

Triptans and migraine agents

The drugs used to abort a migraine attack and the unrelated drugs used to stop attacks happening, held together on one page because the choice between them turns almost entirely on whether a patient can safely be given a cranial vasoconstrictor.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/triptans-and-migraine-agents>

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Quick revision

One Liner: Acute migraine drugs and preventive migraine drugs share an indication and nothing else, and the single fact that organises the acute half is whether the agent constricts cranial vessels.

1. Triptans are 5-HT_{1B/1D} receptor agonists acting on intracranial vessels and trigeminal sensory nerves, causing cranial vasoconstriction and pro-inflammatory neuropeptide inhibition. [1][2]
2. Seven triptans are marketed: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan. [12]
3. The sumatriptan label contraindicates ischaemic coronary artery disease, coronary artery vasospasm including Prinzmetal's angina, and uncontrolled hypertension. [1]
4. A history of stroke or transient ischaemic attack, and hemiplegic or basilar migraine, are also triptan contraindications, because those patients carry a higher risk of stroke. [1]
5. Ergotamine carries a boxed warning that serious or life-threatening peripheral ischaemia has followed its coadministration with potent CYP3A4 inhibitors. [3]
6. Recent use of an ergotamine-containing or ergot-type medicine, meaning within twenty-four hours, is a contraindication to sumatriptan, and the same interval separates any two 5-HT₁ agonists. [1]
7. Lasmiditan binds the 5-HT_{1F} receptor, its label lists no contraindications at all, and patients are advised against hazardous activity for at least eight hours after each dose. [4]
8. Ubrogapant and rimegepant are calcitonin gene-related peptide receptor antagonists, and gepants together with lasmiditan do not cause vasoconstriction. [5][6][12]
9. Using acute migraine drugs on ten or more days per month may lead to exacerbation of headache, the state called medication overuse headache. [1][4]
10. Erenumab is a human monoclonal antibody that binds the CGRP receptor and is given by subcutaneous injection for preventive treatment. [7]
11. Oral prevention borrows from four unrelated classes, using propranolol, topiramate, amitriptyline, candesartan and flunarizine. [8][9][11][10]

Overview

1. Migraine pharmacology divides into two halves that share an indication and almost no mechanism. Acute treatment aborts an attack already under way; preventive treatment reduces how often attacks arrive. The propranolol label states the division outright, noting that efficacy in the treatment of a migraine attack that has started has not been established and that the drug is not indicated for such use. [8]
2. Within the acute half, agents are grouped by the receptor they occupy. Sumatriptan exerts its effects through agonism at 5-HT_{1B/1D} receptors on intracranial vessels and trigeminal sensory nerves, and zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. Ergot alkaloids act far less selectively, and their characteristic toxicity is ergotism, manifested by intense arterial vasoconstriction. Lasmiditan occupies 5-HT_{1F} instead, while ubrogapant and rimegepant antagonise the calcitonin gene-related peptide receptor. [1][2][3][4][5][6]
3. A single safety boundary organises the older acute drugs. Triptans are contraindicated in patients with

cardiovascular disease, peripheral vascular disease, cerebrovascular disease and uncontrolled hypertension, because of the potential for ischaemia. Gepants and lasmiditan do not cause vasoconstriction, and were developed as alternatives for patients who do not tolerate triptans. That is why the newer acute agents matter clinically rather than merely commercially. [12]

4. Prevention is assembled largely from drugs whose principal use lies elsewhere: a beta-blocker, an antiepileptic, a tricyclic antidepressant, an angiotensin receptor blocker, and a mixed sodium and calcium channel blocker. The CGRP monoclonal antibodies are the exception, developed for migraine and administered subcutaneously. None of these preventive agents will stop an attack that has already begun. [8][9][11][10][7]

Classification and drug examples

Intro: Divided first by purpose, acute or preventive, and then by molecular target within each half. That order matters because the target determines the contraindications, and the contraindications are what decide which acute drug a given patient can have.

1. Name: Triptans, the 5-HT_{1B/1D} receptor agonists

1. Note: The reference agents for acute treatment. Seven are marketed, and all carry the vascular restrictions that follow from a mechanism involving cranial vasoconstriction.

1. Name: Sumatriptan

Sumatriptan succinate

1. Route: Oral

1. Note: The prototype. Its label describes binding with high affinity to human cloned 5-HT_{1B/1D} receptors, with effects on intracranial vessels and trigeminal sensory nerves that cause cranial vasoconstriction and pro-inflammatory neuropeptide inhibition. [1]

2. Name: Zolmitriptan

Zomig

2. Route: Oral

2. Note: Binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. Atypical sensations and pain or pressure sensations were the most frequently reported complaints in its trials. [2]

3. Name: Rizatriptan

3. Route: Oral

3. Note: One of the seven marketed triptans, sharing the receptor target and the ischaemic restrictions of the group. [12]

4. Name: Naratriptan

4. Route: Oral

4. Note: Also among the seven available triptans, and subject to the same cardiovascular and cerebrovascular exclusions. [12]

5. Name: Eletriptan

5. Route: Oral

5. Note: A further member of the marketed triptan group; the potential for ischaemia applies to it as to the rest. [12]

6. Name: Frovatriptan

6. Route: Oral

6. Note: Counted among the seven triptans available for acute migraine, with the class restriction in uncontrolled hypertension. [12]

7. Name: Almotriptan

7. Route: Oral

7. Note: The remaining marketed triptan, listed alongside the other six in reviews of acute migraine treatment. [12][1]

2. Name: Ditans, the selective 5-HT_{1F} agonists

2. Note: A single agent defined by moving one receptor subtype away from the triptans and losing the vasoconstrictor action in the process.

