Best Practices in the Treatment of Nausea and Vomiting

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Disclosures

• I have no relevant conflicts of interest to disclose.

At the conclusion of this activity, the learners will be able to:

1. Understand the pathophysiology of nausea/vomiting.
2. Identify common causes of nausea and vomiting in the palliative care setting.
3. Identify the different treatment options available in the management of nausea and vomiting.
Nausea and Vomiting

- Nausea and vomiting are common and distressing symptoms affecting the majority of palliative and hospice patients.
- Prevalence does increase as one gets closer towards the end of life.
- If one understands the pathophysiology of nausea and vomiting, it makes treatment selection much easier.

Why is nausea and vomiting difficult to manage?

- Failure to identify and target the cause
- Use of wrong antiemetic medication
  - Failure to match the treatment to the cause
  - Use of multiple medications that has the same mechanism of action
- Inadequate dose
  - Medications not given often enough (sometimes need scheduled)
  - Failure to increase dose when appropriate
- Inappropriate route
  - Oral medication + Vomiting patient = Fail
  - Rectal medication + Diarrhea patient = Fail
Getting the treatment of nausea and vomiting right……

• A very important step is understanding the pathophysiology of nausea and vomiting…..

Let’s Review the Pathophysiology of Nausea and Vomiting

What are the main neurotransmitters in the pathophysiology of nausea?

• Acetylcholine (M1)
• Dopamine (D2)
• Histamine (H1)
• Serotonin (5HT3)
Some others are:

- Gamma-Aminobutric acid (GABA<sub>A</sub> and GABA<sub>B</sub> receptors)
- Substance P (Neurokinin 1 Receptor/NK1)
- Cannabinoid type 1 (CB1)
- Endogenous opioids

Where is the Chemoreceptor trigger zone?

- The CTZ is located in the area postrema, on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle.
Main Receptors in the CTZ Zone

- Dopamine (D$_2$
- Serotonin (5-HT$_3$
- Substance P (Neurokinin 1 Receptor (NK$_1$
- Cannabinoid type 1 (CB$_1$

Neural pathways project from the CTZ to the nucleus tractus solitarius and the reticular formation of the medulla oblongata, which is the location of the vomiting center (VC).

CTZ Zone

- Most medications that induce nausea affect the chemoreceptor trigger zone.
- In addition, biochemical changes and electrolyte abnormalities.
- Treatment should focus on agents that affect dopamine and serotonin.

Labyrinth

- Inside the labyrinth is the vestibule, which is important for balance.
- Abnormalities trigger the vestibular cochlear nerve (VIII) which goes to the brain stem to an area called Vestibular Nuclei located in the Pons.
Vestibular Nucleus

- Vestibular Nuclei have receptors for Histamine (H1) and Muscarinic receptors (Acetylcholine), which ultimately activates the vomiting center to trigger the vomiting reflex.
- Triggers: motion sickness, BPPV, tumors, medications (opioids), infection (e.g. Meniere’s disease)
- Treatment should focus on agents that affect histamine and acetylcholine.

Cerebral Cortex

- Triggers that affect the higher brain centers are emotional factors (e.g. anxiety), pain, CNS tumors, meningeal irritation, increased ICP, repulsive smells, and repulsive sights.
- When activates it sends a signal to the vomiting center which is often GABA and Histamine (H1) mediated.

Gastrointestinal Tract

- In the stomach, we have pits and glands that have enterochromaffin cells.
- This cells have chemoreceptors that release serotonin and dopamine which activates the vomiting center via the vagus nerve (CNX).
- There are also mechanoreceptors trigger by constipation/obstruction, gastric stasis, or infections which also activates the vomiting center.
Gastrointestinal Tract

• The main neurotransmitters released are Serotonin (5HT3&5HT4) and Dopamine (D2).

• Treatment should focus on agents that affect Dopamine and Serotonin.

So CTZ, Vestibular Nucleus, GI tract and Cerebral cortex all trigger the vomiting center

Vomiting Center

• Vomiting Center is located in the Medulla oblongata

• The vomiting center has receptors for
  – Histamine
  – Acetylcholine
  – Serotonin

• Once activated, it starts the vomiting reflex cascade.
Vomiting Reflex

• Lower esophageal sphincter relaxes
• Diaphragm and abdominal muscles contract
• This leads to increased intraabdominal pressure
• You will also see autonomic changes like tachycardia and increased salivation.
• Glottis then closes and then one vomits.

