

Antihistamines

Medicines that block the histamine H1 receptor, divided into an older generation that reaches the brain and therefore sedates and dries, and a newer generation that penetrates the central nervous system poorly and is the usual daytime choice.

Online guide: <https://www.medguideglobal.com/pharmacology/respiratory-and-allergy/antihistamines>

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Quick revision

One Liner: Every drug on this page blocks the same receptor; what separates the two generations is how much of the drug reaches the brain.

1. First-generation agents including chlorphenamine, cinnarizine, diphenhydramine, hydroxyzine and promethazine are the ones the NHS classes as making you drowsy. [14]
2. Acrivastine, cetirizine, fexofenadine and loratadine sit in the non-drowsy group, which the NHS calls generally the best option because sleepiness is less likely. [14]
3. Diphenhydramine's label describes it as an antihistamine with anticholinergic (drying) and sedative effects, which is the whole first-generation problem in one phrase. [9]
4. Promethazine carries a boxed warning against use below two years of age because of the potential for fatal respiratory depression. [1]
5. Radiolabelled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier, and no sedative effects were seen. [6]
6. Cetirizine is the second-generation agent whose over-the-counter label still states plainly that drowsiness may occur. [5][8]
7. Hydroxyzine is contraindicated where the QT interval is already prolonged, which sets it apart from the rest of the older group. [3]
8. Muscarinic blockade explains the dry mouth, blurred vision and difficulty passing urine that follow the older agents around. [14][16]
9. The same molecules are sold as night-time sleep aids and in cough and cold remedies, where a reader may not register that an antihistamine is involved at all. [10][15]
10. In a driving-simulator trial, steering was worse after diphenhydramine than at a blood alcohol content one-eighth of the legal limit. [17]

Overview

1. Histamine acting at the H1 receptor produces the sneezing, itch, weal and flare of an allergic response. Every agent on this page occupies that receptor instead. Older labels put it as competition with histamine for cell receptor sites on effector cells; newer ones describe selective H1-receptor antagonist activity. Either way the drug relieves the symptom and leaves the sensitisation untouched. [9][6]
2. The class then splits on a single pharmacological property: how much drug gets into the brain. Fexofenadine's label reports that rat distribution studies indicated it does not cross the blood-brain barrier and that no sedative or other central nervous system effects were observed. Desloratadine's label reports rat and guinea-pig work showing it did not readily cross the blood brain barrier, and then adds that the clinical significance of this finding is unknown. The regulators have not claimed more than the animal data support, and neither should a student. [6][7]
3. What the older drugs do reach the brain to do is documented directly. Promethazine is described as an H1 receptor blocking agent that, in addition to its antihistaminic action, provides clinically useful sedative and antiemetic effects. That single sentence explains why the first generation survives at all: sedation and antiemesis are exactly what is

wanted for motion sickness, for a night-time sleep preparation, and for pruritus that keeps a patient awake. [1][12][10]
 4. Two safety statements dominate the class. Promethazine must not be given to a child under two years because of fatal respiratory depression, and the injectable form carries a second boxed warning about severe tissue injury. Hydroxyzine is contraindicated when the QT interval is prolonged. Everything else on the page is a matter of degree; those three are absolute. [1][2][3]

Classification and drug examples

Intro: Grouped by central nervous system penetration, because that one property predicts sedation, antimuscarinic burden, and whether an agent belongs anywhere near a working day.

1. Name: First-generation (sedating) antihistamines

1. Note: Older agents that reach the brain. They sedate, they block muscarinic receptors alongside H1, and several are sold without prescription for sleep, colds or travel sickness rather than for allergy.

