

Antiemetics

Nausea and vomiting are driven by at least four separate receptor systems, and antiemetics are chosen by which one is firing: serotonin 5-HT₃ receptors after chemotherapy or surgery, dopamine D₂ receptors in the chemoreceptor trigger zone, histamine H₁/muscarinic receptors in the vestibular pathway of motion sickness, or substance P/neurokinin-1 receptors in delayed chemotherapy-induced nausea - each answered by a structurally different drug with its own defining harm.

Online guide: <https://www.medguideglobal.com/pharmacology/gastrointestinal/antiemetics>

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Quick revision

One Liner: Antiemetics are organised by the receptor driving the nausea, not by the drug class name: 5-HT₃ antagonists for chemotherapy/postoperative nausea, dopamine D₂ antagonists for the chemoreceptor trigger zone, H₁/muscarinic antagonists for motion sickness, and NK₁ antagonists for delayed chemotherapy-induced nausea - and each group carries a defining, receptor-linked harm rather than a generic side-effect list.

1. Ondansetron and the other 5-HT₃ antagonists block serotonin receptors both peripherally on vagal afferents in the gut and centrally in the chemoreceptor trigger zone, and prolong the QT interval in a dose-dependent way, with postmarketing Torsades de Pointes reported. [1]
2. Metoclopramide is a dopamine D₂ antagonist with prokinetic gut effects, but it carries a boxed warning for tardive dyskinesia, a movement disorder that is often irreversible, whose risk rises with treatment duration and cumulative dose - treatment beyond 12 weeks is specifically discouraged for that reason. [2]
3. Prochlorperazine, a phenothiazine dopamine antagonist related to the antipsychotics, treats nausea through the same D₂-blocking chemoreceptor-trigger-zone mechanism and shares the class's risk of extrapyramidal reactions and tardive dyskinesia with prolonged use. [3]
4. Promethazine and meclizine are H₁-antihistamines with anticholinergic activity that act on the vestibular apparatus and vomiting centre, making them the drugs of choice for motion sickness rather than for chemotherapy-induced nausea. [4]
5. Promethazine injection carries a boxed warning for severe tissue injury, including gangrene, if it leaks outside the vein (extravasation) or is injected intra-arterially or subcutaneously; it must be given by deep intramuscular injection or through a running IV line. [4]
6. Aprepitant and its prodrug fosaprepitant are neurokinin-1 (NK₁) receptor antagonists used specifically to prevent delayed chemotherapy-induced nausea and vomiting, and they are clinically significant CYP3A4 substrates, inhibitors and inducers with real drug-interaction potential. [5]
7. The organising exam logic is "which nausea, which receptor": vestibular/motion nausea responds to H₁/muscarinic blockade, chemotherapy/postoperative nausea to 5-HT₃ or dopamine blockade, and delayed chemotherapy nausea specifically to NK₁ blockade - picking the wrong receptor family for the wrong trigger is the commonest conceptual error. [10]

Overview

1. Nausea and vomiting are not produced by a single pathway, which is why antiemetics cannot be organised the way, say, antibiotics are. At least four separate receptor systems converge on the brainstem's vomiting centre and chemoreceptor trigger zone: serotonin (5-HT₃) receptors, activated heavily by chemotherapy and surgery through vagal afferents in the gut wall and directly in the trigger zone; dopamine (D₂) receptors, densely expressed in the chemoreceptor trigger zone itself; histamine (H₁) and muscarinic acetylcholine receptors, central to the vestibular pathway that produces motion sickness; and neurokinin-1 (NK₁) receptors, bound by substance P and specifically

implicated in the delayed phase of chemotherapy-induced nausea that starts more than a day after treatment. A rational choice of antiemetic starts with identifying which of these systems is actually driving the nausea in front of the clinician. [10]

