

PainWeek®

The L-Shaped Room: Challenges and Advances in the Diagnosis and Treatment of Migraine

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Disclosure

- Contracted Research (Principal Investigators must provide information, even if received by the institution): Eli Lilly site principal investigator (no payment)

Learning Objectives

- Explain diagnostic criteria for episodic and chronic migraine
- Identify patients who require preventive treatment
- Outline available treatments for migraine
- Summarize the efficacy of new treatments

Outline

- Diagnosis
- Pathophysiology
- Preventive treatments
- Acute treatments
- Non-pharmacologic treatments



Approach to Diagnosis

ICHD-3

	Migraine	TTH
Duration (untreated)	4-72h (>72h = Status migrainosus)	30min to 7d
2/4 Characteristics	<ol style="list-style-type: none"> 1. Unilateral 2. Pulsating 3. Moderate – Severe 4. Affected by activity 	<ol style="list-style-type: none"> 1. Bilateral 2. Non-pulsating 3. Mild to moderate 4. Not affected by activity
Associations	<ol style="list-style-type: none"> 1. Nausea &/or vomit AND/OR 2. Photo- + Phonophobia 	<ol style="list-style-type: none"> 1. No Nausea/Vomit AND 2. Photo, Phono, or none
Types	<p>Episodic: <15d per month</p> <p>Chronic: 15+d per month (8+ migraine days)</p>	<p>Infrequent: <1/mo</p> <p>Frequent: 1-14/mo</p> <p>Chronic 15+/mo</p>

Medication Overuse Headache

- Headache >15 days per month
- Regular overuse for >3 month
- Examples:
 - 15+ days of simple analgesia
 - 10+ days of triptans, opioids, butalbital, or combo meds
 - Likely less for opioids and butalbital

Secondary Headaches

SNOOP4 = Red Flags

- Systemic Symptoms / Signs
- Neurologic Symptoms / Signs
- Onset > 50y
- Onset = Thunderclap
- Pattern Change:
 - i. Postural headache
 - ii. Progressive headache
 - iii. Papilledema
 - iv. Precipitated by Valsalva
 - v. (Pregnancy)

Migraine Pathophysiology

Migraine Phases



❖ **PREMONITORY PHASE**

❖ **AURA PHASE**

❖ **HEADACHE PHASE**

❖ **POSTDROME PHASE**

Migraine Phases

❖ **PREMONITORY
PHASE**



PREMONITORY PHASE



Poor concentration
Fatigue
Depression
Elation
Irritability



Photophobia



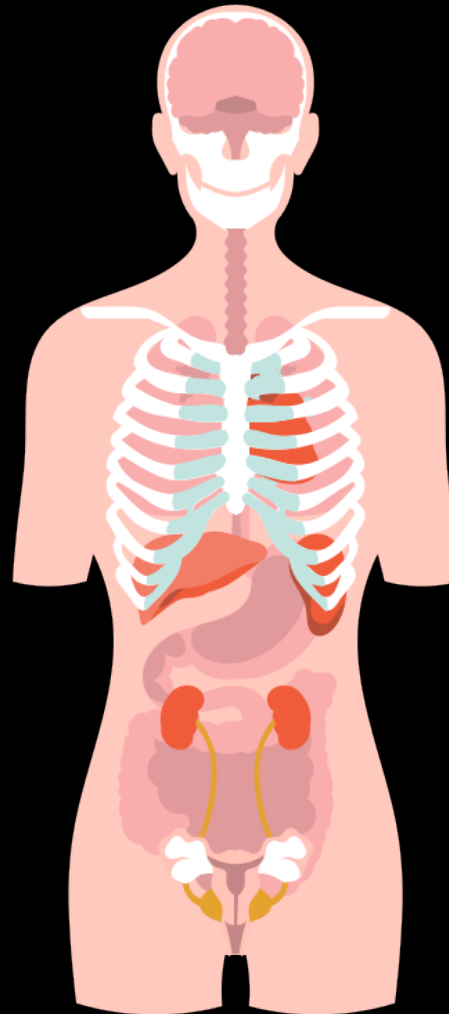
Phonophobia



Osmophobia



Neck stiffness



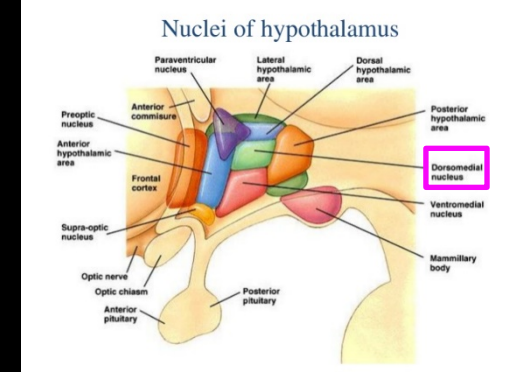
Yawning
Sleep impairment



Food cravings
Nausea
Diarrhea
Constipation



Thirst
Urinary frequency

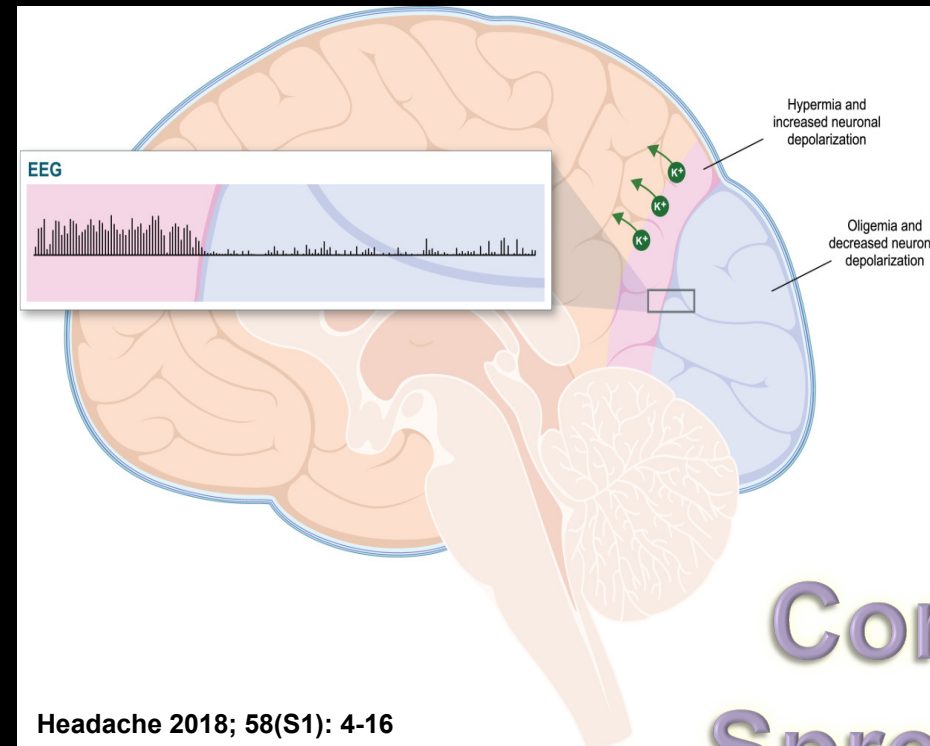
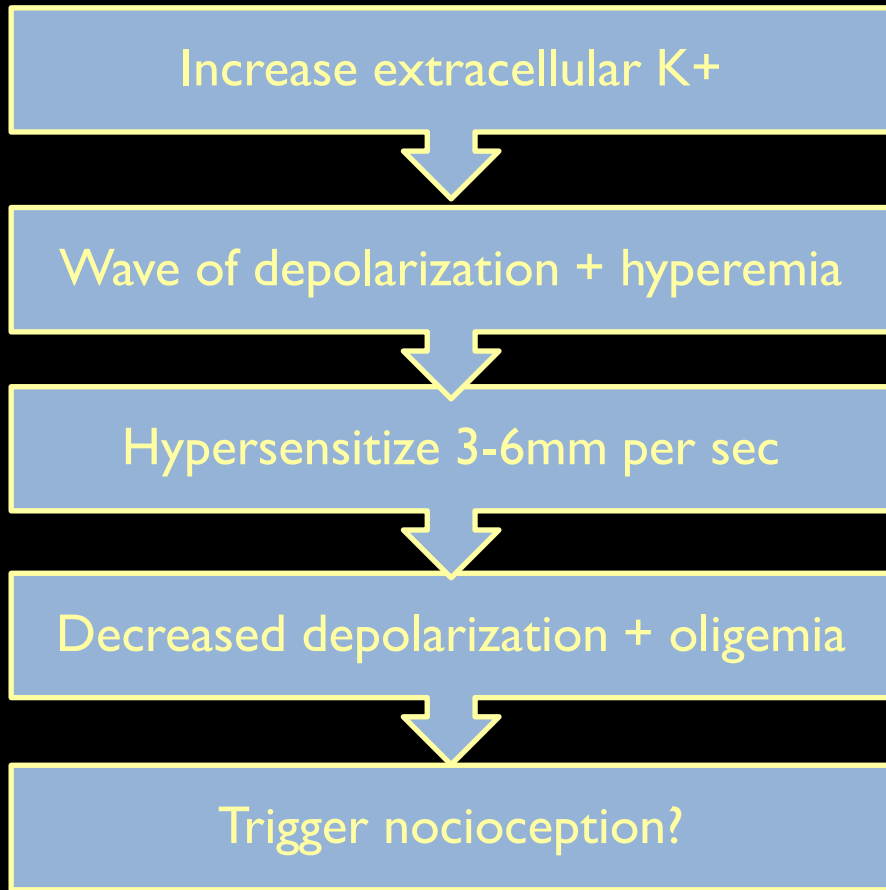