1. Name: Chlorphenamine

1. Chlorpheniramine maleate

2. Piriton

1. Route: Oral

1. Note: Its label warns that drowsiness may occur, that excitability may occur especially in children, and instructs plainly: do not use to make a child sleepy. [11]

2. Name: Diphenhydramine

Benadryl

2. Route: Oral, topical and injectable

2. Note: The archetype of the group, and the active ingredient of a great many products whose purpose line reads nighttime sleep-aid rather than antihistamine. [9][10]

3. Name: Promethazine

Phenergan

3. Route: Oral and injectable

3. Note: A phenothiazine derivative used for allergic rhinitis, motion sickness, nausea after anaesthesia and light sleep; it carries the most serious paediatric warning in the class. [1]

4. Name: Hydroxyzine

4. Route: Oral

4. Note: Licensed for pruritus of allergic origin, for anxiety and for preoperative sedation; its label attributes the effect to suppression of activity in certain key regions of the subcortical area of the central nervous system. [3]

5. Name: Dimenhydrinate

5. Route: Oral

5. Note: Sold under the purpose line antiemetic rather than antihistamine, for the nausea, vomiting and dizziness of motion sickness. [12]

6. Name: Cinnarizine

6. Route: Oral

6. Note: Grouped by the NHS with the drowsy antihistamines and used chiefly for vestibular symptoms; no released medicine page exists here yet. [14] [14][9]

2. Name: Second-generation (non-sedating) antihistamines

2. Note: Later agents that penetrate the central nervous system poorly and are the routine first choice for allergic rhinitis and chronic urticaria. Non-sedating is a relative claim, not an absolute one.

1. Name: Cetirizine

Zyrtec

1. Route: Oral

1. Note: The residual-sedation outlier of the group: its over-the-counter warnings state that drowsiness may occur and

advise care when driving a motor vehicle or operating machinery. [5]

2. Name: Levocetirizine

Xyzal

2. Route: Oral

2. Note: The active enantiomer of cetirizine, with an affinity for the human H1-receptor two-fold higher than that of cetirizine; somnolence was reported in 6% of adults against 2% on placebo. [4]

3. Name: Loratadine

1. Claritin

2. Clarityn

3. Route: Oral

3. Note: Marketed as non-drowsy with an asterisk reading when taken as directed, and warning separately that taking more than directed may cause drowsiness. [8]

4. Name: Desloratadine

Clarinx

4. Route: Oral

4. Note: A long-acting tricyclic histamine antagonist that is itself a major metabolite of loratadine; somnolence occurred in 2.1% of recipients against 1.8% on placebo. [7]

5. Name: Fexofenadine

1. Allegra

2. Telfast

5. Route: Oral

5. Note: The major active metabolite of terfenadine, and the agent with the clearest label statement that it does not enter the brain. [6]

6. Name: Rupatadine

6. Route: Oral

6. Note: A newer oral second-generation agent available in the United Kingdom; it has no United States label, so no claim about it is made on this page. [14] [14][6]

3. Name: Topical ocular and nasal H1 antagonists

3. Note: Applied straight onto the affected mucosa, which treats the symptom where it arises and keeps systemic exposure low.

Name: Ketotifen

Alaway

Route: Ophthalmic

Note: An over-the-counter antihistamine eye drop for the temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander. [13] [13]

Mechanism of action

Summary: All members are H1 receptor antagonists. The first generation adds muscarinic blockade and, because it enters the brain, central H1 blockade as well; the second generation was designed to keep out of the central nervous system and largely does.

Target: The histamine H1 receptor, with additional muscarinic acetylcholine receptor blockade by the older agents

Cidal Static: Symptom-suppressing rather than disease-modifying

Kill Kinetics: Effect tracks receptor occupancy, and therefore plasma or local tissue concentration

1. Step: 1

1. Title: Competition with histamine at the H1 receptor

1. Detail: The diphenhydramine label describes antihistamines as competing with histamine for cell receptor sites on effector cells. Occupying the receptor prevents histamine from producing vasodilatation, increased permeability,

sensory nerve stimulation and glandular secretion, so the sneeze, the itch and the runny nose are blunted. [9]

2. Step: 2

2. Title: Selectivity for H1 over the other histamine receptors

2. Detail: Fexofenadine is described as an antihistamine with selective H1-receptor antagonist activity, and desloratadine as a long-acting tricyclic histamine antagonist with selective H1-receptor histamine antagonist activity. Because H2 receptors are left alone, none of these drugs suppresses gastric acid. [6][7]

