
- Titrate and administer around the clock
- Reassess

How do we choose a medication?

- We can choose a medication based on the pathophysiology of nausea and vomiting.
- The main mediators of nausea:
  - Dopamine →Dopamine antagonists
    - Phenothiazines (compazine)
    - Butyrophenones (haldol)
    - Substituted Benzamides (reglan)
    - Atypical neuroleptics (olanzapine, risperidone)
  - Histamine (5HT4) → Antihistamines (benadryl, phenergan)
  - Acetylcholine → Anticholinergics (scopolamine, levsin)
  - Serotonin (5HT3) →Serotonin receptor antagonists (zofran, kytril, aloxi)
  - NK1 receptor Antagonists (emend)

How do we choose a medication?

- Others antiemetics
  - Benzodiazepines (Ativan)
  - Cannabinoids (Marinol)
  - Corticosteroids (Decadron)
  - Thalidomide
  - Mirtazepine
  - Octreotide
  - Erythromycin

There are four types of Dopamine blockers

1. **Phenothiazines:**
   - *D2 antagonists (CTZ >peripheral) , does not increase GI motility*
   - *Dopaminergic, cholinergic, histamine and alpha-1-adrenergic receptor antagonism*
     - *Side effects: extrapyramidal reactions (akathisia, dystonia), hypotension, urinary retention, dry mouth, sedation*
   - *Chlorpromazine (Thorazine), prochorperazine (Compazine), promethazine (Phenergan)*

Dopamine Antagonists

2. Butyrophenones:

- *Haloperidol (Haldol)*
- *almost exclusively dopamine blocker, not sedating*
- *Safe in renal failure*
- *0.5 – 2mg q 4 hours*
- *Side Effects: postural hypotension, akathisia, dystonia, prolonged QT*
- *Evidence for haldol: uncontrolled case studies*

Dopamine Antagonists

3. Benzamides:

- *Metoclopramide (Reglan)*
  - *Blocks dopamine in the gut > CTZ; also has prokinetic activity via the cholinergic system in the myenteric plexus to promote motility (via increase in 5-HT4)*
  - *At higher doses (greater than 120mg/24 hours) becomes a 5-HT3 receptor antagonist acting centrally or in the gut*
  - *Antiemetic doses are greater than prokinetic doses*
  - *Anticholinergic medications will antagonize prokinetic effect*
  - *Short half-life (3 hours)*
  - *Side effects: dystonia, akathisia, sedation, tachycardia, hypotension*
  - *May have appetite stimulant effect*
  - *Avoid in complete bowel obstruction*

Dopamine Antagonists

4. Thienobenzodiazepines:

Olanzapine (Zyprexa, Zydis)

- Atypical neuroleptic
- Block dopamine, acetylcholine, histamine and serotonin receptors
- Effective in managing acute and delayed CINV
- Refractory N/V: in one study effective 30% of the time when all other therapies failed
- Effective for nausea, anxiety, delirium
- 1.25 – 5 mg q HS; max dose 10 – 15 mg/day; may use in divided doses
- Side effects: dry mouth, sedation

Antihistamines and Anticholinergics

- *Act on the vomiting center*
- *Especially useful if vestibular component to nausea identified*
- *Decreases peristalsis and colic*
- *Dephenhydramine may help prevent/treat EPS secondary to dopamine antagonists*
- *Side effects: **sedation,** dry mouth, ileus, urinary retention, blurred vision, confusion*
- *Tertiary derivatives: atropine and scopolamine*
  - *Lipophilic, causing sedation and confusion*
- *Quaternary derivatives: hyoscyamine and glycopyrrolate*
  - *Does not cross blood-brain barrier*

Steroids

- Unclear method of action; may act by modulation of prostaglandin release, decrease permeability of blood-brain barrier to emetogenic stimuli
- Decrease in peri-tumor inflammation and edema:hepatic capsular stretch, radiation effects, increased intracranial pressure, partial small bowel obstruction
- CINV: clear advantage over placebo; acute and delayed CINV (acute: 12 – 20 mg/day with 5HT3 antagonist, delayed: 4 – 8 mg/day)
- NV associated with advanced cancer (especially if associated with pain): 2 – 8 mg/day
- Improved symptom control when added to metoclopramide in advanced cancer
- SE: increased appetite, insomnia, dysphoria, psychosis, agitation, confusion. Long term SE include gastric ulcers, proximal muscle weakness,osteopenia, weight gain, diabetes.

