Nausea, emesis, and antiemetics

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Differential diagnosis of nausea and vomiting

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5HT3 antagonists (especially ondansetron)

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PDF of this chapter

medications which may cause nausea

- Chemotherapy
- Analgesics

https://emcrit.org/ibcc/antiemetic/
- Aspirin
- NSAIDs
- Opioids
- Antibiotics
  - Erythromycin
  - Sulfonamides
  - Acyclovir
- Cardiovascular
  - Antiarrhythmics
  - Antihypertensives (beta-blockers, calcium channel blockers)
  - Digoxin
  - Diuretics
- Endocrine
  - Oral contraception
  - Oral antidiabetic agents
- Neurology
  - Anticonvulsants
  - Parkinson's disease medications (dopaminergic)

**endocrine / metabolic**
- Pregnancy (generally within the first nine weeks of pregnancy)
- Uremia
- Fulminant hepatic failure
- Ketoacidosis (e.g., diabetic ketoacidosis)
- Hyperparathyroidism, hypoparathyroidism
- Hyperthyroidism
- Addison's disease

**gastrointestinal**
- Obstruction (e.g., intestinal obstruction, gastric outlet obstruction)
- Hypomotility (e.g., gastroparesis, ileus)
- Acute gastroenteritis
- Pancreatitis
- Cholecystitis
- Mesenteric ischemia
- Appendicitis

**central nervous system**
- Ear and labyrinthine disorders (often associated with vertigo)
  - Vestibular neuronitis
  - Meniere's disease
  - Otitis media
- Intracranial pressure elevation
- Migraine
- Cyclic vomiting syndrome, cannabinoid hyperemesis syndrome

### evaluation of the patient with nausea and vomiting

History and physical examination are the highest yield investigations. In many cases, these may reveal the etiology without additional evaluation. For patients in whom initial investigation is unrevealing, the following studies may be considered (with an evaluation tailored to the patient).
physical examination

- Neurologic examination
  - If concern for elevated intracranial pressure, assess this using optic nerve ultrasonography. (https://emcrit.org/pulmcrit/pulmcrit-algorithm-diagnosing-icp-elevation-ocular-sonography/)
- Abdominal examination, ideally using ultrasonography
  - i) Gastric ultrasonography (http://www.gastricultrasound.org/) may estimate size and contents of the stomach.
  - ii) Small bowel peristalsis may be assessed, to evaluate for obstruction.
- Measurement of gastric residual volume (for intubated patients with a gastric tube)

laboratory studies

- Chemistries (including Ca/Mg/Phos)
- Liver function tests
- Lipase, if clinical concern for pancreatitis
- Cortisol level, if adrenal insufficiency is suspected
- TSH, if hyperthyroidism is suspected
- Pregnancy testing, as appropriate

imaging studies

- Abdominal X-ray may be considered, to evaluate for obstruction or ileus.
- Neuroimaging, if history and physical examination suggest elevated intracranial pressure.

treatment

Ideally, the treatment would involve specific resolution of the underlying cause. Contributory factors should be addressed as possible (e.g., reduction of opioid dose by using adjunctive analgesics).

Realistically, it is often difficult to immediately identify and reverse the cause. Nausea and vomiting are enormously uncomfortable and potentially dangerous (e.g., due to aspiration or inability to take oral medication). Therefore, symptomatic treatment is often valuable, using one or more antiemetic agents.

pharmacological fundamentals

pathophysiology of emesis

- Treatment of emesis involves understanding the neural pathways involved. Blocking receptors involved in these pathways may alleviate emesis.
- Vestibular etiologies of nausea involve H1 histamine and M1 muscarinic acetylcholine receptors. Consequently, antihistamine and anticholinergic medications may be useful to treat these etiologies of nausea.
- Most other causes of nausea seem to involve several receptors (especially the SHT-3 serotonin receptors, D2 dopamine receptors, M1 muscarinic acetylcholine receptors, and the H1 histamine receptors). Consequently, most broad-spectrum antiemetic drugs will inhibit one or more of these receptors.
construction of antiemetic regimens

