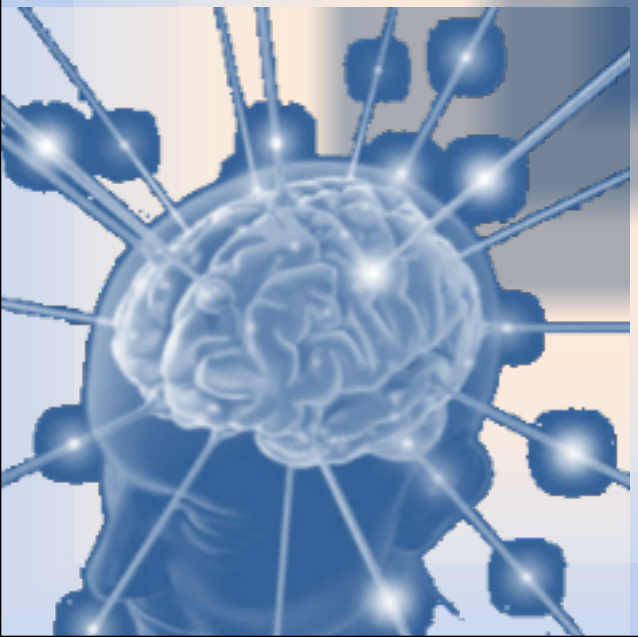
DRUGS USED IN HEADACHE AND MIGRAINE



Dr. Ishfaq Bukhari

ILOs

- Differentiate between types of headache regarding their symptoms, signs and pathophysiology.
- Recognize drugs used to prevent migraine
- Identify drugs used to rescue and abort migraine
- Elaborate on the pharmacokinetics, dynamic and toxic profile of some of these drugs.

HEADACHE

Pain anywhere in the region of the head or neck

It is caused by disturbance of the
Pain – Sensitive Structures around the brain

Within the cranium

(blood vessels, meninges, cranial nerves)

Outside the cranium

(muscles, nerves , arteries ,veins, subcutaneous tissues ,eyes, ears and other tissues)

MIGRAINE

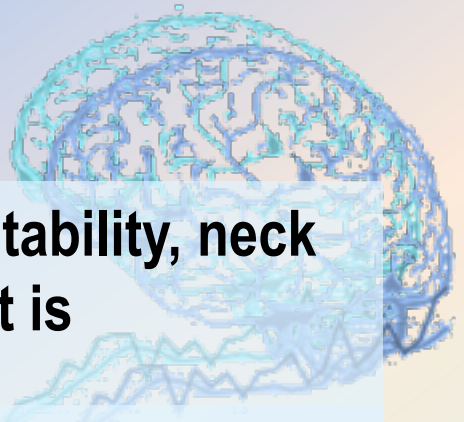
Recurrent attacks of throbbing headache
Unilateral / or on both sides
Lasting from > 2 up to 72 hrs.
± Preceded *(or accompanied)* by AURA

Perceptual disturbance of motor < sensory nature
visual [Photophobia (↑sensitivity to light)]
auditory [Phonophobia (↑ sensitivity to sound)]
olfactory unpleasant smell ….
Sensory; abnormal sensation of at face,extremeties.
Develops over 5-20 min. & last fewer than 60 min.

Aura: flashes of light, blind spots or tingling in your arm.

Migraine pain is usually on one side of head with facial and neck pain and nausea and vomiting.

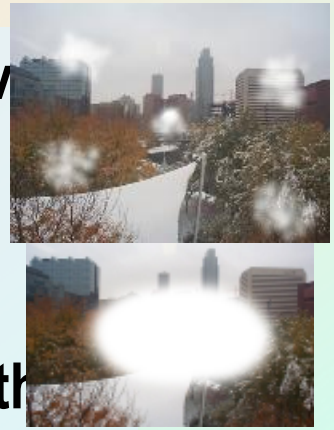
Phases of Migraine



1. Prodrom Phase; a change in mood or behavior (irritability, neck stifness) that starts hours or days before headache. It is experienced by 60% of migraineurs.

2. Aura Phase; Sensory > motor symptoms starts 5-20 min before the migraine attack. It is experienced by 20% of migraineurs.

