Pediatric Migraine: An Update

PROJECT ECHO

May 29, 2025

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With slide credit to:

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Diclosures

Relevant relationships with commercial entities:

None

Potential for conflicts within this presentation:

None

Steps taken to review and mitigate potential bias:

We will discuss off label migraine therapies in children and adolescents.

We will only present published data on migraine medications

Learning Objectives

Recognize	Review	Apply
Recognize the scope, distribution, and burden of diagnosed and undiagnosed headache disorders and migraine in children and youth	Review updates on acute and preventive therapies in the treatment of pediatric migraine	Apply evidence-based strategies for managing and preventing disability related to migraine in children and adolescents

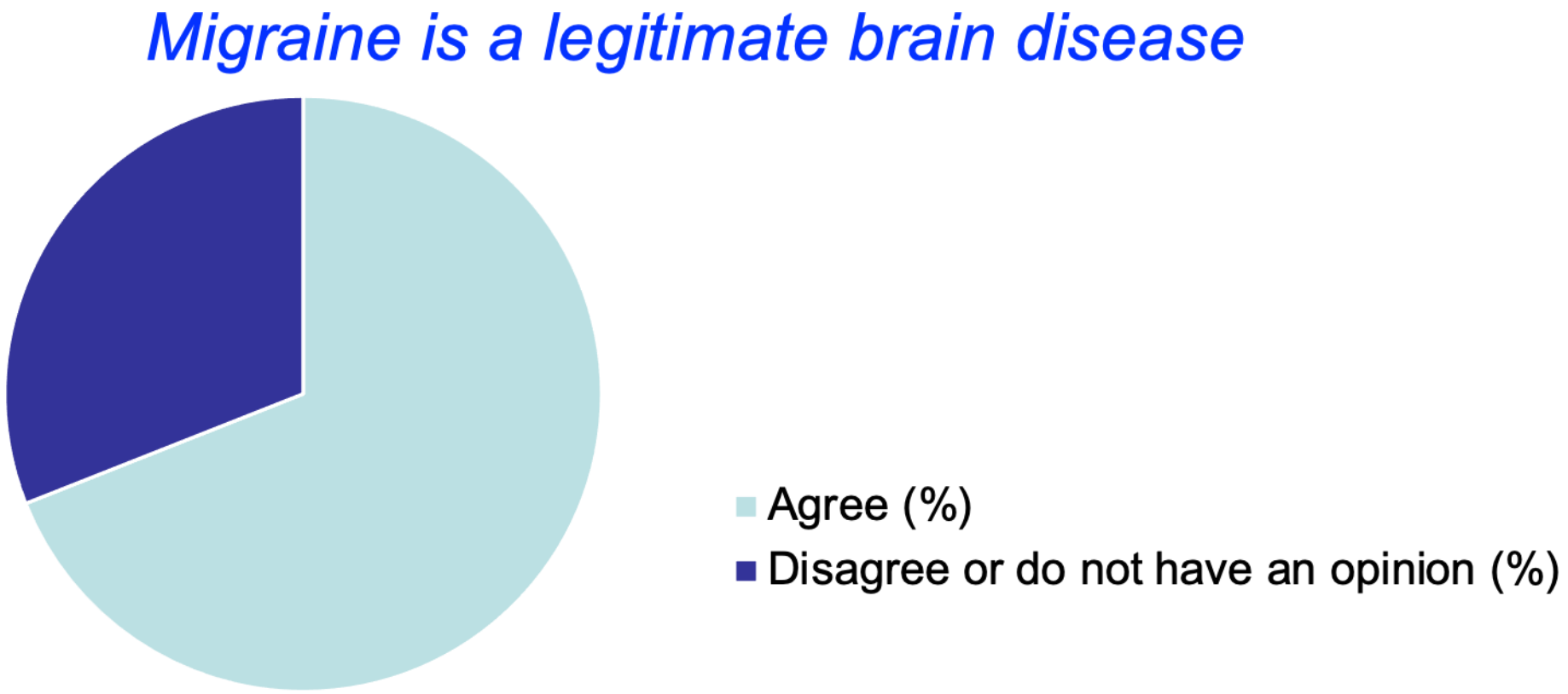
Q: I am comfortable managing children and youth with headache

A. Yes, I usually feel confident managing these patients

B. No, I usually feel uncomfortable managing these patients

C. I often feel uncertain as to how to manage these patients

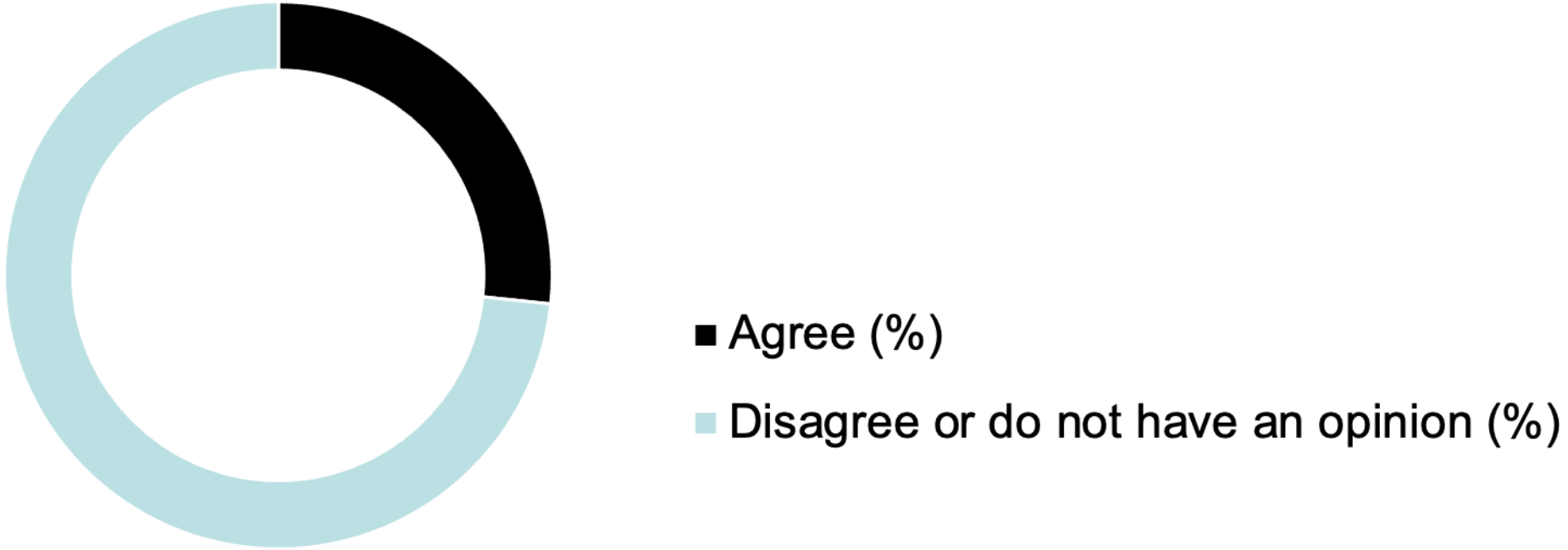
Migraine Attitudes, Knowledge, and Practice Patterns (MKAPP) Survey