3. Step: 3

3. Title: Entry into the brain decides whether the drug sedates

3. Detail: For fexofenadine, rat distribution studies indicated no crossing of the blood-brain barrier and no sedative or other central nervous system effects were observed. For desloratadine, rat and guinea-pig studies showed it did not readily cross the blood brain barrier, though the label states that the clinical significance of this finding is unknown. [6][7]

4. Step: 4

4. Title: Central H1 blockade produces sedation and antiemesis

4. Detail: Where a drug does reach central receptors, the consequences are therapeutic as often as they are adverse. Promethazine's label states that in addition to its antihistaminic action it provides clinically useful sedative and antiemetic effects, which is why it appears in preparations for travel sickness and for postoperative vomiting. [1]

5. Step: 5

5. Title: Muscarinic blockade adds the drying effects

5. Detail: Diphenhydramine is characterised on its label as having anticholinergic (drying) as well as sedative effects. Clinically this shows as a dry mouth, blurred vision and difficulty passing urine, and it is why the older agents are cautioned in glaucoma, in prostatic enlargement and in bladder-neck obstruction. [9][14][11]

6. Step: 6

6. Title: Route of application changes the exposure

6. Detail: An eye drop or a nasal spray delivers the antagonist to the tissue that itches while keeping systemic concentrations low, which is the rationale for topical ketotifen in seasonal eye symptoms rather than an oral tablet. [13]

Major clinical uses

1. Drug: Fexofenadine

1. Organism: Not applicable

1. Indication: Seasonal allergic rhinitis and chronic idiopathic urticaria

1. Line: first line

1. Note: Licensed for relief of seasonal allergic rhinitis symptoms and for the uncomplicated skin manifestations of chronic idiopathic urticaria from six years of age. [6]

2. Drug: Levocetirizine

2. Organism: Not applicable

2. Indication: Seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria

2. Line: first line

2. Note: Indicated for relief of symptoms associated with seasonal and perennial allergic rhinitis, and for uncomplicated skin manifestations of chronic idiopathic urticaria from six months of age. [4]

3. Drug: Desloratadine

3. Organism: Not applicable

3. Indication: Perennial allergic rhinitis and chronic idiopathic urticaria in young children

3. Line: first line

3. Note: Approved for seasonal allergic rhinitis from two years of age, and for perennial allergic rhinitis and chronic idiopathic urticaria from six months of age. [7]

4. Drug: Promethazine

4. Organism: Not applicable
4. Indication: Motion sickness, and prevention and control of nausea and vomiting associated with certain types of anaesthesia and surgery
4. Line: selected situations
4. Note: The same label also covers perennial and seasonal allergic rhinitis, allergic conjunctivitis, and sedation with relief of apprehension and production of light sleep. [1]
5. Drug: Hydroxyzine
5. Organism: Not applicable
5. Indication: Pruritus due to allergic conditions, anxiety, and preoperative sedation
5. Line: selected situations
5. Note: A useful illustration that the sedative property is sometimes the point rather than the price, though the QT contraindication limits where it can be used. [3]
6. Drug: Dimenhydrinate
6. Organism: Not applicable
6. Indication: Prevention and treatment of nausea, vomiting and dizziness associated with motion sickness
6. Line: over the counter
6. Note: Vestibular symptoms respond to central H1 and muscarinic blockade, which is why an antihistamine is labelled here as an antiemetic. [12]
7. Drug: Diphenhydramine
7. Organism: Not applicable
7. Indication: Relief of occasional sleeplessness, sold over the counter as a nighttime sleep-aid
7. Line: over the counter
7. Note: The label carries its own limit: if sleeplessness persists continuously for more than two weeks, insomnia may be a symptom of serious underlying medical illness. [10][16]
8. Drug: Ketotifen
8. Organism: Not applicable
8. Indication: Temporary relief of itchy eyes due to ragweed, pollen, grass, animal hair and dander
8. Line: over the counter
8. Note: Contact lenses are removed before instillation and reinserted no sooner than ten minutes afterwards, and persistent eye pain or visual change means stopping and seeking advice. [13]

