PHARMACOLOGY

Drugs for Headache

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate drugs and drug classes for treating/managing headaches
2. Explain the mechanism of action of triptans, ergots, selective serotonin agonists, and calcitonin gene related peptide (CGRP) antagonists
3. Describe adverse effects and contraindications to triptans, ergots, selective serotonin agonists, and calcitonin gene related peptide (CGRP) antagonists
4. Describe the clinically important drug interactions of triptans, ergots, selective serotonin agonists, and calcitonin gene related peptide (CGRP) antagonists

PATHOPHYSIOLOGY RELEVANT TO PHARMACOLOGY

Multiple primary neuronal impairments → intra- and extracranial changes that cause migraine

Activation of multiple brain regions

- Hypothalamus, brain stem, cortex

Depressed neuronal activity spreads across brain

Trigeminovascular system becomes overactive → release of vasoactive peptides (e.g., calcitonin gene-related peptide (CGRP), neurokinin A, and substance P)

- Vasoactive peptides produce sterile inflammation causing sensation of pain

Probably a result of imbalance in sensation of pain and CNS blood vessel tone, which is controlled by noradrenergic and serotonergic neurons

NEUROPEPTIDES ASSOCIATED WITH MIGRAINE

Serotonin

- Role controversial
- Hypothesized that most or every neuron in brain may be in contact with a serotonergic projection fiber

Calcitonin gene-related peptide (CGRP)

Pituitary adenylate cyclase-activating polypeptide (PACAP)

MIGRAINE MANAGEMENT

Acute or abortive

- Acetaminophen and NSAIDs
- Triptans
- Ditans
- CGRP antagonists
- Ergot alkaloids

Prophylactic

- Valproate, divalproex sodium – A
- Topiramate – A
- Metoprolol, propranolol, timolol – A
- Frovatriptan (menstrual-related) – A
- Amitriptyline – B
- Atenolol – B
- Nadolol – B
- Venlafaxine – B
- Atogepant
- CGRP monoclonal antibodies

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TRIPTANS

Pharmacology

INTERACTIVE QUESTION

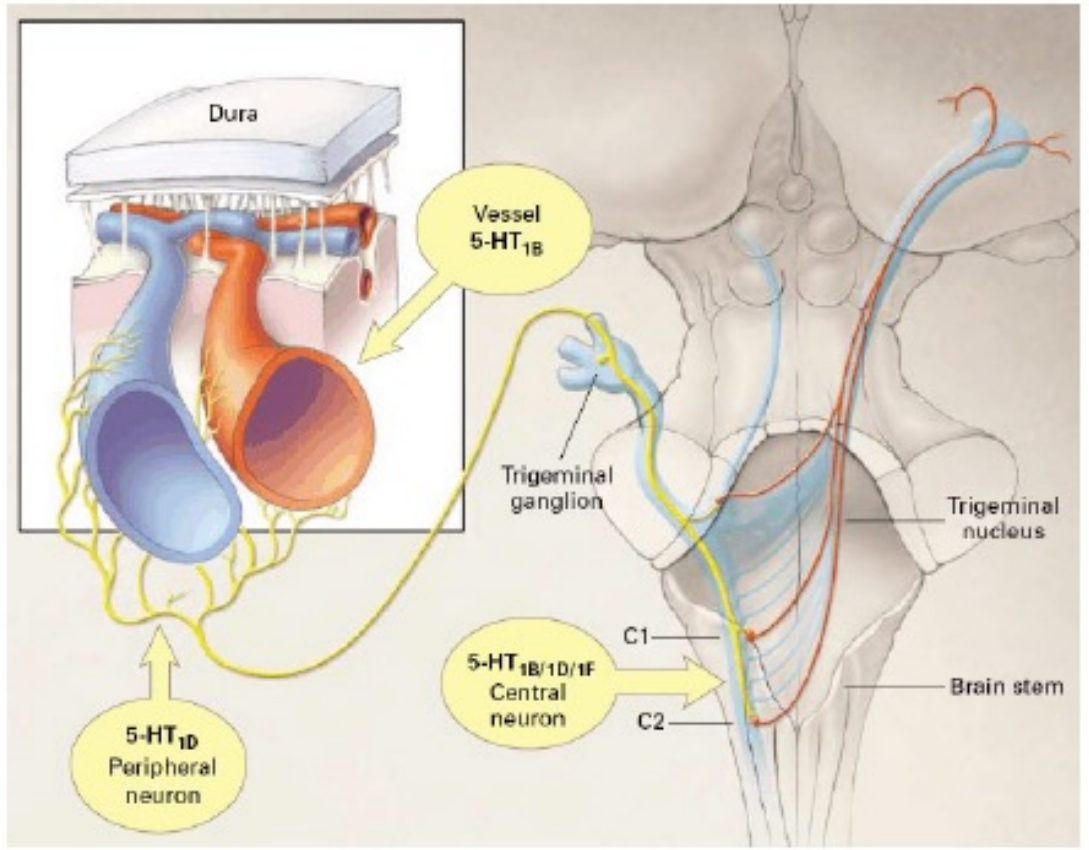
HA is a 36-year-old female with a PMH significant for dysmenorrhea and migraine. HA's migraines have progressed to moderate to severe and they require medication beyond NSAIDs. HA's PCP prescribes sumatriptan. What is sumatriptan's mechanism of action? Based on sumatriptan's mechanism of action, which adverse effects could HA potentially experience?