Lipton et al. Neurology (2004)

Migraine Attitudes, Knowledge, and Practice Patterns (MKAPP) Survey

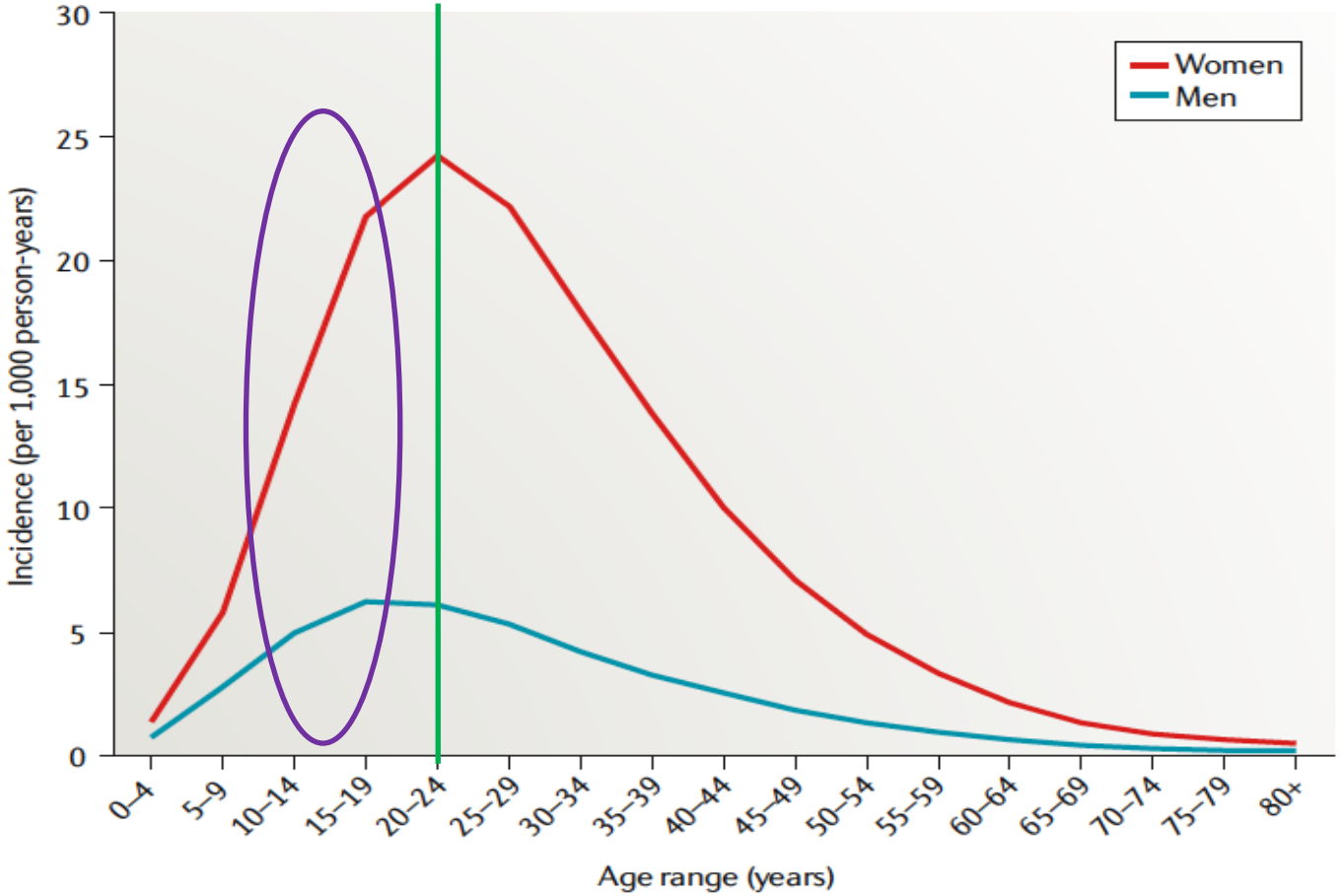
Patients with headache are motivated to maintain their disability



Lipton et al. Neurology (2004)

Migraine Incidence by Age and Gender

Orr et al. Nat Rev Neurol (2018)



Impact

- Quality of life (QoL) measure studies have likened the impact of QoL in children with migraine to that in children with **diabetes**, **arthritis**, and **cancer**

Antonaci et al. The Journal of Headache and Pain (2014)