Name: Lasmiditan

Reyvow

Route: Oral

Note: Binds with high affinity to the 5-HT_{1F} receptor, though its label states that the precise mechanism is unknown. It is a Schedule V controlled substance and its label lists no contraindications. [4] [4][12]

3. Name: Gepants, the small-molecule CGRP receptor antagonists

3. Note: Oral antagonists of the calcitonin gene-related peptide receptor. Their interactions are metabolic rather than vascular, which changes the questions asked before prescribing.

1. Name: Ubrogapant

Ubrelvy

1. Route: Oral

1. Note: A calcitonin gene-related peptide receptor antagonist for acute use only; its label states that it is not indicated for the preventive treatment of migraine. [5]

2. Name: Rimegepant

Nurtec ODT

2. Route: Oral or sublingual, as an orally disintegrating tablet

2. Note: The unusual member that holds both indications, being licensed for acute treatment and for preventive treatment of episodic migraine in adults. [6] [5][6]

4. Name: Ergot alkaloids

4. Note: The historic acute treatment, displaced by the triptans. Non-selective vasoconstriction and a boxed interaction warning explain why they are now reserved.

1. Name: Ergotamine

1. Ergotamine tartrate

2. Ergomar

1. Route: Sublingual

1. Note: Indicated as therapy to abort or prevent vascular headache. Its label states that it should not be used for chronic daily administration, and caps the number of tablets permitted in any one week. [3]

2. Name: Dihydroergotamine

DHE

2. Route: Parenteral and intranasal

2. Note: Named in the sumatriptan label as an example of an ergot-type medication, recent use of which within twenty-four hours is a contraindication to the triptan. [1] [3][1]

5. Name: Oral preventive agents

5. Note: Drugs repurposed from cardiology, epilepsy and psychiatry. They reduce attack frequency and have no role once an attack is under way.

1. Name: Propranolol

Inderal LA

1. Route: Oral

1. Note: A non-selective beta-blocker indicated for the prophylaxis of common migraine headache. Its label is explicit that it is not indicated for an attack that has started. [8]

2. Name: Topiramate

Topamax

2. Route: Oral

2. Note: Indicated for the prophylaxis of migraine headache in adults; its usefulness in acute treatment has not been studied. Its adverse-effect profile is covered in depth on the antiepileptics page. [9]

3. Name: Amitriptyline

3. Route: Oral

3. Note: A tricyclic antidepressant used preventively; a systematic review of randomised trials records monthly migraine day reductions ranging from one to almost eight days, with widely varying adverse-event rates. [11]

4. Name: Candesartan

4. Route: Oral

4. Note: An angiotensin receptor blocker, included in systematic reviews of episodic migraine prevention with a reported reduction of about two monthly migraine days at twelve weeks. [11]

5. Name: Flunarizine

5. Route: Oral

5. Note: Described as a mixed sodium and calcium channel blocker, and not marketed in the United States. Mild daytime sedation and weight gain were the commonest reasons for stopping it in trials. [10] [8][11]

6. Name: CGRP monoclonal antibodies

6. Note: Injectable biologics designed for migraine rather than borrowed from another specialty, and the only preventive group whose target matches that of the gepants.

Name: Erenumab

1. Erenumab-aooe

2. Aimovig

Route: Subcutaneous injection

Note: A human monoclonal antibody that binds the calcitonin gene-related peptide receptor and antagonises its function, licensed for preventive treatment of migraine in adults. [7] [7]

Mechanism of action

Summary: Four distinct acute mechanisms and a scatter of preventive ones. Triptans agonise 5-HT_{1B/1D} receptors, producing cranial vasoconstriction and neuropeptide inhibition; ergots vasoconstrict without that selectivity; lasmiditan agonises 5-HT_{1F}; gepants and erenumab block the CGRP receptor from outside and inside the vessel wall respectively. Prevention works through beta-adrenoceptor blockade, mixed antiepileptic actions, channel blockade and CGRP receptor antagonism.