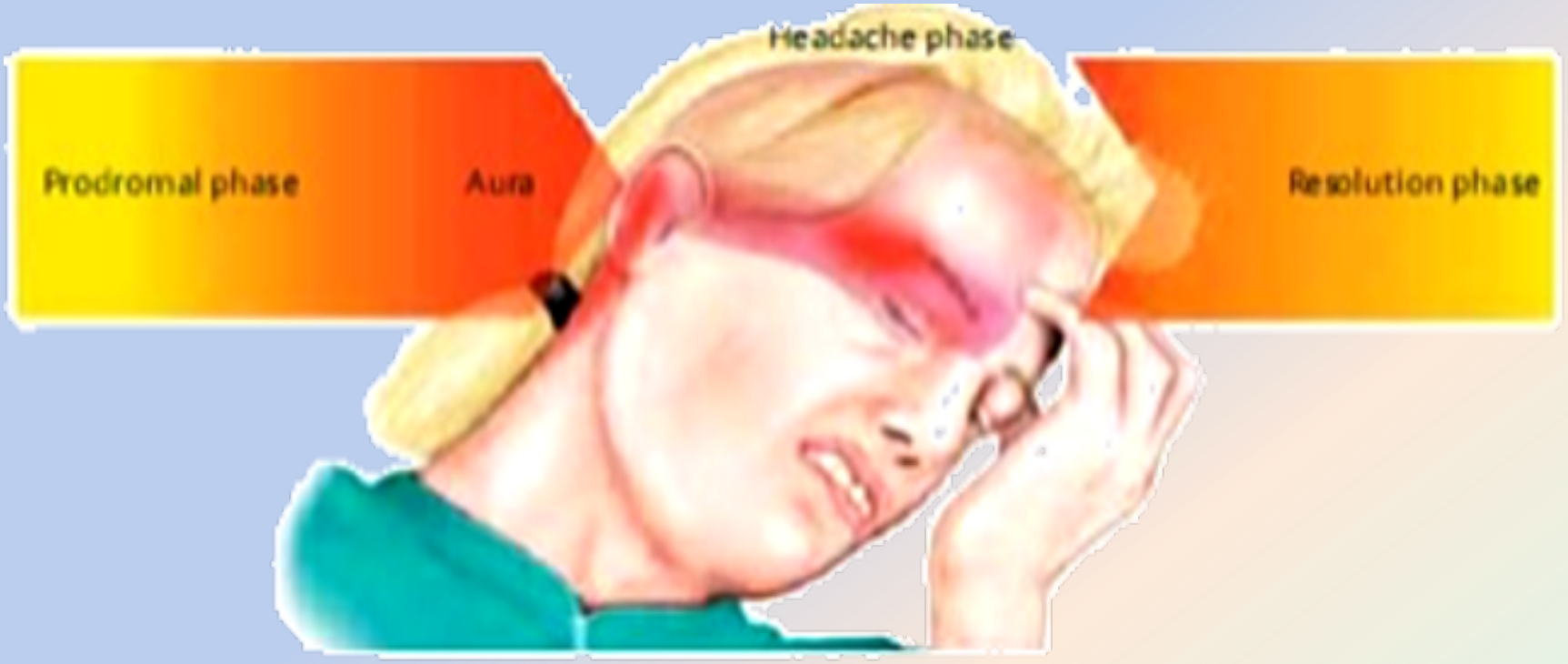
3. Headache Phase; moderate to severe pain, ↑ with activ



+ anorexia, vomiting,
Intolerance to light, sounds, odors
Blurry vision /Blocked nose /Pale face
Sensations of heat or coldness /Sweating /Tenderness of th
scalp

4. Postdrom Phase: still not normal, either;

•More likely fatigued → irritability /impaired concentration /scalp tenderness /mood changes / GIT symptoms, ……



Curtain like effect over one eye

TYPES OF MIGRAINE

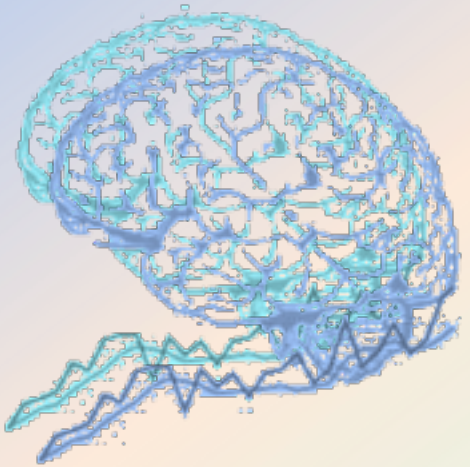
COMMON

Without Aura [80%]

CLASSIC

With Aura [20%]