Migraine Phases

❖ AURA PHASE



AURA PHASE



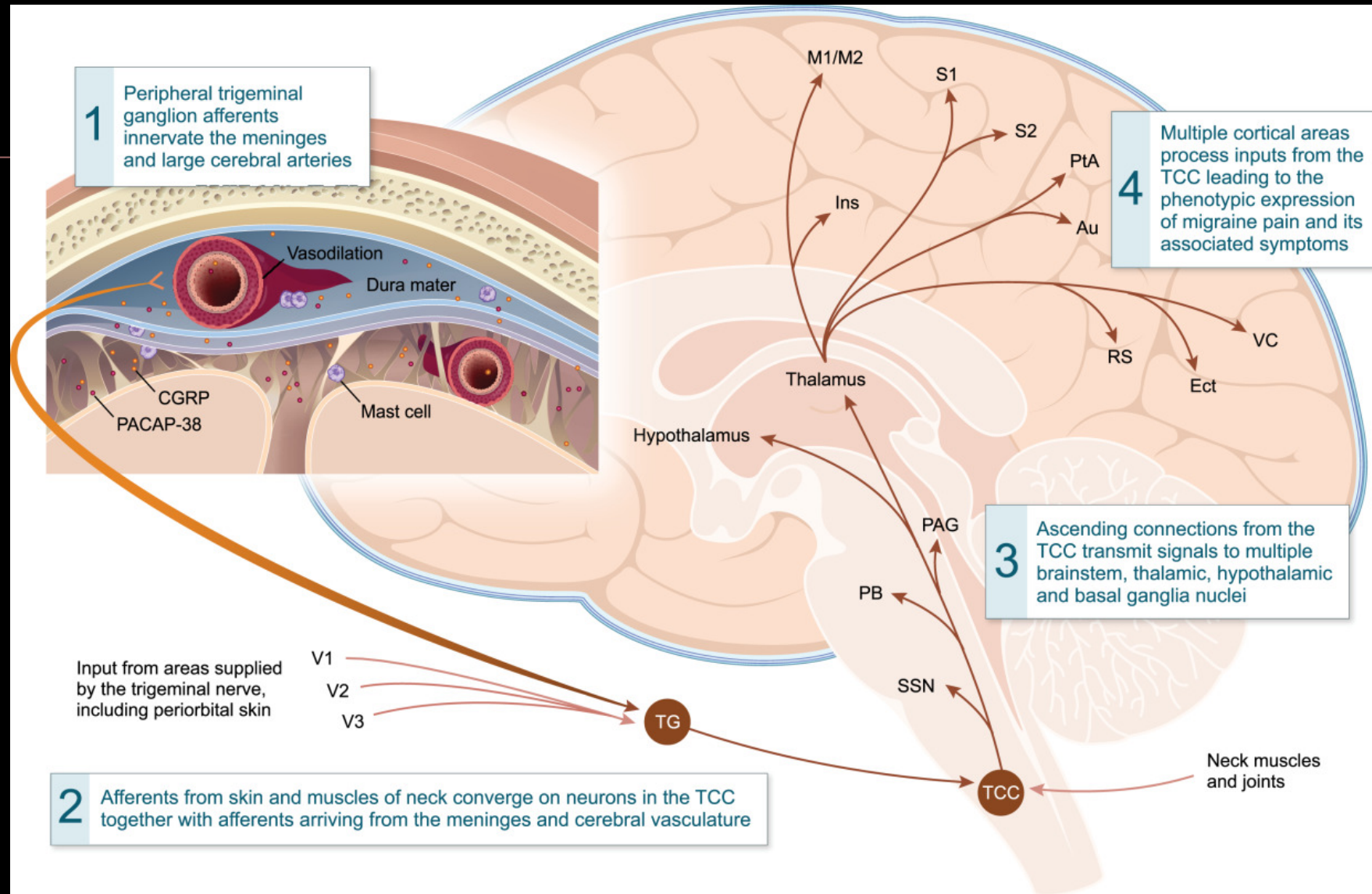
Cortical
Spreading
Depression

Migraine Phases

❖ HEADACHE PHASE



HEADACHE PHASE



Migraine Phases

❖ POSTDROME PHASE



POSTDROME PHASE

- Global reduction in blood flow
 - Locus ceruleus (NE) ?
 - Alpha2 mediated vasoconstriction
- Relationship with CSD?
- Shared mechanisms with premonitory phase?