Pharmacokinetics

1. Drug: Fexofenadine
1. Route: Oral
1. Absorption: Reduced by grapefruit, orange and apple juice and by aluminium- and magnesium-containing antacids
1. Csf Penetration: Rat distribution studies indicated it does not cross the blood-brain barrier
1. Metabolism: Little metabolic transformation; it is itself the major active metabolite of terfenadine
1. Elimination: Largely unchanged
1. Half Life: Prolonged where renal function is decreased
1. Dose Adjust: The label sets a lower starting point in adults with decreased renal function, based on increases in bioavailability and half-life. [6]
2. Drug: Levocetirizine
2. Route: Oral
2. Absorption: Rapid and extensive after oral intake
2. Csf Penetration: Limited; somnolence nonetheless exceeded placebo in trials
2. Metabolism: Minimal
2. Elimination: Substantially excreted by the kidneys

2. Half Life: Extended in renal impairment
2. Dose Adjust: Adjustment is graded by creatinine clearance and the drug is contraindicated in end-stage renal disease; the calculation belongs to the treating clinician. [4]
3. Drug: Desloratadine
3. Route: Oral
3. Absorption: Well absorbed orally
3. Csf Penetration: Did not readily cross the blood brain barrier in animal studies, with the clinical significance stated to be unknown
3. Metabolism: Extensively metabolised to 3-hydroxydesloratadine, an active metabolite
3. Elimination: Hepatic and renal
3. Half Life: Long enough for once-daily use
3. Dose Adjust: About 6% of the general population are poor metabolisers, with median exposure roughly sixfold that of normal metabolisers. [7]
4. Drug: Loratadine
4. Route: Oral
4. Absorption: Rapid after an oral dose
4. Csf Penetration: Low at labelled intake, which is the basis of the non-drowsy claim
4. Metabolism: Converted to desloratadine, which carries much of the activity
4. Elimination: Hepatic and renal
4. Half Life: Supports once-daily use
4. Dose Adjust: The over-the-counter label directs anyone with liver or kidney disease to ask a doctor, who should determine whether a different dose is needed. [8][7]
5. Drug: Diphenhydramine
5. Route: Oral, topical and injectable
5. Absorption: A single oral dose is quickly absorbed
5. Csf Penetration: Sufficient to produce marked sedation
5. Metabolism: Hepatic
5. Elimination: Hepatic and renal
5. Half Life: Maximum activity at about one hour, with activity lasting some four to six hours
5. Dose Adjust: Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients, so caution rises with age. [9]
1. This page gives no dose regimens. Choice of agent, timing and any adjustment for renal or hepatic function rest with the treating clinician and the current national formulary.
2. Figures quoted here are reproduced as the labels report them, and a label's own hedging is kept rather than smoothed away.

Adverse effects

1. Effect: Sedation and impaired performance
1. Detail: Somnolence, fatigue and asthenia are reported with the sedating agents and, less often, with cetirizine and levocetirizine. The levocetirizine label reports somnolence in 6% of treated adults against 2% on placebo and cautions against hazardous occupations requiring complete mental alertness and motor coordination. [4][14]
2. Effect: Antimuscarinic effects
2. Detail: Dry mouth, blurred vision and difficulty passing urine are listed for the drowsy group, and dryness of the nose and throat is common. Constipation follows from the same receptor blockade. [14][16]
3. Effect: Reduced coordination, reaction speed and judgement
3. Detail: The NHS lists these alongside sleepiness for the drowsy agents and advises against driving or using machinery after taking them. [14]

4. Effect: Headache, dry mouth and nausea with the newer agents

4. Detail: The second generation is not free of adverse effects; drowsiness remains possible even though it is less common than with the older group. [14]

5. Effect: Paradoxical excitability in children

5. Detail: Chlorphenamine's label warns that excitability may occur, especially in children, so a sedating antihistamine may agitate rather than settle a young child. [11]

1. Effect: Fatal respiratory depression in young children

1. Detail: The promethazine boxed warning states that the tablets should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Above that age the label directs use of the lowest effective amount and avoidance of other drugs with respiratory depressant effects.