2. Ondansetron is the prototype 5-HT₃ antagonist and the drug most associated with preventing chemotherapy-induced and postoperative nausea and vomiting. Its defining risk is cardiac rather than gastrointestinal: the drug prolongs the QT interval in a dose-dependent manner, and postmarketing reports include Torsades de Pointes. This led the FDA to remove the single 32 mg intravenous dose from the label and to specifically recommend ECG monitoring in patients with electrolyte abnormalities such as hypokalaemia or hypomagnesaemia, congestive heart failure, bradyarrhythmias, or those taking other QT-prolonging drugs, and to avoid the drug altogether in congenital long QT syndrome. [1]

3. Metoclopramide and prochlorperazine both work by blocking dopamine D₂ receptors in the chemoreceptor trigger zone, but that same receptor blockade produces extrapyramidal symptoms because D₂ receptors are also central to normal motor control in the basal ganglia. Metoclopramide's label carries a boxed warning specifically for tardive dyskinesia, a repetitive, involuntary movement disorder that is often irreversible once established; the risk increases with both the duration of treatment and the total cumulative dose, which is why the label recommends against using metoclopramide for longer than 12 weeks except in rare cases where the benefit is judged to outweigh the risk. Prochlorperazine, a phenothiazine structurally related to the antipsychotics, carries a comparable extrapyramidal and tardive dyskinesia risk through the same dopamine-blocking mechanism, alongside its own sedative and anticholinergic effects. [2][3]

4. Promethazine and meclizine belong to a mechanistically different group: H₁-antihistamines with meaningful anticholinergic activity, acting on the vestibular apparatus and the vomiting centre rather than primarily on the chemoreceptor trigger zone. This is why they are the standard choice for motion sickness rather than for chemotherapy-induced nausea, and why sedation and dry mouth, not extrapyramidal symptoms, dominate their side-effect profile. Promethazine carries its own distinct and unrelated hazard: given intravenously it can cause severe tissue injury, including gangrene, if it leaks outside the vein or is inadvertently given intra-arterially or subcutaneously, which is why its label requires deep intramuscular injection or administration through a running, clearly patent intravenous line, and carries a boxed warning to that effect. [4]

5. Aprepitant, and its injectable prodrug fosaprepitant, target yet another receptor: neurokinin-1, bound by substance P, specifically implicated in the delayed phase of chemotherapy-induced nausea and vomiting that 5-HT₃ antagonists alone control less well. Rather than a receptor-linked toxicity, this drug's defining pharmacological feature is drug-drug interaction potential: aprepitant is a substrate, moderate inhibitor and inducer of CYP3A4, so it is combined with chemotherapy and other drugs metabolised through that enzyme only with attention to the resulting interactions, and its labelling specifically flags reduced efficacy when co-administered with strong CYP3A4 inducers such as rifampin. [5]

Classification and drug examples

Intro: Antiemetics are grouped by the receptor they block, because that receptor also predicts both which type of nausea the drug treats well and which specific harm it carries.

1. Name: 5-HT₃ (serotonin) receptor antagonists

1. Note: Block serotonin receptors on vagal afferents and in the chemoreceptor trigger zone; the class-defining risk is dose-dependent QT prolongation.

1. Name: Ondansetron

Zofran

1. Route: Oral, IV, orally disintegrating tablet

1. Note: The 32 mg single IV dose was removed from the label after being linked to significant QT prolongation. [1]

2. Name: Granisetron

Kytril

2. Route: Oral, IV, transdermal

2. Note: Same 5-HT₃ mechanism as ondansetron; also used for chemotherapy- and radiation-induced nausea. [6]

3. Name: Palonosetron (as netupitant/palonosetron)

Akynzeo

3. Route: Oral, IV

3. Note: A longer-acting 5-HT₃ antagonist marketed combined with the NK₁ antagonist netupitant for both acute and delayed chemotherapy-induced nausea. [7] [1]

2. Name: Dopamine D₂ receptor antagonists

2. Note: Block D₂ receptors in the chemoreceptor trigger zone; the same mechanism that controls nausea also risks extrapyramidal symptoms and tardive dyskinesia.