Other consideration

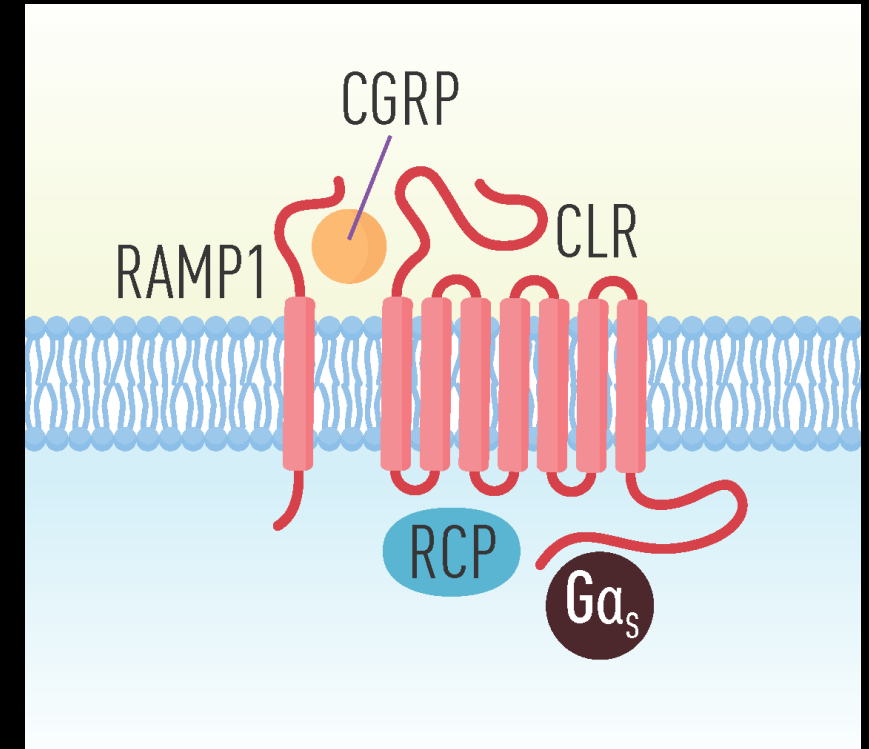
Calcitonin
Gene-Related
Peptide
(CGRP)

Serotonin
Related Medications

Genetics

Calcitonin Gene-Related Peptide (CGRP)

- Potent vasodilator
- Elevated in migraine attacks
- IV CGRP triggers migraine attack
 - Only if PMH Migraine
 - Not in controls
- Likely peripheral & central effects
 - CGRP mAb responders: ↓ Hypothalamic response to pain



Edvinsson, L. (2018). "The CGRP Pathway in Migraine as a Viable Target for Therapies." *Headache* **58 Suppl 1: 33-47**.
Dodick, D. W. (2018). "A Phase-by-Phase Review of Migraine Pathophysiology." *Headache* **58 Suppl 1: 4-16**.
Goadsby PJ. Headache research in 2020: disrupting and improving practice. *Lancet Neurol.* 2021 Jan;20(1):7-8.

Ergots
VS
Triptans
VS
Ditans

Ergots

- 5HT₁ agonist
- 5HT₂, DA & Adrenergic

Triptans

- 5HT_{1B/1D} agonist
+/- 1F affinity

Ditans

- 5HT_{1F} agonist

Migraine Management

Preventive Treatment

Nonspecific oral

OnabotulinumtoxinA

Nerve blocks

Gepants

Devices

CGRP Monoclonal Antibodies

Preventive Treatment

When to start a preventive treatment?

- 4 to 6 d/mo
- Patient preference
- Disabling attacks
- Acute Rx side effects
- MOH risk

**How do
I know
if it is
Working?**

Goal = 50% Response

3 month trial or A/E

Non-specific Oral Preventive Medications

<i>Established Efficacy*</i>	<i>Probably Effective</i>
Candesartan	Amitriptyline
Divalproex	Atenolol
Metoprolol	Lisinopril
Propranolol	Memantine
Timolol	Nadolol
Topiramate	Venlafaxine

*Frovatriptan for menstrual migraine

Other Non-Specific Preventive Medications*

- Acetazolamide
- Cyproheptadine
- Duloxetine
- Gabapentin
- Nortriptyline
- Pregabalin
- Zonisamide

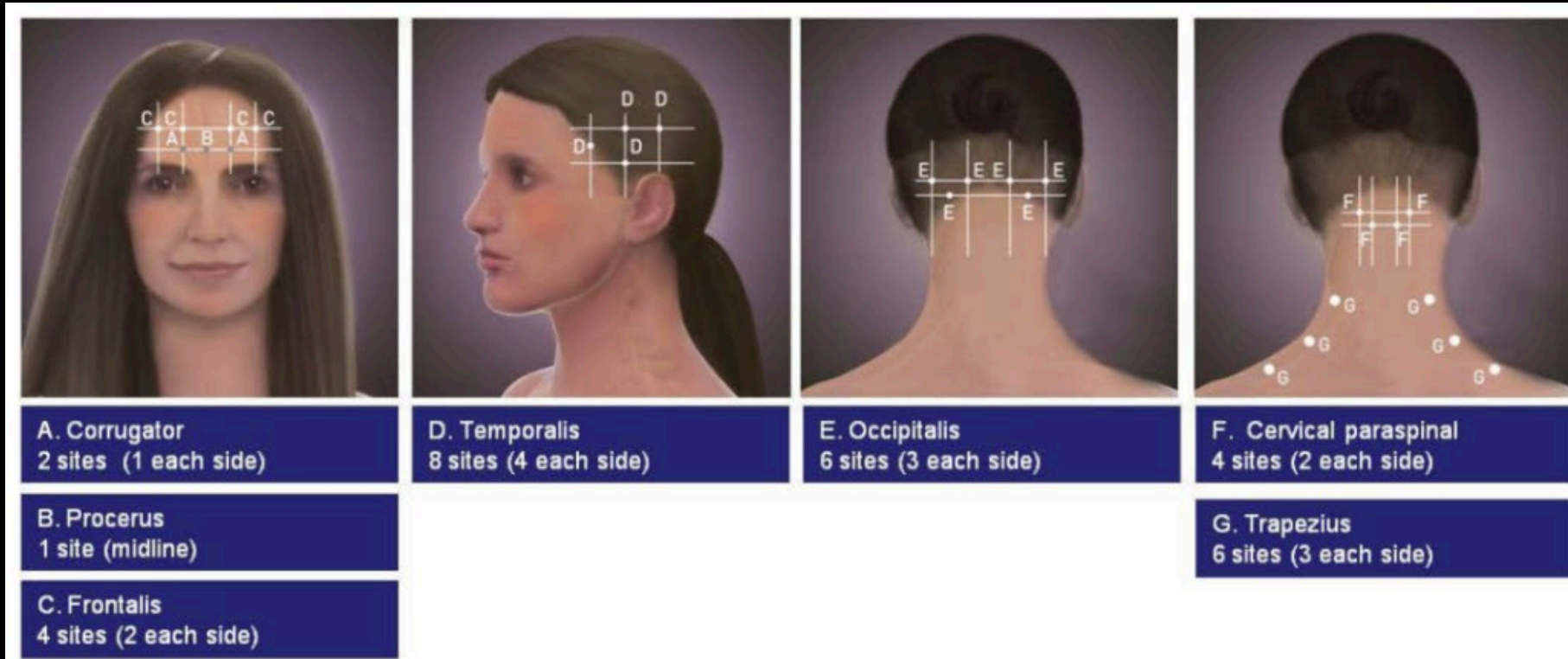
*Limited evidence → consider for refractory patients not responding to firstline options