1. Action: An absolute age limit rather than a caution; recognition of it is the single most important safety point on this page. [1]

2. Effect: Severe tissue injury with promethazine injection

2. Detail: The injectable boxed warning reads that severe chemical irritation and damage to tissues regardless of the route of parenteral administration has been reported, including gangrene, tissue necrosis, and thrombophlebitis. Intra-arterial administration is not to be used because of severe arteriospasm and possible resulting gangrene.

2. Action: Persistent or worsening pain or burning at the injection site is reported immediately; the preferred route is deep intramuscular administration. [2]

3. Effect: QT prolongation and torsade de pointes

3. Detail: Reported during post-marketing use of hydroxyzine, mostly in patients with other risk factors such as pre-existing heart disease, electrolyte imbalance or concurrent arrhythmogenic drugs.

3. Action: Contraindicated where the QT interval is prolonged, and used cautiously in congenital long QT syndrome, recent myocardial infarction, uncompensated heart failure and bradyarrhythmia. [3]

4. Effect: Overdose in infants and children

4. Detail: The diphenhydramine label warns that antihistamines in overdosage may cause hallucinations, convulsions, or death in this age group. Over-the-counter availability makes accidental ingestion the practical route to this outcome.

4. Action: Suspected ingestion is a medical emergency; child-resistant packaging is part of the regulatory response to it. [9][15]

1. Drug: Cetirizine

1. Effect: Uniquely among the widely used second-generation agents, the over-the-counter warnings state that drowsiness may occur, and that alcohol, sedatives and tranquilizers may increase drowsiness. [5]

2. Drug: Levocetirizine

2. Effect: Somnolence, fatigue and asthenia have been reported in clinical trials, and the label notes an increased risk of somnolence above the recommended intake. [4]

3. Drug: Loratadine

3. Effect: The non-drowsy claim is qualified on the packet itself by an asterisk reading when taken as directed, with a separate warning that more than directed may cause drowsiness. [8]

4. Drug: Promethazine

4. Effect: May cause marked drowsiness or impair the mental or physical abilities required for potentially hazardous tasks such as driving a vehicle or operating machinery. [1]

5. Drug: Dimenhydrinate

5. Effect: Marked drowsiness may occur, which is easily overlooked because the product is bought for travel rather than for allergy. [12]

6. Drug: Diphenhydramine in older people

6. Effect: Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients, and MedlinePlus states that diphenhydramine should generally not be used in older adults except to manage serious allergic reactions. [9][16]

Contraindications, precautions and interactions

1. Promethazine is contraindicated below two years of age, the tablets carrying a boxed warning about potentially fatal respiratory depression in that group. [1]
2. Hydroxyzine is contraindicated in patients with a prolonged QT interval. [3]
3. Promethazine injection must never be given intra-arterially because of the likelihood of severe arteriospasm and the possibility of resultant gangrene, and subcutaneous injection is not recommended. [2]
1. Drugs with anticholinergic properties are used with caution in narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction. [1][11]
2. A breathing problem such as emphysema or chronic bronchitis appears on the over-the-counter labels as a reason to seek advice before an older antihistamine is used. [11][12]
3. Older people tolerate the first generation poorly, and diphenhydramine is generally not recommended for them outside the management of serious allergic reactions. [16][9]
4. United Kingdom regulators concluded that over-the-counter cough and cold preparations containing brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine or triprolidine should no longer be used below six years of age. [15]
5. Levocetirizine is substantially excreted by the kidneys, so the risk of adverse reactions is greater where renal function is impaired. [4]
6. Anyone with liver or kidney disease is directed by the loratadine label to seek medical advice on whether a different amount is appropriate. [8]
1. With: Alcohol and other central nervous system depressants
1. Effect: Concurrent use should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur; the same caution appears on over-the-counter cetirizine, where alcohol, sedatives and tranquilizers may increase drowsiness. [4][5]
2. With: Aluminium- and magnesium-containing antacids
2. Effect: Given within fifteen minutes of fexofenadine, such an antacid decreased fexofenadine AUC by 41% and Cmax by 43%, and the over-the-counter label simply says not to take the two at the same time. [6]
3. With: Grapefruit, orange and apple juice
3. Effect: Fruit juices may reduce the bioavailability and exposure of fexofenadine, and weal and flare were significantly larger when it was given with grapefruit or orange juice than with water. [6]
4. With: Other QT-prolonging drugs and electrolyte disturbance
4. Effect: Most post-marketing reports of torsade de pointes on hydroxyzine arose in patients with additional risk factors, including concomitant arrhythmogenic drug use. [3]
5. With: Sedating antihistamines already present in a combination product
5. Effect: Cough and cold remedies frequently contain one of these agents, so a patient taking a separate antihistamine can double the sedative and antimuscarinic load without realising it. [15][10]

