

### Serotonin Pathophysiology (5HT)

Serotonin is synthesized from L-tryptophan

Free Serotonin is either stored in vesicles, or it is rapidly inactivated by MAO.

In the pineal gland, serotonin is a precursor to Melatonin (sleep).

L-tryptophan->Serotonin->Melatonin

Over 90% of serotonin in mammals is found in enterochromaffin cells in the gut, where it regulates peristalsis.

Serotonin is also found in the blood in platelets (makes them sticky) and in the brain.

Brain serotonin neurons are involved in mood, sleep, appetite, temperature regulation, pain, blood pressure regulation, and vomiting. (It may also play a role in aggression.)

Serotonin leads to platelet aggregation.

Serotonin directly causes contraction of VASCULAR smooth muscle and is a powerful VASOCONSTRICTOR, except in skeletal muscle and the heart where it is a vasodilator.

5HT is involved in the mechanisms of depression, anxiety, and migraine.

### Triptans- Serotonin Agonist Drug Therapy

These drugs are agonists of 5HT<sub>1B</sub> and 5HT<sub>1D</sub> to inhibit the release of CGRP, substance P, and neurokinin A.

### Triptans- Serotonin Agonist Drug Therapy (cont)

MOA: 5HT<sub>1B</sub> and 5HT<sub>1D</sub> agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT<sub>1F</sub> receptors on CNV nerve terminals preventing CGRP release.

Rizatriptan, Sumatriptan, and Zolmitriptan are **contraindicated** with MAOIs.

Indicated for acute migraine management.

**Contraindicated** with IHD, angina, history of a stroke, CVD, uncontrolled HTN, ischemic bowel disease, use with ergots, use with other triptans within 24 hours, QT prolongation, pregnancy (causes contraction of the uterine smooth muscle), hepatic failure, renal failure, and basilar migraines (brainstem origin)

Consider a triptan with a nasal spray or injectable formulation in patients with severe nausea/vomiting, migraines that quickly intensify, or patients who awake with migraines (these formulations allow for a faster onset of action)

Almo, Suma, Riza, and Zolmi have a shorter life so they may require multiple doses to prevent off periods.

Frovatriptan is the longest acting but least effective triptan.

### Almotriptan (Axert)

MOA: 5HT<sub>1B</sub> and 5HT<sub>1D</sub> agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT<sub>1F</sub> receptors on CNV nerve terminals preventing CGRP release.

Indications: Acute migraine management

Formulations: Oral

Side Effects: Dry mouth, paresthesia, dizziness, tachycardia, muscle weakness, triptan sensations (burning, flushing, tingling, and tightness of face)

Contraindications: CI with MAOIs

Considerations: Better tolerated than sumatriptan, only FDA approved triptan for children, best tolerated overall.

### Eletriptan (Relpax)

MOA: 5HT<sub>1B</sub> and 5HT<sub>1D</sub> agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT<sub>1F</sub> receptors on CNV nerve terminals preventing CGRP release.

Indications: acute migraine management

Formulations: oral

Side Effects: dry mouth, paresthesias, dizziness, tachycardia, muscle weakness, triptan sensations.



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### Eletriptan (Relpax) (cont)

Contraindications: CI within 72 hours of CYP3A4 inhibitors (clarithromycin, azoles, ritonavir), CI in hepatic or renal impairment.

Considerations: NOT CI with MAOIs. Has the highest potential for drug interactions.

### Zolmitriptan (Zomig)

MOA: 5HT1B and 5HT1D agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT1F receptors on CNV nerve terminals preventing CGRP release.

Indications: acute migraine management

Formulations: oral or oral dissolving tablet

Side Effects: dry mouth, parasthesias, dizziness, tachycardia, muscle weakness, triptan sensations

Contraindications: CI with MAOIs in the past 2 weeks

Considerations: used when others failed

### Sumatriptan (Imitrex)

MOA: 5HT1B and 5HT1D agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT1F receptors on CNV nerve terminals preventing CGRP release.