Disability of Migraine and TTH by Age

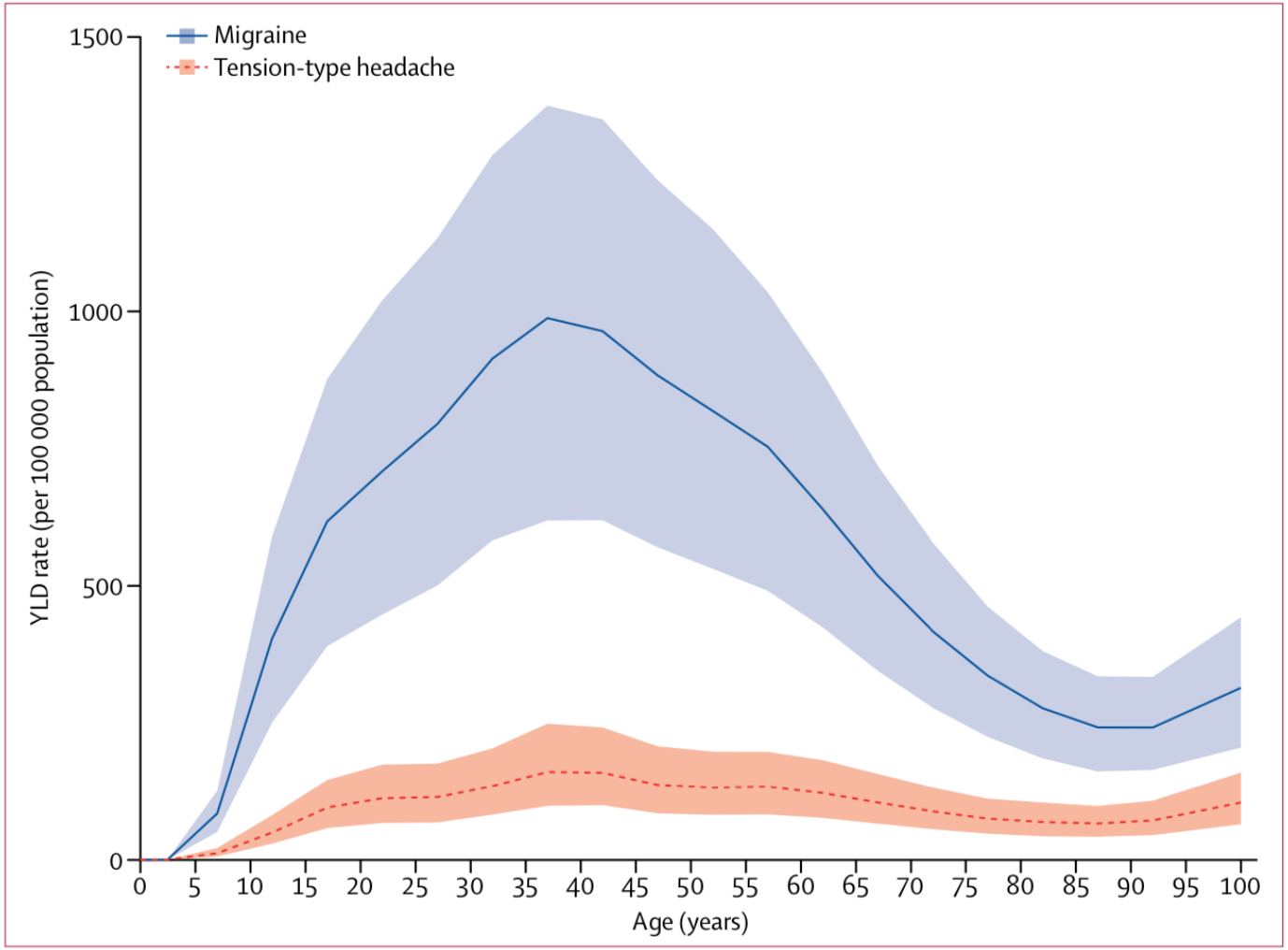


Figure 4: **Global years of life lived with disability (YLD) rate per 100 000 population due to migraine and tension-type headache by age, 2016**

Shaded areas show 95% uncertainty intervals. Values are plotted at the midpoint of 5-year age categories.

Lancet Neurology (2017)

Early Diagnosis is Neccessary

Predictor for persistent headache and chronic migraine

Shorter duration between first attack and time of diagnosis predicts better headache freedom at 1 year?

Early diagnosis and intervention improves the prognosis of migraine

Kienbacher et al. Cephalalgia (2006)
Galiski et al. Pediatric Neurology (2015)

Migraine in Children

- **Attacks can be brief** - ICHD-3 criteria define a minimum of 2 hours for
- Photo/phonophobia can be **inferred through behavior**
- 80% of children report **bilateral pain**
- Younger children have more GI presentation (**vomiting**) compared to lower children
- Aura + dizziness increase with age
- Younger children have more **symptomatic overlap with tension-type HA**

International Classification of Headache Disorders (ICHD-3)

Migraine is an episodic headache lasting 2-72 hours with:

Any 2

- ❑ unilateral (often bilateral in younger children)
- ❑ throbbing (often non-throbbing in children)
- ❑ worsened by activity
- ❑ moderate or severe

Any 1

- ❑ nausea or vomiting
- ❑ photophobia and phonophobia (often inferred from behavior)

- ❑ At least 5 attacks
- ❑ Not due to other disorder

2+1 = Migraine

IHS, ICHD-3, Cephalalgia, 2018, Vol. 38(1) 1–211

General Principles

Majority of children and youth who seek outpatient evaluation of headache will have migraine

Education as intervention

Multidisciplinary approach

Migraine Diary

Canadian Migraine Tracker

RED: I have to STOP

YELLOW: I have to SLOW down

GREEN: I can GO

3-Month Headache Diary

Month:	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	T
Headache 0/1/2/3/*																																
Period																																
Tx:																																
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Tx:																																
Effects Acute Tx:																																
Preventives																																
Notes																																