OnabotulinumtoxinA

CHRONIC MIGRAINE

PRE-EMPT = 155u q12wks

Follow The Pain = 195u q12wks



Appropriate trial is 3 sessions

Nerve Blocks

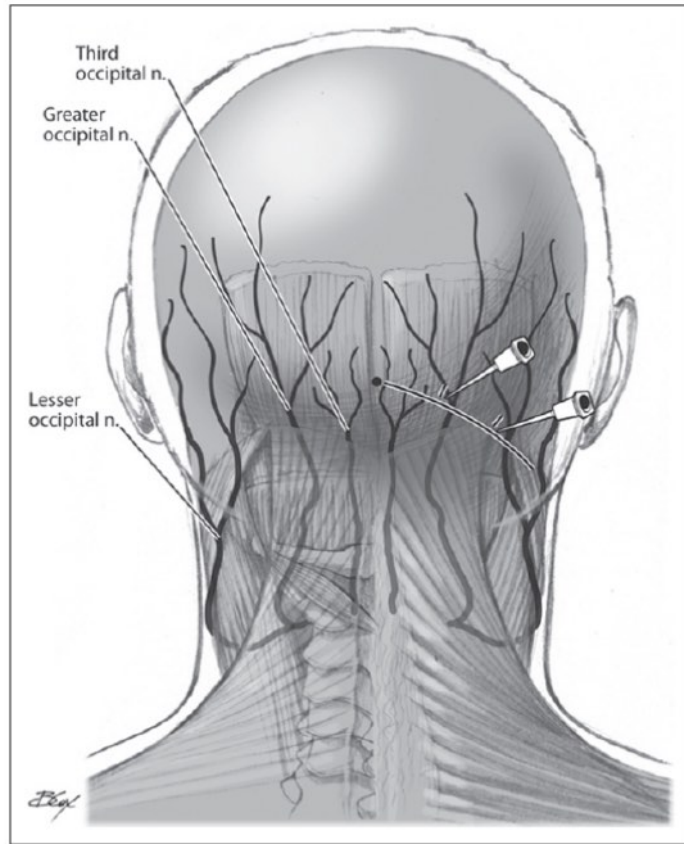


Fig 1.—Greater and lesser occipital nerve blocks.

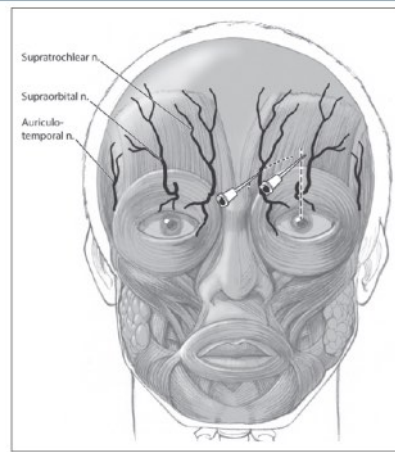


Fig 2.—Supratrochlear and supraorbital nerve blocks.

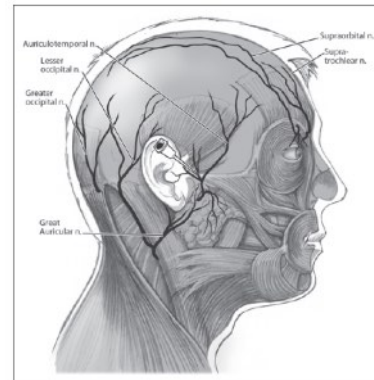


Fig 3.—Auriculotemporal nerve block.

- -Volumes vary greatly
- -Frequency varies greatly
- -Options include bupivacaine and lidocaine
- Steroids:
 - Cluster headache
 - Migraine = poor evidence
 - Never in the face
- Cervicogenic: Diagnostic blocks +/- RFA ?

CGRP Monoclonal Antibodies

CGRP Receptor antibody

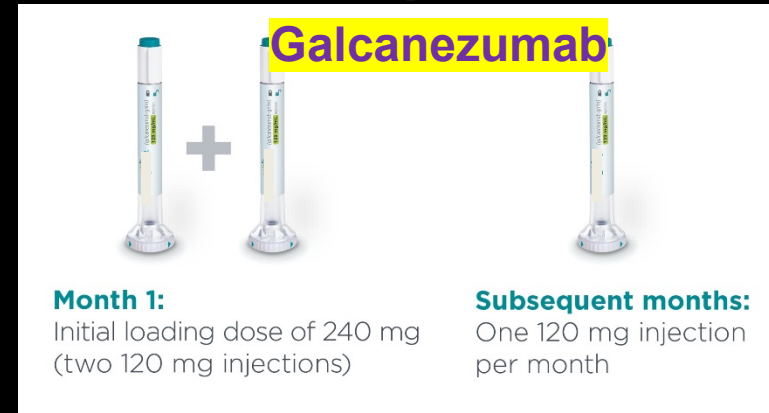


Erenumab

70-140mg sc qMo
ARISE & NCT02456740
Extra A/E: Constipation & HTN

**50% responder rates
of ~60%**

CGRP Ligand antibody



Month 1:
Initial loading dose of 240 mg
(two 120 mg injections)

Subsequent months:
One 120 mg injection
per month

EVOLVE-1 & -2, REGAIN

*Main A/E =
Injection
Site Reaction*



Fremanezumab

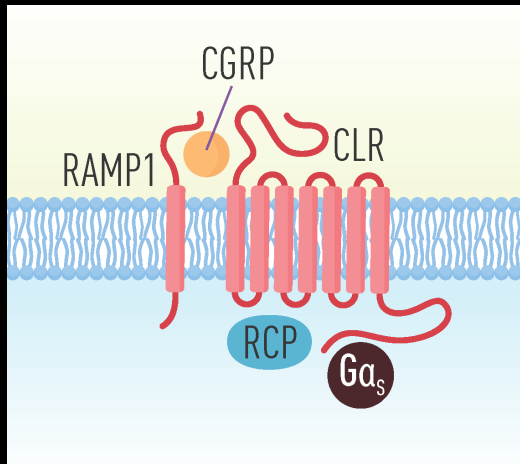
225mg qMo –or- 675mg q3mo
NCT02621931 & NCT02629861



Eptinezumab

100-300mg IV q3mo
PROMISE-1 & -2

Gepants as Preventive (CGRP Receptor Antagonist)



Rimegepant

- FDA approval: Episodic migraine
- 75mg ODT q2d
- Migraine days: -4.3

Pending FDA

Atogepant

Phase 3 ADVANCE

10mg, 30mg, 60mg

Zavegepant

Phase 2/3 in progress

100mg, 200mg

Migraine Management

Acute Treatment

NSAIDs

Triptans

DHE

Gepants

Ditans

Devices

Migraine Management

Acute Treatment

Triptans

~40-75% 2h pain relief

Sumatriptan	PO= 25mg, 50mg, 100mg IN= 10mg (<i>Tosymra</i>); 11mg (<i>Onzetra</i>); 5 & 20mg SC = 3mg (<i>Zembrace</i>); 4 & 6mg	Oldest High A/E rate
Almotriptan	6.25 - 12.5mg po	Fast, low A/E
Eletriptan	20 - 40mg po	Fast, mod A/E
Frovatriptan	2.5mg po	Long, low A/E
Naratriptan	1 - 2.5mg po	Long, low A/E
Rizatriptan	5 - 10mg po/ODT	Fast, mod A/E
Zolmitriptan	2.5 - 5mg po/OD/IN Pending = Qtrypta patch (<i>microneedles</i>)	Fast, mod A/E
Suma + Naproxen	Sumatriptan 85mg + Naproxen 500mg	Combo med
Riza + Meloxicam	Pending = AXS-07	New & Faster

Combo with triptans =
60-80% 2h headache relief

NSAIDs

Naproxen

- 500mg prn

Indomethacin

- 25-75mg prn

Diclofenac po or Cambia (powdered diclofenac)

- 50mg prn

Ketorolac

- 10mg po; 15.75mg IN; 30-60mg IM

Dihydroergotamine (DHE)