1. Name: Metoclopramide

Reglan

1. Route: Oral, IV, IM

1. Note: Boxed warning for tardive dyskinesia; treatment beyond 12 weeks is specifically discouraged. [2]

2. Name: Prochlorperazine

Compazine

2. Route: Oral, IM, IV, rectal

2. Note: A phenothiazine antipsychotic-family drug used at antiemetic doses; shares the class's tardive dyskinesia risk with prolonged high-dose use. [3] [2]

3. Name: H₁-antihistamine / anticholinergic antiemetics

3. Note: Act on the vestibular pathway rather than the chemoreceptor trigger zone; the drugs of choice for motion sickness rather than chemotherapy-induced nausea.

1. Name: Promethazine

Phenergan

1. Route: Oral, rectal, IM, IV

1. Note: Boxed warning for severe tissue injury, including gangrene, with extravasation or improper injection route. [4]

2. Name: Meclizine

1. Antivert

2. Bonine

2. Route: Oral

2. Note: OTC antihistamine specifically marketed for prevention and treatment of motion sickness; not separately profiled with a registry medicine page on this site. [8]

3. Name: Dimenhydrinate

Dramamine

3. Route: Oral

3. Note: A diphenhydramine salt with the same vestibular H₁/anticholinergic mechanism, also used for motion sickness. [9] [4]

4. Name: NK₁ (neurokinin-1) receptor antagonists

4. Note: Block substance P signalling implicated specifically in delayed chemotherapy-induced nausea and vomiting; defined by CYP3A4 interaction potential rather than a receptor-linked toxicity.

Name: Fosaprepitant

Emend for injection

Route: IV

Note: A prodrug converted to aprepitant within about 30 minutes of infusion; carries the same CYP3A4 interaction profile as oral aprepitant. [5] [5]

Mechanism of action

Summary: Each antiemetic subclass blocks a different receptor along the pathway that produces nausea and vomiting:

5-HT₃ receptors on vagal afferents and in the chemoreceptor trigger zone, dopamine D₂ receptors in the chemoreceptor trigger zone, histamine H₁ and muscarinic receptors along the vestibular pathway to the vomiting centre, and neurokinin-1 receptors bound by substance P, which are particularly implicated in the delayed phase of chemotherapy-induced emesis. Which receptor is actually driving a given episode of nausea determines which class will work.

Target: 5-HT₃ receptors (serotonin antagonists); dopamine D₂ receptors (dopamine antagonists); histamine H₁ and muscarinic acetylcholine receptors (antihistamine/anticholinergic antiemetics); neurokinin-1 receptors (NK1 antagonists)

Cidal Static: Not applicable - these are receptor antagonists acting on the patient's own neural pathways, not on a pathogen

Kill Kinetics: Onset within roughly 30 minutes to 2 hours for oral/IV dosing across the class; duration tracks each drug's own half-life rather than a shared kinetic profile

1. Step: 1

1. Title: Chemotherapy, surgery or gut irritation releases serotonin from enterochromaffin cells

1. Detail: Serotonin released from the gut wall activates 5-HT₃ receptors on vagal afferent nerves, which relay the signal to the brainstem, and also acts directly on 5-HT₃ receptors in the chemoreceptor trigger zone. [10]

2. Step: 2

2. Title: 5-HT₃ antagonists block that serotonin signal at both sites

2. Detail: Ondansetron and related drugs competitively block 5-HT₃ receptors peripherally on vagal afferents and centrally in the chemoreceptor trigger zone, interrupting the nausea signal at its source and at its relay point. [1]

3. Step: 3

3. Title: Circulating toxins and drugs activate dopamine D₂ receptors in the chemoreceptor trigger zone

3. Detail: The chemoreceptor trigger zone sits outside the blood-brain barrier and is rich in dopamine D₂ receptors, which is why circulating drugs and toxins can trigger nausea through this route. [10]

