

Challenges and Advances in the Diagnosis and Treatment of Migraine

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painweek

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Disclosure

Nothing to disclose

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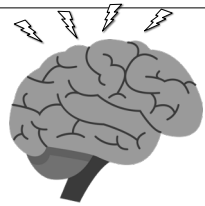
Learning Objectives

- Explain diagnostic criteria for episodic and chronic migraine
- Identify patients with migraine who need preventative therapy based on clinical presentation and diagnostic criteria
- Outline available medications for migraine treatment and prevention
- Summarize the efficacy, safety, and mechanism of action of newly-approved or emerging treatment options for migraine

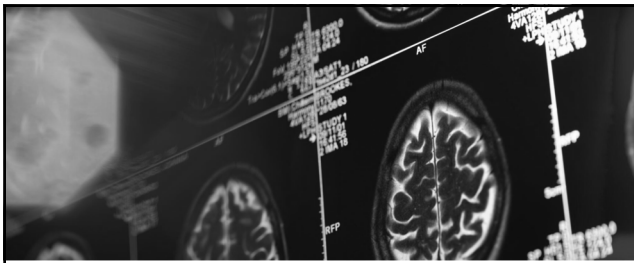
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Outline

- Approach to diagnosis
- Migraine pathophysiology
- Preventive, acute, and nonpharmacologic treatments



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Approach to diagnosis

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ICHD-3

	Migraine	TTH
Duration (untreated)	4-72h (>72h = Status migrainosus)	30min to 7d
2/4 Characteristics	1. Unilateral 2. Pulsating 3. Moderate to severe 4. Affected by activity	1. Bilateral 2. Nonpulsating 3. Mild to moderate 4. Not affected by activity
Associations	1. Nausea and/or vomit AND/OR 2. Photo- and phonophobia	1. No nausea/vomit AND 2. Photo, phono, or none
Types	Episodic: <15d per month Chronic: 15+d per month (8+ migraine days)	Infrequent: <1/mo Frequent: 1-14/mo Chronic 15+/mo

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Medication Overuse Headache
 Headache on >15 days per month
 Regular overuse for >3 months

Examples:

- 15+ days of simple analgesia
- 10+ days of triptans, opioids, butalbital, combo meds
 - Likely even less needed for opioids & butalbital

ICHD-3

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New Daily Persistent Headache

- A. Persistent headache fulfill criteria B & C
- B. Distinct onset with pain constant in 24h
- C. >3 months
- D. No better diagnosis

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New Daily Persistent Headache

- A. Persistent Headache fulfill criteria B & C
- B. Distinct onset with pain constant in 24h
- C. >3 months
- D. No better diagnosis

Rule out MOH, CSF leak, and onset from trauma

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Secondary Headaches

SNOOP4 = red flags

- Systemic symptoms/signs
- Neurologic symptoms/signs
- Onset >50y
- Onset = thunderclap
- Pattern change:
 - Postural headache
 - Progressive headache
 - Papilledema
 - Precipitated by valsalva
 - (Pregnancy)

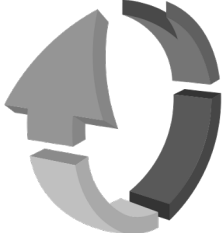
Dodick 2010

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Migraine Pathophysiology

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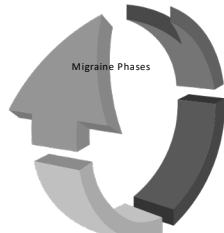
Migraine Phases



- ❖ PREMONITORY PHASE
- ❖ AURA PHASE
- ❖ HEADACHE PHASE
- ❖ POSTDROME PHASE

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Migraine Phases



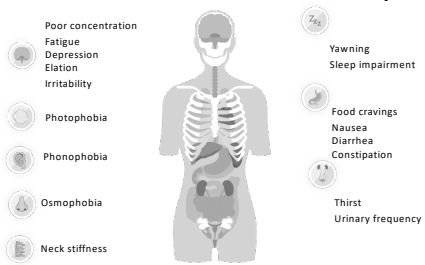
❖ **PREMONITORY PHASE**

- ❖ AURA PHASE
- ❖ HEADACHE PHASE
- ❖ POSTDROME PHASE

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Premonitory Phase

Can start up to 3 days before!