Migraine Triggers



Diet

Aged cheese, Alcohol, Chocolate, Caffeine, Hot dogs, Avocado,

Stresses

Hormonal changes: Menstrual migraine Most common

Climate

Diseases

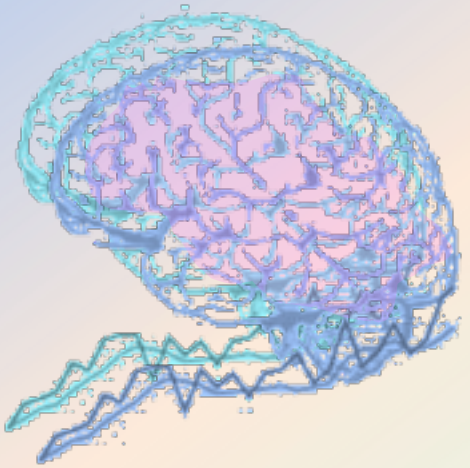
Therapy

Antibiotics, Antihypertensives, H_2 blockers, Vasodilators, Oral contraceptives

Life Style

Theories

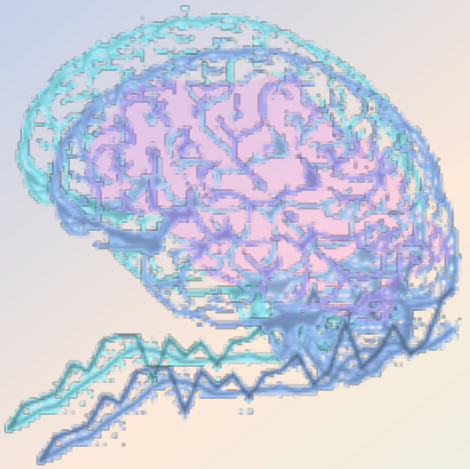
Migraine Causal Theories



- Vascular
- Cortical Spreading Depression
- Neurovascular theory ?
- Mediators [Serotonin]
- Dopaminergic Hypersensitivity

Migraine Causal Theories

Vascular



Triggers

↓

Intracranial vasoconstriction → migraine aura

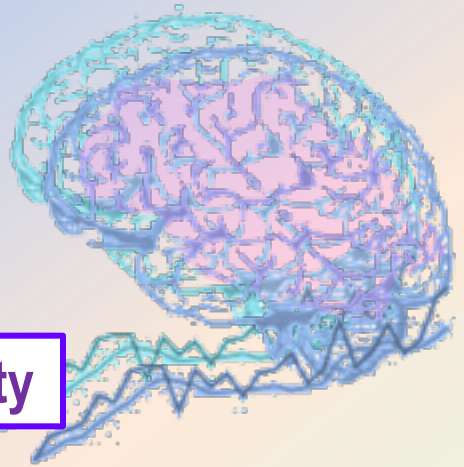
↓

focal ischemia → ↑ mediators → rebound vasodilatation → ↑ permeability & leak → inflammatory reaction → activates perivascular nociceptive nerves → migraine headache

↓

It throbs as blood flow at these sensitive area with each heart beat

Migraine Causal Theories



Vascular

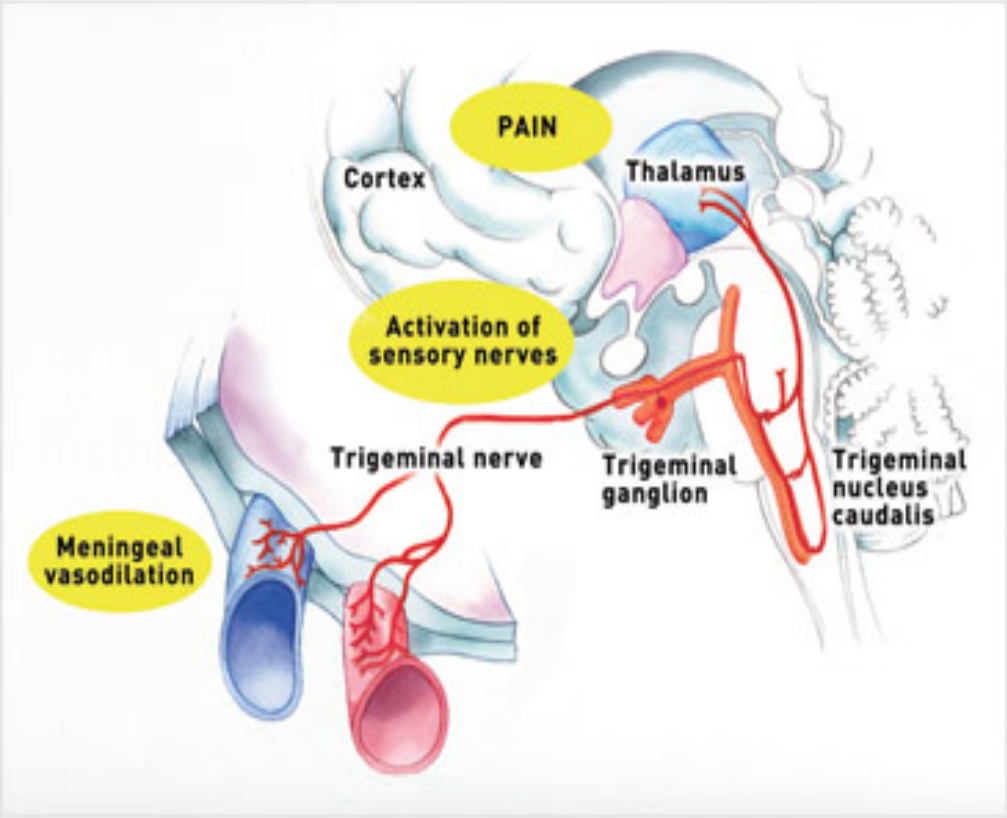
Neurovascular theory ?