4. Step: 4

4. Title: Dopamine antagonists block that D₂ signal, but the same receptor family runs motor control

4. Detail: Metoclopramide and prochlorperazine block D₂ receptors in the chemoreceptor trigger zone to suppress nausea, but D₂ receptors are also central to the nigrostriatal motor pathway, which is the anatomical basis for the extrapyramidal symptoms and tardive dyskinesia risk shared by this subclass. [2]

5. Step: 5

5. Title: Vestibular stimulation activates histamine H₁ and muscarinic receptors

5. Detail: Motion sickness arises from a mismatch of vestibular and visual input that signals through H₁ and muscarinic pathways to the vomiting centre, which is why antihistamines with anticholinergic activity, not 5-HT₃ or D₂ antagonists, are the standard treatment for this specific trigger. [4]

6. Step: 6

6. Title: Substance P activates NK₁ receptors, especially in delayed chemotherapy-induced nausea

6. Detail: Substance P release and NK₁ receptor activation are particularly implicated in the delayed phase of chemotherapy-induced nausea and vomiting, occurring more than 24 hours after chemotherapy, a phase that 5-HT₃ antagonism alone controls less effectively. [5]

7. Step: 7

7. Title: NK₁ antagonists block that substance P signal

7. Detail: Aprepitant and fosaprepitant (its prodrug, converted to aprepitant within about 30 minutes of infusion) block NK₁ receptors, extending antiemetic coverage into the delayed phase when added to a 5-HT₃ antagonist and a corticosteroid. [5]

Major clinical uses

1. Drug: Ondansetron / granisetron / palonosetron

1. Organism: Not applicable
1. Indication: Prevention of chemotherapy-induced and radiation-induced nausea and vomiting; prevention and treatment of postoperative nausea and vomiting
1. Line: first-line for chemotherapy- and surgery-related nausea
1. Note: ECG monitoring recommended in patients with electrolyte abnormalities, heart failure, bradyarrhythmia, or on other QT-prolonging drugs. [1]
2. Drug: Metoclopramide
2. Organism: Not applicable
2. Indication: Gastroparesis (short-term), gastroesophageal reflux (short-term), and prevention of chemotherapy-induced nausea
2. Line: second-line, short-term use given the tardive dyskinesia risk with prolonged treatment
2. Note: Not recommended for longer than 12 weeks of treatment except in select cases. [2]
3. Drug: Prochlorperazine
3. Organism: Not applicable
3. Indication: Control of severe nausea and vomiting; short-term management of non-psychotic anxiety at low dose
3. Line: used for nausea not adequately controlled by other agents, or where a sedating antiemetic is wanted
3. Note: Also has genuine antipsychotic indications outside its antiemetic use. [3]
4. Drug: Promethazine / dimenhydrinate / meclizine
4. Organism: Not applicable
4. Indication: Motion sickness prevention and treatment; nausea and vomiting associated with anaesthesia and surgery (promethazine specifically)
4. Line: first-line for motion sickness; promethazine also used perioperatively
4. Note: Sedation is a prominent, expected effect of this subclass. [4][8]
5. Drug: Fosaprepitant (aprepitant prodrug)
5. Organism: Not applicable
5. Indication: Prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic chemotherapy, in combination with a 5-HT₃ antagonist and a corticosteroid
5. Line: add-on to a 5-HT₃ antagonist/corticosteroid regimen for delayed-phase coverage
5. Note: Real CYP3A4 interaction potential with concomitant chemotherapy and other drugs. [5]