So let's recap......
The main neurotransmitters in the pathophysiology of nausea and vomiting are:

- Acetylcholine (M1)
- Dopamine (D2)
- Histamine (H1)
- Serotonin (5HT3)

So now we understand the pathophysiology of nausea and vomiting..... Now let's discuss the common etiologies.
Key Point

- Nausea and Vomiting are symptoms of a diagnosis....
- They are not the diagnosis

What is the most common cause of Nausea and Vomiting at the end of life?


Increases closer to death:

- Nausea and vomiting do appear to become more common as death approaches
- so it is not surprising that nausea has been found to be a predictor of a shortened survival
  - 62% at 1–2 months before death
  - 71% in the final week of life
- However, in one study, the prevalence of nausea peaked in patients with a Karnofsky performance status score of 40, then decreased as performance status declined further.
Step 1: Assess the patient

Nausea and Vomiting Assessment using Acronym O,P, Q, R, S, T, U and V

<table>
<thead>
<tr>
<th>O (Onset)</th>
<th>What did it begin? How long does it last? How often does it happen? Is it there all the time?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (Proximal)</td>
<td>What brings it on? What makes it better? What makes it worse?</td>
</tr>
<tr>
<td>Q (Quality)</td>
<td>What does it feel like? Can you describe it?</td>
</tr>
<tr>
<td>R (Radiation)</td>
<td>Do you have nausea with or without vomiting?</td>
</tr>
<tr>
<td>S (Severity)</td>
<td>Where is the intensity of this symptom? On a scale of 0-10, how bad is it? How does it affect your ability to function? Does the symptom add to your distress?</td>
</tr>
<tr>
<td>T (Treatment)</td>
<td>What symptoms and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?</td>
</tr>
<tr>
<td>U (Understanding Impact on Values)</td>
<td>What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom? On a scale of 0 to 10, with 0 being none and 10 being worst possible? Are there any other issues or concerns that the symptom that are important to you or your family?</td>
</tr>
<tr>
<td>V (Values)</td>
<td>What does it mean to you?</td>
</tr>
</tbody>
</table>

Step 2: Examine the Patient

- **Appearance and Vital signs**
  - Pale, jaundice?
  - Fever, tachycardia, hypotension?
- **Lung**
  - Fluid overload?
- **Skin and mucous membranes**
  - Increased salivation?
  - Sweating?
  - Dry mouth?
- **Abdominal exam**
  - Tenderness?
  - Distension/masses?
  - Bowel sounds?
- **Extremities**
  - Peripheral edema?
- **Rectal exam (In limited patients-also depends of prognosis)**
  - If severe constipation to look for impaction
  - If having rectal bleeding
Step 3: Identify the possible cause(s)

VOMIT Mnemonic

- V = Vestibular
- O = Obstruction
- M = Motility Disorder
- I = Infection, Inflammation, Increased ICP
- T = Toxins

V-Vestibular

- Motion Sickness
- Benign paroxysmal positional vertigo
- Meniere’s disease
- Tumor
- Inner ear infection/inflammation (e.g. labyrinthitis)
- Medications (e.g. opioids)

- Key Neurotransmitters: Acetylcholine and Histamine
O-Obstruction

- Constipation
- Ileus, Intestinal pseudo-obstruction (Ogilvie’s)
- Partial or full bowel obstruction
- Intraabdominal Mets
- Ascites
- Adhesion
- Biliary/pancreatic duct

- Key Neurotransmitters: Serotonin & Dopamine

M-Motility Disorder

- Gastroparesis (e.g. Diabetes Mellitus)
- Neurological Disorders (e.g. Parkinson disease, spinal cord injury)
- Irritable bowel syndrome (IBS)
- Medications (e.g. opioids)
- Hypo/hyperthyroidism
- GERD, Gastroenteritis
- Scleroderma

- Key Neurotransmitters: Serotonin & Dopamine

I-Infection/Inflammation/Increased ICP

- Bacterial or Viral infection
- Stroke
- Concussion
- Brain Tumor
- Radiation
- Chemotherapy (direct GI effects)
- Gastroenteritis, pancreatitis, cholecystitis

- Key Neurotransmitters: Serotonin & Dopamine
T-Toxins

- Metabolic disorders
- Medications
- Organ failure
  - Liver and Renal
- Poisoning
- Substance Abuse