Comparison tables

1. Title: First generation against second generation
1. Caption: One property, central nervous system penetration, generates almost every difference in the table below.
1. Key: feature
1. Label: Feature
1. Is Row Header: true
2. Key: first
2. Label: First generation
3. Key: second
3. Label: Second generation

1. Feature: Brain penetration
1. First: Enough to produce sedation and antiemesis
1. Second: Poor; animal data for fexofenadine and desloratadine show little or no crossing [1][6][7]
2. Feature: Sedation
2. First: Expected, and marked with promethazine, diphenhydramine and dimenhydrinate
2. Second: Uncommon, but cetirizine and levocetirizine still carry drowsiness wording [1][12][5][4]
3. Feature: Antimuscarinic effects
3. First: Dry mouth, blurred vision and difficulty passing urine are characteristic
3. Second: Dry mouth may occur, but the muscarinic burden is not a feature of the group [14][9]
4. Feature: Everyday role
4. First: Sleep preparations, travel sickness, cough and cold mixtures, pruritus at night
4. Second: Daytime control of allergic rhinitis and chronic urticaria [10][12][6][4]
5. Feature: Advice on driving
5. First: The NHS says not to drive or use machinery after taking them
5. Second: Generally compatible with driving, though caution still applies to cetirizine [14][5]
6. Feature: Restriction in young children
6. First: Promethazine barred below two years; United Kingdom cough and cold products barred below six
6. Second: Licensed down to six months for several agents [1][15][7][4]
2. Title: What separates the newer agents from each other
2. Caption: They are near-interchangeable for symptom control, so the discriminators are handling, interactions and the residual sedation signal.
1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: sedation
2. Label: Sedation signal on the label
3. Key: handling
3. Label: Handling point
1. Drug: Cetirizine
1. Sedation: Drowsiness may occur, stated outright
1. Handling: Alcohol, sedatives and tranquilizers may increase the effect [5]
2. Drug: Levocetirizine
2. Sedation: Somnolence in 6% of adults against 2% on placebo
2. Handling: Substantially renally excreted; contraindicated in end-stage renal disease [4]
3. Drug: Loratadine
3. Sedation: Non-drowsy when taken as directed; more than directed may cause drowsiness
3. Handling: Liver or kidney disease prompts medical advice before use [8]
4. Drug: Desloratadine
4. Sedation: Somnolence in 2.1% against 1.8% on placebo
4. Handling: Roughly 6% of people are poor metabolisers with much greater exposure [7]
5. Drug: Fexofenadine
5. Sedation: No sedative or other central nervous system effects observed
5. Handling: Absorption cut by fruit juices and by aluminium- and magnesium-containing antacids [6]

High-yield exam pearls

1. Pearl: The generation split is about pharmacokinetics, not receptor pharmacology; both generations antagonise the same H1 receptor.

