

H2-receptor antagonists

Reversible, competitive blockers of the histamine H2 receptor on the gastric parietal cell - faster-acting and shallower than proton pump inhibitors, and a class whose modern shape was set by the 2020 withdrawal of ranitidine over carcinogenic contamination.

Online guide: <https://www.medguideglobal.com/pharmacology/gastrointestinal/h2-receptor-antagonists>

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Quick revision

One Liner: H2-receptor antagonists reversibly and competitively block histamine at the H2 receptor on the parietal cell - a shallower, faster-acting alternative to PPIs, with the class's clinical picture dominated by two facts that only apply to specific members: cimetidine's heavy cytochrome P450 interaction burden, and ranitidine's 2020 withdrawal over NDMA contamination.

1. Mechanism: competitively bind H2 receptors on the basolateral membrane of gastric parietal cells, blocking histamine-driven acid secretion. [1][2]
2. Famotidine and cimetidine remain in routine use; ranitidine was withdrawn from the US market in 2020 after NDMA contamination was found to increase with storage time and temperature. [1][4]
3. Famotidine's most common adverse reactions in clinical trials were headache, dizziness, constipation and diarrhoea, each occurring in 1% or more of treated patients. [3]
4. Cimetidine, not the class as a whole, carries a clinically significant cytochrome P450 interaction burden - it inhibits CYP1A2, CYP2C9 and CYP2D6, raising levels of drugs including warfarin, theophylline, phenytoin and several benzodiazepines. [2]
5. High-dose cimetidine (above 5 g/day) can cause reversible gynaecomastia or impotence through antiandrogenic activity, an effect not shared to the same degree by famotidine. [2]
6. Confusion, delirium, hallucinations and agitation are recognised H2RA adverse effects in elderly or renally impaired patients, requiring dose reduction in renal impairment. [3]
7. H2RAs act faster than proton pump inhibitors but suppress acid less completely, because they block only one of several inputs to the acid-secreting pump rather than the pump itself. [1]

Overview

1. H2-receptor antagonists competitively and reversibly block histamine at the H2 receptor on the basolateral membrane of the gastric parietal cell, reducing basal and stimulated gastric acid secretion, volume and acidity. Because histamine is only one of the signals - alongside gastrin and acetylcholine - that drive the parietal cell's acid-secreting pump, H2RAs suppress acid less completely than proton pump inhibitors, but they take effect faster. [1]
2. Famotidine and cimetidine remain the two H2RAs in routine current use; ranitidine, once one of the most widely used members of the class, was withdrawn from the US market in April 2020 after the FDA found that N-nitrosodimethylamine (NDMA), a probable human carcinogen, forms within the ranitidine molecule and increases with storage time and elevated temperature. That withdrawal was a contamination and stability finding specific to ranitidine's chemistry, not evidence against the H2-blocking mechanism itself. [1][4]
3. The two remaining members are not clinically interchangeable. Cimetidine carries a clinically significant cytochrome P450 interaction burden - inhibiting CYP1A2, CYP2C9 and CYP2D6 - and, at high doses, an antiandrogenic effect that can cause gynaecomastia or impotence. Famotidine does not carry either of these to the same degree, which is a large part of why it is now the more commonly used H2RA in practice. [2]

Classification and drug examples

Intro: Two members remain in routine use; a third, once the class leader, was withdrawn for a contamination reason unrelated to its mechanism.

1. Name: H2RAs currently in routine use

1. Note: Both act on the same H2 receptor, but differ sharply in their off-target pharmacology.

1. Name: Famotidine

Pepcid

1. Route: Oral/IV

1. Note: Lower cytochrome P450 interaction burden than cimetidine; the more commonly used H2RA in current practice. [2]

2. Name: Cimetidine

Tagamet

2. Route: Oral/IV

2. Note: Clinically significant CYP1A2/CYP2C9/CYP2D6 inhibitor; high doses can cause antiandrogenic effects. [2]

3. Name: Nizatidine

Axid

3. Route: Oral

3. Note: Shares the class's core H2-receptor mechanism; renally eliminated. [1] [1][2]

2. Name: Withdrawn member

2. Note: Removed from the US market for a stability/contamination reason, not a mechanistic safety failure of H2 blockade itself.

Name: Ranitidine

Zantac

Route: Historically oral/IV

Note: Withdrawn from the US market in April 2020 after NDMA, a probable human carcinogen, was found to form and increase with storage time and temperature. [4] [4]

Mechanism of action

Summary: H2-receptor antagonists competitively and reversibly bind the histamine H2 receptor on the basolateral membrane of the gastric parietal cell, blocking histamine-driven activation of the acid-secreting pathway and reducing basal, nocturnal and stimulated gastric acid secretion, volume and acidity.