- Antiemetics generally have similar efficacy, so selection is based largely on selecting medications with the most favorable side effect profiles. However, one exception to this is that certain conditions may be more sensitive to specific agents. For example:
  - Vestibular etiologies may respond best to anticholinergic or antihistamine agents.
  - Gastroparesis may be best treated by metoclopramide and perhaps haloperidol/droperidol as a 2nd line agent.
  - Migraine headache may respond to prochlorperazine or metoclopramide, perhaps with the addition of ondansetron.
- If a single antiemetic agent is ineffective, then a second agent may be added to it (ideally targeting a different receptor).
- Ondansetron is often chosen as a front-line agent, due largely to its lack of serious side effects. However, ondansetron can prolong QT interval and increase the risk of Torsade de Pointes (more on this below).
- Drugs with activity against the D2 receptor are often added as second-line agents (e.g., haloperidol, olanzapine, or prochlorperazine). An exception to this would patients with Parkinson's disease, in whom D2 receptor antagonism should be avoided.
- Sniffing isopropyl alcohol pads has been demonstrated to be effective in some studies. Aromatherapy is doubtless the safest medical intervention for treatment of nausea/vomiting. Thus, it may be reasonable to add this as a co-intervention with a front-line parenteral antiemetic.
**general comments**

- Ondansetron is a fairly safe and broad-spectrum antiemetic. Unlike many other antiemetic agents, there are no sedative or extrapyramidal side effects.
- Ondansetron is often used as front-line therapy for management of nausea/vomiting.

**dosing**

- 8 mg PO/IV q8hr PRN. Infuse or slowly push each dose over 15 minutes.
- Oral disintegrating tablet (ODT) may be useful in patients unable to swallow (8 mg ODT q8hr PRN).
- Renal impairment: No adjustment
- Significant liver dysfunction (Child class C cirrhosis): max 8 mg per 24 hours.

**cautions & contraindications**

- Contraindication: QT prolongation or high risk of Torsade de Pointes (e.g., untreated hypokalemia).
  - Ondansetron can prolong QT interval and cause Torsade de Pointes. ([29259513](https://pubmed.ncbi.nlm.nih.gov/29259513/))
  - Among commonly utilized antiemetics, ondansetron might carry a relatively higher risk of Torsade de Pointes than other agents. In contrast, there is widespread concern regarding haloperidol or droperidol, but the risk of Torsade de Pointes is probably minimal at the tiny doses of droperidol or haloperidol which are used to treat nausea.
  - Although ondansetron might be riskier than some other antiemetics, the absolute risk of arrhythmia remains low. Ondansetron is one of the most widely utilized medications, yet relatively few reports exist of its causing Torsade de Pointes. ([24314899](https://pubmed.ncbi.nlm.nih.gov/24314899/)) Interestingly, many of these events occurred within 1-2 minutes of rapidly pushing ondansetron—an unnecessarily risky practice which should probably be avoided (figure above).
- The most common side effects are mild headache (1/36 patients) and constipation (1/23 patients).

**palonosetron**

- Palonosetron is a second-generation 5HT3 antagonist, with the following advantages compared to ondansetron:
  - Absence of QT prolongation (perhaps the greatest advantage). ([26111957](https://pubmed.ncbi.nlm.nih.gov/26111957/))
  - Longer half-life (~40 hours).
  - Superior efficacy compared to ondansetron (especially the 8-mg dosing of ondansetron).
- 0.25 mg palonosetron IV is a commonly used dose for prevention of chemotherapy-induced nausea and vomiting. ([26345982](https://pubmed.ncbi.nlm.nih.gov/26345982/))
- There are no real contraindications to palonosetron (aside from a history of anaphylaxis to the drug).
The main drawback is cost and availability. Palonosetron is a bit more expensive than ondansetron (a single 0.25 mg dose costs $130 according to goodrx.com). However, improved efficacy and reduced need to redose palonosetron can render it cost-effective. (17532704)

More: MedScape monograph on palonosetron

**butyrophenones (haloperidol & droperidol)**

**general comments**

- There don’t appear to be any substantive differences between these two agents regarding antiemetic efficacy. Haloperidol is one half as potent as droperidol, so twice as large a dose will be required.
- Advantages of these agents include their being ubiquitously available and their ability to provide titrated intravenous administration (most units should have at least one of them on hand).