• Key Neurotransmitters: Serotonin & Dopamine

So let’s recap……

VOMIT Mnemonic

- Vestibular
  - Motion Sickness, Benign paroxysmal positional vertigo, Meniere’s disease, Tumor, Inner ear infection/inflammation (e.g. labyrinthitis), Medications (e.g. opioids)
- Obstruction
  - Constipation, ileus, Intestinal pseudo-obstruction (Ogilvie’s), Partial or full bowel obstruction, Intraabdominal Mets, Ascites, Adhesion, Biliary/pancreatic duct
- Motility Disorder
  - Gastroparesis (e.g. Diabetes Mellitus), Neurological Disorders (e.g. Parkinson disease, spinal cord injury), Irritable bowel syndrome (IBS), Medications (e.g. opioids), Hypo/hyperthyroidism, GERD, Gastroenteritis, Scleroderma
- Infection, Inflammation, Increased ICP
  - Bacterial or Viral infection, Stroke, Concussion, Brain Tumor, Radiation, Chemotherapy (direct GI effects), Gastroenteritis, pancreatitis, cholecystitis
- Toxins
  - Metabolic disorders, Medications, Organ failure, Poisoning, Substance Abuse
What are common medications that cause nausea and vomiting?

- Cytotoxic chemotherapy
- Opioids
- NSAIDS, Aspirin
- Digitalis
- Iron
- Antibiotics
- Theophylline
- Antidepressants (SSRI, SNRI)
- Anticonvulsants (e.g. carbamazepine, phenytoin)

So we reviewed the pathophysiology of nausea and vomiting and common etiologies.... Let's now review some cases
For these Cases I want you to think about the following:

- **What area is being affected?**
  - Chemoreceptor Trigger zone
  - Vestibular Nucleus
  - Gastrointestinal Tract
  - Higher Brain Center/Cerebral Cortex

- **Which receptors should we target?**
  - Dopamine
  - Serotonin
  - Histamine
  - Acetylcholine
  - GABA
  - Other

34 year old female presents with intermittent nausea associated with early satiety and postprandial fullness or bloating. The nausea is relieved by vomiting that is usually small volume, occasionally forceful, and sometimes contain food.

- **What area do you think is being affected?**
- **Which receptors should we target for our treatment?**

- **What area is being affected?**

- **Which receptors should we target?**
62 year old male with PMHX of NSCLC persistent nausea, aggravated by the sight and smell of food, unrelieved by vomiting. He is currently not on chemotherapy or radiation. His medications are morphine SA + morphine IR, Pepcid, and Norvasc.

What area do you think is being affected?
Which receptors should we target for our treatment?

72 year old male presents with intermittent nausea associated with abdominal cramps and altered bowel habit. The nausea is relieved by vomiting and sometimes the vomit is bilious in nature.

What area do you think is being affected?
Which receptors should we target for our treatment?
• What area is being affected?

• Which receptors should we target?

56 year old female presents with nausea aggravated by movement, even just turning the head.

• What area do you think is being affected?
• Which receptors should we target for our treatment?

• What area is being affected?

• Which receptors should we target?
• 45 year old female who has stage IV cervical cancer has uncontrolled nausea prior to starting cisplatin therapy.
  • What area do you think is being affected?
  • Which receptors should we target for our treatment?

• 43 year old male presents with early morning nausea and vomiting associated with headaches.
  • What area do you think is being affected?
  • Which receptors should we target for our treatment?
• What area is being affected?

• Which receptors should we target?

What about Radiation?

• The incidence and severity of RT-induced nausea and vomiting (RINV) are both treatment-related (irradiated site and volume, single and total dose, fractionation schedule, techniques) and patient-related. The most important factor appears to be the radiation field.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk score</th>
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<tbody>
<tr>
<td>Age</td>
<td>2</td>
</tr>
<tr>
<td>Sex</td>
<td>3</td>
</tr>
<tr>
<td>Treatment</td>
<td>1</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>2</td>
</tr>
<tr>
<td>Performance status</td>
<td>1</td>
</tr>
<tr>
<td>Previous RT history</td>
<td>1</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>2</td>
</tr>
</tbody>
</table>

Data from: Han et al. (2004); H3 Chabot L.S., and Han K. et al. Support Care (2007; 1512).

Focus Treatment on:

• Serotonin and Dopamine
Chemotherapy induced depends on emetogenicity of chemotherapy drug

- Highest are: (>90%)
  - Anthracycline/cyclophosphamide for breast cancer
  - Carmustine
  - Cisplatin
  - Dacarbazine
  - Mechlorethamine
  - Stretozocin
  - Altretamine
  - Procarbazine

RELATED TO CHEMO:

- Acute N&V: N&V experienced during the first 24-hour period after chemotherapy administration is considered acute N&V.