Target: 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors, the calcitonin gene-related peptide receptor, beta-adrenoceptors, and neuronal sodium and calcium channels

Cidal Static: Attack-aborting or attack-preventing rather than disease-modifying

Kill Kinetics: Acute agents act within hours of a single administration; preventive agents require sustained exposure over weeks

1. Step: 1

1. Title: Agonism at 5-HT_{1B} and 5-HT_{1D} receptors

1. Detail: Sumatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors and exerts its effect through agonism at those receptors on intracranial vessels and trigeminal sensory nerves. Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. [1][2]

2. Step: 2

2. Title: Cranial vasoconstriction and neuropeptide inhibition

2. Detail: Two consequences follow that binding: constriction of cranial vessels, and inhibition of the release of pro-inflammatory neuropeptides from trigeminal sensory nerve endings. The vascular half of that pair is also the source of the class's cardiac and cerebrovascular restrictions. [1]

3. Step: 3

3. Title: Non-selective ergot vasoconstriction

3. Detail: Ergotamine aborts vascular headache but without the receptor selectivity of a triptan. Its label describes ergotism as intense arterial vasoconstriction producing signs and symptoms of peripheral vascular ischaemia, and

states that gangrene can result. [3]

4. Step: 4

4. Title: Selective 5-HT_{1F} agonism without vasoconstriction

4. Detail: Lasmiditan binds with high affinity to the 5-HT_{1F} receptor and is presumed to act through agonism there, although its label states that the precise mechanism is unknown. Unlike the triptans it does not cause vasoconstriction. [4][12]

5. Step: 5

5. Title: Blockade of the CGRP receptor by small molecules

5. Detail: Ubrogapant and rimegepant are both calcitonin gene-related peptide receptor antagonists. Because they interrupt the neuropeptide signal rather than constricting a vessel, they were developed as alternatives for patients who do not tolerate triptans. [5][6][12]

6. Step: 6

6. Title: Blockade of the same receptor by an antibody

6. Detail: Erenumab is a human monoclonal antibody that binds the calcitonin gene-related peptide receptor and antagonises its function. The molecular target is shared with the gepants, but the antibody format means subcutaneous administration and a preventive rather than acute role. [7]

7. Step: 7

7. Title: Preventive mechanisms borrowed from other classes

7. Detail: Propranolol acts through beta-adrenoceptor blockade, topiramate through the mixed antiepileptic actions described on its own class page, and flunarizine as a mixed sodium and calcium channel blocker whose therapeutic effect is thought unlikely to depend on calcium antagonism in cerebral vessels. [8][9][10]

Major clinical uses

1. Drug: Sumatriptan

1. Organism: Not applicable

1. Indication: Acute treatment of migraine with or without aura in adults

1. Line: first-line acute

1. Note: The label restricts it to acute treatment in adults and gives no preventive indication. A cardiovascular evaluation is directed in triptan-naïve patients who have multiple cardiovascular risk factors. [1]

2. Drug: Zolmitriptan

2. Organism: Not applicable

2. Indication: Acute treatment of migraine with or without aura in adults

2. Line: first-line acute

2. Note: An alternative triptan where a patient responds poorly to another member of the group, carrying the same receptor mechanism and the same exclusions. [2]

3. Drug: Lasmiditan

3. Organism: Not applicable

3. Indication: Acute treatment of migraine with or without aura in adults

3. Line: acute, where a vasoconstrictor is unsuitable

3. Note: Its label states that it is not indicated for the preventive treatment of migraine. Sedation and driving impairment, rather than vascular risk, are what limit its use. [4]

4. Drug: Ubrogapant

4. Organism: Not applicable

4. Indication: Acute treatment of migraine with or without aura in adults

4. Line: acute alternative

4. Note: Confined to acute use by its own label. Its principal prescribing constraint is metabolic: it is contraindicated with concomitant use of strong CYP3A4 inhibitors. [5]

5. Drug: Rimegepant
5. Organism: Not applicable
5. Indication: Acute treatment of migraine, and preventive treatment of episodic migraine in adults
5. Line: acute and preventive
5. Note: The only agent on this page licensed on both sides of the acute and preventive divide, which is the detail most often tested about it. [6]
6. Drug: Ergotamine
6. Organism: Not applicable
6. Indication: Therapy to abort or prevent vascular headache, including migraine and its variants
6. Line: reserved
6. Note: Its indication is broader than a triptan's, but the boxed interaction warning and the prohibition on chronic daily administration have pushed it out of routine use. [3]
7. Drug: Propranolol
7. Organism: Not applicable
7. Indication: Prophylaxis of common migraine headache
7. Line: first-line preventive
7. Note: The label directs that therapy is discontinued if a satisfactory response is not obtained within four to six weeks of reaching the maximal dose, which sets the expected trial period for a preventive agent. [8]
8. Drug: Topiramate
8. Organism: Not applicable
8. Indication: Prophylaxis of migraine headache in adults
8. Line: first-line preventive
8. Note: Usefulness in acute migraine has not been studied. Its ophthalmic, metabolic and cognitive adverse effects are the reason it is monitored closely, and those are set out on the antiepileptics page. [9]
9. Drug: Flunarizine
9. Organism: Not applicable
9. Indication: Preventive treatment of migraine, where it is available
9. Line: preventive, regionally variable
9. Note: A European Headache Federation appraisal found insufficient data to support Level A evidence for efficacy despite its long-standing first-line use, and notes that it is not marketed in the United States. [10]
10. Drug: Erenumab
10. Organism: Not applicable
10. Indication: Preventive treatment of migraine in adults
10. Line: preventive biologic
10. Note: Given subcutaneously into the abdomen, thigh or upper arm. It is the preventive option whose target is the migraine pathway itself rather than a repurposed cardiovascular or antiepileptic action. [7]
11. Drug: Candesartan and amitriptyline
11. Organism: Not applicable
11. Indication: Preventive treatment of episodic migraine
11. Line: alternative preventive
11. Note: Both appear in systematic reviews of randomised preventive trials, candesartan as an angiotensin receptor blocker and amitriptyline as a tricyclic, with reported monthly migraine day reductions overlapping those of propranolol. [11]