### Sumatriptan (Imitrex) (cont)

Indications: acute migraine management

Formulations: Oral, Spray, SQ injection, combo products

Side Effects: dry mouth, paresthesias, dizziness, tachycardia, muscle weakness, triptan sensations

Contraindications: CI with MAOIs within 2 weeks, CI in hepatic impairment

Considerations: fastest onset of orals, highest potency with SQ injection, only triptan that is safe in pregnancy/breastfeeding

### Rizatriptan (Maxalt)

MOA: 5HT1B and 5HT1D agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT1F receptors on CNV nerve terminals preventing CGRP release.

Indications: acute migraine management

Formulations: Oral or Oral Dissolving Tablet

Side Effects: dry mouth, paresthesias, dizziness, tachycardia, muscle weakness, triptan sensations

Contraindications: CI with MAOIs in the past two weeks

Considerations: better when given prior to an event (such as with menstruation)

### Frovatriptan (Frova)

MOA: 5HT1B and 5HT1D agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT1F receptors on CNV nerve terminals preventing CGRP release.

Indications: acute migraine management

Formulations: oral

Side effects: dry mouth, paresthesias, dizziness, tachycardia, muscle weakness, triptan sensations

Contraindications: CI in peripheral vascular disease

Considerations: NOT CI with MAOIs, longest 1/2 life, slower onset of action

### Naratriptan (Amerge)

MOA: 5HT1B and 5HT1D agonist active the receptors on the presynaptic trigeminal nerve endings and inhibit the release of vasodilating peptides, also leads to vasoconstriction by preventing the vasodilation and stretching of pain nerve endings. It also inhibits histamine release from mast cells, blocking inflammation in the brain. It can also stimulate 5HT1F receptors on CNV nerve terminals preventing CGRP release.

Indications: acute migraine management

Formulations: oral

Side effects: dry mouth, paresthesias, dizziness, tachycardia, muscle weakness, triptan sensation



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### Venlafaxine er (Effexor XR)- Prophylaxis (cont)

Side Effects: Nausea, vomiting, drowsiness, dizziness, blurry vision

Contraindications: CI with MAOIs within 2 weeks

Considerations: caution in patients with HTN, and seizure disorders

### Valproic Acid/Divalproex- Prophylaxis

MOA for migraine prophylaxis: increases GABA action (inhibitory NT centrally), suppresses migraine events, slows nociceptive transmission

Indications: first line, consider using with BB to increase efficacy

Formulations: Oral

Side Effects: GI, sleepiness, weight gain, hair loss, tremor, thrombocytopenia, rare hepatotoxicity, caution in liver disease

Contraindications: CI in women that may become pregnant (Teratogenic)

Considerations: FDA approved for migraine prophylaxis

### TCA (Tricyclic Antidepressant)-Prophylaxis

Drugs Used: Amitriptyline

MOA for migraine prophylaxis: inhibits 5HT reuptake (leads to vasoconstriction), decreases excitability, intensifies inhibition on nociceptive pathways

Indications: first or second line, consider for patients with insomnia or depression, also good for tension type headaches, consider using with BB, topiramate to increase efficacy

### TCA (Tricyclic Antidepressant)-Prophylaxis (cont)

Formulation: oral

Side Effects: anticholinergic effects (**weight gain**, blurry vision, constipation, sedation, **drowsiness**) arrhythmias

Contraindications:

Considerations: Amitriptyline has the most data of the class and the only one FDA approved for this indication

### Topiramate (Topamax)- Prophylaxis

MOA for migraine prophylaxis: blocks multiple voltage gated channels (Na and Ca<sup>2+</sup>) leading to decreased excitability, facilitates GABA mediated inhibition, reduces CGRP secretion from trigeminal neurons

Indications: first line therapy, may be beneficial in chronic migraine (15 or more HA/month), can be used with BB or TCA to increase efficacy.

Formulation: oral

Side Effects: fatigue, HA, dizziness, nausea, weight loss, glaucoma, metabolic acidosis, kidney stones

Contraindications:

Considerations: Consider in patients worries about weight gain, FDA approved for prophylaxis

### Beta Blockers- Prophylaxis

Drugs Used: Metoprolol, Propranolol, Timolol (\*propranolol and timolol are FDA approved for migraine prevention)

### Beta Blockers- Prophylaxis (cont)

MOA in migraine prophylaxis: reduces neuronal activity and excitability (decreased NE release), membrane stabilizing

Indication: considered 1st line agent, especially for patients who already need a BB for another reason (HTN, angina)