- Delayed (or late) N&V: N&V that occurs more than 24 hours after chemotherapy administration

- Anticipatory nausea and vomiting (ANV): ANV is nausea and/or vomiting that occurs prior to the beginning of a new cycle of chemotherapy

- Chronic N&V

Step 4: Direct the treatment toward the cause

So once you figure out the cause and then target treatment to hit that receptor
Dopamine Antagonist

- **Mechanism:**
  - Blocks dopamine at the dopamine (D2) receptor
- **Drugs:**
  - Metoclopramide (Reglan)
  - Haloperidol
  - Olanzapine
  - Prochlorperazine (Compazine)
  - Promethazine (Phenergan)
  - Chlorpromazine (Thorazine)

Side Effects

- Sedation, dizziness, Dry mouth
- Extrapyramidal symptoms: tremor, rigidity, etc.
- QT prolongation
- Tardive dyskinesia-repetitive, involuntary movements like lip smacking
- Weight gain, hyperglycemia
- DVT/PE, elevated prolactin (atypicals)
- Neutropenia (watch ANC<1000)

Anticholinergics

- **Mechanism:**
  - Blocks acetylcholine (ACH) at the muscarinic (M1) receptor
- **Drugs:**
  - Scopolamine
  - Hyoscyamine (Levsin)
  - Glycopyrrolate (Robinul)
  - Olanzapine
  - Chlorpromazine (thorazine)
  - Prochlorperazine (Compazine)
- **Side Effects:**
  - Dry mouth, Constipation, Confusion/delirium, Urinary retention
Antihistamines

- **Mechanism:**
  - Block histamine at H1 receptor
  - Many also block acetylcholine (M1) receptor
- **Drugs:**
  - Meclizine
  - Diphenhydramine (Benadryl)
  - Hydroxyzine (Atarax)
  - Cyclizine
  - Doxepin
  - Hydroxyzine (Phenergan)
- **Side Effects:**
  - Sedation, blurry vision, dizziness, dry mouth, UA retention, confusion.

Serotonin Antagonist

- **Mechanism:**
  - Block serotonin at 5-HT3 receptor
- **Drugs:**
  - “Setrons”: Ondansetron (Zofran), Palonosetron, Granisetron, dolasetron, tropisetron
  - Mirtazapine (5HT2 and 5HT3)
  - Olanzapine (5HT2)
- **Side Effects:**
  - Headache, flushing, dizziness, itching, UA retention, constipation/diarrhea, rarely QT prolongation.

Substance P Antagonist

- **Mechanism:**
  - Block Substance P at the NK-1 Receptor
- **Drug:** only used for chemotherapy induced
  - Aprepitant (Emend), fosaprepitant, rolapitant, netupitant, casopitant
- **Side Effects:**
  - Headache, GI upset, elevated LFTs, dizziness, hiccups, asthenia
Corticosteroids

- **Mechanism:**
  - Not well understood, may prevent release of arachidonic acid (anti-inflammatory effects)

- **Drugs:**
  - Dexamethasone, methylprednisolone

- **Side Effects:**
  - Edema, insomnia, agitation, psychosis, adrenal insufficiency, GI upset/PUD, elevated FBG, infection, muscle weakness, osteoporosis, avascular necrosis, bleeding.

Cannabinoids

- **Mechanism:**
  - Affects cannabinoid receptors in vomiting center

- **Drugs:**
  - Natural or synthetic cannabinoids
  - Dronabinol (Marinol)
  - Nabilone (Cesamet)
  - Nabiximols (Sativex): Intranasal

- **Side Effects:**
  - Sedation, dizziness, agitation, hallucinations, seizures, (rare-cyclic vomiting syndrome)

Benzodiazepines

- **Mechanism:**
  - Enhance effects of GABA by binding to benzodiazepine receptors in the brain

- **Medications:**
  - Lorazepam: PO, IV
  - Alprazolam: PO
  - Diazepam: PO, IV, PR
  - Midazolam: PO, IV, PR, intranasal, SL

- **Side Effects:**
  - Sedation, dry mouth, dizziness, paradoxical agitation
Main drugs for chemo induced N/V

- **5HT3**
  - Ondansetron, granisetron (patch), dolasetron, palonosetron, tropisetron, ramosetron

- **Steroids**
  - Dexamethasone with or without NK1

- **NK1 antagonist**
  - Aprepitant, fosaprepitant, rolapitant

- **NEPA (Netupitant + palonosetron)**
  - Netupitant is NK1 antagonist

- **Cannabinoid receptors (CB1) antagonist**
  - Nabilone, or dronabinol.

- **Dopaminergic antagonist**
  - Metoclopramide, prochlorperazine, Olanzapine

Malignant Bowel Obstruction

- Malignant bowel obstruction occurs in 3–15% in patients with cancer.