1. Why: It explains in one move why the older drugs sedate, why they dry, and why the newer ones do neither to any comparable degree. [6][9]
2. Pearl: Promethazine's boxed warning is an age limit, not a dose caution: below two years it is simply not used.
2. Why: Examiners test the absolute nature of the restriction, and the reason given on the label is potentially fatal respiratory depression. [1]
3. Pearl: Cetirizine and levocetirizine are the second-generation agents whose labels still carry sedation wording.
3. Why: A question asking which non-sedating antihistamine may still make a driver sleepy is asking about this pair. [5][4]
4. Pearl: Fexofenadine absorption is reduced both by aluminium- and magnesium-containing antacids and by common fruit juices.
4. Why: It is the one routinely examined absorption interaction in the class, and the juice effect was demonstrated on weal and flare size. [6]
5. Pearl: Hydroxyzine is the antihistamine with a cardiac contraindication.
5. Why: A prolonged QT interval rules it out, which no other agent in routine allergy use does. [3]
6. Pearl: Desloratadine is the major active metabolite of loratadine, and fexofenadine is the major active metabolite of terfenadine.
6. Why: Both were developed as the active metabolite of an earlier drug, which is a favourite one-line question. [7][6]
7. Pearl: A patient's own sense of drowsiness is a poor guide to how impaired they actually are.
7. Why: Subjective signs such as yawning or drooping eyelids may not be apparent when driving and psychomotor function are already affected. [17]

Common exam traps

1. Trap: Treating non-sedating as meaning never sedating.
1. Correction: The loratadine packet qualifies its non-drowsy claim with when taken as directed, and cetirizine's warnings state that drowsiness may occur. [8][5]
2. Trap: Assuming an over-the-counter sleep aid or cold remedy contains no antihistamine worth thinking about.
2. Correction: Many are diphenhydramine under a purpose line reading nighttime sleep-aid, and they carry the same glaucoma, prostate and breathing cautions as an allergy tablet. [10][15]
3. Trap: Reaching for a sedating antihistamine to settle an unsettled child.
3. Correction: Excitability may occur especially in children, and the chlorphenamine label states directly that it is not to be used to make a child sleepy. [11]
4. Trap: Claiming that second-generation agents are proven not to enter the human brain.
4. Correction: The evidence cited on the labels is animal distribution and receptor-binding work, and the desloratadine label says the clinical significance of the finding is unknown. [7][6]
5. Trap: Thinking the promethazine injection warning is only about the child under two.
5. Correction: There is a second boxed warning on the injectable form about severe chemical irritation and damage to tissues, including gangrene and tissue necrosis. [2]
6. Trap: Prescribing an older antihistamine for an elderly patient because it is familiar and cheap.
6. Correction: Dizziness, sedation and hypotension are more likely with age, and diphenhydramine is generally not recommended in older adults outside serious allergic reactions. [9][16]

Self-test questions

1. Question: A three-month-old infant is brought to a rural clinic with vomiting, and a relative suggests a promethazine syrup left over from an older sibling. What is the correct response?
1. Promethazine must not be used at this age because of potentially fatal respiratory depression
2. Promethazine is acceptable if the amount is halved for body weight
3. Promethazine is acceptable provided the infant is observed for one hour

4. Promethazine is acceptable because syrups are safer than tablets

1. Explanation: The boxed warning states the product should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. No adjustment or observation makes it acceptable below that age. [1]

2. Question: Which single property best explains why diphenhydramine causes sedation while fexofenadine does not?

1. Penetration of the central nervous system

2. Affinity for the H1 receptor

3. Duration of receptor occupancy

4. Selectivity for H2 over H1 receptors

2. Explanation: Both are H1 antagonists. Rat distribution studies indicated fexofenadine does not cross the blood-brain barrier and no sedative or other central nervous system effects were observed, whereas diphenhydramine is labelled as having sedative effects. [6][9]

3. Question: A patient taking fexofenadine for hay fever reports that it seems to have stopped working since they began a morning routine of indigestion remedy and a glass of orange juice. What is the most likely explanation?