**~40% 2h Pain
freedom***

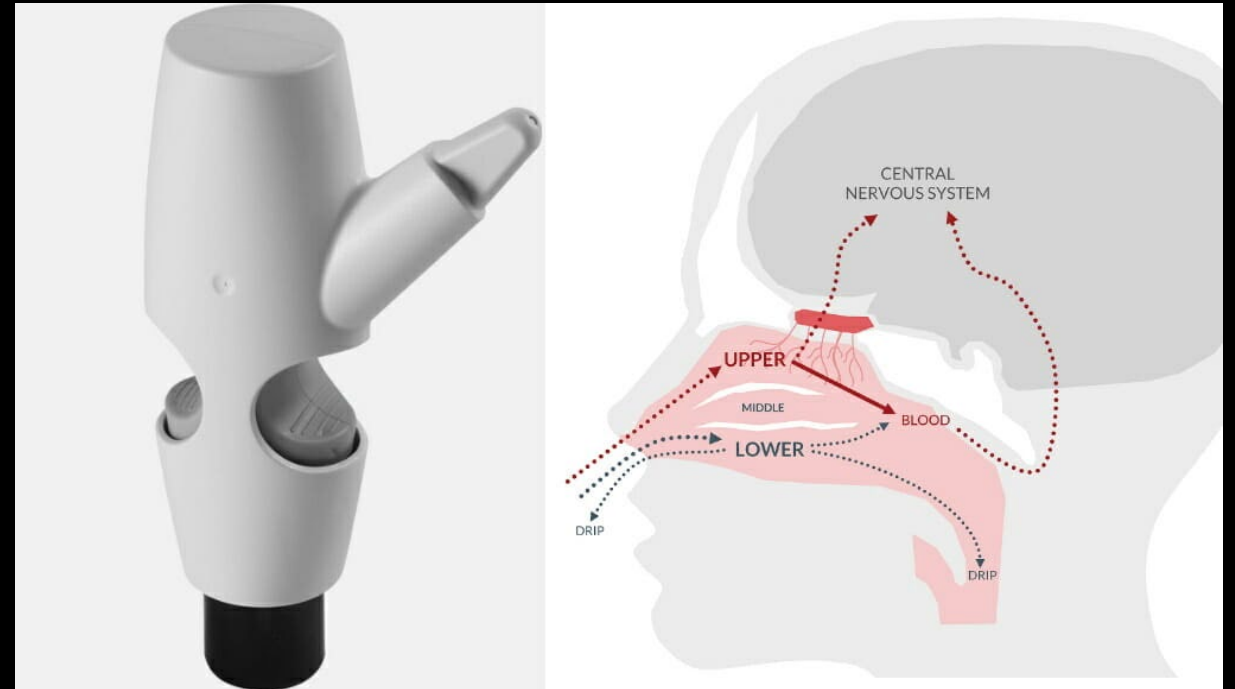
■ Nasal

- Old = Migranal
- New POD device = TRUDHESA
 - Pending FDA approval
 - Drug levels similar to IV

■ Parenteral

- 1mg SC/IM
- 1mg IV q8h or continuous IV
- A/E = Nausea

■ NOT within 24h of a triptan



Gepants

- **UBROGEPANT** (NCT02828020 & NCT02867709)
 - 50-100mg po
 - Repeat after 2h
- **RIMEGEPANT** (NCT03461757)
 - 75mg ODT
 - Acute and preventive
 - Can repeat after 24h
- Zavegapent po & IN
 - Still in clinical trials
- Pipeline: FE 205030 sc

~20% 2h Pain
freedom*

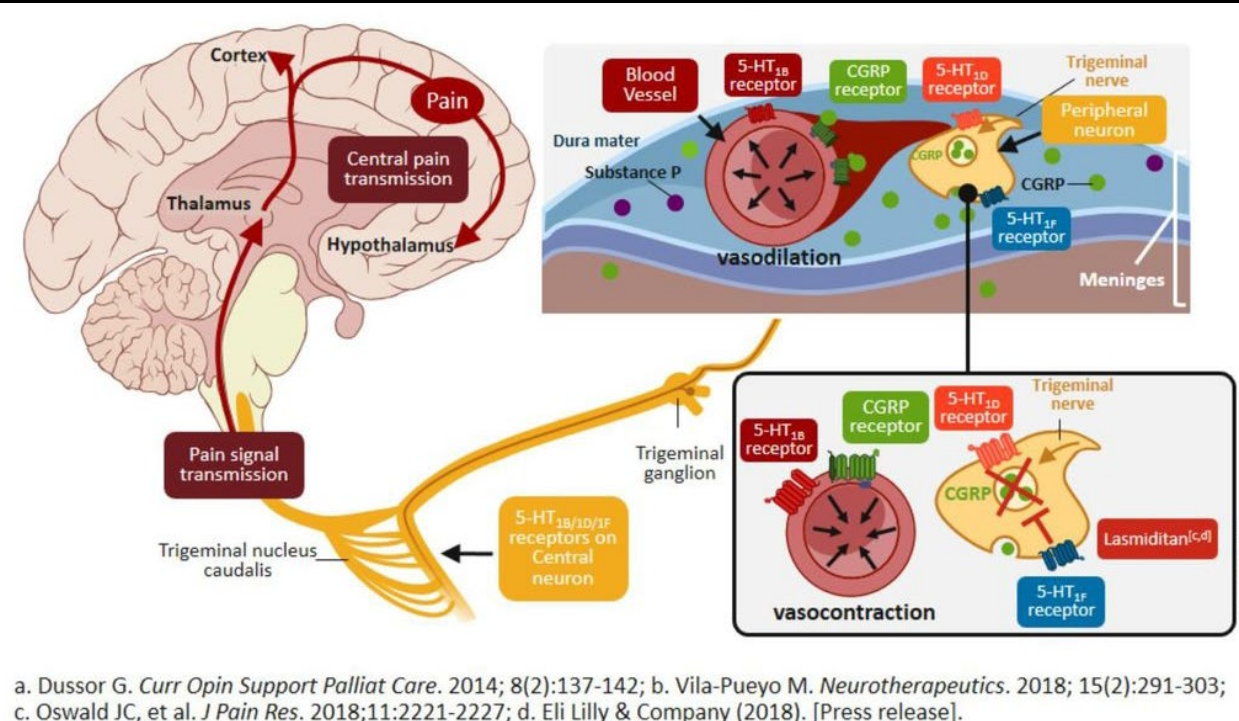


*Placebo was about 11-14%

Ditans

~30-40% 2h pain freedom

- Triptans = 5HT-1B/1D agonist
 - Vasoconstriction due to 1B
- Ditans = 5HT-1F agonist
 - No vasoconstriction
- Lasmiditan
 - Can repeat after 24h
 - 8h driving restriction
 - Schedule 5 med



50 mg 100 mg 200 mg
(100 mg x2)

PainWeek *Placebo was about 20%

Kuca, B., et al. (2018). "Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study." *Neurology* **91(24)**: e2222-e2232.

Daily severe headache....