- This is higher in patients with:
  - ovarian (20–50%) and colon cancer (10–29%).

Malignant Bowel Obstruction

- **Receptors:** Dopamine, Serotonin, somatostatin, Acetylcholine

- **Treatment:**
  - **First line:** Haloperidol + Dexamethasone + Ranitidine or PPI + anti-secretory +/- antispasmodic agents +/- Reglan
    - **Anti-secretory:** hyoscine (scopolamine) hydrobromide 0.2 to 0.4 mg every six to eight hours subcutaneously; or transdermal scopolamine, or glycopyrronium or octreotide, or cyclizine
    - **Anti-spasmodic:** hyoscine (scopolamine), dicyclomine, hyoscyamine.
    - **Promotility:** in patients who have no colic, a prokinetic (eg metoclopramide) is recommended, to help relieve a partial or functional obstruction
  - **Second Line:** Chlorpromazine, prochlorperazine

- **Surgical:** can consider debulking, stenting, Venting G Tube

- **Radiation:** depending on cancer and location.
Palliative Sedation?

- Intractable nausea and vomiting - Rare
  - 4% of cases when palliative sedation has been used was secondarily to nausea/vomiting
- Use of Propofol has been used since it affects GABA and 5HT3 in the CTZ along with anti-dopaminergic effects.
- Also midazolam, and levomepromazine has been used.


Other treatments/options

- Acupuncture
- Herbs: Ginger, Peppermint
- Vitamin B6 (pyridoxine): motion sickness
- Progressive muscle relaxation, biofeedback, CBT, systematic desensitization, guided imagery, hypnosis, music
- Nometex

Conclusion

- Nausea and vomiting is a common and distressing symptoms affecting the majority of palliative and hospice patients.
- Prevalence does increase as one gets closer towards the end of life.
- Key is once you figure out the cause, is to then target treatment to hit that receptor(s).
Thanks!

Any questions?
You can find me at:
- Email: jgabbard@wakehealth.edu

Credits
Special thanks to The Carolina Center for sponsoring this lecture

Helpful Tables for you

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medications</th>
</tr>
</thead>
</table>
| Dopamine Antagonists | - Metoclopramide (Reglan) 10 - 20 mg po/qs/pr q4-8h  
- Haloperidol 0.5 - 1 mg po/sq/lv q6-12h  
- Prochlorperazine (Compazine) 5 - 20 mg po/pr/lv q4-8h  
- Olanzapine – start with 2.5 - 5 mg once/day  
- Promethazine (Phenergan) 12.5-25mg po/lv IV Q6 hour  
- Chlorpromazine (Thorazine): 10-25mg Po/M Q4-6 hour |
| Prokinetic | - Metoclopramide 10 - 20 mg po/qs/pr q4-8h |
| Anticholinergic | - Scopolamine patch (Transderm-NF) 1-3 Q1/2 hours  
- Scopolamine 0.1-0.4 S/CIV Q4 hours  
- Hyoscymine (Levsin): 0.125-0.25mg Q6-8 Q8 hour  
- Glycopyrrolate (Robinul): 1 mg orally or 0.2 mg subcutaneously or intravenously every four to eight hours as needed  
- Olanzapine: 5-10mg po daily  
- Chlorpromazine (Thorazine): 10-25mg Po/M Q4-6 hour  
- Prochlorperazine (Compazine) 5 - 20 mg po/lv q4-8h |
### H1 Antagonists
- Promethazine (Phenergan): 25 mg po/iv q4-6h
- Meclizine (Dramamine): 25-50 mg po q6-12h
- Diphenhydramine (Benadryl): 25-50 mg po/sc/iv daily
- Hydroxyzine (Atarax): 25-50 mg po Q6 hour
- Cyclizine (not in the US)
- Chlorpheniramine: 3.5 - 5 mg once/day
- Dimenhydrinate: 3-6 mg po QPM

### Serotonin Antagonists
- Ondansetron: 4 - 8 mg bid-tid po/sc/iv
- Granisetron: 0.5–1 mg po/sc/iv OD – bid
- Dolasetron (Anzemet)/Palonosetron (Aloxi®)
- Mirtazapine: 7.5-15 mg po QPM

### Cannabinoids
- Nabilone: 1 – 2 mg po bid
- Dronabinol: 2.5 mg po bid, titrated up

### Miscellaneous
- Dexamethasone: 2 - 8 mg po/sc/iv OD-qid
- Lorazepam: 0.5 - 1 mg po/sc/iv q4-12h
- Octreotide: 100-400 mcg SC Q8 hour (bowel obstructions)

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### Helpful Tables for you