Formulation: oral

Side Effects: BB blues, bradycardia, impotence, bronchoconstriction, AV blocks, fatigue, hypotension

Contraindications: Caution in patients with asthma (nonselective), PDV, and heart blocks

Considerations: Can use with TCA, topiramate to increase efficacy

### Lasmiditan (Reyvow) 5HT<sub>1F</sub> Agonist

MOA: 5HT<sub>1F</sub> specific agonist, lacks the vasoconstrictive effects of triptans because it is selective for 1F (suggests it may be safer for cardio), **overall it reduces trigeminal nerve stimulation**

Indications: used when patient has failed 2 triptans or are unable to tolerate triptans

Formulation: Oral

Side Effects: dizziness, hallucinations, sedation, nausea, vomiting, tachycardia, palpitations, euphoria (**do not drive for 8 hours post dose**)

Contraindications:

Considerations: **a controlled substance-> CV**. There is a risk of serotonin syndrome ALONE OR if used in combo with other serotonergic drugs (SSRIs, ergots, triptans, ect)



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### Serotonin Syndrome

The accumulation of too much serotonin in the brain synapses.

Most at risk patients are those on multiple medications that will elevate serotonin levels.

**Watch for drug induced** (Tryptans, antidepressants like SSRIs/SNRIs, cocaine, ondansetron, ect).

### Migraine Pathophysiology

Migraine Headaches are most often unilateral (hemiplegic), pulsating, and can last anywhere from 2 hours to 72 hours.

Symptoms include nausea, vomiting, sensitivity to light, sound, and smell, pain is often made worse by physical activity.

Migraines are more common in females and there tends to be a genetic component.

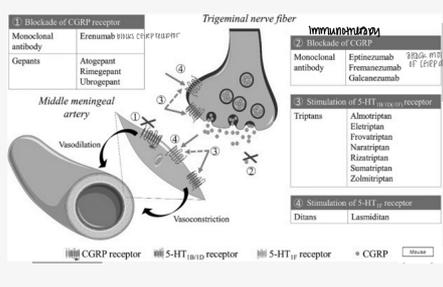
There are two types those that are preceded by an aura, and those that are without aura (more common ~85%)

Those that are preceded by an aura experience and sensory episode. There is often burning, itching, numbness, speech problems, visual symptoms, flickering lights, blinds pots, and even vision loss.

Those that are not preceded by an aura, usually experience a prodrome of fatigue and irritability.

Possible triggers are thought to be increased stress, changes in sleep patterns, and fluctuations in estrogen during the menstrual cycle.

### Overview



### Ergotamine tartrate/Dihydroergotamine

MOA: the fungus releases histamine, Ach, and tyramine. These all affect alpha, dopamine, and 5HT receptors.

Indications: migraine in prodrome, in severe cases

Formulations: sublingual tablet (Ergomar/-Cafergot), suppository, IV/IM in severe cases in ED

Side Effects: nausea, vomiting, dizziness, abdominal pain, weakness, **serious if signs of ergotism**

Contraindications: CI in pregnancy, PDV, severe atherosclerosis, Raynaud's syndrome, CyP3A4 inhibitors (increases levels of ergotamine) (also duh severe vasoconstriction)

Considerations: Provides **long lasting vasoconstriction** and it accumulates. Patient education is key for them not to exceed 6mg/attack and no more than 10mg/week

### Ergot Alkaloids

Ergot alkaloids are created by the fungus *Claviceps purpurea* (found on grains)

MOA: the fungus releases histamine, Ach, tyramine. This affects all alpha, dopamine, and 5HT receptors.

Accidental injection can lead to ergotism. Toxicity leads to hallucinations, vasospasms, can lead to painful ischemia and gangrene.

### Ergot Alkaloids (cont)

#### A very potent vasoconstrictor

LSD is a synthetic ergot- powerful CNS hallucinogen

Ergots are not used for analgesic properties in any other condition.

Ergots are most effective when given during the prodrome. The effectiveness decreases the longer you wait-> **for acute only**

#### not first line, save for severe cases

Hyperprolactinemia can occur due to secreting tumors of the pituitary or by using DA antagonist. Bromocriptine is used to decrease prolactin levels and also helps in tumor regression. Bromocriptine, Cabergoline, and Pergolide have the highest pituitary DA pituitary DA pituitary receptor affinity of ergots.