Total # of days with any acute medication intake	# of days for each HA severity				
	0	1	2	3	Tot

Month:	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	T
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Total # of days with any acute medication intake	# of days for each HA severity				
	0	1	2	3	Tot

Legend:

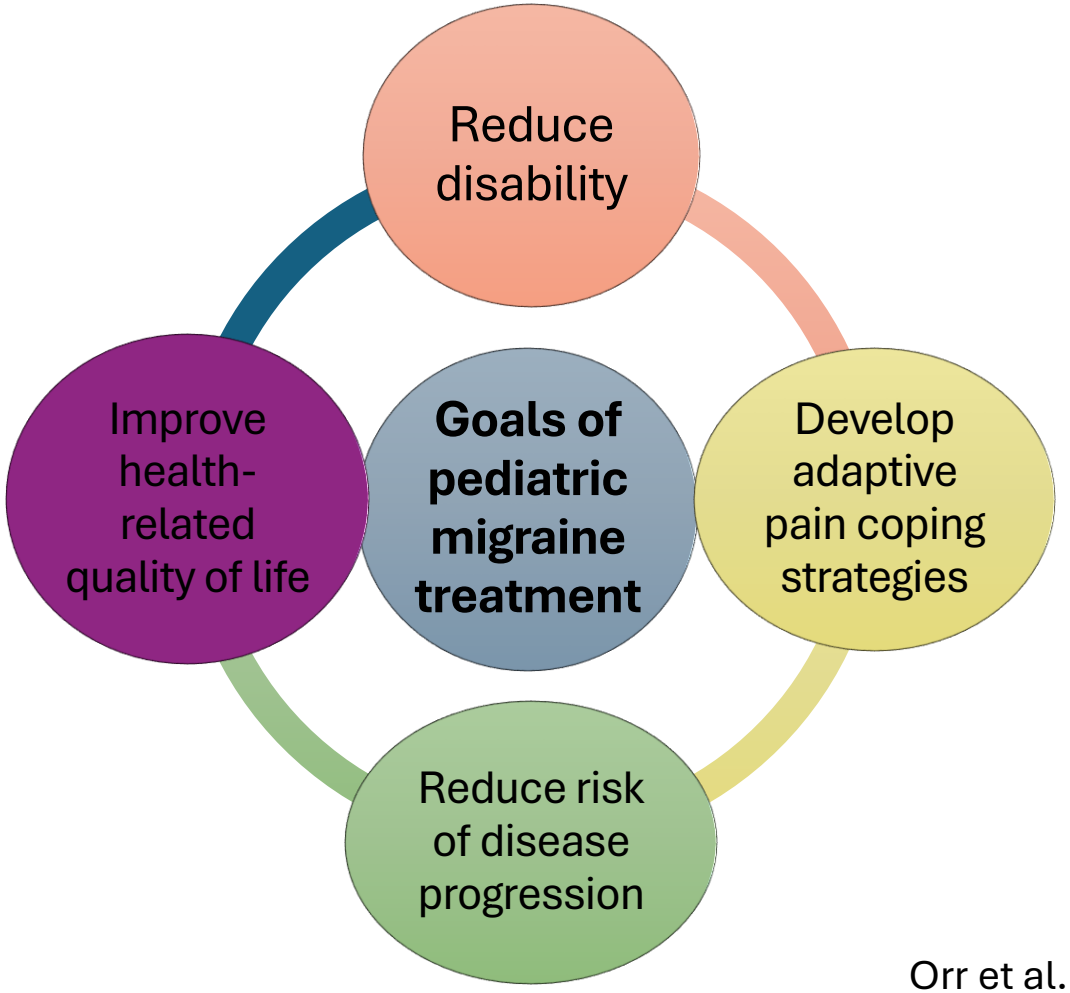
Headache severity scale:
- 0 = headache free
- 1 = mild, can function
- 2 = moderate, slowed
- 3 = severe cannot function
- * = miss work or personal activity

Effectiveness of acute tx:
- S = success
- P = partal benefit
- F = failure
- R= recurrence of HA
- E = side effects

Tx: treatment

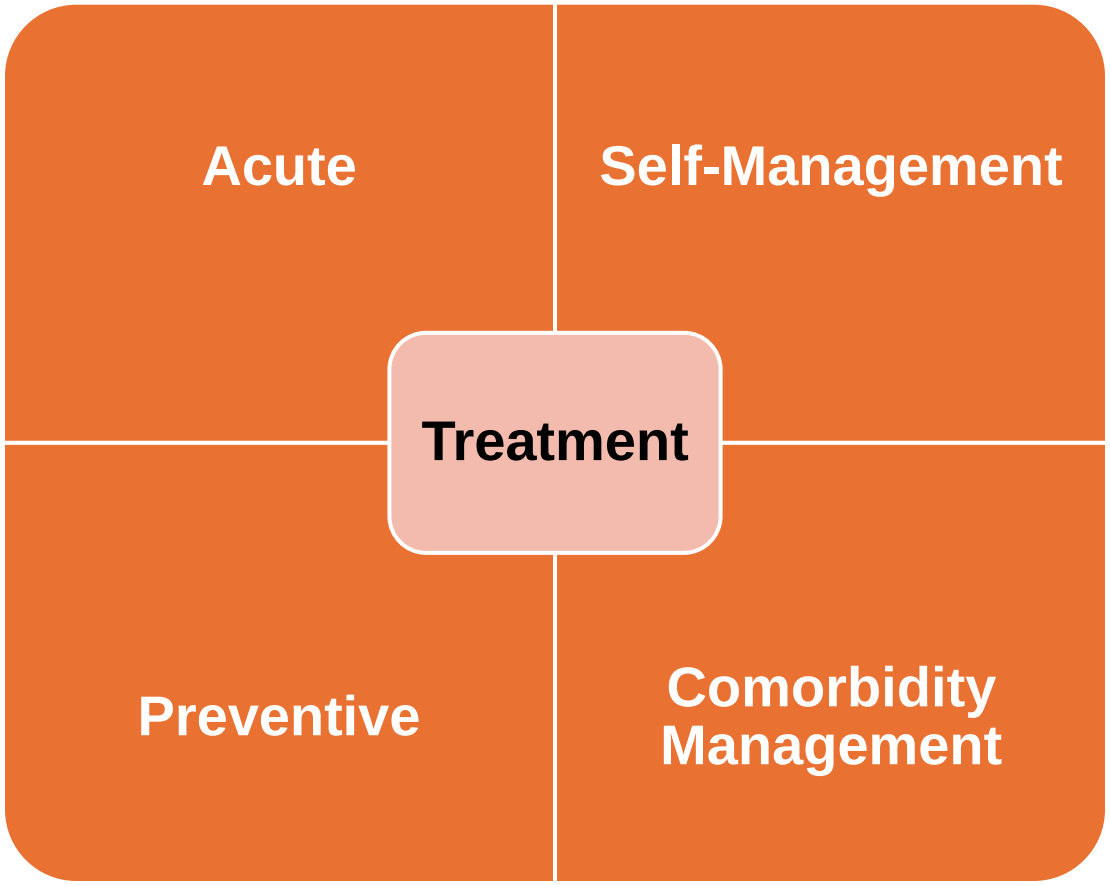
Activate Windows
Go to Settings to activate Windows.