Pharmacokinetics

1. This page gives no dose regimens or titration schedules. Choosing between an acute and a preventive agent, and monitoring either, belongs to the treating clinician working from a current prescribing reference and the individual

patient's cardiovascular history.

2. The interactions that matter most in this class are metabolic rather than pharmacodynamic. Ergotamine's boxed warning concerns coadministration with potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics, and ubrogepant is contraindicated outright with strong CYP3A4 inhibitors. [3][5]
3. Rimegepant's label advises avoiding concomitant strong CYP3A4 inhibitors, avoiding strong or moderate CYP3A4 inducers, and avoiding a further dose within forty-eight hours where a moderate CYP3A4 inhibitor or a potent P-glycoprotein inhibitor has been given. [6]
4. Organ impairment sets separate limits: rimegepant is to be avoided in severe hepatic impairment and in end-stage renal disease, while sumatriptan tablets are contraindicated in severe hepatic impairment. [6][1]
5. Erenumab is a monoclonal antibody, so it is delivered by subcutaneous injection rather than absorbed orally, and anti-erenumab antibodies developed in 11.1 percent of patients in a long-term study. [7]

Adverse effects

1. Effect: Sensory and pressure symptoms with triptans
 1. Detail: In the zolmitriptan trials, pain or pressure sensations were reported by 22 percent and atypical sensations by 18 percent, with dizziness in 10 percent, somnolence in 8 percent and nausea in 6 to 9 percent. [2]
2. Effect: Chest, throat, neck or jaw tightness
 2. Detail: The sumatriptan label carries a dedicated warning for pain, tightness or pressure at these sites, which sits directly alongside its warnings on myocardial ischaemia and other vasospasm reactions. [1]
3. Effect: Sedation and dizziness with lasmiditan
 3. Detail: Dizziness, fatigue, paraesthesia and sedation were the reactions reported in at least 5 percent of patients and more often than with placebo. [4]
4. Effect: Nausea with the gepants
 4. Detail: Nausea and somnolence were the commonest reactions with ubrogepant. With rimegepant used acutely, nausea occurred in 2 percent against 0.4 percent on placebo, and nausea with abdominal pain or dyspepsia predominated in preventive use. [5][6]
5. Effect: Injection site reactions and constipation with erenumab
 5. Detail: These are the two most frequently reported reactions to the antibody, and the constipation is not always trivial. [7]
1. Effect: Myocardial ischaemia, myocardial infarction and Prinzmetal's angina
 1. Detail: The first warning in the sumatriptan label, and the reason the drug is contraindicated in ischaemic or vasospastic coronary artery disease. Arrhythmias, cerebrovascular events and other vasospasm reactions follow it as separate warnings.
 1. Action: A cardiovascular evaluation is performed in triptan-naïve patients with multiple cardiovascular risk factors before the drug is given; the assessment and any change of treatment rest with the treating clinician. [1]
2. Effect: Peripheral ischaemia and gangrene from ergotism
 2. Detail: Ergotism presents as numbness or tingling in the fingers and toes, muscle pain in the arms and legs, and coldness and pallor of the digits. The label states that gangrene can result.
 2. Action: Ergotamine is not given with other vasoconstrictors, and concomitant potent CYP3A4 inhibitors are contraindicated. [3]
3. Effect: Medication overuse headache
 3. Detail: Overuse of acute migraine drugs such as ergotamine, triptans or opioids, or a combination of them, on ten or more days per month may lead to exacerbation of headache.
 3. Action: Detoxification including withdrawal of the overused drug may be necessary, and often involves a transient worsening of headache; this is a decision for the treating clinician. [1][4]
4. Effect: Serotonin syndrome
 4. Detail: A recognised risk when a triptan is combined with a serotonergic agent such as an SSRI, an SNRI, a tricyclic

or a monoamine oxidase inhibitor. Lasmiditan carries its own serotonin syndrome warning.

4. Action: The labels direct that the drug is discontinued if serotonin syndrome is suspected. [1][4]

5. Effect: Constipation with serious complications from erenumab

5. Detail: Severe constipation has developed after the antibody, in some cases requiring hospitalisation or surgery, and most often after the first dose.

5. Action: New or worsening hypertension is a separate labelled risk, typically appearing within seven days of dosing and occasionally leading to hospitalisation. [7]

6. Effect: Acute myopia with secondary angle-closure glaucoma from topiramate

6. Detail: A syndrome of acutely decreased visual acuity with or without ocular pain. Untreated raised intraocular pressure of any cause can lead to permanent vision loss.