Parkinson's disease: Bromocriptine (D2 agonist) helps to stop the release of too much prolactin. Rarely used now.

### NSAIDs

MOA: reduces pain and inflammation through prostaglandin inhibition

Indications: no specific NSAIDs are FDA approved for migraines EXCEPT for **Cambia** (diclofenac powder for oral solution) and **Elyxyb** (celecoxib oral solution) **Ibuprofen and Naproxen are most used for mild migraines**

Formulations: depends on drug- many available

Side effects: bleeding risk for patients on blood thinners, stomach ulcers, caution in asthmatics **celecoxib has a BBW for CV events**



### NSAIDs (cont)

Contraindications: CI in pregnancy after 20 weeks, NSAID allergy, and severe renal impairment

Considerations: Acetaminophen/ASA/caffeine=excedrin (OTC migraine cocktail), APAP and ASA alone can also be tried for OTC migraine management

### Eptinezumab (Vyephti) CGRP Antibodies

MOA: Blocks the CGRP receptor

Indications: consider in patients with inadequate response after an 8 week trial of at least 2 first line oral meds or med combinations at optimal doses, OR if oral non-CGRP medications are not tolerated

Formulation: Infusion given every 3 months in office

Considerations: can be combined with non-CGRP oral medications for acute (ie. triptan, NSAIDs). Information is lacking on taking CGRP antagonist for both acute treatment and prophylaxis.

### Erenumab (Aimovig) -CGRP antibody

MOA: CGRP receptor blocker

Indications: consider in patients with inadequate response after an 8 week trial of at least 2 first line oral meds or med combinations at optimal doses, OR if oral non-CGRP medications are not tolerated

Formulation: autoinjector, SQ once monthly

Contraindications: Special warning label for worsening HTN, and Latex allergy

Considerations: can be combined with non-CGRP oral medications for acute (Triptans, NSAIDs)

### Fremanezumab (Ajovy)- CGRP Antibody

MOA: CGRP receptor blocker

Indications: consider in patients with inadequate response after an 8 week trial of at least 2 first line oral meds or med combinations at optimal doses, OR if oral non-CGRP medications are not tolerated

Formulation: autoinjector, SQ monthly (1injection), or every 3 months (3 injections at once)

Considerations: can be combined with non-CGRP oral medications.

### Galcanexumab (Emgality)- CGRP Antibody

MOA: Blocks the CGRP receptor

Indications: consider in patients with inadequate response after an 8 week trial of at least 2 first line oral meds or med combinations at optimal doses, OR if oral non-CGRP medications are not tolerated

Formulation: Prefilled syringe/or autoinjector, SQ once monthly

Considerations: can be combined with non-CGRP oral medications for acute.

### Rimegepant (Nurtec)-CGRP antagonist

MOA: CGRP is a peptide released from sensory nerves in the brain, it dilates blood vessels and centrally modulates nociception. These medications antagonize this peptide and prevent its dilatory effects. It also decreases nociception response leading to decreased pain.

Indications: consider for patients that can't use triptans or have failed 2 triptans

Formulations: oral dissolving tablet

### Rimegepant (Nurtec)-CGRP antagonist (cont)

Side Effects: nausea, hypersensitivity reactions, sedation, dry mouth, abdominal pain/dyspepsia

Contraindications: CI in hepatic impairment, and with CYP3A4 inhibitors or inducers **look for drug interactions**

Considerations: Long 1/2 life (11 hours). FDA approved for both prevention (prophylaxis) and treatment. **Max of 18 doses per month (one tablet qod)**

### Ubrogepant (Ubrovelvy)- CGRP antagonist

MOA: CGRP is a peptide released from sensory nerves in the brain, it dilates blood vessels and centrally modulates nociception. These medications antagonize this peptide and prevent its dilatory effects. It also decreases nociception response leading to decreased pain.

Indications: consider for a patients that can't use triptans or have failed two triptans. Consider an alternative to injectable CGRP antagonist.

Formulations: Oral

Side Effects: nausea, hypersensitivity reactions, sedation, dry mouth

Contraindications: CI with strong CYP3A4 inhibitors **look for drug interactions**

Considerations: only used for treatment, not used for prevention



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