- Poor concentration
- Fatigue
- Depression
- Elation
- Irritability
- Photophobia
- Phonophobia
- Osmophobia
- Neck stiffness
- Yawning
- Sleep impairment
- Food cravings
- Nausea
- Diarrhea
- Constipation
- Thirst
- Urinary frequency

Karsan et al. 2018

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Premonitory Phase

Activation of the hypothalamus as a trigger for migraine pain

Theory 1: *The hypothalamus-brainstem axis affects pain signals from thalamus to the cortex → Homeostatic changes lower threshold*

Theory 2: *Parasympathetic hypothalamic activation of the SSN & SPG activate the trigeminovascular system*
-Triggers vasodilation and proinflammatory chemical release Gago-Veiga & Sobrado 2019

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Premonitory Phase

Symptom	Anatomical area
Cognition	Hypothalamus and frontal lobe
Fatigue, mood	Hypothalamus → limbic
-Phobias	Locus ceruleus, occipital, temporal, insula
Neck stiff	Hypothalamus + TCC
Yawn / sleep	Hypothalamus, ventral tegmental
Cravings	Ventral tegmental area, nucleus accumbens, amygdala
Nausea / GI	Hypothalamus, brainstem, insula
Thirst, urination	Hypothalamus

Gago-Veiga & Sobrado 2019

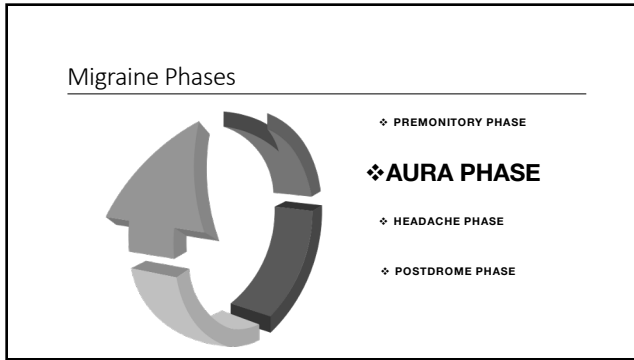
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Premonitory Phase

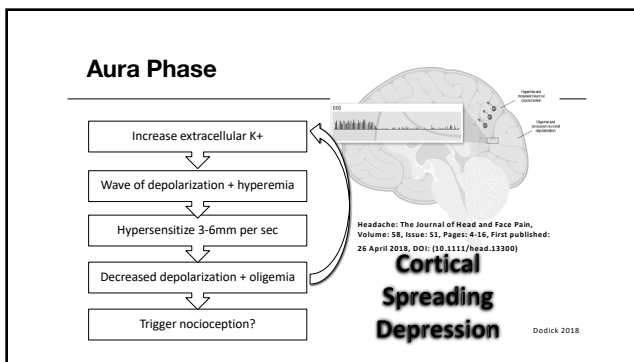
Dopamine	Orexin	NE	ADH
<ul style="list-style-type: none"> • Cognition • Fatigue • Yawn • Cravings • Mood • Nausea 	<ul style="list-style-type: none"> • Sleep changes 	<ul style="list-style-type: none"> • Photo- • Phono- • Osmo- 	<ul style="list-style-type: none"> • Thirst • Urination