Pharmacokinetics

1. Drug: Ondansetron
1. Route: Oral, IV, orally disintegrating tablet
1. Absorption: Well absorbed orally
1. Csf Penetration: See prescribing reference
1. Metabolism: Hepatic, primarily CYP3A4 with contributions from CYP1A2 and CYP2D6
1. Elimination: Hepatic, with renal excretion of metabolites
1. Dose Adjust: Hepatic impairment; QT-prolonging comedications; congenital long QT syndrome is a contraindication [1]
2. Drug: Metoclopramide
2. Route: Oral, IV, IM
2. Absorption: Well absorbed orally
2. Csf Penetration: Crosses into the CNS, which underlies both its antiemetic action and its extrapyramidal risk
2. Metabolism: Limited hepatic metabolism
2. Elimination: Primarily renal
2. Dose Adjust: Renal impairment; total treatment duration capped because of tardive dyskinesia risk [2]
3. Drug: Promethazine

- 3. Route: Oral, rectal, IM, IV
- 3. Absorption: Well absorbed orally
- 3. Csf Penetration: Crosses into the CNS, producing sedation as an expected effect
- 3. Metabolism: Hepatic
- 3. Elimination: Hepatic and renal
- 3. Dose Adjust: IV administration requires a patent, running line or deep IM injection because of extravasation/tissue-injury risk [4]
- 4. Drug: Fosaprepitant / aprepitant
- 4. Route: IV (fosaprepitant); oral (aprepitant)
- 4. Absorption: Fosaprepitant is converted to aprepitant within about 30 minutes of IV infusion
- 4. Csf Penetration: See prescribing reference
- 4. Metabolism: Hepatic, via CYP3A4, with aprepitant itself acting as a CYP3A4 substrate, inhibitor and inducer
- 4. Elimination: Hepatic
- 4. Dose Adjust: Concomitant strong CYP3A4 inducers reduce efficacy; concomitant CYP3A4 substrates may need dose adjustment [5]
- 1. This page gives no dose regimens by design. Dose selection depends on the indication, the emetogenic trigger, renal/hepatic function and concomitant drugs, and belongs in a current prescribing reference used by the treating clinician.
- 2. Only the NK1 antagonist subclass has meaningful CYP3A4 drug-interaction potential as its defining pharmacokinetic feature; the other three subclasses are differentiated mainly by receptor target and CNS penetration rather than by enzyme interactions. [5]

Adverse effects

- 1. Effect: Headache and constipation
- 1. Detail: Common with 5-HT₃ antagonists such as ondansetron, reported in a meaningful minority of patients. [1]
- 2. Effect: Sedation and dry mouth
- 2. Detail: Expected with the H₁-antihistamine/anticholinergic subclass (promethazine, dimenhydrinate, meclizine) because of their central antihistaminergic and anticholinergic activity. [4]
- 3. Effect: Restlessness and mild extrapyramidal symptoms
- 3. Detail: Reported with metoclopramide and prochlorperazine even at short-term, therapeutic dosing, distinct from the longer-term tardive dyskinesia risk. [2]
- 1. Effect: QT prolongation and Torsades de Pointes
- 1. Detail: Ondansetron prolongs the QT interval in a dose-dependent manner; postmarketing cases of Torsades de Pointes have been reported, which is why the single 32 mg IV dose was removed from the label.
- 1. Action: ECG monitoring is recommended in patients with electrolyte abnormalities, heart failure, bradyarrhythmia or concomitant QT-prolonging drugs; the drug is avoided in congenital long QT syndrome. [1]
- 2. Effect: Tardive dyskinesia
- 2. Detail: Metoclopramide carries a boxed warning for tardive dyskinesia, a movement disorder that is often irreversible; risk rises with treatment duration and cumulative dose. Prochlorperazine carries a related risk through the same D₂-blocking mechanism.
- 2. Action: Treatment beyond 12 weeks is specifically discouraged for metoclopramide; therapy is discontinued immediately if signs of tardive dyskinesia appear. [2][3]
- 3. Effect: Severe tissue injury, including gangrene, with promethazine extravasation
- 3. Detail: Promethazine given intravenously can cause severe chemical irritation and tissue damage, including gangrene, if it leaks outside the vein or is inadvertently given intra-arterially or subcutaneously.
- 3. Action: The label requires deep intramuscular injection or administration only through a clearly patent, freely running intravenous line, and carries a boxed warning to that effect. [4]