**dosing for nausea/vomiting**

- **Droperidol**
  - The usual dose is 0.625-1.25 mg IV. An additional dose may be provided if needed after 20-30 minutes. Subsequently, the effective dose may be repeated q4 hours PRN.
  - Each dose may be given as a slow IV push over ~5 minutes.
  - More: MedScape monograph on droperidol

- **Haloperidol**
  - The usual dose is 2-3 mg IM/IV. An additional dose may be provided if needed after 20-30 minutes. Subsequently, the effective dose may be repeated q4 hours PRN.
  - Each dose may be given as a slow IV push over ~5 minutes.
  - More: MedScape monograph on haloperidol

**cautions & contraindications**

- Contraindications
  - Parkinson's disease.
  - Tenuous mental status, causing a risk of oversedation.
  - QT prolongation. Note, however, that their effect on QT interval will be minimal and likely clinically insignificant at the low doses used for nausea/vomiting.
- Side effects: sedation, extrapyramidal symptoms.

**phenothiazines (prochlorperazine, chlorpromazine, promethazine)**

**general comments**

Prochlorperazine (COMPAZINE) is more selective for D2 receptors. This comes with advantages and disadvantages:

- Advantage - Less sedation than other phenothiazines.
- Disadvantage – Higher rate of extrapyramidal side effects (e.g., akathisia, dystonia).
- Prochlorperazine is available over the counter in the United States, implying a reasonable safety profile.
- Promethazine (PHENERGAN)
  - Disadvantage – Can cause tissue damage if extravasation, so generally shouldn't be given intravenously.

- Chlorpromazine (THORAZINE)
  - It is not typically used for treatment of nausea/vomiting. However, chlorpromazine is overall quite similar to promethazine.
  - Chlorpromazine could be considered as an alternative to promethazine, especially if intravenous administration is required.

**dosing**

- Promethazine (PHENERGAN)
  - **dosing**
  - 5-10 mg IV q4-6 hours PRN (max 40 mg total daily).

- Chlorpromazine (THORAZINE)
  - 25 mg IM/IV q4-8 hours PRN.

- Promethazine (PHENERGAN)
  - 12.5-25 mg PO/IM q4-6hr PRN (max 25 mg/dose, max 100 mg/day).
  - 25 mg per rectum q12 hours PRN.
  - IV administration is avoided, since severe tissue damage can occur. ([25841474](https://pubmed.ncbi.nlm.nih.gov/25841474/))

**cautions & contraindications**

- General contraindications to these agents:
  - Parkinson's disease
  - Somnolence, with a risk of respiratory suppression
  - Chlorpromazine (THORAZINE): May cause neutropenia, so it's contraindicated in leukopenia.
  - Chlorpromazine (THORAZINE) and promethazine (PHENERGAN) may prolong the QT interval.

**general comments**

- Advantages
  - Olanzapine does not cause clinically relevant prolongation of QT or Torsade de Pointes (discussed [here](https://emcrit.org/pulmcrit/intravenous-olanzapine-haloperidol/)).
  - Olanzapine has a lower risk of extrapyramidal effects, compared to agents with greater action on the D2 receptors (e.g., droperidol and haloperidol).

- Disadvantages
  - Olanzapine does cause some sedation.
  - Olanzapine is generally less readily available than haloperidol (olanzapine will typically need to be ordered from central pharmacy, as opposed to haloperidol, which is ubiquitous).

**dosing**

- 2.5 mg IV/IM q4 hours PRN (max 20 mg/day).
- If giving intravenously, provide as a slow IV push over ~5 minutes (similar to haloperidol). Although olanzapine is labeled for IM use, it can be given intravenously (discussed [here](https://emcrit.org/pulmcrit/intravenous-olanzapine-haloperidol/), and [here](https://emcrit.org/pulmcrit/v-olanzapine/)).
- Higher doses (e.g., 5 mg) could be considered if the patient has concurrent agitation or anxiety. Alternatively, 2.5 mg may be given as an initial dose, then followed with a subsequent dose after about half an hour if there is inadequate response.

**cautions & contraindications**

- The main concern is the possibility of oversedation.
Extrapyramidal side effects may occur, but these are generally less problematic than with agents that act more potently on D2 receptors (e.g., haloperidol, droperidol).

Olanzapine does not cause clinically relevant prolongation of QT or risk of Torsade de Pointes. This is especially true at the low doses used for treatment of nausea and vomiting.

Olanzapine (https://emcrit.org/pulmcrit/intravenous-olanzapine-haloperidol/) does not cause clinically relevant prolongation of QT or risk of Torsade de Pointes. This is especially true at the low doses used for treatment of nausea and vomiting.