Gago-Veiga & Sobrado 2019

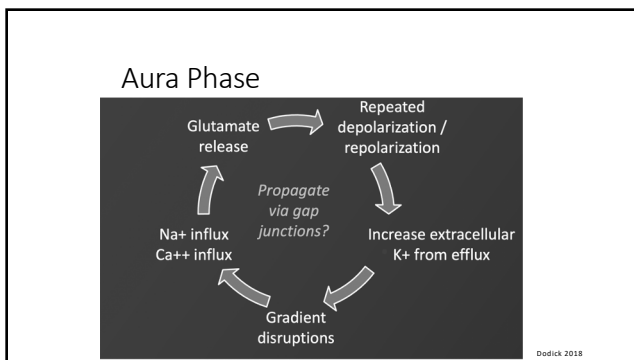
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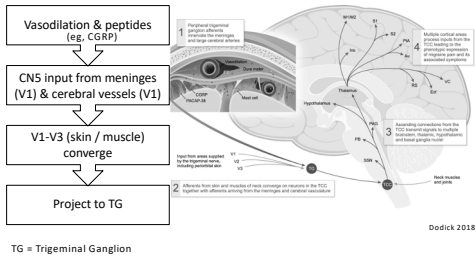
Migraine Phases



- ◆ PREMONITORY PHASE
- ◆ AURA PHASE
- ◆ **HEADACHE PHASE**
- ◆ POSTDROME PHASE

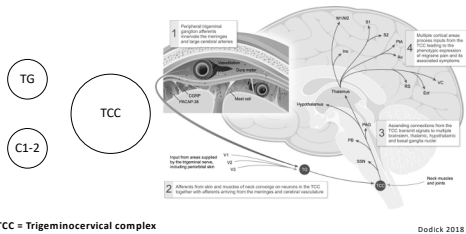
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Headache Phase – Step 1



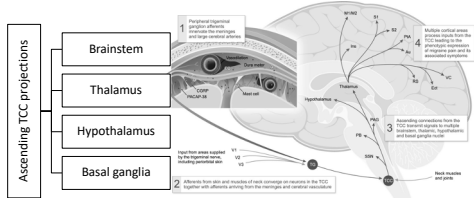
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Headache Phase – Step 2



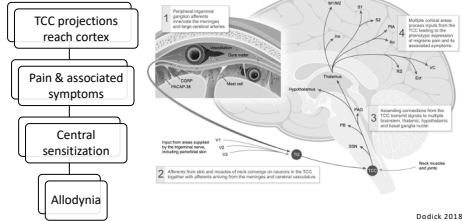
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Headache Phase – Step 3



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Headache Phase – Step 4



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Migraine Phases

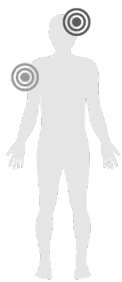


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Postdrome Phase

- Global reduction in blood flow
 - Possible role of locus ceruleus (norepinephrine)
 - Alpha2 mediated vasoconstriction
- Possible relationship to cortical spreading depression
- Possible shared mechanisms with premonitory phase

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Peripheral vs Central Sensitization

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Peripheral Sensitization

Activation of peripheral trigeminovascular neurons

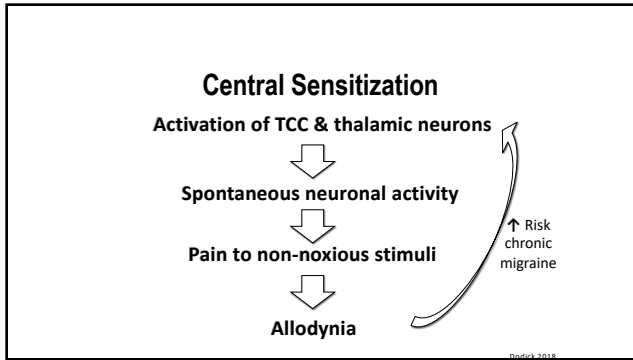
↓ threshold & ↑ magnitude of nociception

Throbbing pain & bend/cough pain

*Chemicals including CGRP influence this process

Dodick 2018

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Calcitonin Gene-Related Peptide

1. Potent vasodilator
2. Neurotransmitter
 - Affected by glutamate
3. **Elevated** in migraine attacks
4. IV CGRP **triggers migraine**
 - Only if PMH of migraine
 - Does not occur in controls

Receptor = CLR + RAMP1

Dodick 2018, Edvinsson 2018

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Meningeal CGRP

Activation via hypothalamus?