- 4. Effect: Reduced antiemetic efficacy from CYP3A4 drug interaction
- 4. Detail: Concomitant strong CYP3A4 inducers such as rifampin can meaningfully reduce aprepitant/fosaprepitant plasma concentrations and antiemetic efficacy.
- 4. Action: Concomitant medications are reviewed for CYP3A4 interaction before starting an NK1 antagonist regimen. [5]

1. Drug: Ondansetron

- 1. Effect: The only drug in this class whose label change (removal of the 32 mg IV dose) was driven directly by a cardiac safety signal rather than an efficacy finding. [1]

2. Drug: Metoclopramide

- 2. Effect: The only member with an explicit maximum-duration recommendation (12 weeks) written directly into its boxed warning. [2]

3. Drug: Promethazine

- 3. Effect: The only member whose boxed warning concerns the injection technique itself rather than a systemic drug effect. [4]

4. Drug: Fosaprepitant/aprepitant

- 4. Effect: The only member whose defining pharmacological property is CYP3A4 substrate/inhibitor/inducer behaviour rather than a receptor-linked organ toxicity. [5]

Contraindications, precautions and interactions

- 1. Ondansetron: concomitant apomorphine (risk of profound hypotension and loss of consciousness); congenital long QT syndrome. [1]

- 2. Metoclopramide: history of tardive dyskinesia; conditions where increased gastrointestinal motility is dangerous, such as GI haemorrhage, obstruction or perforation. [2]

- 3. Promethazine: use in children under 2 years of age; subcutaneous or intra-arterial injection. [4]

- 1. 5-HT₃ antagonists are used cautiously with other QT-prolonging drugs and in patients with electrolyte disturbance, heart failure or bradyarrhythmia. [1]

- 2. Dopamine antagonists are used at the lowest effective dose for the shortest necessary duration given the tardive dyskinesia risk shared by the subclass. [2][3]

- 3. Promethazine and other sedating antihistamine antiemetics are used cautiously in patients with respiratory compromise, in the elderly, and alongside other CNS depressants. [4]

- 4. Concomitant medications are reviewed for CYP3A4 interaction before and during aprepitant/fosaprepitant therapy, particularly chemotherapy agents metabolised through that enzyme. [5]

1. With: Other QT-prolonging drugs

- 1. Effect: Additive QT prolongation risk with ondansetron and related 5-HT₃ antagonists. [1]

2. With: Other CNS depressants

- 2. Effect: Additive sedation with promethazine, dimenhydrinate and meclizine. [4]

3. With: Strong CYP3A4 inhibitors or inducers

- 3. Effect: Alter aprepitant/fosaprepitant exposure and efficacy, and aprepitant itself can raise plasma levels of other CYP3A4-metabolised drugs, including some chemotherapy agents. [5]

4. With: Other dopamine antagonists or antipsychotics

- 4. Effect: Additive extrapyramidal symptom risk with metoclopramide or prochlorperazine. [2]

Comparison tables

Title: Which nausea, which receptor

Caption: Choice of antiemetic subclass is driven by the clinical trigger for the nausea, because each receptor family answers a different trigger and carries a different defining risk.

1. Key: subclass

1. Label: Subclass
2. Key: receptor
2. Label: Receptor blocked
3. Key: best_for
3. Label: Best-matched trigger
4. Key: defining_risk
4. Label: Defining risk
1. Subclass: 5-HT3 antagonists
1. Receptor: Serotonin 5-HT3
1. Best For: Chemotherapy- and surgery-related nausea
1. Defining Risk: Dose-dependent QT prolongation [1]
2. Subclass: Dopamine antagonists
2. Receptor: Dopamine D2
2. Best For: Chemoreceptor-trigger-zone-driven nausea, gastroparesis
2. Defining Risk: Extrapyramidal symptoms and tardive dyskinesia [2]
3. Subclass: H1-antihistamines/anticholinergics
3. Receptor: Histamine H1 and muscarinic
3. Best For: Motion sickness
3. Defining Risk: Sedation; promethazine specifically risks tissue injury from improper IV administration [4]
4. Subclass: NK1 antagonists
4. Receptor: Neurokinin-1 (substance P)
4. Best For: Delayed-phase chemotherapy-induced nausea
4. Defining Risk: CYP3A4 drug-drug interactions [5]