Target: Histamine H2 receptor on the basolateral membrane of the gastric parietal cell

Cidal Static: not applicable (not an antimicrobial class)

Kill Kinetics: not applicable (not an antimicrobial class)

1. Step: 1

1. Title: Histamine normally drives acid secretion

1. Detail: Histamine released near the parietal cell binds the H2 receptor, one of the three physiological inputs (with gastrin and acetylcholine) that activate acid secretion via the H⁺/K⁺-ATPase. [1]

2. Step: 2

2. Title: The drug competes with histamine at the H2 receptor

2. Detail: H2RAs bind the same receptor competitively and reversibly, displacing or blocking histamine without triggering the receptor's normal signal. [1]

3. Step: 3

3. Title: Acid secretion falls, but incompletely

3. Detail: Because gastrin and acetylcholine can still drive the pump through their own receptors, blocking histamine alone reduces basal, nocturnal and stimulated acid output without abolishing it the way irreversible pump inhibition

does. [1]

4. Step: 4

4. Title: The block is reversible

4. Detail: Because binding is competitive rather than covalent, the effect tracks drug concentration far more closely than a proton pump inhibitor's does, giving faster onset and a shorter duration of action. [1]

Major clinical uses

1. Drug: Famotidine

1. Indication: Active duodenal ulcer, active gastric ulcer, symptomatic non-erosive GERD, and biopsy-confirmed erosive oesophagitis due to GERD in patients 40 kg and above

1. Line: first-line/second-line

1. Note: Labelled indications; specific choice and duration are set by the treating clinician. [3]

2. Drug: Famotidine

2. Indication: Pathological hypersecretory conditions and prevention of duodenal ulcer recurrence in adults

2. Line: targeted

2. Note: Adult-specific labelled indications. [3]

3. Drug: H2RAs as a class

3. Indication: On-demand or short-term heartburn relief, including over-the-counter use

3. Line: as-needed

3. Note: Their faster onset relative to PPIs suits intermittent, symptom-triggered dosing. [1]

4. Drug: H2RAs as a class

4. Indication: Stress ulcer prophylaxis in critically ill patients (off-label/institutional use)

4. Line: adjunct

4. Note: A recognised off-label application alongside the labelled indications. [1]

Pharmacokinetics

1. Drug: Famotidine

1. Route: Oral/IV

1. Absorption: Oral bioavailability moderate; not dependent on acid-catalysed activation the way PPIs are

1. Csf Penetration: Confusion/delirium reported in elderly and renally impaired patients, consistent with some CNS penetration

1. Metabolism: Minimal hepatic metabolism

1. Elimination: Primarily renal

1. Half Life: See prescribing reference

1. Dose Adjust: Substantial dose reduction required once creatinine clearance falls below 60 mL/min [3]

2. Drug: Cimetidine

2. Route: Oral/IV

2. Absorption: Well absorbed orally

2. Csf Penetration: CNS effects (delirium, drowsiness) documented, especially in the elderly and renally impaired

2. Metabolism: Hepatic, and the drug itself inhibits CYP1A2, CYP2C9 and CYP2D6

2. Elimination: Renal

2. Half Life: See prescribing reference

2. Dose Adjust: Renal and hepatic impairment; review interacting medicines before use [2]

1. Renal elimination dominates this class, and confusion or delirium at unadjusted doses is a specifically documented risk in elderly or renally impaired patients - a dosing-table adjustment, not just a general caution. [3]

2. This page gives no dose regimens by design. Doses depend on indication, renal function, age and the treating clinician's assessment, and belong in a current prescribing reference.

Adverse effects

Effect: Headache, dizziness, constipation and diarrhoea

Detail: The most common famotidine adverse reactions in clinical trials, each occurring in 1% or more of treated patients. [3]

1. Effect: Confusion, delirium, hallucinations, disorientation, agitation, seizures and lethargy
1. Detail: Documented specifically in elderly patients and those with renal impairment, particularly at unadjusted doses.
1. Action: New confusion or behavioural change in an older or renally impaired patient on an H2RA warrants prompt medical assessment. [3]
2. Effect: Thrombocytopenia
2. Detail: A recognised though uncommon adverse reaction reported with famotidine.
2. Action: Unexplained bleeding or bruising warrants medical evaluation. [3]
3. Effect: Symptomatic response does not exclude gastric malignancy
3. Detail: Improvement of symptoms on an H2RA does not rule out an underlying gastric cancer.
3. Action: Persistent or alarm gastrointestinal symptoms need proper clinical evaluation rather than continued self-treatment. [3]
1. Drug: Cimetidine
1. Effect: Reversible gynaecomastia or impotence at doses above roughly 5 g/day, through antiandrogenic activity plausibly mediated by increased prolactin; also hepatitis, haemolytic anaemia and vitamin B12 malabsorption have been documented. [2]
2. Drug: Ranitidine (historical)
2. Effect: Not a pharmacodynamic adverse effect but a manufacturing/stability finding: N-nitrosodimethylamine (NDMA) contamination that increased with storage time and temperature, leading to market withdrawal. [4]