CSD?

Meningeal artery

Trigeminal afferent A δ fiber

Trigeminal afferent C-fiber

CGRP

TRP

CGRP Receptor

ion channel

Antidromic Peripheral release:

- 1) Triggers vasodilation
- 2) Triggers sterile inflammation

Dodick 2018

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Botox vs Anti-CGRPs

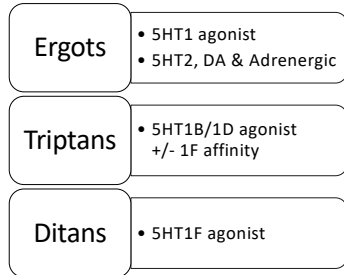
C Fibers	Aδ Fibers
Small, unmyelinated, and slow conduction	Large, myelinated, and fast conduction
Blunt & dull	Sharp & localized
Synapse on WDR neurons	Synapse on HT neurons
Contain CGRP	CGRP receptors
Botox blocks CGRP release	Blocked by mAbs & gepants

WDR = Wide dynamic range; HT = High Threshold Diener AHS conference 2020

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Ergots vs Triptans vs Ditans

Bemenei et al 2017



Bemenei et al 2017

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FHM1 = CACNA1A
Voltage gated Ca⁺⁺ Channel
Controls synaptic NT release
Unregulated glutamate release
Causes hyperexcitability

FHM2 = ATP1A2
Glial Na⁺/K⁺ ATPase
Affects glutamate reuptake
Causes hyperexcitability

FMH3 = SCN1A
Voltage gated Na⁺ channel
Found on inhibitory interneurons
Unregulated firing of excitatory neurons

GWAS loci findings
Glutamate regulation
Synaptic plasticity
Ion homeostasis ...

Medina 2018

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Migraine Management

PREVENTIVE TREATMENT

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When to start a preventive treatment?

- 4 to 8 headache days per month
- Patient preference
- Severe or disabling attacks / aura (eg, hemiplegic)

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How do I know if it is working?

- Goal = 50% response
- 3 month trial of appropriate dose

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1st Line Oral Meds

- Amitriptyline**
-Start 10-25mg QHS
- Propranolol**
-Start 60mg ER or 10mg QHS-BID
- Topiramate**
-Start 15-25mg QHS (aim for 100mg/d)
- Venlafaxine**
-Start 37.5mg ER or 25mg BID
- Divalproex**
-Start 250mg QHS then BID

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2nd Line Oral Meds

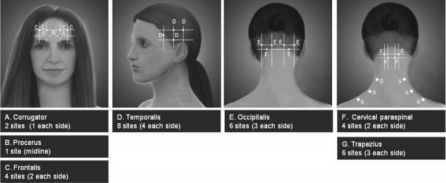
- Memantine**
-Start 5mg QHS → 10mg BID
- Gabapentin**
-Start 100-300mg QHS. Max 3600mg/d
- Cyproheptadine**
-Start 4mg TID
- Zonisamide**
-Start 25mg QHS → 100mg
- Acetazolamide**

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For CHRONIC MIGRAINE
PRE-EMPT trial protocol = 155 units q3mo
Follow the Pain = 195 units q3mo

****Appropriate trial is 3 sessions**

OnabotulinumtoxinA



A. Corrugator 2 sites (1 each side)	D. Temporets 8 sites (4 each side)	E. Occipitals 8 sites (4 each side)	F. Cervical paraspinal 4 sites (2 each side)
B. Proccus 1 site (midline)			G. Trapezius 8 sites (4 each side)
C. Frontalis 4 sites (2 each side)			

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Nerve Blocks

Fig 1—Greater and lesser occipital nerve blocks.