Goals of Migraine Treatment



Orr et al. Nature Reviews Neurology (2018)

Anatomy


Acute
Self-Management
Treatment
Preventive
Comorbidity Management

CASE 1: Jorge

14y M with episodic migraine without aura since age 8

Migraine attacks: moderate to severe, bilateral frontal pressure headache

Frequency/duration: 3-4 days a month/ lasting 6-8 hours

Associated features:

- light and sound bothersome
- prefers to rest during attacks when severe
- nausea within 15 mins from headache onset

Medications: acetaminophen and ibuprofen (no longer working)

PMHx: asthma, motion sickness, infant colic

Exam: unremarkable

Q: What would you offer for acute therapy?

A. Sumatriptan nasal spray

B. Almotriptan tablet

C. Rizatriptan tablet

D. Zolmitriptan nasal spray

E. None of the above *(I am not comfortable trying any of these options)*

What are acute therapies?

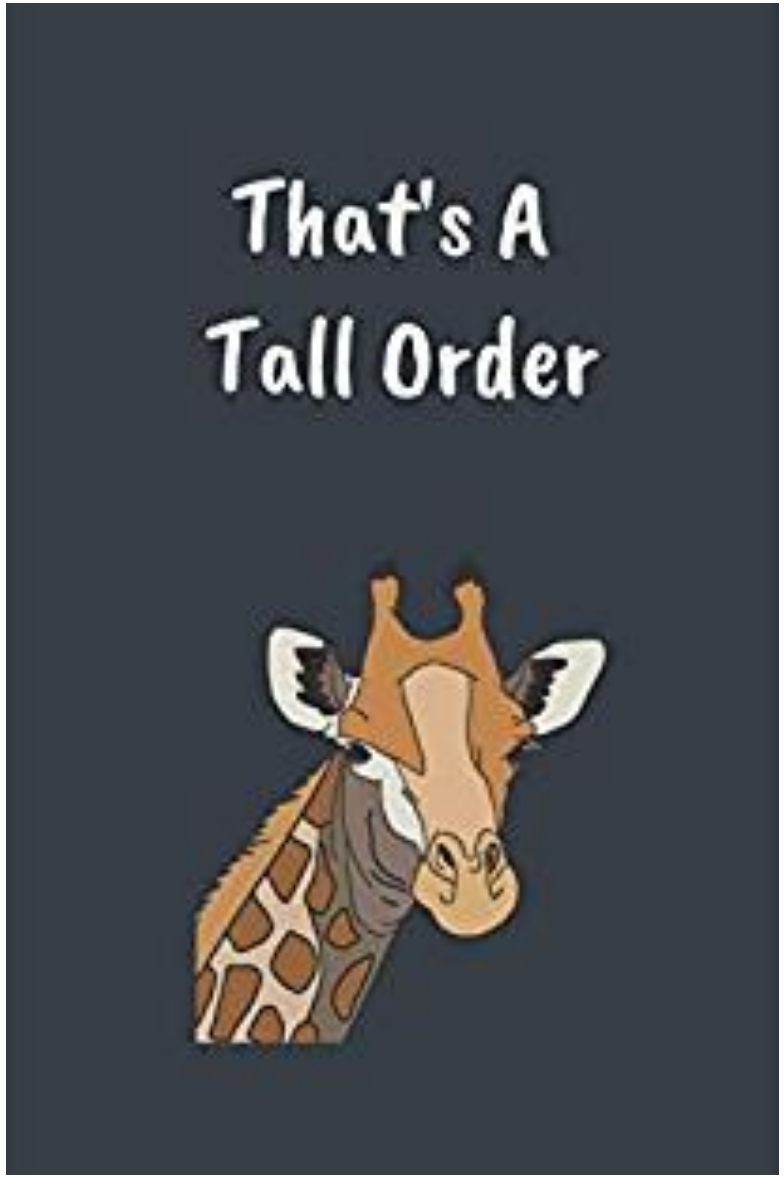
Why are they important?

- Modifiable risk factors for progression:
  - Headache frequency
  - Headache-related disability
  - **Ineffective acute treatment**
  - Opioids/barbituates
    - *Excessive opioid use is a risk factor for migraine progression to chronic migraine*

Bigal et al. Headache (2008)
Lipton et al. Neurology (2015)

Effective acute treatment

- Rapid and consistent freedom from pain and most bothersome symptoms (MBS) without recurrence
- Restored ability to function
- Minimal need for repeat dosing or rescue medications
- Optimal self-care and reduced subsequent use of resources (e.g. ED visits)
- Minimal or no adverse effects



American Headache Society. Headache (2019)

Challenges

- Heterogeneous population
- Difficulty with case definitions
- Outcome measures
- Confounders, confounders, confounders
- Placebo/ nocebo effects

Where to start?