Contraindications, precautions and interactions

Known hypersensitivity to the specific H2RA or its excipients, with recognised potential cross-sensitivity among H2RAs. [1]

1. Renal impairment, given the class's substantial reliance on renal elimination and the documented confusion/delirium risk at unadjusted doses. [3]
2. Hepatic impairment with cimetidine specifically, given its hepatic metabolism and enzyme-inhibiting activity. [2]
1. With: Warfarin, tricyclic antidepressants, lidocaine, calcium channel blockers, quinidine, oral sulfonylureas, phenytoin, theophylline, benzodiazepines and beta blockers (with cimetidine)
1. Effect: Cimetidine's inhibition of CYP1A2, CYP2C9 and CYP2D6 can raise plasma levels of these drugs, producing clinically significant interactions. [2]
2. With: Tizanidine (with famotidine)
2. Effect: Concomitant use is not recommended because of risk of hypotension and bradycardia related to CYP1A2 effects. [3]
3. With: Dasatinib, delavirdine, cefditoren, fosamprenavir (pH-dependent absorption drugs)
3. Effect: Reduced gastric acidity from famotidine significantly reduces their absorption. [3]

Comparison tables

Title: Famotidine versus cimetidine: where the class actually differs

Caption: The two H2RAs in routine current use share a mechanism but not a safety profile. A prescribing reference and the treating clinician govern actual therapy choices.

1. Key: drug
1. Label: Drug

1. Is Row Header: true
2. Key: cyp_interactions
2. Label: CYP450 interaction burden
3. Key: endocrine
3. Label: Antiandrogenic effect
4. Key: current_use
4. Label: Current role
1. Drug: Famotidine
1. Cyp Interactions: Comparatively low
1. Endocrine: Not a significant feature
1. Current Use: The more commonly used H2RA in current practice [2]
2. Drug: Cimetidine
2. Cyp Interactions: Clinically significant (CYP1A2, CYP2C9, CYP2D6)
2. Endocrine: Reversible gynaecomastia/impotence at high doses
2. Current Use: Used with more caution because of its interaction and endocrine profile [2]

High-yield exam pearls

1. Pearl: H2RAs block a receptor, not the pump.
1. Why: Histamine is only one of several signals (alongside gastrin and acetylcholine) that drive the parietal cell's H⁺/K⁺-ATPase, so blocking the H2 receptor reduces acid secretion without shutting the pump down completely the way a PPI does. [1]
2. Pearl: The class's biggest drug-interaction risk belongs to one member, not all of them.
2. Why: Cimetidine inhibits CYP1A2, CYP2C9 and CYP2D6 clinically significantly; famotidine does not share this burden to the same degree, which is why cimetidine is the one that raises levels of warfarin, theophylline, phenytoin and several other narrow-therapeutic-index drugs. [2]
3. Pearl: Gynaecomastia with an H2RA points to cimetidine, not the whole class.
3. Why: High-dose cimetidine's antiandrogenic activity, plausibly mediated by raised prolactin, is a recognised cause of reversible gynaecomastia or impotence - a class-defining exam trap because it is a cimetidine-specific effect rather than a generic H2RA one. [2]
4. Pearl: Ranitidine's exit was about contamination, not the drug's own pharmacology.
4. Why: Ranitidine was withdrawn because N-nitrosodimethylamine (NDMA), a probable human carcinogen, was found to form within the tablet and increase with storage time and temperature - a manufacturing/stability finding, not evidence that the H2-blocking mechanism itself was unsafe. [4]
5. Pearl: Renal impairment is a dosing trigger, not just a caution.
5. Why: Famotidine's labelled dosing table cuts the maintenance dose substantially once creatinine clearance falls below 60 mL/min, and confusion/delirium is a recognised risk in elderly or renally impaired patients at unadjusted doses. [3]

Common exam traps

1. Trap: "All H2-receptor antagonists carry the same cytochrome P450 interaction risk."
1. Correction: The clinically significant CYP1A2/CYP2C9/CYP2D6 inhibition profile is specifically documented for cimetidine. Treating this as a flat class effect would wrongly flag famotidine for interactions it does not carry to the same extent. [2]
2. Trap: "Ranitidine was withdrawn because H2-blockers are dangerous."
2. Correction: The withdrawal was driven by NDMA, a contaminant that increases within the ranitidine molecule during storage, not by the H2-antagonist mechanism itself. Famotidine and cimetidine remain in routine, FDA-authorised use. [4]