Fig 2—Trigeminal and occipital nerve blocks.

Fig 3—Hypoglossal and vagus nerve blocks.

- Volumes vary greatly
- Frequency varies greatly
- Options include bupivacaine and lidocaine
- Steroids:
 - Cluster headache
 - Migraine = poor evidence
 - Never in the face
- Especial cervicogenic:
 - Consider sending for diagnostic blocks and RFA

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CGRP Receptor Antibody

Erenumab 70-140mg sc qMo

CGRP Ligand Antibody

Galcanezumab

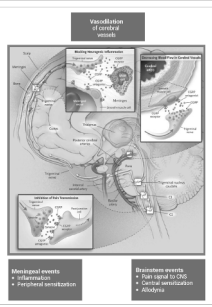
Month 1: Initial loading dose of 240 mg (two 120 mg injections)

Subsequent months: One 120 mg injection per month

Fremanezumab 225mg sc qMoc

Eptinezumab 100-300mg IV q3mo

Figure 6. Migraine pathogenesis—activation of the trigeminovascular system



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Acute Treatment

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Triptans

Ineffective in ~40% of patients!

Sumatriptan	PO = 25 to 100mg IN = 11-22mg (nasal powder), 20mg (oral) SC = 4-6mg (oral), 3mg (injection)	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	Fast, mod A/E
Suma + Naproxen	Sumatriptan 85mg + naproxen 500mg	Combo med

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NSAIDs

Consider combo treatment with triptans to increase response!

- Naproxen
• 500mg prn
- Indomethacin
• 25-75mg prn
- Diclofenac po or Cambia (powdered diclofenac)
• 50mg prn
- Ketorolac
• 10mg po; 15.75mg IN; 30-60mg IM

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Dihydroergotamine (DHE)

Migranal = nasal

DHE available as SC / IV

A/E esp parenterally: nausea

Do NOT use within 24h of a triptan



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Gepants

CGRP receptor antagonists


- Well tolerated
- Less effective than triptans?

Ubrogepant 50 - 100mg po

- Can repeat after 2h

Rimegepant

- 75mg ODT
- Can repeat after 24h



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Ditans

Triptans = 5HT-1B/1D agonist

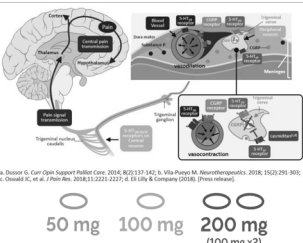
- Vasoconstriction due to 1B

Ditans = 5HT-1F agonist

- No vasoconstriction

Lasmiditan

- Can repeat after 24h
- 8h driving restriction
- Schedule 5 med




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Daily severe headache.... What to do with rescues

Step 1 (Daily)	<ul style="list-style-type: none"> -Devices (Cefaly, Nerivio, gammaCore, sTMS) -Compounded nasal sprays like lidocaine or ketamine -Muscle relaxants like tizanidine, cyclobenzaprine, baclofen -Gabapentin, timolol eye drops, acetazolamide
Step 2 (10d/mo)	<ul style="list-style-type: none"> -Triptans, gepants, ditans -NSAIDs, acetaminophen -Anti-dopaminergics, ondansetron -DHE (IN/SC) -Isometheptene mucate, dichloralphenazone and acetaminophen (compounded) -Butalbital -Ketorolac po/IN/SC -Dexamethasone 4mg -Oral combo (eg, VPA, anti-dopamine, dimenhydramine) <p>**My approach - not evidence based</p>
Step 3 (3d/mo)	<ul style="list-style-type: none"> -Anti-psychotic -Hydroxyzine -Butalbital-containing agents, DHE -Infusion clinic

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**NOT Recommended:
OPIOIDS & BULTALBITAL**

- ↓ Treatment Response
- Risk of Chronic Daily Headache
- Tolerance, Withdraw, Abuse, Overdose
- Increased Sensitization