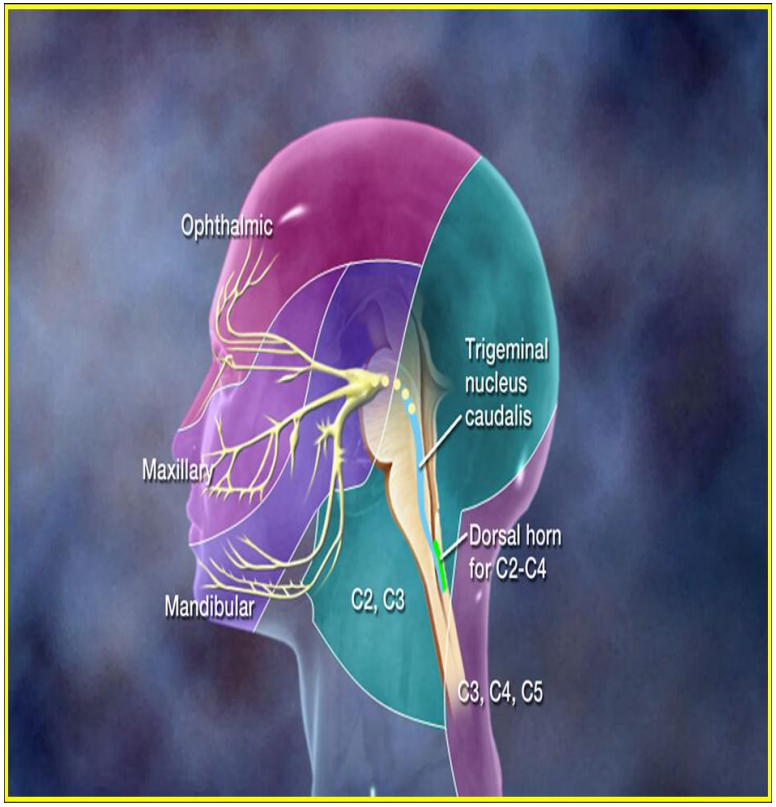
Mediators [Serotonin]

Dopaminergic Hypersensitivity

Triggers
↓
Release K / glutamates
↓
Creates a slowly well-defined depolarizing wave → depolarize adjacent tissues → propagating at a rate of 2-6 mm/min → vasoconstriction → migraine aura
↓
→ activate trigeminovascular complex → vasodilation → migraine headache

Which is Pry
Which is secondary





Stimulation of the trigeminal nerve causes the release of vasoactive peptides; this is responsible for the head pain, as well as the facial and neck pain, experienced during migraine

TREATMENT STRATEGY

ACUTE ATTACK

Controls attack

- **RESCUE THERAPY**
  - Non-specifically target individual symptoms i.e. alleviating pain, emesis and associated symptoms
  - Mild-Moderate
- **ABORTIVE THERAPY**
  - They specifically target pathways of migraine by ↓ meningeal dilatation & ↓ neural activation via $5HT_1$ agonism → i.e. stopping headache as it is evolving.
  - Abortive medications > effective if taken early, just before the pain starts, losing effectiveness once the attack has begun
  - So they must be rapidly acting
  - Severe/ Disabling

PREVENT RECURRENCE

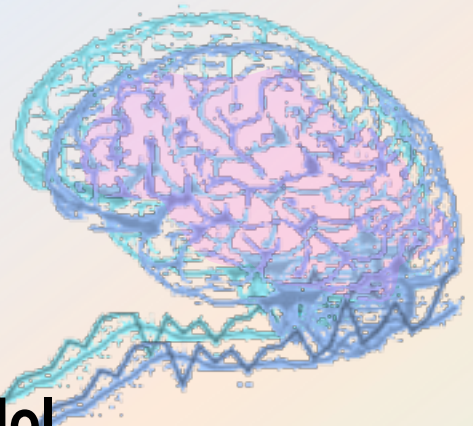
↓recurrence frequency, severity, duration & / or disability