Metoclopramide (https://emcrit.org/?attachment_id=477788)

Metoclopramide may be generally conceptualized as a combination of haloperidol plus a little ondansetron and some pro-kinetic activity (see receptor table above).

- Many antiemetics have both anti-D2 activity plus anticholinergic activity (e.g., olanzapine, prochlorperazine, promethazine). This intrinsic anticholinergic activity may reduce the rate of extrapyramidal symptoms caused by D2 antagonism (because anticholinergics can be used to treat extrapyramidal symptoms!). Agents with anti D2 activity that lack anticholinergic activity may tend to have the highest rate of extrapyramidal symptoms (e.g., haloperidol, droperidol, and metoclopramide).
- Metoclopramide’s pattern of predominant D2 antagonism suggests that it will be an effective antiemetic, but it will also cause extrapyramidal side effects. Alternatively, if metoclopramide is dosed low enough to avoid any potential extrapyramidal side effects, then it will cease to work as an antiemetic (more on this below).

Strengths
- Pro-kinetic properties may be beneficial for patients with gastroparesis.
- Lack of anticholinergic or antihistamine effects make metoclopramide non-sedating.

Dosing

- Background on dosing: Traditionally, 10 mg IV q4-6hrs PRN has often been used. However, this may be too low of a dose to have a substantial effect. An RCT evaluating the prevention of postoperative nausea and vomiting found no efficacy from 10 mg metoclopramide, with increasing efficacy at 25-mg or 50-mg doses (figure below). (16861255) Historically, doses as high as 200 mg q4hr have been used, but these doses were associated with higher rates of extrapyramidal effects (25841470). Doses of 1-2 mg/kg are currently recommended for prevention of chemotherapy-related emesis.
- One reasonable approach might be:
  - 20 mg or 25 mg IV q4-6hrs PRN
  - Slow intravenous infusion over 15 minutes reduces side effects (akathisia) without affecting efficacy.
- Reduce dose by half among patients with GFR 10-40 ml/min; reduce the dose by 75% if GFR <10 ml/min.
cautions & contraindications

- Side effects
  - Extrapyramidal effects can occur.
  - QT prolongation.

other agents

glucocorticoids

- These are not used as front-line agents, but can be useful in combination with other agents (e.g., ondansetron). They require ~4-5 hours to take effect, making them a poor choice for a patient with active emesis. [25841470](https://pubmed.ncbi.nlm.nih.gov/25841470/)
- Glucocorticoids have been investigated primarily for prevention of chemotherapy-induced nausea/vomiting. Among patients in the ICU, glucocorticoids could play a palliative role for patients with advanced malignancy and refractory nausea/vomiting.
- The mechanism of action is unknown.
- The most commonly investigated agent appears to be dexamethasone at doses of ~8 mg.

antihistamines

- Their benefit seems restricted mostly to nausea/vomiting due to vestibular abnormality and post-operative emesis.
- Antihistamines may be useful in patients with Parkinson's disease, who are at increased risk of extrapyramidal symptoms due to most other classes of antiemetics.
- Use of antihistamines in the ICU is limited by their promotion of delirium.

dronabinol

- Dronabinol is not generally used as an antiemetic in critical illness, but could be considered as a palliative measure in patients with malignancy.
- Side effects include sedation, tachycardia, dry mouth, and visual hallucinations.

summary table

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If the patient doesn't respond to one antiemetic, switching to a different agent may not work (especially to a different agent with a similar mechanism of action). Rather, it may be more effective to add a second agent that acts at a different receptor. (25841474)

Avoid rapid IV pushes of antiemetic agents, as this may increase the risk of side effects (especially QT prolongation with ondansetron, or extrapyramidal side effects with D2 receptor antagonists).

Avoid D2 receptor antagonists in patients with Parkinson's disease.

Be extremely cautious about the intravenous use of promethazine (or perhaps avoid this entirely). Extravasation or inadvertent intra-arterial administration of promethazine can cause tissue necrosis.

**Going further:**

- EM Cases: [Drugs that work and Drugs that don't](https://emergencymedicinecases.com/em-drugs-that-work-part-2/): Antiemetics, Angioedema, Oxygen (Anton Helman)
references


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.