What to do with Rescues

Step one (Daily)

- Devices (Cefaly, Nerivio, gammaCore, sTMS, Relivion)
- Compounded nasal sprays like lidocaine or ketamine
- Muscle relaxants like tizanidine, cyclobenzaprine, baclofen
- Gabapentin, timolol eye drops, acetazolamide

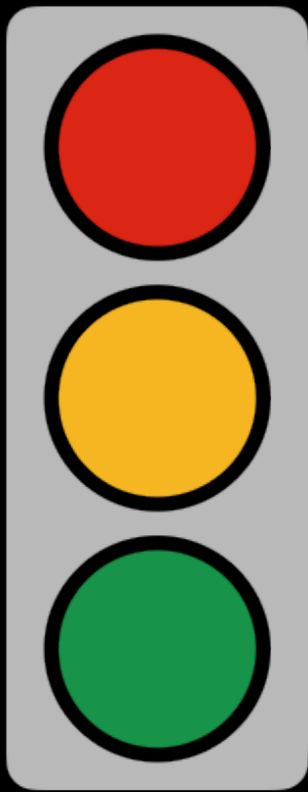
Step 2 (10d/mo)

- Triptans, **Gepants, Ditans**
- NSAIDs + Acetaminophen added in combo
- Anti-dopaminergics, ondansetron
- DHE (IN/SC/IM)
- Isometheptene mucate, dichloralphenazone and acetaminophen (compounded)

Step 3 (3d/mo)

- Ketorolac po/IN/SC
- DHE IN/SC/IM
- Dexamethasone 4mg
- Oral combo (eg VPA, anti-dopamine, dimenhydramine)
- Anti-psychotic
- Hydroxyzine
- Butalbital-containing agents
- Infusion clinic

****My approach -
not evidence based**



**NOT Recommended:
OPIOIDS & BULTALBITAL**

↓ Treatment Response

Risk of Chronic Daily Headache

Tolerance, Withdraw, Abuse, Overdose

Increased sensitization

Migraine Management

Non-Pharmacologic Treatments

**Neuromodulation
Devices**

**Lifestyle
“SEEDS”**

Migraine Management

Non-Pharmacologic Treatments

Cefaly = supraorbital eTENS

Prevention:
20min QHS



Acute:
1 h prn

eTENS = external trigeminal nerve stimulator

Nerivio = Remote Electrical Neuromodulation (REN)

Stimulation in arm -> trigeminocervical complex -> Inhibit migraine pain



Acute:
45min prn

GammaCore = Non-invasive Vagal Nerve Stimulation

PNS activates vagus → Inhibit TNC → Inhibit pain

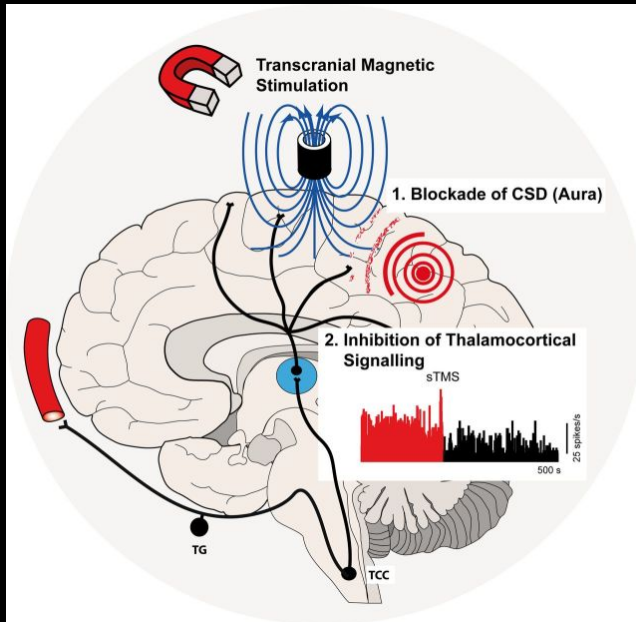


TNC = trigeminal nucleus caudalis

Prevention: 2min stim x 2 TID

Acute: 2min stim x 2 prn
-Repeat after 20min & 2h

Single pulse TransMagnetic Stimulation (sTMS)



Prevention BID:

- 2 pulses – wait 15min – 2 pulses

Acute prn:

- 3 pulses q15min



Relivion = Non-invasive OS-TNS

RCT with n=55 for 1h OS-TNS vs Sham

- **50% Responder rate =**
 - 67% for OS-TNS
 - 20% for Sham
- **Pain free at 2h =**
 - 43% for OS-TNS
 - 11% for Sham

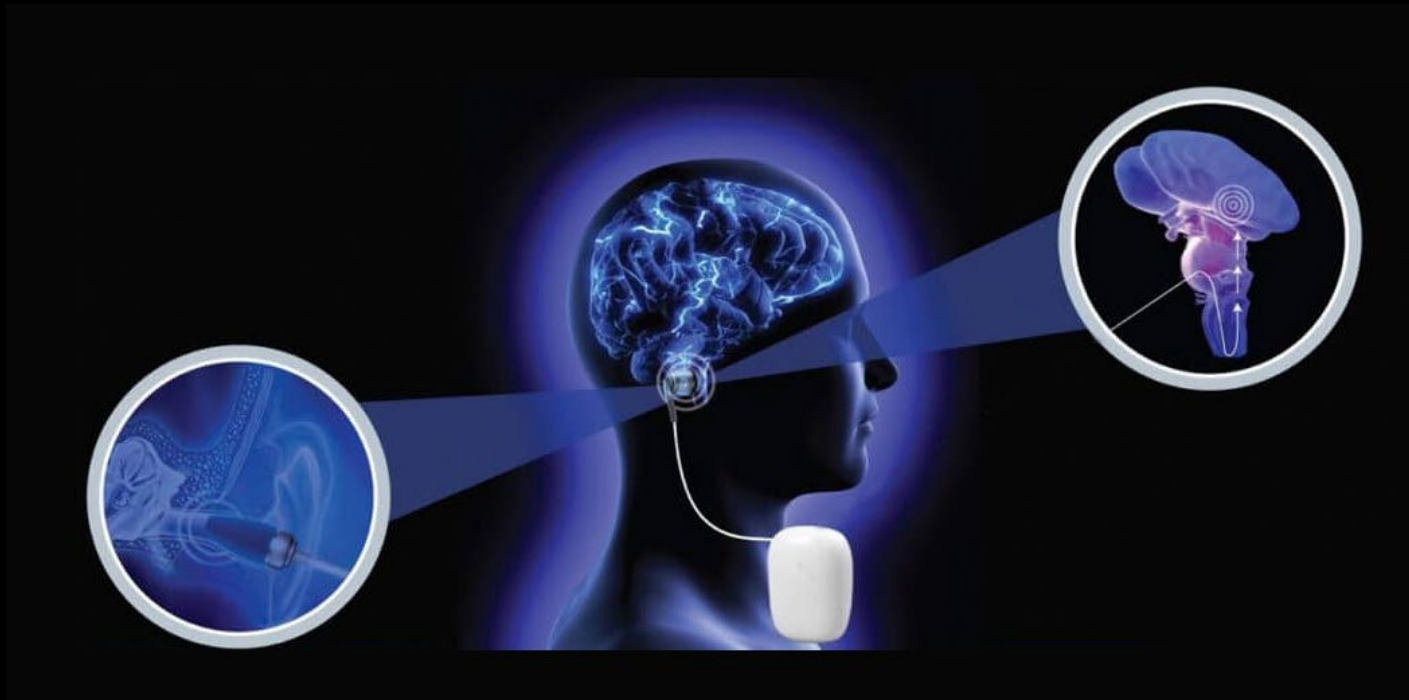
Newly FDA approved
with release pending!