↑responsiveness to abortive therapy

N.B. *Full effect of therapy needs several weeks to manifest & should continue for 6 m. & can be repeated*

TREATMENT of Acute Attack

RESCUE THERAPY



➔ Analgesics

- NSAIDs / Acetaminophen
- (ibuprofen , naproxen for mild to moderate attack with no nausea and vomiting)
- Non-opioid:weak μ agonist;Tramadol
- Tramdol also inhibits serotonin reuptake

➔ Antiemetics

- Dopamine Antagonists
  - Domperidone
  - Phenothiazines
  - Promethazine
- $5HT_3$ antagonists (for severe nausea and vomiting
  - Ondanseteron
  - Granisetron
- H_1 antagonist
  - Meclizine, diphenhydramine

+ ***Gastro-prokinetic***

↑ *Absorption & bioavailability of abortive therapy*

Dopamine antagonists + Sedation

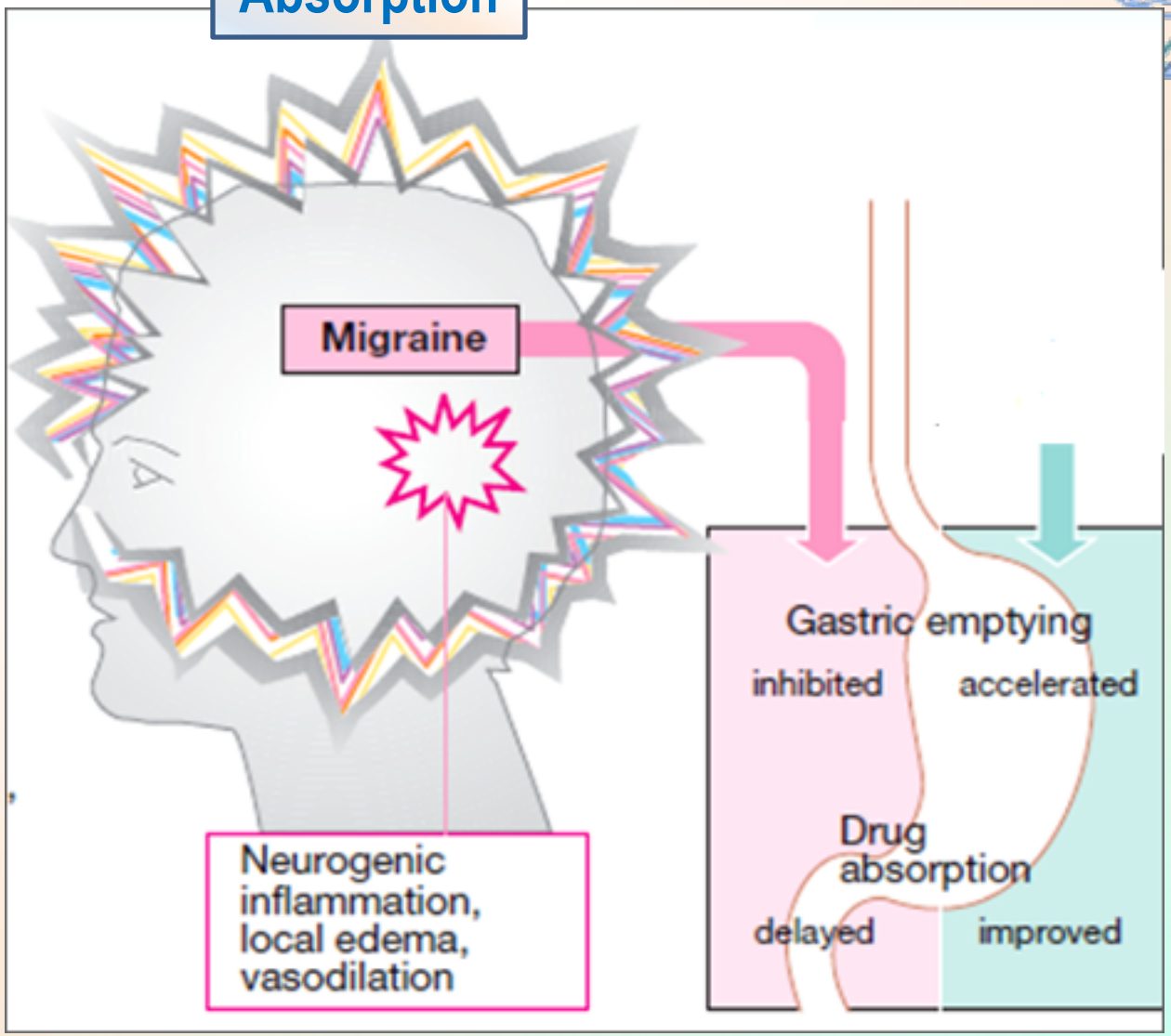
Antihistamine +sedation Anticholinergic

TREATMENT of Acute Attack

Prokinetics;
Domperidone

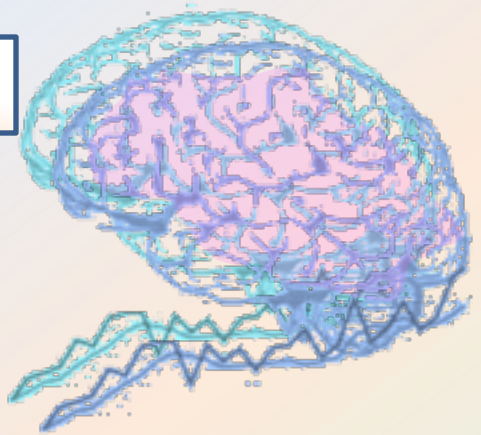
Help Absorption

ABORTIVE THERAPY



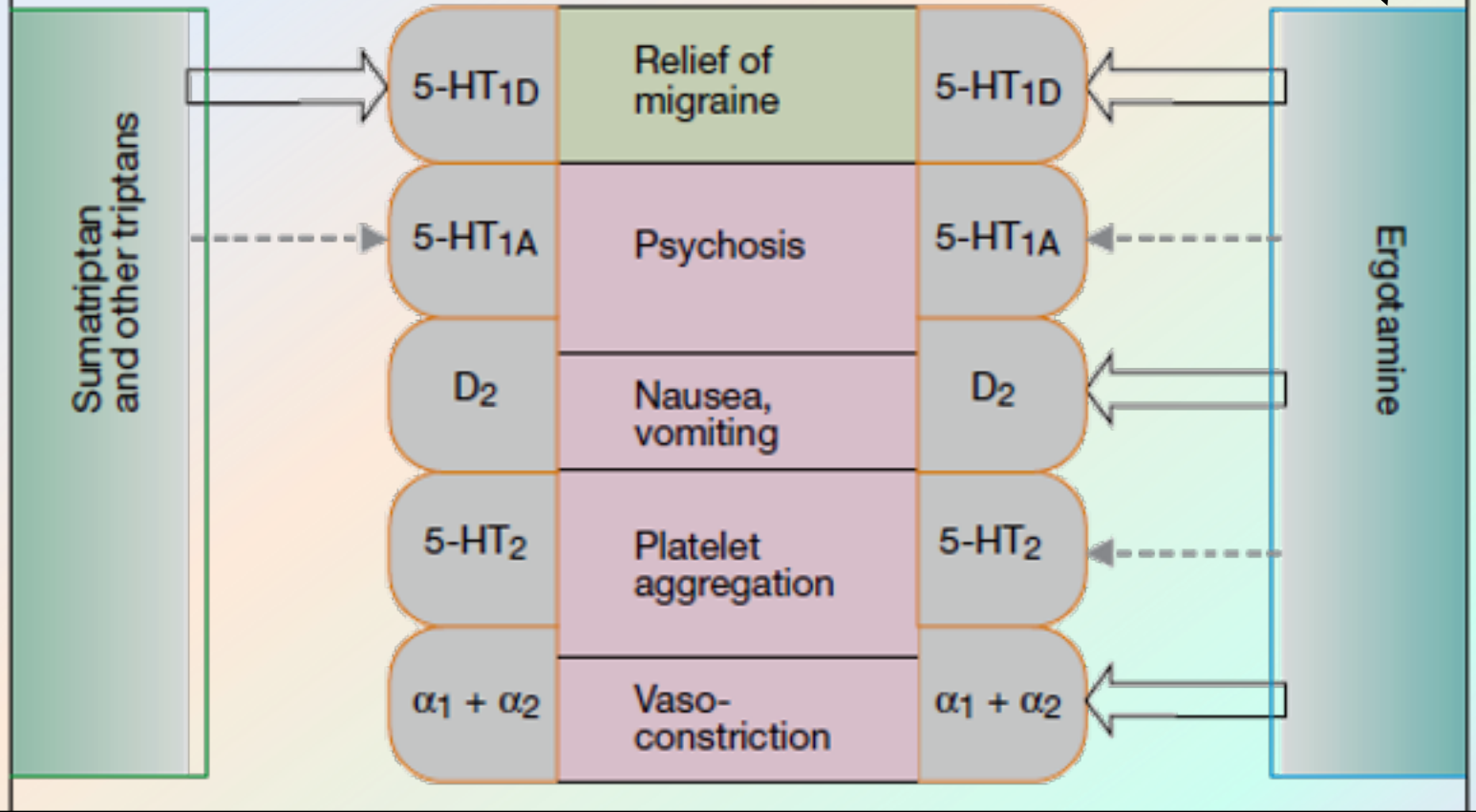
TREATMENT of Acute Attack

ABORTIVE THERAPY



➔ $5HT_1$

- **AGONISTS** ➔ **TRIPTANS**
  > selective
- **PARTIAL AGONISTS** ➔ **ERGOTS**
  non-selective



TREATMENT of Acute Attack

ABORTIVE THERAPY

ERGOTS