MECHANISM OF ACTION

Agonists of **5-HT1B** and **5-HT1D** serotonin receptors

- ↓ excitability of neurons in the trigeminovascular system (via stimulation of brainstem 5-HT1B/1D receptors)
- ↓ release of neuropeptides with inflammatory and vasodilating properties, ie, CGRP, substance P, and neurokinin A (via presynaptic 5-HT1D receptor effect)
- Vasoconstriction of cerebral and extracerebral vessels (via stimulation of vascular 5-HT1B)

Low or no affinity for other 5-HT, alpha-1 and alpha-2 adrenergic, beta adrenergic, dopaminergic, muscarinic cholinergic, or benzodiazepine receptors



Serotonin Receptor Subtypes[a]

SUBTYPE	SIGNALING EFFECTOR	LOCALIZATION	FUNCTION	AGONISTS	ANTAGONISTS
$5HT_{1A}$	↓ AC	Raphe nuclei, cortex, hippocampus	Somatodendritic autoreceptor	8-OH-DPAT, buspirone	WAY 100135
$5HT_{1B}$	↓ AC	Subiculum, globus pallidus, substantia nigra	Presynaptic autoreceptor	Sumatriptan, CP94253	GR-55562
$5HT_{1D}$	↓ AC	Cranial vessels, globus pallidus, substantia nigra	Presynaptic autoreceptor, vasoconstriction	Sumatriptan	SB 714786
$5HT_{1E}$	↓ AC	Cortex, striatum	—	—	—
$5HT_{1F}$	↓ AC	Dorsal raphe, hippocampus, periphery	—	LY334370	—

TRIPTANS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Almotriptan (Axert) Eletriptan (Relpax) Frovatriptan (Frova) Naratriptan (Amerge) Rizatriptan (Maxalt) **Sumatriptan (Imitrex)** Zolmitriptan (Zomig)	Uncontrolled hypertension Prinzmetal angina Peripheral or cerebral vascular disease **Coronary Artery Disease (may cause myocardial infarction**) May cause serotonin syndrome	Paresthesia Dizziness Fatigue Chest discomfort Heaviness sensation Mild pain or burning (injection) Bitter taste (nasal spray)	Concomitant use with ergot alkaloids or other triptans because vasoconstriction could be additive Drugs that modulate serotonin (ie, SSRIs, SNRIs, TCAs, MAOIs)

SEROTONIN SYNDROME

Potentially life-threatening condition by use of serotonergic drugs

- Generalized excess of 5-HT at 5-HT receptors

Symptoms range from mild to fatal

- Neurobehavioral (confusion, agitation, coma, seizures)
- Autonomic (hyperthermia, diaphoresis, tachycardia, hypertension)
- Neuromuscular (myoclonus, rigidity, tremor, ataxia, shivering, nystagmus)

Precipitating drugs

- SSRIs
- Second generation antidepressants
- MAOIs
- Linezolid
- Tramadol
- Meperidine, fentanyl
- Ondansetron
- Sumatriptan
- MDMA, LSD
- St. John's wort, ginseng

SEROTONIN SYNDROME MANAGEMENT

Sedation (benzodiazepines)

Paralysis

Intubation, and ventilation

Consider 5HT2 block with cyproheptadine or chlorpromazine

CLINICAL USE & ADME

Cluster headache (acute)

Migraine (moderate to severe, acute)

Dosage forms

- Oral administration (nausea, vomiting)
- Injection pen device for self subcutaneous administration (mild pain or redness at injection site)
- Nasal spray (bitter, unpleasant taste)

Metabolized in the liver mainly by monoamine oxidase A

Individual repones may way

- Failure of one does not preclude efficacy of another

DOSAGE FORM EXAMPLES

Images from WebMD

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LASMIDITAN ("DITANS")