Serotonin Antagonists

- Ondansetron (Zofran), Granisetron (Kytril), Dolasetron (Anzemet),Tropisetron (Navoban)
- Palonsetron (Aloxi) second generation
  - Longer half-life
- Act on serotonin receptors in CTZ, evidence suggests receptors also present in the gut
  - Serotonin in gut released in response to insults such as radiation and chemotherapy
- Indicated for chemotherapy or surgery induced nausea and vomiting
- Efficacy improved when given with corticosteroids
- Expense
- Side effects: constipation, headache

Benzodiazepines

- Lorazepam, Diazepam
- Act centrally on cortex to decrease cortical triggers for nausea
- Useful if anxiety or anticipatory nausea are a factor
- Provide sedation, amnesia
- May cause confusion and paradoxical excitement, especially in elderly
- Ativan most commonly used:0.5-2 mg q 4 – 6 hours PRN

Cannabinoids

- Thought to work through brainstem cannabinoid receptors
- Effective in CINV, AIDS-related cachexia, N/V
- Side effects: somnolence, confusion, perceptual disturbance, dysphoria, dizziness, especially in the elderly
- Not first line anti-emetic
- Cost

Other Medications

- Thalidomide
  - Central antiemetic and sedative effects
  - Immunomodulatory, antipyretic; possible analgesic, antidiaphoretic and antiangiogenic actions
  - In advanced cancer: low dose improved appetite, nausea, and sense of well-being (n = 37)
- Erythromycin
  - Bacteriostatic macrolide with prokinetic properties
  - Potent motilin agonist
  - Tachyphylaxis may occur
- Mirtazepine
  - Antidepressant affecting histamine and multiple types of serotonin receptors
  - Also useful for refractory itching

Octreotide

- Somatostatin analogue
- Inhibits gastric, pancreatic and intestinal secretions and reduces GI motility
- Useful in intestinal obstruction
- Consider use of anticholinergics for same indication
- Side Effects: diarrhea, anorexia, headache

Nonpharmacologic Therapy

- Dietary
- Avoidance of emetogenic sights, sounds, smells
- Acupuncture
- TENS
- Hypnosis or relaxation
  - Particularly for anticipatory CINV

How do you choose?

- Reglan: works in the brain and the gut to improve motility; therefore good for gastroparesis, ileus, partial small bowel obstruction.
- Haldol: very powerful dopamine antagonist; works well for all kinds of nausea since it acts on the CTZ in the brain and on D2 receptors in the gut.
- Scopolamine/Levsin: if nausea is related to secretions or if it is related to bowel. inflammation, as in peritoneal carcinomatosis. Decrease peristalsis and good for cramping.

How do you choose?

- Dexamethasone: unclear how it works, good for all nausea but not a first line agent due to side effects. Cannot use for prolonged period of time. Especially good for liver mets causing capsular stretch, inflammation from radiation, and increased intracranial pressure.
- Zofran: role is mostly for chemotherapy, surgery or radiation related nausea. Causes constipation so can worsen motility problems.

How do you choose?

- Compazine: a good dopamine blocker with some histamine and acetylcholine effects; also good for most types of nausea but not as effective as haldol
- Phenergan: more of an antihistamine than a dopamine antagonist; therefore better for intestinal inflammation and control of secretions or vertigo/positional nausea
- Ativan: acts to decrease cortical input and helps with anticipatory nausea

When do you use ABHR?

- Ativan/Benadryl/Haldol/Reglan (0.5mg/12.5mg/0.5mg/10mg)
- Kitchen sink approach
- Very good for emergencies/uncontrolled symptoms with extensive suffering
- If all else fails

What should we do for Ms. R?

Stepwise Approach

- Start simple
  - One narrow spectrum antiemetic
- Try 2nd antiemetic if not effective
- Try combination regimen
  - Consider mechanism of action, side effects, administration, cost effectiveness
- Use multipurpose drugs
  - Haloperidol, metoclopramide, decadron, olanzapine
- Use measures to manage underlying causes
  - Judicious fluids, reglan or erythromycin to increase gastric emptying, Levsin to decrease GI secretions, etc

What should we do for Ms. R?

Reglan 10 mg QID for gastroparesis and ileus (will help move bowels and empty stomach and also decrease nausea in general)

Senna/colace/lactulose to move bowels

Discontinue zofran: causing constipation and no indication. She has not had surgery, radiation or chemo.

If no improvement…

- Add Haldol 1-2 mg q 6 hours standing for opioid related nausea; can also opioid rotate from morphine to oxycodone or methadone

Establishing a Treatment Plan

- Collaborative/Team Approach
- Rationale for antiemetic regimen
  - Scientific evidence
  - Clinical judgement
  - Risk factors
  - Past experience
  - Probable pathophysiology

Establishing a Treatment Plan

- Establish patient-centered goals
  - Teach importance of prevention
  - Non pharmacologic treatments : small meals, avoid acidic foods
  - Explore complementary methods- acupuncture

Red Flags: Who/When to Call

- Persistent unrelieved nausea for 24 hours
- Greater than 2 vomiting episodes in 24 hours despite antiemetics
- Inability to eat/drink, sense of dryness
- Signs/symptoms of dehydration: lightheaded or dizzy, low urine output, postural signs
- Unanticipated side effects form antiemetics

Rationale for Drug Choices

- N/V is often multifactorial, particularly in patients with multi-focal or advanced illness
- Necessitates combining agents with different pharmacologic activity