Product of *Claviceps purpurea;* a fungs growing on rye/ grains

Non-Selective

Agonism at $5HT_1$ receptors (5HT-1D/1B found in cerebereal And menigeal vessels)

↓release of vasodilating peptides

↓excessive firing of nerve endings

At blood vessels → ↓vasodilation & stretching of the pain endings

Partial agonist effect on α-adrenoceptors → vasoconstriction

Ergotamine tartarate (resticted use)

Oral, sublingual, rectal suppository, inhaler

Caffeine → Cafergot

Dihydroergotamine

Nasal spray, inhaler & injectable forms (good to use if patient is vomiting)

ERGOTS

Ergotamine tartarate (rare clinical use due to sever adverse effects

Oral absorption Incomplete (erratic) + slow → low bioavailability

Despite $t_{1/2}$ nearly 2 hours, ergotamine produces vasoconstriction → 24 hours or longer due to high and long tissue binding ability.
Ergotamine tartrate has significant side effects, and may worsen the nausea and vomiting associated with migraine

Dihydroergotamine (preferred in clinical setting

Given parenterally, Dihydroergotamine is eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance and has less adverse effects.

Indications

They are only used to abort the attacks [*Exception Dihydroergotamine can be given for severe, recurrent attacks not responding to other drugs*]
Their use is restricted to patients with frequent, moderate attack or infrequent but severe attacks.

ADRs

- GIT upset
- Feeling of cold and numbness of limbs, tingling
- anginal pain due to coronary spasm, and disturbed cardiac rhythm (tachycardia or bradycardia)
- Prolong use → rebound headache due to vasodilatation followed by vasoconstriction.
- Prolong use and high dose → paraesthesia (tingling or burning sensation)

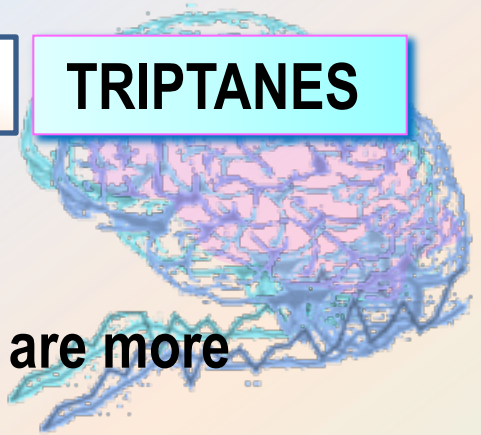
Contraindications

- Pregnancy; fetal distress and miscarriage (ergot is uterine stimulant and vasoconstrictor)
- Peripheral and coronary vascular diseases
- Hypertension
- Liver and kidney diseases
- prophylaxis of migraine.
- In concurrent use with triptans(at least 6 hrs from last dose of tryptans or 24 hrs from stopping ergotamine and β-blockers

TREATMENT of Acute Attack

ABORTIVE THERAPY

TRIPTANES



Selective

Agonism at $5HT_1$ receptors

Same as discussed for ergotamine except that triptans are more selective as serotonergic agonist.

No α_1, α_2, β –adrenergic , dopamine or muscarinic receptors.

Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem . Triptans inhibit transmission in the trigeminal nucleus caudalis

SUMATRIPTAN *Present in →oral, nasal spray, and injectable forms*

Oral bioavailability low / Subcutaneous bioavailability is 97%, peaks after 2 min & $t_{1/2}$ nearly 2 hours (fast action with Sc, good for patient with vomiting)

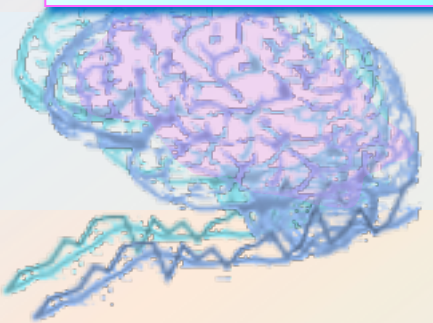
ZOLMITRIPTAN *Present in →nasal spray, and injectable forms*

Oral bioavailability 40%, peaks after 2 hrs & $t_{1/2}$ nearly 3 hours

NARATRIPTAN *Present in addition → + Oral preparations*

Oral bioavailability 70%, peaks after 2 hrs & $t_{1/2}$ nearly 6 hours (slower onset , less side effects)

TRIPTANES



Indications

- To abort attacks in patients with frequent, moderate or infrequent but severe attacks.
- In cluster headache

ADRs

- most of adv are the same as with ergot but triptans are better tolerated.
- Mild pain and burning sensation at the site of injection.
- Vasospasm, Ischemic heart; Angina and Arrhythmias

ZOLMITRIPTAN

- Chest & neck tightness
- Coronary vasospasm
- Somnolence

Contraindications

- Peripheral vasospastic diseases
- Uncontrolled hypertension
- History of ischemia
- Cerebrovascular disorders
- In concurrent use with ergots or others inducing vasospasm
- In concurrent use with MAOIs, lithium, SSRIs, ….→(5HT increased to toxic level))
- Renal or hepatic impairment

DECIDING WHETHER BETTER WITH A TRIYPTAN OR WITH DHE.

For patients with headache episodes lasting 2 or 3 days at a time, DHE is often the optimal choice because it has longer $t_{1/2}$

For patients with migraines a day or less and need rapid relief of pain, triptans are often a better choice

For pregnant women: paracetamol or intranasal sumitriptan and or diphenhydramin, meclizine are safe to be used.

The form of drug preparation could influence the choice

Injectable sumatriptan reaches T_{max} the fastest followed by DHE nasal spray and rizatriptan

CHOOSING A TRIPTANS

- Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.
- Differences in $t_{1/2}$ → a clinical effect in terms of recurrence of headache

Pharmacokinetics

Medication	T_{max}(h)	$t_{1/2}$(h)
DHE	1	10
Sumatriptan SQ	0.25	2
Rizatriptan	1-1.5	2-3
Zolmitriptan	2.5	3
Naratriptan	2-3	6
Eletriptan	2.8	4
Frovatriptan	2-3	26

CHOOSING A TRIPTANS

- **Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.**
- **Differences in $t_{1/2}$ → a clinical effect in terms of recurrence of headache**

For extremely fast relief within 15 min. injectable sumatriptan is the only choice.

If expected re-dosing is needed & / or recurrence of headache Naratriptan , frovatriptan, have slower onset, fewer side effects, and a lower recurrence rate

Menstraul migraine: Frovatriptan (longer half life (26 hrs) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine and continuing for six days

TREATMENT STRATEGY

ACUTE ATTACK

Antiepileptics;

Block Na channel & augment GABA at GABA-A receptors

Topiramate;

Valproic;

PREVENT RECURRENCE

Antidepressants

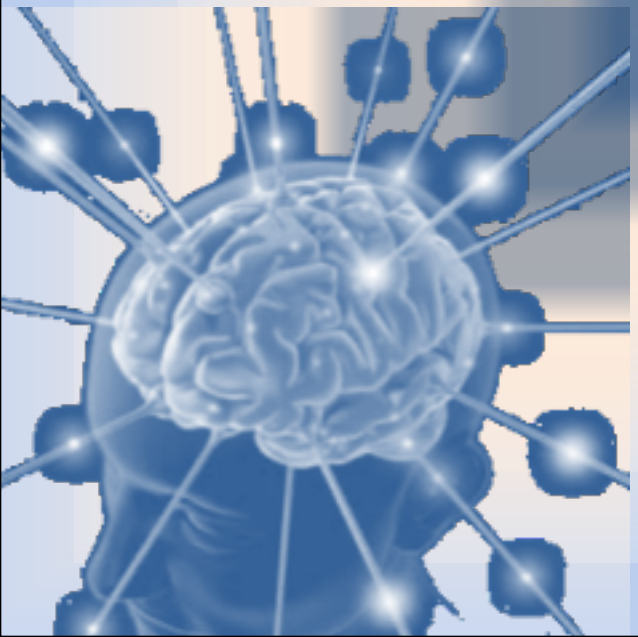
TCA; amitryptylin and nortryptyline

Antihypertensives

βblockers; propranolol

.Propranolol is commonly used in pophylaxis of migraine attack

DRUGS USED IN HEADACHE AND MIGRAINE



GLUCOOD