3. Trap: "H2RAs and PPIs are interchangeable, just with different brand names."

3. Correction: They act on different targets by different chemistry - H2RAs reversibly and competitively block the histamine H2 receptor upstream of acid secretion, while PPIs irreversibly disable the H⁺/K⁺-ATPase itself. H2RAs act faster but suppress acid less completely. [1]

Self-test questions

1. Question: What is the mechanistic difference between an H2-receptor antagonist and a proton pump inhibitor?

1. There is no difference; both irreversibly inhibit the H⁺/K⁺-ATPase
2. H2RAs reversibly and competitively block the histamine H2 receptor on the parietal cell; PPIs irreversibly inhibit the H⁺/K⁺-ATPase pump itself
3. H2RAs act on the pump; PPIs act on the H2 receptor
4. H2RAs are prodrugs requiring acid activation; PPIs are not

1. Explanation: H2RAs block one of the inputs (histamine) that drives the parietal cell's acid-secreting pump, competitively and reversibly. PPIs act further downstream, irreversibly disabling the pump itself - which is why PPIs achieve deeper, longer acid suppression. [1]

2. Question: A patient on warfarin is prescribed an H2-receptor antagonist for reflux. Which agent is most likely to raise the warfarin level through a cytochrome P450 interaction?

1. Famotidine
2. Nizatidine
3. Cimetidine
4. All H2RAs equally

2. Explanation: Cimetidine inhibits CYP1A2, CYP2C9 and CYP2D6, and warfarin metabolism depends partly on CYP2C9 - this interaction is specifically documented for cimetidine rather than the class as a whole. [2]

3. Question: Why was ranitidine withdrawn from the US market in 2020?

1. It was found to cause severe hepatotoxicity
2. N-nitrosodimethylamine (NDMA), a probable human carcinogen, was found to form and increase with storage time and temperature
3. It was replaced by a more effective H2RA
4. It failed a routine efficacy re-evaluation

3. Explanation: The FDA's action followed laboratory findings of unacceptable NDMA levels forming under both controlled and uncontrolled storage conditions, leading the agency to advise prescribers to stop prescribing it and to request its removal from the market. [4]

4. Question: A male patient on long-term high-dose cimetidine develops gynaecomastia. What is the most likely explanation?

1. A class-wide effect shared equally by famotidine
2. Cimetidine's antiandrogenic activity, plausibly mediated by increased prolactin, at doses above roughly 5 g/day
3. An unrelated endocrine tumour that must be assumed
4. Gastric acid suppression itself causing hormonal disruption

4. Explanation: High-dose cimetidine is specifically documented to cause reversible gynaecomastia or impotence through antiandrogenic activity, an effect that is not a generic property of the H2RA class. [2]

5. Question: Which patient population needs H2RA dose adjustment because of a recognised confusion/delirium risk at standard doses?

1. Young healthy adults
2. Elderly patients and those with renal impairment
3. Patients with well-controlled asthma
4. Patients taking calcium carbonate antacids

5. Explanation: Confusion, delirium, hallucinations, disorientation, agitation, seizures and lethargy are recognised

H2RA adverse effects specifically flagged in elderly and renally impaired patients, and labelled dosing tables reduce the maintenance dose as creatinine clearance falls. [3]

Frequently asked questions

1. Question: Are H2-receptor antagonists the same as proton pump inhibitors?

1. Answer: No. H2RAs reversibly and competitively block the histamine H2 receptor, one of several inputs to acid secretion. PPIs irreversibly disable the acid-secreting pump itself. H2RAs act faster but suppress acid less completely. [1]

2. Question: Why is famotidine used more often than cimetidine today?

2. Answer: Famotidine does not carry cimetidine's clinically significant cytochrome P450 interaction burden or its high-dose antiandrogenic effects, which makes it easier to combine safely with other medicines. [2]

3. Question: Why is ranitidine no longer available?

3. Answer: The FDA requested its withdrawal from the US market in April 2020 after finding that N-nitrosodimethylamine (NDMA), a probable human carcinogen, forms within the ranitidine molecule and increases with storage time and higher temperature. This was a contamination and stability finding, not evidence that H2 blockade itself is unsafe. [4]

4. Question: Can an H2-receptor antagonist cause confusion in an elderly patient?

4. Answer: Yes. Confusion, delirium, hallucinations and agitation are documented adverse effects, particularly in elderly or renally impaired patients at unadjusted doses, which is why renal dosing tables reduce the dose as kidney function declines. [3]

References

[1] Famotidine (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK534778/>

[2] Cimetidine (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK544255/>

[3] PEPCID (famotidine) tablets, FDA prescribing information (DailyMed). U.S. National Library of Medicine / FDA 2024. <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a06502d9-7903-4f37-833e-e5763d502def>

[4] N-nitrosodimethylamine (NDMA) contamination of ranitidine products. PubMed Central, National Library of Medicine 2022. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9261846/>

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.