High-yield exam pearls

1. Pearl: "Which nausea, which receptor" is the organising logic of this whole class.
1. Why: Motion sickness, chemotherapy nausea and delayed chemotherapy nausea are driven by different receptor systems, so the same antiemetic will not work equally well for all three. [10]
2. Pearl: Ondansetron's defining risk is cardiac, not gastrointestinal.
2. Why: Dose-dependent QT prolongation, not a GI adverse effect, is why the 32 mg single IV dose was removed from the label. [1]
3. Pearl: Metoclopramide's boxed warning specifies a 12-week treatment ceiling.
3. Why: This is one of the few boxed warnings that names an explicit duration limit rather than just a risk category, directly reflecting that tardive dyskinesia risk tracks cumulative exposure. [2]
4. Pearl: Promethazine's boxed warning is about how it is injected, not what it does systemically.
4. Why: Severe tissue injury/gangrene from extravasation or wrong-route injection is a technique-linked hazard, distinct from the drug's antihistaminergic pharmacology. [4]
5. Pearl: Aprepitant/fosaprepitant's defining property is CYP3A4 interaction, not organ toxicity.
5. Why: It is the only antiemetic subclass here whose main prescribing hazard is a pharmacokinetic interaction rather than a direct receptor-linked adverse effect. [5]

Common exam traps

1. Trap: Reaching for a 5-HT3 antagonist for motion sickness.
1. Correction: Motion sickness is driven by the vestibular H1/muscarinic pathway, not serotonin release from the gut, so an antihistamine like promethazine or meclizine is the better-matched choice. [4]
2. Trap: Assuming metoclopramide's extrapyramidal risk only matters with long-term use.
2. Correction: Restlessness and mild extrapyramidal symptoms are reported even at short-term therapeutic dosing,

distinct from the longer-term, often-irreversible tardive dyskinesia the boxed warning addresses. [2]

3. Trap: Treating ondansetron as risk-free because it is not sedating and not a dopamine antagonist.

3. Correction: Its own defining risk, dose-dependent QT prolongation with reported Torsades de Pointes, is a real and label-driving cardiac hazard, not a benign trade-off for avoiding sedation or extrapyramidal effects. [1]

4. Trap: Assuming aprepitant/fosaprepitant's only concern is nausea control.

4. Correction: Its CYP3A4 substrate/inhibitor/inducer behaviour can meaningfully alter concomitant chemotherapy drug levels, which is arguably the more clinically important prescribing issue than its own antiemetic efficacy. [5]

Self-test questions

1. Question: A patient develops nausea from motion during a long car journey. Which antiemetic class is best matched to the mechanism?

1. 5-HT₃ antagonists
2. NK₁ antagonists
3. H₁-antihistamines/anticholinergics
4. Dopamine D₂ antagonists

1. Explanation: Motion sickness arises through the vestibular pathway signalling via histamine H₁ and muscarinic receptors, which is why antihistamines with anticholinergic activity such as promethazine or meclizine, not 5-HT₃, NK₁ or dopamine antagonists, are the standard choice. [4]

2. Question: Why was the 32 mg single intravenous dose of ondansetron removed from its label?

1. It was found to be ineffective
2. It was linked to significant dose-dependent QT-interval prolongation
3. It caused unacceptable sedation
4. It interacted with all chemotherapy agents

2. Explanation: Ondansetron prolongs the QT interval in a dose-dependent manner, and the 32 mg single IV dose was specifically associated with a clinically significant QT effect, leading to its removal from the label. [1]