Stratified care

- Severity
- Onset
- Associated symptoms/ MBS
- Duration of attacks

RED: I have to STOP

YELLOW: I have to SLOW down

GREEN: I can GO

Lagman-Bartolome et al. Headache (2019)

Acute Treatment in Pediatric Migraine: Stratified Approach

Traffic Light of Migraine Action Plan (TRALI-MAP)

How to choose your acute/rescue medication?

I have to **STOP**

RED
Or
Headache upon waking up in AM

TRIPTAN 1st dose → (2-4 hours*; Red Yellow) → TRIPTAN 2nd dose (Red Yellow Green)

\+

NSAID 1st dose → (_____ hours**; Green) → NSAID 2nd dose

I have to **SLOW** down

YELLOW

TRIPTAN 1st dose → (15-30 mins; Red Yellow Green) → NSAID 1st dose (Green)

TRIPTAN 1st dose → (2-4 hours*; Red/Yellow) → TRIPTAN 2nd dose

____ hours** → NSAID 2nd dose (Red Yellow Green)

I can **GO**

GREEN

NSAID 1st dose → (15-30 mins; Red Yellow) → TRIPTAN 1st dose

NSAID 1st dose → (____ hours**; Green) → NSAID 2nd dose

2-4 hours* → TRIPTAN 2nd dose (Red/Yellow)

TRIPTAN 2nd dose → NSAID 2nd dose (Red Yellow Green)

Lagman-Bartolome AM, Lay C.Headache.2019;59(2):250-252. doi: 10.1111/head.13428. Epub 2018 Oct 27. PMID: 30367814.

Medications	Level of Recommendation	DOSE (mg)		Age (years)
TRIPTANS	**2019 AAN Guidelines**	<40 kg	≥40 kg	
Sumatriptan	**B** (nasal)	5 mg	10-20 mg	≥12
	tablet	12.5-25 mg (0.06 mg/kg/dose)	50-100 mg	≥12
	SQ inj	0.1 mg/kg	4-6 mg	-
Sumatriptan+Naproxen	**B** (tablet)	10/85 mg	85/500 mg	≥12 (FDA)
Almotriptan	**B** (tablet)	6.25	12.5 mg	≥12 (FDA/HC)
Zolmitriptan	**B** (nasal)	2.5 mg	5 mg	≥12 (FDA)
	melt, tablet	2.5 mg	5 mg	-
Rizatriptan	**B** (ODT)	5 mg	10 mg	≥6 (FDA)
NSAIDs				
Ibuprofen	**B**	10 mg/kg/dose	800	Any age
Anti-emetics	**B**			

NSAIDs

Ibuprofen 7. 5 – 10 mg/kg as first line in children

Other NSAIDs with efficacy shown in adult studies also used in:

(i) Children - naproxen (liquid formulation available), indomethacin (caution- GI)

(ii) Adolescents – CAMBIA (diclofenac), mefenamic acid, nabumetone…

Triptans

- **PO:**
  - Sumatriptan/Naproxen
  - Rizatriptan *
  - Almotriptan
- **IN:**
  - Sumatriptan
  - Zolmitriptan
- Safety demonstrated for Eletriptan + Sumatriptan, Zolmitriptan PO
- Pharmacokinetic data available for long-acting triptans (Frovatriptan, Naratriptan)

	Route	Notes
Sumatriptan	PO, IN, SC	• Biggest dose range (25mg, 50mg, 100mg PO; 5mg, 20mg NS) • Oldest- “first generation”- tends to have more SE
Zolmitriptan	PO (+ODT), IN	• 2.5 mg PO, 5 mg IN • IN typically tolerated better vs Suma IN
Eletriptan	PO	• 20 mg, 40 mg • Reduced recurrence within 24h • Potent
Rizatriptan	PO (+ODT)	• 5 mg, 10 mg • “Gateway triptan” • Quick onset of action (PO Tmax 1h) • Well tolerated
Almotriptan	PO	• 6.25 mg, 12.5 mg • Most SE neutral
Naratriptan	PO	• Long acting • Well tolerated