6. Action: An abrupt visual change in a patient taking topiramate is treated as urgent; the antiepileptics page covers this and the drug's other systemic effects in full. [9]

7. Effect: Anaphylaxis and other hypersensitivity reactions

7. Detail: Serious hypersensitivity, including anaphylaxis, dyspnoea and rash, has occurred with rimegepant, and can appear days after administration. Ubrogepant has been associated with anaphylaxis, dyspnoea, facial or throat oedema, rash, urticaria and pruritus.

7. Action: A serious or severe reaction prompts discontinuation and appropriate treatment. [6][5]

8. Effect: Bronchospasm with propranolol

8. Detail: Bronchial asthma is a listed contraindication, and the label warns that the drug may provoke a bronchial asthmatic attack in patients with bronchospastic lung disease.

8. Action: Exacerbation of angina and myocardial infarction have followed abrupt withdrawal, so discontinuation is a supervised process rather than an immediate stop. [8]

1. Drug: Lasmiditan

1. Effect: Significant driving impairment. In a driving study, single doses significantly impaired the ability to drive, and patients are advised against hazardous activity requiring complete alertness for at least eight hours after each dose. [4]

2. Drug: Lasmiditan

2. Effect: Central nervous system depression, with caution advised where it is combined with alcohol or other depressants. It is scheduled as a controlled substance in the CV category. [4]

3. Drug: Ergotamine

3. Effect: Extreme elevation of blood pressure when used with sympathomimetic pressor agents, and a prohibition on chronic daily administration with a fixed ceiling on tablets per week. [3]

4. Drug: Flunarizine

4. Effect: Mild daytime sedation and weight gain were the commonest adverse events leading to discontinuation in trials. [10]

5. Drug: Topiramate

5. Effect: Hyperchloraemic non-anion-gap metabolic acidosis, and oligohidrosis with decreased sweating that has infrequently led to hospitalisation. [9]

6. Drug: Candesartan

6. Effect: Dizziness was the commonest adverse event in a placebo-controlled preventive trial, affecting roughly 30 percent of those on candesartan against 13 percent on placebo. [11]

Contraindications, precautions and interactions

1. Sumatriptan is contraindicated in ischaemic coronary artery disease, meaning angina pectoris, previous myocardial infarction or documented silent ischaemia, and in coronary artery vasospasm including Prinzmetal's angina. [1]

2. It is further contraindicated in Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders. [1]

3. A history of stroke or transient ischaemic attack, or of hemiplegic or basilar migraine, excludes the drug, because such patients are at higher risk of stroke. [1]
 4. Peripheral vascular disease, ischaemic bowel disease and uncontrolled hypertension complete the vascular exclusions, alongside severe hepatic impairment and hypersensitivity to the drug. [1]
 5. Use of an ergotamine-containing or ergot-type medication, or of another 5-HT₁ agonist, within the preceding twenty-four hours is contraindicated because the vasospastic effects may be additive. [1]
 6. Ergotamine must not be given with potent CYP3A4 inhibitors, and its own contraindications include peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy. [3]
 7. Ubrogapant is contraindicated with concomitant use of strong CYP3A4 inhibitors, and in patients with a history of serious hypersensitivity to it. [5]
 8. Propranolol is contraindicated in cardiogenic shock, in sinus bradycardia and heart block greater than first degree, in bronchial asthma, and in known hypersensitivity. [8]
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1. The triptan class as a whole is avoided in cardiovascular disease, peripheral vascular disease, cerebrovascular disease and uncontrolled hypertension because of the potential for ischaemia. [12]
 2. Where a triptan-naïve patient has multiple cardiovascular risk factors, a cardiovascular evaluation is performed before the first dose is given. [1]
 3. Rimegepant is to be avoided in severe hepatic impairment and in end-stage renal disease with a creatinine clearance under 15 mL per minute. [6]
 4. Erenumab can cause new-onset or worsening hypertension, usually within seven days of a dose, so blood pressure is a relevant thing to keep under review during treatment. [7]
 5. Lasmiditan requires that driving and machinery are avoided for at least eight hours after a dose, and patients unable to follow that advice should not be given it. [4]
 6. Flunarizine is not marketed in the United States and its availability varies between European countries, so recommendations built around it do not transfer everywhere. [10]
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1. With: Monoamine oxidase A inhibitors
 1. Effect: Concurrent administration, or use within two weeks of stopping such an inhibitor, is contraindicated with both sumatriptan and zolmitriptan. [1][2]
 2. With: Ergot-containing and ergot-type drugs
 2. Effect: These have been reported to cause prolonged vasospastic reactions, so their use within twenty-four hours of sumatriptan is contraindicated; the zolmitriptan label directs that the same pairing be avoided. [1][2]
 3. With: Another 5-HT_{1B/1D} agonist
 3. Effect: Concomitant use within twenty-four hours of zolmitriptan is not recommended, and is contraindicated with sumatriptan, on the grounds of additive vasospastic effect. [2][1]
 4. With: Potent CYP3A4 inhibitors, including protease inhibitors and macrolides
 4. Effect: Serious or life-threatening peripheral ischaemia has been associated with their coadministration with ergotamine tartrate, which is the substance of that drug's boxed warning. [3]
 5. With: Strong CYP3A4 inhibitors such as ketoconazole, itraconazole or clarithromycin
 5. Effect: Ubrogapant should not be used with them at all, and rimegepant's label directs that concomitant administration be avoided. [5][6]
 6. With: P-glycoprotein inhibitors and moderate CYP3A4 inhibitors
 6. Effect: A further dose of rimegepant is avoided within forty-eight hours when a potent P-glycoprotein inhibitor or a moderate CYP3A4 inhibitor has been given. [6]
 7. With: Other vasoconstrictors and sympathomimetic pressor agents
 7. Effect: Ergotamine should not be administered with other vasoconstrictors, and combination with pressor agents may cause extreme elevation of blood pressure. [3]
 8. With: Serotonergic antidepressants
 8. Effect: Serotonin syndrome may occur when a triptan is combined with an SSRI, an SNRI, a tricyclic antidepressant