ICHD-3; Choosing Wisely


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Nonpharmacologic Treatment

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Cefaly = Supraorbital eTNS

Prevention: 20min QHS



Acute: 1h prn

eTNS = external trigeminal nerve stimulator

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Nerivio = Remote Electrical Neuromodulation (REN)

Stimulation in arm → trigeminocervical complex → inhibit migraine pain



Acute:
45min prn

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GammaCore = Noninvasive Vagal Nerve Stimulation

PNS activates vagus → inhibits TNC → inhibit migraine pain



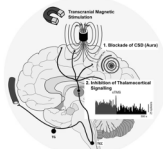
Prevention: 2min stim x 2 TID

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

TNC = trigeminal nucleus caudalis

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Single Pulse TransMagnetic Stimulation (sTMS)



Prevention BID:
2 pulses – wait 15min – 2 pulses



Acute prn:
3 pulses q15min

***Company went bankrupt. Not currently available*

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S Sleep **E** Exercise **E** Eat & Drink **D** Diary **S** Stress

Robblee & Starling 2019

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S **Sleep** **Stopbang Score**

- Common comorbid sleep disorders
 - Insomnia
 - Sleep apnea
 - Restless leg syndrome
- Behavioral modifications for sleep
 - Stimulus control therapy
 - Sleep restriction

S = Snoring
T = Tired (daytime)
O = Observed apnea/choke/gasp
P = Pressure (hypertension)
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

Robblee & Starling 2019; www.stopbang.ca/osa/screening.php

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E **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

* Calcitonin gene-related peptide = CGRP
 **Endocannabinoid ligand anandamide = AEA

Köseoglu et al 2003

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E **Systematic Review**

5 RCTs & 1 nonrandomized controlled trial
 Moderate level evidence
 ↓ Monthly migraine days by 0.6±0.3

2 studies
 Equivalent benefit vs topiramate / amitriptyline
 Amitriptyline + exercise = synergistic

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E

Trigger

Premonitory phase

True ↓ Migraine threshold?
 -Red wine?
 -Caffeine withdrawal?

e.g. Sweet craving like chocolate?
 -or-
 Misattribute like MSG?

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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	+

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E

- Dehydration is associated with headache
- Unknown if rehydration reduces migraine
 - Posthoc analysis:
 - IV fluids alone did not ↓ migraine
 - One study showed benefit with 4L/day
- General health studies: 1.8L/d hydration

Robblee & Starling 2019

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E

- Caffeine
 - Nonspecific adenosine receptor antagonist
- Analgesic at 65 to 200mg
- High use = chronification of headache
- <200mg is recommended based on ICHD-3 (caffeine withdrawal headache)

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D

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			

= Bedbound
 = Reduced Function
 = No reduced Function

∇ = Abortive Medication used (Aim is <10/mo)

***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.

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S **Stress Management in Migraine** **Also consider DBT**

Biofeedback	Cognitive Behavioral Therapy	Mindfulness
<ul style="list-style-type: none"> Behavioral + Autonomic measures Types: <ul style="list-style-type: none"> EMG EEG Temperature Sweat sensors Heart rate Blood volume pulse feedback Respiration bands 	<ul style="list-style-type: none"> Thoughts & Behavioral therapy to Δemotions May aid coping? Helps mood disorders Individual or group 	<ul style="list-style-type: none"> Awareness of thoughts, feelings & sensations Present moment No judgement Mindfulness-based stress reduction (MBSR) ?Pain acceptance

Robblee & Starling 2019

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Summary

Diagnosis	Pathophysiology	Treatment
<ul style="list-style-type: none"> ICHD-3.org Don't forget: <ul style="list-style-type: none"> MOH NDPH CSF leak SNOOP4 	<ul style="list-style-type: none"> 4 phases Trigeminovascular activation 	<ul style="list-style-type: none"> Firstline orals Botox CGRP mAbs Triptans, ditans, and gepants Devices SEEDS

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Thank you!

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