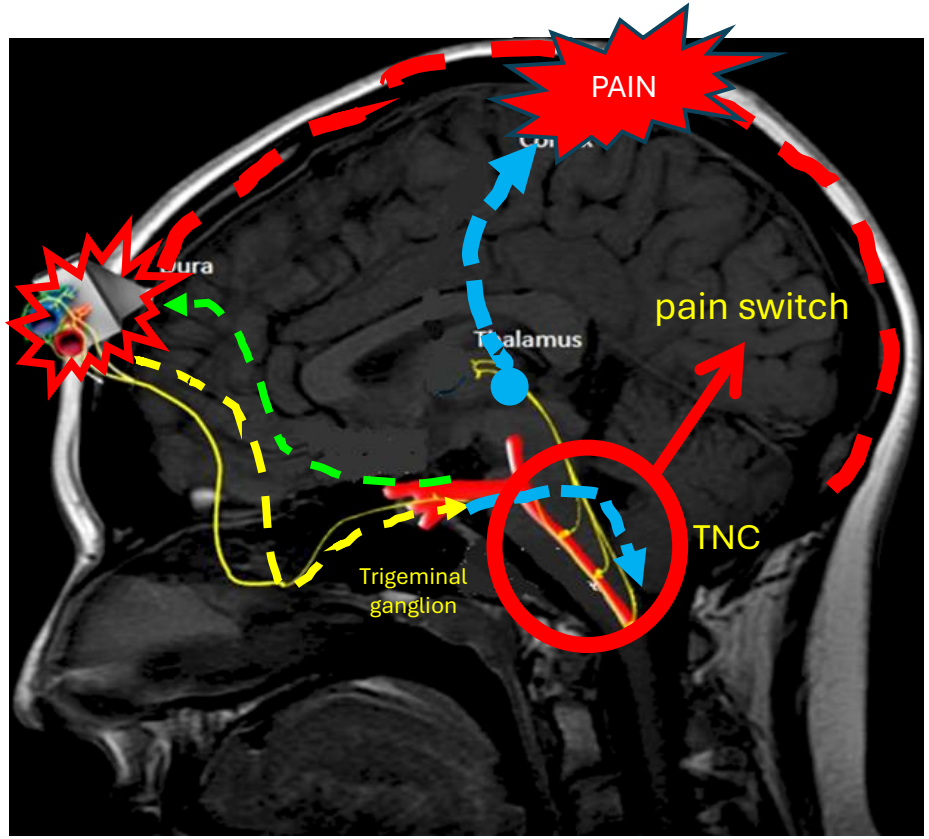
Anti-emetics

- Dopamine (D2) antagonists may help with nausea + symptoms of migraine
  - Metoclopramide- PO
  - Prochlorperazine- PO/PR
  - Promethazine- PO/PR
- Monitor for akathisia, EPS
  - Benadryl PRN
- Specific anti-emetics may also be used (e.g Ondansetron)

Timing Matters

Treatment success drops from 80% to 50% as central sensitization occurs within 30-60 minutes from attack onset

TGVS activation[2]



CSD[1]

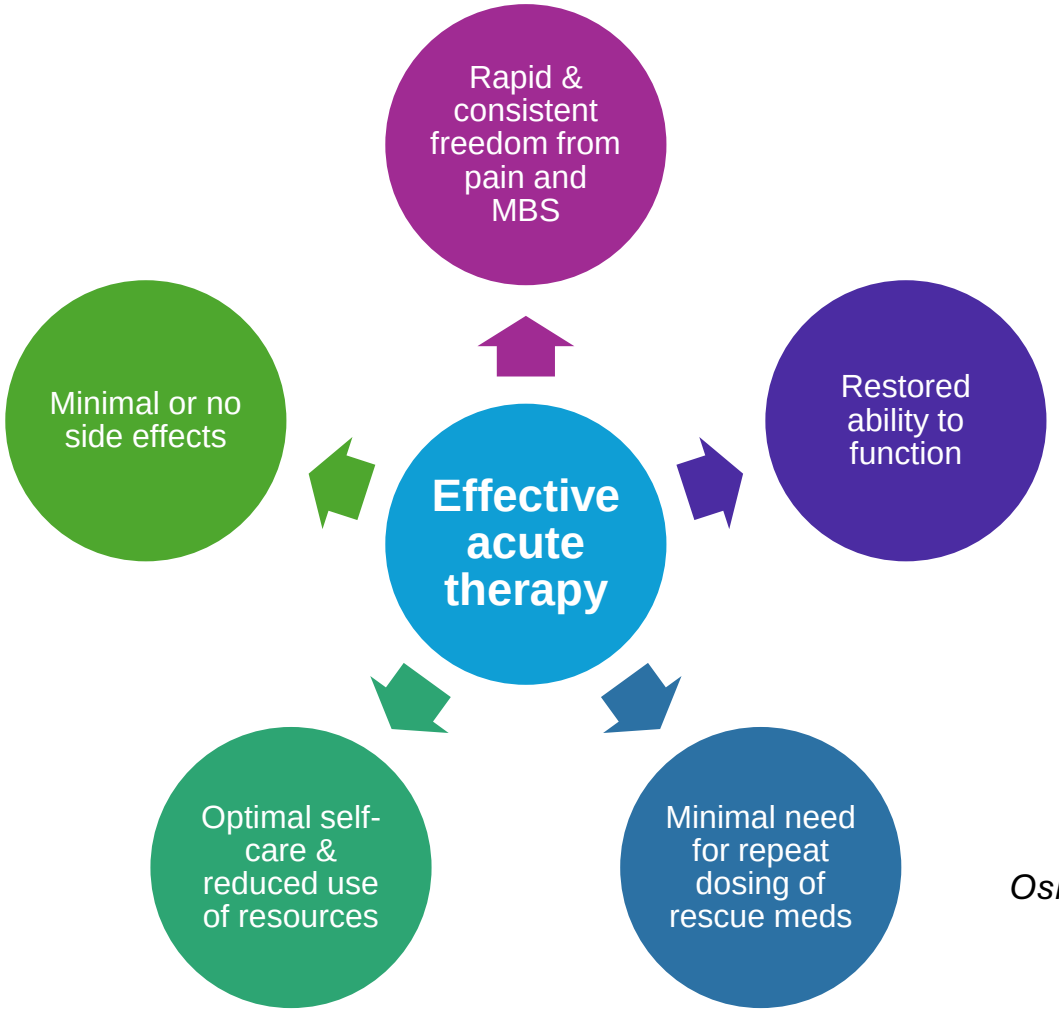
Early treatment

- greater % of patients achieving a 2-hour pain-free response (60% vs 32%)[3]
- lower recurrence rate (13% vs 33%)
- lower adverse event rate (14% vs 29%)

TGVS: Trigeminovascular system
CSD: cortical spreading depression
TNC: trigeminal nucleus caudalis