Pharmacology

LASMIDITAN MECHANISM OF ACTION

Selective 5-HT1F agonist

Does not cause vasoconstriction

LASMIDITAN

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Lasmiditan (Reyvow)	No contraindications Cautions: CNS depression Heart disease Severe hepatic impairment Serotonin syndrome	Dizziness Fatigue Paresthesia Sedation Driving impairment 90 min to 8 hours after dose	May enhance effect of other CNS depressants May enhance arrhythmogenic effects of bradycardia-causing agents

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ERGOT ALKALOIDS (ERGOTS)

Pharmacology

MECHANISM OF ACTION

Agonists of 5-HT receptors (non-specific)

- 5-HT1 and 5-HT2
- May also be partial agonists of alpha-adrenergic receptors and potent agonists or dopamine receptors

Produced by fungus (*Claviceps purpurea*) found in wet or spoiled grain

Image credit

INTERACTIVE QUESTION

HA read online about a more “natural” treatment for migraines called ergots. HA wonders if ergots could be a better choice since they are considering trying to become pregnant. Would ergots be a reasonable option for HA? Defend your answer.

ERGOT ALKALOID COMPARISON

Ergot Alkaloid	Alpha Receptor (α_1)	Dopamine Receptor (D_2)	Serotonin Receptor ($5\text{-}HT_2$)	Uterine Smooth Muscle Stimulation
Bromocriptine	−	+ + +	−	0
Ergonovine	+ +	− (PA)	+ + +	+ +
Ergotamine	PA	0	PA	+ + +
Lysergic acid diethylamide (LSD)	0	+ + +	− −/+ + in CNS	+

Agonist effects are indicated by +, antagonist by −, no effect by 0. Relative affinity for the receptor is indicated by the number of + or − signs.

PA, partial agonist.

From: Katzung BG, Vanderah TW: *Basic & Clinical Pharmacology,* 15th ed. New York, NY: McGraw Hill; 2021.

MAIN ADVERSE EFFECTS OF ERGOTS

BLOOD VESSELS

ALPHA-1 ADRENERGIC RECEPTOR MEDIATED VASOCONSTRICTION

(ISCHEMIA, GANGRENE)

UTERUS

UTERINE CONTRACTION

(MISCARRIAGE, ABORTION)

BRAIN

REBOUND HEADACHE

GASTROINTESTINAL

NAUSEA, VOMITING COMMON

ERGOTS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Ergotamine Dihydroergotamine	Cardiac, peripheral, and cerebral vascular disease Uncontrolled hypertension **Pregnancy** Liver impairment Sepsis **Inhibitors of CYP3A4 (ie, erythromycin, azole antifungals) d/t acute ergot toxicity**	**Nausea/vomiting** **Vasoconstriction** **Contractions of uterine smooth muscle** Leg weakness Muscle pain Flushing Sweating **Rebound headache**	Inhibitors of CYP3A4 can prolong the action of ergotamine Drugs that cause vasoconstriction (ie, alpha blockers, beta blockers, triptans) Drugs that modulate serotonin (ie, SSRIs, SNRIs, TCAs, MAOIs)

CLINICAL USES OF ERGOTAMINE/ DIHYRDOERGOTAMINE

Treatment of migraine

Treatment of cluster headache

INTERACTIVE QUESTION

Drug Class	Impact on 5-HT Receptors
Ergots	
Triptans	
Lasmiditan	

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MODULATORS OF CGRP SIGNALING

CALCITONIN GENE-RELATED PEPTIDE (CGRP)