or a monoamine oxidase inhibitor. [1]

Comparison tables

1. Title: The acute agents compared

1. Caption: The decisive column is the third one: whether the mechanism involves constricting a vessel is what governs who can be given the drug. Selection remains a matter for the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: target

2. Label: Molecular target

3. Key: vasoconstriction

3. Label: Vasoconstrictor action

4. Key: limit

4. Label: Principal limiting factor

1. Drug: Sumatriptan

1. Target: 5-HT_{1B/1D} receptors

1. Vasoconstriction: Yes, cranial vasoconstriction is part of the labelled mechanism

1. Limit: Ischaemic coronary disease, prior stroke or TIA, uncontrolled hypertension [1]

2. Drug: Zolmitriptan

2. Target: 5-HT_{1D} and 5-HT_{1B} receptors

2. Vasoconstriction: Yes, with constriction of cranial vessels

2. Limit: Same vascular exclusions, plus concurrent MAO-A inhibition [2]

3. Drug: Ergotamine

3. Target: Non-selective, with intense arterial vasoconstriction

3. Vasoconstriction: Yes, and least selectively of all

3. Limit: Boxed warning on potent CYP3A4 inhibitors; ergotism and gangrene [3]

4. Drug: Lasmiditan

4. Target: 5-HT_{1F} receptor

4. Vasoconstriction: No

4. Limit: Driving impairment for at least eight hours; controlled substance status [4][12]

5. Drug: Ubrogapant

5. Target: CGRP receptor

5. Vasoconstriction: No

5. Limit: Contraindicated with strong CYP3A4 inhibitors [5][12]

6. Drug: Rimegepant

6. Target: CGRP receptor

6. Vasoconstriction: No

6. Limit: CYP3A and P-glycoprotein interactions; severe hepatic or end-stage renal disease [6][12]

2. Title: The preventive agents compared

2. Caption: Four of these five were developed for something else entirely. None of them has a role in an attack that has already started.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: origin

2. Label: Parent class

- 3. Key: route
- 3. Label: Route
- 4. Key: signature
- 4. Label: Signature drawback
- 1. Drug: Propranolol
- 1. Origin: Non-selective beta-blocker
- 1. Route: Oral
- 1. Signature: Contraindicated in bronchial asthma; angina and infarction after abrupt withdrawal [8]
- 2. Drug: Topiramate
- 2. Origin: Antiepileptic
- 2. Route: Oral
- 2. Signature: Acute myopia with angle closure, metabolic acidosis, oligohidrosis [9]
- 3. Drug: Amitriptyline
- 3. Origin: Tricyclic antidepressant
- 3. Route: Oral
- 3. Signature: Adverse-event rates across randomised trials range from none to universal [11]
- 4. Drug: Candesartan
- 4. Origin: Angiotensin receptor blocker
- 4. Route: Oral
- 4. Signature: Dizziness affected roughly a third of participants in a placebo-controlled trial [11]
- 5. Drug: Flunarizine
- 5. Origin: Mixed sodium and calcium channel blocker
- 5. Route: Oral
- 5. Signature: Daytime sedation and weight gain; unavailable in the United States [10]
- 6. Drug: Erenumab
- 6. Origin: CGRP receptor monoclonal antibody
- 6. Route: Subcutaneous injection
- 6. Signature: Severe constipation, sometimes needing surgery, and new or worsening hypertension [7]

High-yield exam pearls

- 1. Pearl: The triptan mechanism has two arms, not one: agonism at 5-HT_{1B/1D} produces cranial vasoconstriction and also inhibits release of pro-inflammatory neuropeptides.
- 1. Why: Questions often reward the neuropeptide arm, because it explains why a drug acting on vessels relieves the sensitisation as well as the vasodilatation. [1]
- 2. Pearl: Twenty-four hours is the number to remember: that is the separation required between a triptan and an ergot, and between any two 5-HT₁ agonists.
- 2. Why: It is a labelled contraindication rather than a caution, and the interval is exactly the sort of detail a written paper can test unambiguously. [1]
- 3. Pearl: Ergotamine's boxed warning is about a drug interaction: serious or life-threatening peripheral ischaemia with potent CYP3A4 inhibitors including protease inhibitors and macrolides.
- 3. Why: Most boxed warnings describe a direct toxicity, so an interaction-based one stands out, and it is the practical reason ergots have been displaced. [3]
- 4. Pearl: Lasmiditan's label lists no contraindications at all, whereas the sumatriptan label lists ten.
- 4. Why: That contrast is the cleanest single illustration of what removing the vasoconstrictor mechanism buys clinically. [4][1]
- 5. Pearl: Rimegepant holds both an acute and a preventive indication; ubrogepant and lasmiditan are explicitly not indicated for prevention.