3. Question: What does metoclopramide's boxed warning specifically caution against?

1. Severe hepatotoxicity with any use
2. Tardive dyskinesia, with a recommendation against use beyond 12 weeks
3. Anaphylaxis on first exposure
4. Irreversible renal failure

3. Explanation: Metoclopramide's boxed warning addresses tardive dyskinesia, a movement disorder that is often irreversible, whose risk rises with treatment duration and cumulative dose, leading to the 12-week treatment recommendation. [2]

4. Question: Why must promethazine injection be given by deep intramuscular injection or through a clearly running IV line rather than any convenient route?

1. To improve its taste
2. To avoid severe tissue injury, including gangrene, from extravasation or intra-arterial/subcutaneous injection
3. To prevent nausea from the injection itself
4. To speed up hepatic metabolism

4. Explanation: Promethazine carries a boxed warning for severe chemical tissue injury, including gangrene, if it leaks outside the vein or is given by the wrong route, which is why administration technique is specifically restricted. [4]

5. Question: What is the main pharmacological reason aprepitant/fosaprepitant requires careful review of concomitant medications?

1. It is highly protein-bound with no metabolism
2. It is a substrate, inhibitor and inducer of CYP3A4, with real potential to alter levels of co-administered drugs including some chemotherapy agents
3. It has no known drug interactions

4. It is exclusively eliminated unchanged by the kidney
5. Explanation: Aprepitant acts as a CYP3A4 substrate, moderate inhibitor and inducer, giving it meaningful potential to alter plasma levels of other CYP3A4-metabolised drugs, which is the class's defining pharmacokinetic feature. [5]
6. Question: A patient needs an antiemetic for the delayed phase of chemotherapy-induced nausea that a 5-HT₃ antagonist alone has not controlled. Which receptor-targeted class is added specifically for this?
 1. H₁-antihistamines
 2. NK₁ antagonists
 3. Anticholinergics
 4. Saline osmotic agents
6. Explanation: The delayed phase of chemotherapy-induced nausea is particularly linked to substance P and NK₁ receptor activation, which is why NK₁ antagonists such as aprepitant/fosaprepitant are added to a 5-HT₃ antagonist and corticosteroid regimen for this specific phase. [5]

Frequently asked questions

1. Question: Why do different antiemetics work for different kinds of nausea?
 1. Answer: Because nausea and vomiting are produced by at least four separate receptor systems - serotonin (5-HT₃), dopamine (D₂), histamine/muscarinic (vestibular), and neurokinin-1 (substance P) - and each antiemetic class blocks only one of them. Motion sickness, chemotherapy nausea and delayed chemotherapy nausea are driven by different combinations of these systems, so matching the drug to the trigger matters clinically. [10]
 2. Question: Is ondansetron safe for someone with a heart rhythm condition?
 2. Answer: It requires caution. Ondansetron prolongs the QT interval in a dose-dependent way and has been linked postmarketing to Torsades de Pointes, so it is avoided in congenital long QT syndrome and used with ECG monitoring in patients with electrolyte abnormalities, heart failure, bradyarrhythmia or other QT-prolonging medications, per its FDA labelling. [1]
 3. Question: Why is metoclopramide not used for long-term nausea control?
 3. Answer: Its boxed warning specifically addresses tardive dyskinesia, a movement disorder that is often irreversible once it develops, with risk rising alongside treatment duration and cumulative dose. That is why the label recommends against treatment beyond 12 weeks except in rare, carefully weighed cases. [2]
 4. Question: What makes promethazine's injection warning different from other antiemetic warnings on this page?
 4. Answer: It is about administration technique rather than the drug's systemic pharmacology. Promethazine given intravenously can cause severe tissue injury, including gangrene, if it leaks outside the vein or is inadvertently injected intra-arterially or subcutaneously, which is why its label requires deep intramuscular injection or delivery only through a clearly patent, freely running IV line. [4]

References

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