Powerful vasodilator peptide neurotransmitter

Released from neurons in central and peripheral nervous system

- Released from trigeminal nerve fibers during migraine

↑ CGRP levels in migraine

CGRP receptor is complex heterodimer containing GPCRs

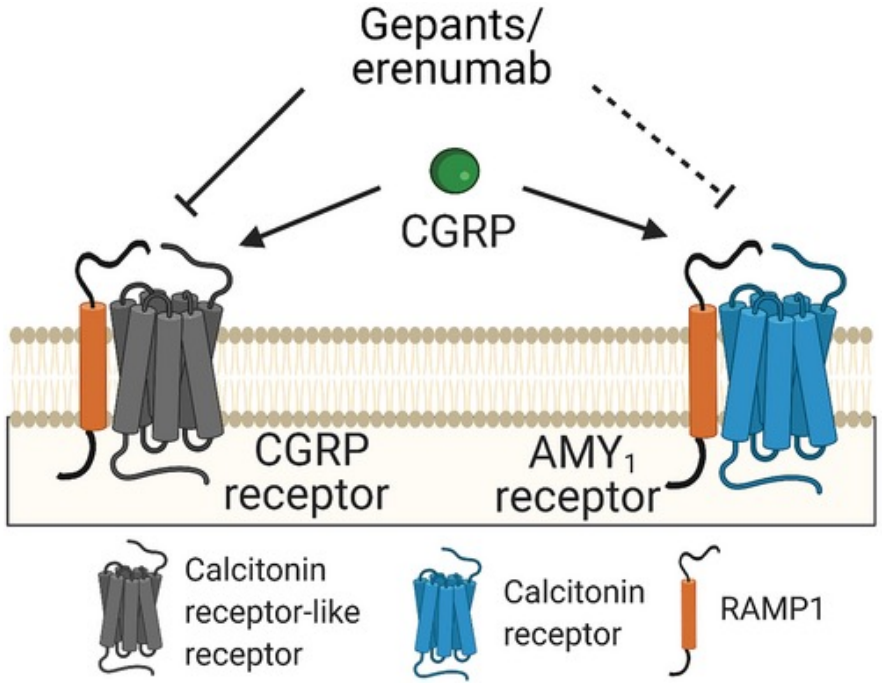

Image credit: Garelja, M. L 2022

DRUGS THAT TARGET CGRP

CGRP receptor antagonists ("Gepants")

Antibodies that bind CGRP peptide

CGRP ANTAGONISTS MECHANISM OF ACTION

Calcitonin gene-related peptide (CGRP) antagonists

Selectively bind to and antagonize the CGRP receptor

- Blocks pain-signaling in trigeminal ganglia

CGRP ANTAGONISTS -GEPANTS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Ubrogepant (Ubrelvy) Rimegepant (Nurtec) Atogepant (Qulipta)	Strong inhibitors of CYP3A4 (e.g., ketoconazole)	Nausea Somnolence Dry mouth	Inhibitors of CYP3A4 (e.g., ketoconazole) increases significantly the exposure to gepant (contraindicated with strong inhibitors, dosage adjustment with others) Strong inducers of CYP3A4 (avoid use) P-gp inhibitors (increase exposure of gepants)

CGRP MONOCLONAL ANTIBODY MOA

Antibodies that prevent endogenous CGRP from binding CGRP receptors

- Erenumab binds CGRP receptor and prevents activation by CGRP
- Fremanezumab and galcanezumab bind CGRP and prevent its binding to and activation of the receptor

CGRP MONOCLONAL ANTIBODIES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Erenumab	Cautions: Constipation	Injection site reaction Hypersensitivity Constipation	None
Fremanezumab Galcanezumab	Cautions: Cardiovascular disease	Injection site reaction Hypersensitivity	

CLINICAL USE & ADME

Migraine treatment
- Ubrogepant
- Rimegepant

Migraine prophylaxis
- Atogepant
- Monoclonal antibodies
  - Erenumab
  - Fremanezumab
  - Galcanezumab

CGRP antagonists
- Orally administered
- Metabolized primarily via CYP3A4
  - Dosage adjustment is necessary when taken with inhibitors and inducers of CYP3A4

CGRP monoclonal antibodies
- Injectable (SQ)

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PROPHYLACTIC THERAPY

MIGRAINE MANAGEMENT

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- Venlafaxine – B
- Atogepant
- CGRP monoclonal antibodies

MIGRAINE PROPHYLACTIC THERAPY

Drug	Mechanism of Action Related to Migraine	Adverse Effects	Notes
Valproate Divalproex sodium	Enhancement of GABA–mediated inhibition, modulation of the excitatory neurotransmitter glutamate, and inhibition of sodium and calcium ion channel activity	Nausea, fatigue, tremor, weight gain and hair loss	Multiple drug interactions Teratogen – avoid in women of childbearing potential
Topiramate (Topamax)	Inhibition of voltage-gated sodium channels, inhibition of high-voltage–activated calcium channels, inhibition of glutamate-mediated neurotransmission	Sedation Slow cognition Kidney stones Weight loss Glaucoma Speech difficulties	Minimal drug interactions

MIGRAINE PROPHYLACTIC THERAPY

Drug	Mechanism of Action Related to Migraine	Adverse Effects	Notes
Propranolol Metoprolol Timolol (beta blocker)	Action is unknown, but beta blockers may raise migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical or subcortical pathways	Fatigue, exercise intolerance, depression and orthostatic hypotension	Caution in patients with asthma

MIGRAINE PROPHYLACTIC THERAPY

Drug	Mechanism of Action Related to Migraine	Adverse Effects	Notes
Amitriptyline (TCA)	May be related to downregulation of central 5-HT2 and adrenergic receptors	Sedation, dry mouth and weight gain	Anticholinergic effects May prolong QT interval
Verapamil (calcium channel blocker)	Beneficial effects may be due to their vasoactive properties, modulation of neurotransmitter release, or a serotonergic effect	Constipation, hypotension, bradycardia, atrioventricular block, and exacerbation of heart failure	May cause gingival hyperplasia Hyperprolactinemia

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ANY QUESTIONS?