OS-TNS = Combined occipital & supraorbital nerve stimulation

Micro-pressure Pulse Insufflator Device (Nocira)

**New in development for acute migraine treatment





Sleep



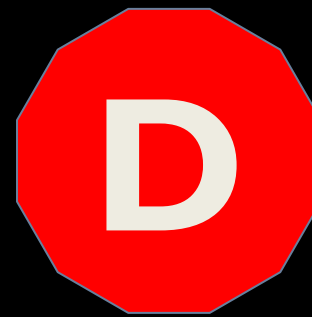
Exercise



Eat

&

Drink



Diary



Stress

S

Sleep

Common comorbid sleep d/o

- Insomnia
 - Sleep apnea
 - Restless leg syndrome
- Stimulus control therapy
- Sleep restriction

www.stopbang.ca/osa/screening.php

STOPBANG Score

- **S** = Snoring
- **T** = Tired (daytime)
- **O** = Observed Apnea/Choke/Gasp
- **P** = Pressure (Hypertension)^{[L][SEP]}
- **B** = BMI > 35 kg/m²
- **A** = Age > 50y
- **N** = Neck size (♂ - 17in, ♀ - 16in)
- **G** = Gender = male
- Low risk = 0-2
- High Risk =
 - 1) 5-6
 - 2) 2/4 STOP + 1/3 BANG



Exercise & Migraine

Sedentary life associated with ↑Migraine

Theory 1: Patient with migraine avoid exercise

Theory 2: Sedentary life increases risk

Prophylactic benefits

Theoretical Pathophysiology:
↑β-endorphins at opioid mu-R
↓Avoidance
↑Lactate
↑CGRP*
↑EAE** pain modulation
↓Inflammation



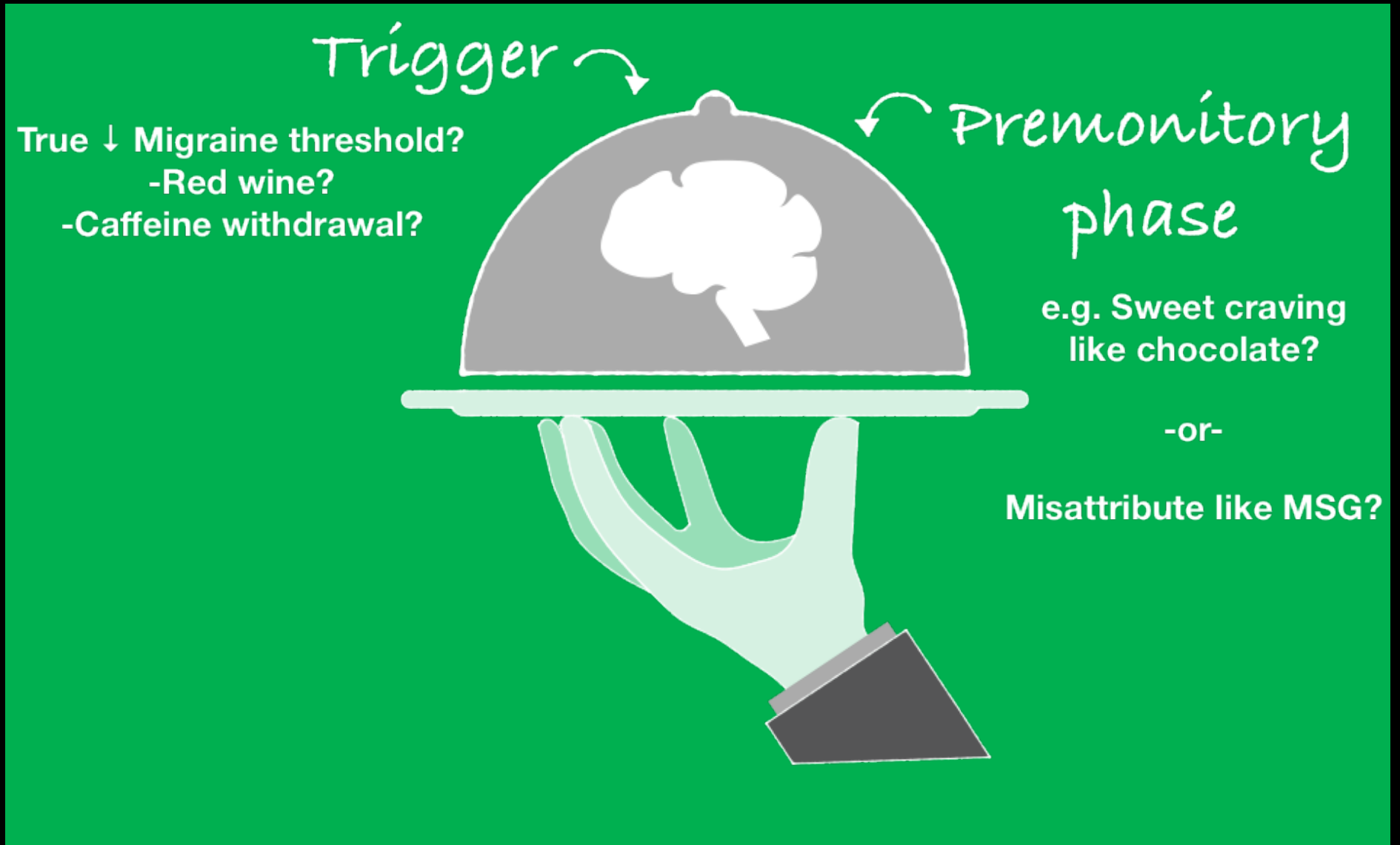
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Exercise & Migraine

- **Systematic Review**
 - 5 RCTs & 1 Non-randomized controlled trial
- Moderate Level evidence
- ↓ Monthly Migraine days by 0.6 ± 0.3

- **2 studies**
- Equivalent benefit vs Topiramate / Amitriptyline
- Amitriptyline + Exercise = Synergistic

E



E

Diets	Studies	Frequency	Duration	Severity
Gluten Free	Systematic Review	+	NA	NA
IgG	RCT x 3	+ (2/3)	NA	NA
Histamine	Prospective	+	-	-
Tyramine	Prospective	NA	-	NA
Ketogenic	RCT x1 Prospective x2	+ (2/3)	+ (x1)	- (x1)
↑ Omega-3 ↓ Omega-6	Systematic Review	-	+	-
Low Sodium	Prospective x2	+ (2/3)	NA	+ (2/3)
Low Fat	RCT x2 Prospective x1	+ (2/3)	+ (x1)	+
Low glycemic	RCT	+	NA	+