1. Reduced absorption caused by both the antacid and the fruit juice

2. Rapid tolerance at the H1 receptor

3. Induction of hepatic metabolism by orange juice

4. Displacement of fexofenadine from plasma protein binding

3. Explanation: An aluminium- and magnesium-containing antacid taken within fifteen minutes decreased fexofenadine AUC by 41% and Cmax by 43%, and grapefruit, orange and apple juice may reduce its bioavailability and exposure. [6]

4. Question: Which antihistamine is contraindicated in a patient with a prolonged QT interval?

1. Hydroxyzine

2. Loratadine

3. Chlorphenamine

4. Ketotifen eye drops

4. Explanation: The hydroxyzine label states that it is contraindicated in patients with a prolonged QT interval, following post-marketing reports of QT prolongation and torsade de pointes. [3]

5. Question: An 82-year-old man with benign prostatic enlargement asks about an over-the-counter tablet for occasional sleeplessness that contains diphenhydramine. Which concern is most relevant?

1. Antimuscarinic effects and sedation are both more troublesome at his age

2. Diphenhydramine has no effect on the bladder

3. The tablet contains no antihistamine because it is sold as a sleep aid

4. Sedation is the only recognised problem in older people

5. Explanation: Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients, and the label lists trouble urinating due to an enlarged prostate gland among the reasons to seek advice first. [9][10][16]

6. Question: Which statement about second-generation antihistamines and the central nervous system is best supported by the product labels?

1. Animal studies show little or no crossing of the blood-brain barrier, and one label calls the clinical significance unknown

2. Human imaging has proved that no drug of the group enters the brain

3. They enter the brain freely but lack activity at central H1 receptors

4. They are converted in the brain to inactive metabolites

6. Explanation: The desloratadine label reports rat and guinea-pig findings that it did not readily cross the blood brain barrier and adds that the clinical significance of this finding is unknown; fexofenadine's label reports the rat distribution result. [7][6]

7. Question: A driver taking a sedating antihistamine says he feels perfectly alert. How should that self-assessment be weighed?

1. It is unreliable, because measurable impairment can occur without obvious drowsiness
2. It is reliable, because drowsiness always precedes impairment
3. It is reliable if he has taken the drug before without incident
4. It is unreliable only if he has also drunk alcohol
7. Explanation: Subjective symptoms such as yawning or drooping eyelids may not be apparent when effects on driving and psychomotor function are already present, and simulator steering after diphenhydramine was worse than at a blood alcohol content one-eighth of the legal limit. [17][14]

Frequently asked questions

1. Question: Why are antihistamines grouped by generation rather than by what they treat?
1. Answer: Because the generation predicts the trouble. Two agents can control the same runny nose while one of them also sedates, dries the mouth and makes driving hazardous. Grouping by indication would hide the difference that actually changes management. [14][9]
2. Question: If a drug is labelled non-drowsy, can it still cause drowsiness?
2. Answer: Yes. The loratadine packet prints its non-drowsy claim with an asterisk reading when taken as directed, and warns that more than directed may cause drowsiness. Cetirizine, in the same generation, warns outright that drowsiness may occur. [8][5]
3. Question: Why does an antihistamine appear in a travel sickness tablet or a sleeping preparation?
3. Answer: Because central H1 blockade produces sedation and antiemesis as well as antihistaminic effects. Dimenhydrinate is labelled as an antiemetic for the nausea, vomiting and dizziness of motion sickness, and diphenhydramine is sold under the purpose line nighttime sleep-aid. [1][12][10]
4. Question: What makes the older agents a particular problem in old age?
4. Answer: Two effects compound. Antihistamines are more likely to cause dizziness, sedation and hypotension in elderly patients, and the antimuscarinic load brings dry mouth, blurred vision, constipation and urinary difficulty on top. MedlinePlus advises that diphenhydramine should generally not be used in older adults except for serious allergic reactions. [9][16][14]
5. Question: Are these medicines suitable for young children with a cough or cold?
5. Answer: United Kingdom regulators concluded there is no robust evidence that such preparations work, that harms have been reported, and that products containing sedating antihistamines should no longer be used below six years of age. Between six and twelve they remain available from pharmacies where advice can be given. [15]
6. Question: Does a topical antihistamine avoid the sedation problem?
6. Answer: Applying the antagonist to the eye or nose treats the symptom where it arises and keeps systemic exposure low, which is the point of an agent such as ketotifen eye drops for itchy eyes in the pollen season. [13]

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