Follow-up Care

- Discuss drug and non-drug measures
- Provide written instruction for self-care
- Phone fu in 24 hours for N/V and effects on ADL's, adverse antiemetic effects, patient rating of plan
- Ongoing evaluation necessary for optimal antiemetic control

Summary of Approach to Nausea and Vomiting

- Take a good history looking for causes of nausea vomiting (secretions, position changes, related to eating, constipation)
- Choose a drug based on the probable pathophysiology
- Assess, assess, and reassess

Constipation

Opioid Induced Constipation

Decreased release of acetylcholine

↓

decreased gut motility; decreased mucosal, pancreatic, and biliary secretions

↓

decreased small bowel propulsion → increased fluid absorption

+

decreased relaxation of rectal musculature =

Opioid Induced Constipation

Desicated stool in the large bowel

Difficulty with evacuation

Prevention is Key

- Senna 2 tabs and docusate 1 tab/cap QD – BID
- Stop insoluble fibers such as Metamucil
- Increase laxative dose if increased dosage of constipating medications such as opioids

Assessment

- Date of last stool
- Stool consistency, amount, frequency
- Sensation incomplete, difficult stool passage
- Presence of pain on defecation, bloating, flatulence, nausea/vomiting
- Medications
- Nutritional intake
- Activity level
- Psychosocial/cognitive
- PMH: hemorrhoids, obstruction, impaction, abdominal surgeries/pathologies

Physical Exam

- Abdomen:
  - Look, listen, touch
  - Presence and quality of bowel sounds; presence of distension, tenderness, masses
  - Rectal: presence of hemorrhoids, fissures, presence of stool in rectal vault
- Diagnostics:
  - KUB to rule out obstruction
  - electrolytes

If not Obstructed or Impacted

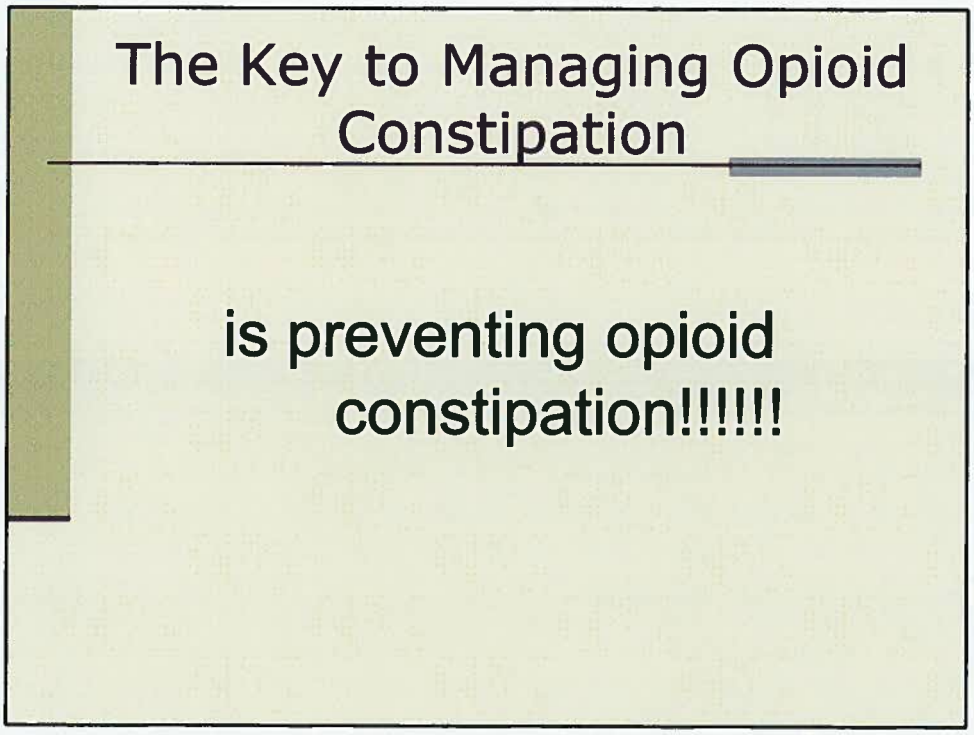
- Non-pharmacological
  - Increase fluids
  - Increase activity
  - Assure privacy for stool evacuation
  - Discontinue medications contributing to constipation if possible

If not Obstructed or Impacted

- Pharmacological Treatment
  - Senna 2 tabs BID + Docusate 1 BID
  - In no stool in 24 – 48 hours:
    - Increase senna to 3 – 4 tabs and docusate 1 tab BID + MOM 30cc or Dulcolax PO q HS or PRN QD
  - If no stool in 48 hours:
    - Stop MOM + add lactulose 30 cc QID or Miralax 17 – 34 gms in 8 – 16 oz of fluid qd

If Impacted:

- Soften stool with glycerin suppository or oil retention enema
- Follow with Fleet or tap water enema
- Manual disimpaction if necessary


The Key to Managing Opioid Constipation
is preventing opioid constipation!!!!!!