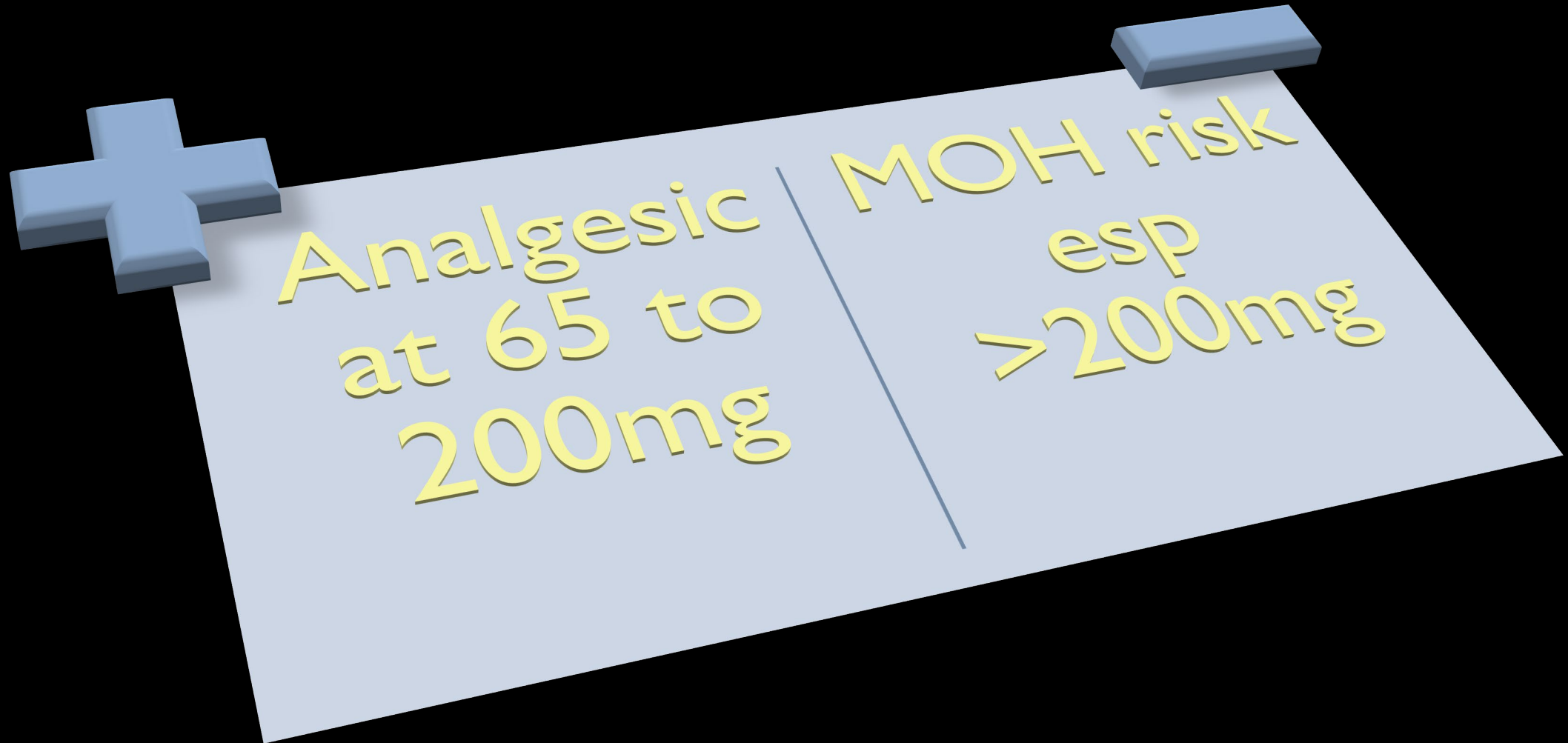
Dehydration association with Headache

Rehydration reduces migraine???

Post hoc analysis: IV fluids alone did not ↓ Migraine	One study: Benefit with 4L/day
--	-----------------------------------

General health recommendation: 1.8L/d hydration

E Caffeine = Nonspecific adenosine receptor antagonist





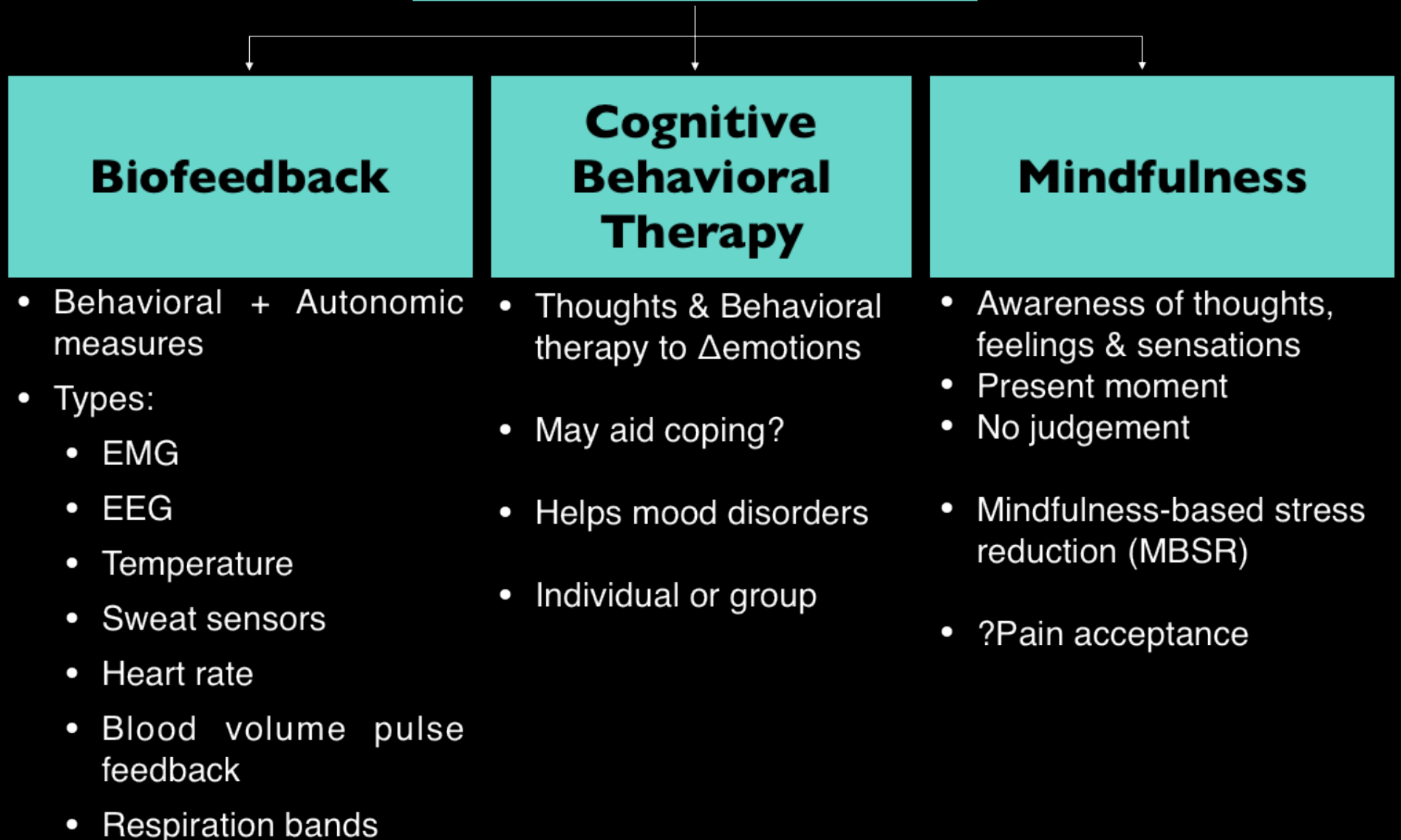
StopLight Headache Diary

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
	1 ✓	2 ✓	3	4 ✓	5	6
7	8	9 ✓	10	11 ✓	12	13
14	15	16 ✓	17	18 ✓	19	20
21	22 ✓	23 ✓	24	25	26	27
28	29	30	31 ✓			
<div style="display: flex; justify-content: space-around;"><div> = Bedbound</div><div> = Reduced Function</div><div> = No reduced Function</div></div> <p style="text-align: center;">✓ = Abortive Medication used (Aim is <10d/mo)</p>						

***This diary shows 4 Red days, 5 yellow days, and 3 green days with 10 abortive treatment days that are not consistently treating the start of headache leading to multiple headaches extending 48-72h. Abortive treatment counseling and starting a preventive would be indicated.



Stress Management in Migraine



Treatment Summary

Acute

- NSAIDs
- Triptans
- Gepants
- Ditans
- DHE
- Devices

Preventive

- Non-specific orals
- OnabotulinumtoxinA
- CGRP mAbs
- Gepants
- Nerve blocks
- Devices
- SEEDS

Pipeline

- New Gepants
 - Atogepant po
 - Zavegepant IN
 - FE 205030 sc
- Triptans
 - Qtrypta (zolmi) patch
 - Riza + meloxicam
- DHE
 - TRUDHESA IN
- Devices
 - Relivion
 - Nocira

PainWeek®

Thank You!

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