5. Why: Candidates commonly assume the gepants behave as one group, and this is where the assumption breaks. [6][5][4]
6. Pearl: Ten or more days of acute treatment per month is the threshold cited in the labels for medication overuse headache.
6. Why: The counter-intuitive idea that the treatment sustains the illness is examined often, and the labels attach a specific frequency to it. [1][4]
7. Pearl: Erenumab and the gepants share a molecular target but not a role: the antibody is preventive and injected, the small molecules are largely acute and oral.
7. Why: It shows that the format of a molecule, not just its target, decides where in a treatment plan it sits. [7][5]

Common exam traps

1. Trap: Treating hemiplegic and basilar migraine as ordinary migraine subtypes that a triptan will help.
1. Correction: Both are listed contraindications in the sumatriptan label, alongside a history of stroke or transient ischaemic attack, because those patients are at higher risk of stroke. [1]
2. Trap: Assuming a preventive drug can be used to rescue an attack in progress.
2. Correction: The propranolol label states that efficacy in treating a migraine attack that has started has not been established and that the drug is not indicated for such use, and topiramate's usefulness in acute migraine has not been studied. [8][9]
3. Trap: Believing that swapping one triptan for another sidesteps the cardiovascular problem.
3. Correction: The restriction is a class property arising from the shared receptor mechanism, and applies across all seven marketed triptans. [12]
4. Trap: Calling lasmiditan a triptan because its name and indication look similar.
4. Correction: It binds the 5-HT_{1F} receptor rather than 5-HT_{1B/1D}, does not cause vasoconstriction, and is a scheduled controlled substance with a driving warning that no triptan carries. [4][12]
5. Trap: Reading ergotamine's boxed warning as a warning about overdose.
5. Correction: It concerns coadministration with potent CYP3A4 inhibitors, and the harm described is serious or life-threatening peripheral ischaemia rather than an effect of excess drug alone. [3]
6. Trap: Assuming the CGRP antibodies are free of systemic effects because they are targeted biologics.
6. Correction: Erenumab's label describes severe constipation that has required hospitalisation or surgery, and new or worsening hypertension usually appearing within seven days of a dose. [7]

Self-test questions

1. Question: Through which receptors does sumatriptan act, according to its label?
1. 5-HT_{1B/1D} receptors on intracranial vessels and trigeminal sensory nerves
2. 5-HT_{1F} receptors on trigeminal ganglion neurons only
3. The calcitonin gene-related peptide receptor
4. Beta-1 adrenoceptors in cranial vessels
1. Explanation: The label states that sumatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors and acts at those receptors on intracranial vessels and trigeminal sensory nerves, causing cranial vasoconstriction and pro-inflammatory neuropeptide inhibition. [1]
2. Question: A patient with documented coronary artery vasospasm asks about an acute migraine treatment. Which agent is contraindicated by its label?
1. Sumatriptan
2. Ubrogapant
3. Rimegepant
4. Lasmiditan
2. Explanation: Coronary artery vasospasm, including Prinzmetal's angina, appears in the sumatriptan

contraindications. Lasmiditan's label lists no contraindications, and the gepants are restricted by hypersensitivity and CYP3A4 interactions rather than by vascular disease. [1][4][5][6]

3. Question: What interval must separate an ergotamine-containing medication from sumatriptan?

1. Twenty-four hours
2. Four hours
3. Two weeks
4. Forty-eight hours

3. Explanation: Recent use, defined as within twenty-four hours, of an ergotamine-containing or ergot-type medication is a contraindication to sumatriptan, because the vasospastic effects of the two may be additive. [1]

4. Question: The boxed warning on the ergotamine tartrate label concerns which combination?

1. Ergotamine with potent CYP3A4 inhibitors such as protease inhibitors and macrolides
2. Ergotamine with a non-steroidal anti-inflammatory drug
3. Ergotamine with an angiotensin receptor blocker
4. Ergotamine with a proton pump inhibitor

4. Explanation: The boxed warning states that serious or life-threatening peripheral ischaemia has been associated with the coadministration of ergotamine tartrate with potent CYP3A4 inhibitors, naming protease inhibitors and macrolide antibiotics. [3]

5. Question: Which agent on this page is licensed both for acute treatment and for preventive treatment of episodic migraine?

1. Rimegepant
2. Ubrogepant
3. Lasmiditan
4. Erenumab

5. Explanation: Rimegepant carries both indications. Ubrogepant and lasmiditan are each stated not to be indicated for prevention, and erenumab is preventive only. [6][5][4][7]

6. Question: A patient taking lasmiditan asks about returning to work as a lorry driver. What does the label direct?

1. Hazardous activity requiring complete mental alertness is avoided for at least eight hours after each dose
2. There is no restriction, as lasmiditan is non-sedating
3. Driving is permitted once the headache has resolved
4. The restriction applies only to the first dose ever taken

6. Explanation: A driving study showed that single doses significantly impaired the ability to drive, and the label advises against driving or operating machinery for at least eight hours after each dose, adding that those unable to follow the advice should not take the drug. [4]

7. Question: At what frequency of acute migraine drug use do the labels warn about exacerbation of headache?

1. Ten or more days per month
2. Two or more days per month
3. Twenty or more days per month
4. Any use on consecutive days

7. Explanation: Both the sumatriptan and lasmiditan labels describe overuse of acute migraine drugs, including ergotamines, triptans and opioids or combinations of them, for ten or more days per month as leading to medication overuse headache. [1][4]

8. Question: Which adverse effect is specifically described in the erenumab label as sometimes requiring hospitalisation or surgery?

1. Severe constipation
2. Acute angle-closure glaucoma
3. Peripheral gangrene
4. Agranulocytosis

8. Explanation: The label warns of constipation with serious complications, noting that severe constipation has developed, sometimes requiring hospitalisation or surgery, most often after the first dose. [7]

Frequently asked questions

1. Question: Why are acute and preventive migraine drugs taught on the same page when they share no mechanism?

1. Answer: Because the clinical decision is a single one. A patient presents with attacks that are too frequent or too severe, and the question is whether to abort each one, to reduce how many arrive, or both. Understanding that propranolol has no effect on an attack in progress, and that a triptan does nothing to reduce attack frequency, is the point of holding the two halves together. [8][1]

2. Question: What exactly makes triptans unsafe in heart disease?

2. Answer: The therapeutic mechanism itself. Constriction of cranial vessels is part of how a triptan works, and that action is not confined to the head. Sumatriptan's label opens its warnings with myocardial ischaemia, myocardial infarction and Prinzmetal's angina, and reviews summarise the class restriction as applying to cardiovascular, peripheral vascular and cerebrovascular disease because of the potential for ischaemia. [1][12]

3. Question: If a patient cannot have a triptan, what remains for an acute attack?

3. Answer: The gepants and lasmiditan. Neither ubrogepant nor rimegepant nor lasmiditan causes vasoconstriction, and they were developed as alternatives for patients who do not tolerate triptans. Their own limits are different in kind: strong CYP3A4 inhibition for ubrogepant, hepatic and renal thresholds for rimegepant, and sedation with driving impairment for lasmiditan. [12][5][6][4]

4. Question: Why have ergot alkaloids largely been abandoned?

4. Answer: Two labelled features rather than a lack of effect. The first is the boxed warning about serious or life-threatening peripheral ischaemia when ergotamine meets a potent CYP3A4 inhibitor. The second is the toxic syndrome itself, described as intense arterial vasoconstriction with numbness, tingling, cold pale digits and, at worst, gangrene. Ergotamine also may not be used for chronic daily administration. [3]

5. Question: Can a triptan be given shortly after an ergot has failed to work?

5. Answer: No. Recent use of an ergotamine-containing or ergot-type medication within twenty-four hours is a contraindication to sumatriptan, on the grounds that vasospastic effects may be additive. The same twenty-four hour separation applies between one 5-HT₁ agonist and another. [1]

6. Question: Does treating attacks promptly ever make migraine worse?

6. Answer: Frequent acute treatment can. Both labels quoted here warn that overusing acute migraine drugs, including triptans, ergotamines and opioids, on ten or more days per month may lead to exacerbation of headache. Withdrawal of the overused drug may be needed, and often brings a transient worsening before improvement, which is why the decision belongs to a clinician. [1][4]

7. Question: How does topiramate fit here when it is an antiepileptic?

7. Answer: It is licensed for the prophylaxis of migraine headache in adults, and its usefulness in acute migraine has not been studied. Its migraine role is preventive only, and the systemic problems that govern its use, from metabolic acidosis to acute myopia with secondary angle closure, are set out on the antiepileptics page rather than repeated here. [9]

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[3] ERGOMAR SUBLINGUAL (ergotamine tartrate) tablet - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a9582fdb-7ddd-4f69-aa7a-66247cdb8c92>

[4] REYVOW (lasmiditan) tablet - prescribing information. DailyMed, U.S. National Library of Medicine .

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aea3358c-ff41-4490-9e6d-c7bf7b3de13f>

[5] UBRELVY (ubrogepant) tablet - prescribing information. DailyMed, U.S. National Library of Medicine .

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fd9f9458-fd96-4688-be3f-f77b3d1af6ab>

[6] NURTEC ODT (rimegepant) orally disintegrating tablet - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=86ef19d2-d6dc-4ac1-a793-dc549cc6bb9b>

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[9] TOPAMAX (topiramate) tablet, coated - prescribing information. DailyMed, U.S. National Library of Medicine .

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