1. Pietrobon D et al. Nat Rev Neuro. (2003)
2. Goadsby. Headache. (2005).

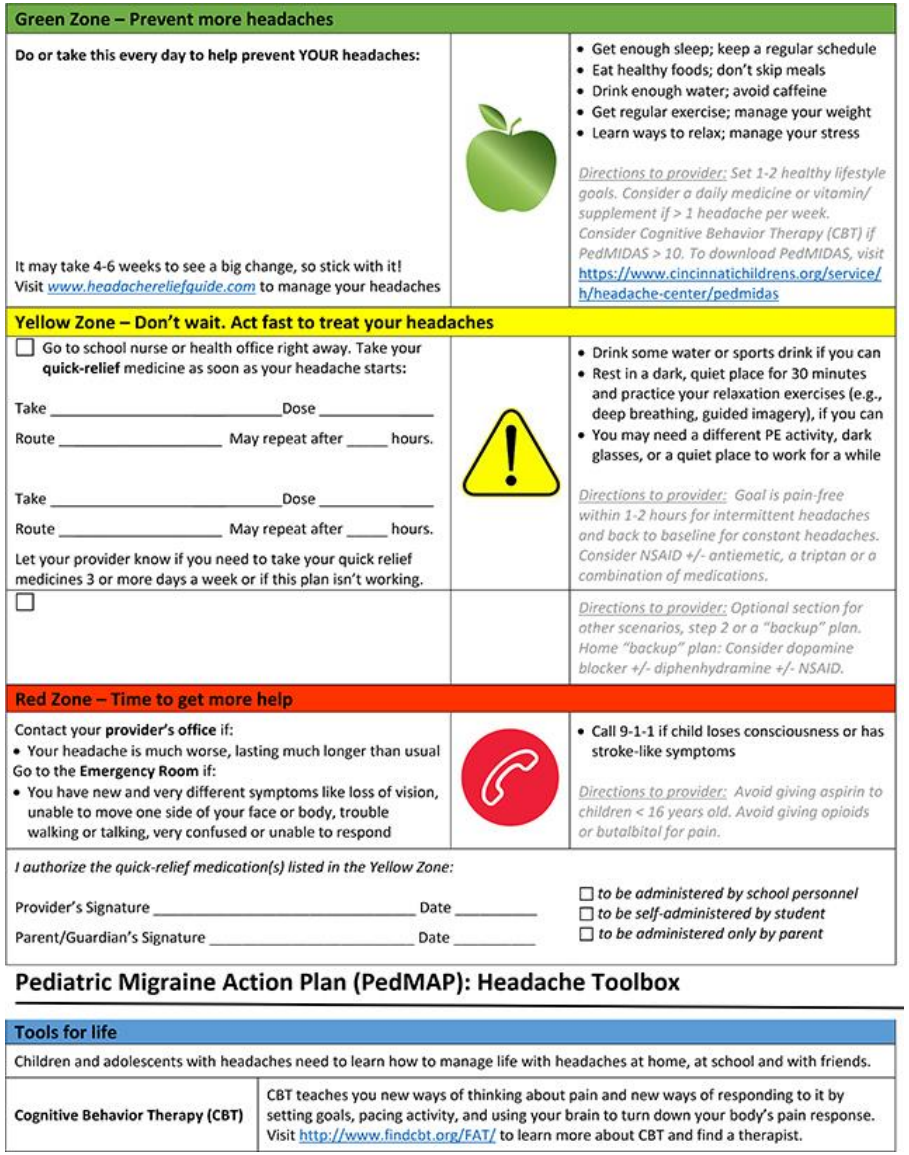
When do you consider acute treatment effective?



Oskoui et al. Headache (2019)

Resource

- Pediatric Migraine Action Plan - *headachejournal.onlinelibrary.wiley.com/doi/epdf/10.1111/head.13681*



Green Zone – Prevent more headaches

Do or take this every day to help prevent YOUR headaches:

- Get enough sleep; keep a regular schedule
- Eat healthy foods; don't skip meals
- Drink enough water; avoid caffeine
- Get regular exercise; manage your weight
- Learn ways to relax; manage your stress

Directions to provider: Set 1-2 healthy lifestyle goals. Consider a daily medicine or vitamin/ supplement if > 1 headache per week. Consider Cognitive Behavior Therapy (CBT) if PedMIDAS > 10. To download PedMIDAS, visit https://www.cincinnatichildrens.org/service/h/headache-center/pedmidas

It may take 4-6 weeks to see a big change, so stick with it!
Visit *www.headachereliefguide.com* to manage your headaches

Yellow Zone – Don't wait. Act fast to treat your headaches

☐ Go to school nurse or health office right away. Take your **quick-relief** medicine as soon as your headache starts:

Take _____ Dose _____
Route _____ May repeat after ____ hours.

Take _____ Dose _____
Route _____ May repeat after ____ hours.

Let your provider know if you need to take your quick relief medicines 3 or more days a week or if this plan isn't working.

- Drink some water or sports drink if you can
- Rest in a dark, quiet place for 30 minutes and practice your relaxation exercises (e.g., deep breathing, guided imagery), if you can
- You may need a different PE activity, dark glasses, or a quiet place to work for a while

Directions to provider: Goal is pain-free within 1-2 hours for intermittent headaches and back to baseline for constant headaches. Consider NSAID +/- antiemetic, a triptan or a combination of medications.

☐

Directions to provider: Optional section for other scenarios, step 2 or a "backup" plan. Home "backup" plan: Consider dopamine blocker +/- diphenhydramine +/- NSAID.

Red Zone – Time to get more help

Contact your **provider's office** if:
- Your headache is much worse, lasting much longer than usual

Go to the **Emergency Room** if:
- You have new and very different symptoms like loss of vision, unable to move one side of your face or body, trouble walking or talking, very confused or unable to respond

- Call 9-1-1 if child loses consciousness or has stroke-like symptoms

Directions to provider: Avoid giving aspirin to children < 16 years old. Avoid giving opioids or butalbital for pain.

I authorize the quick-relief medication(s) listed in the Yellow Zone:

Provider's Signature _____ Date _____
Parent/Guardian's Signature _____ Date _____

☐ *to be administered by school personnel*
☐ *to be self-administered by student*
☐ *to be administered only by parent*

Pediatric Migraine Action Plan (PedMAP): Headache Toolbox

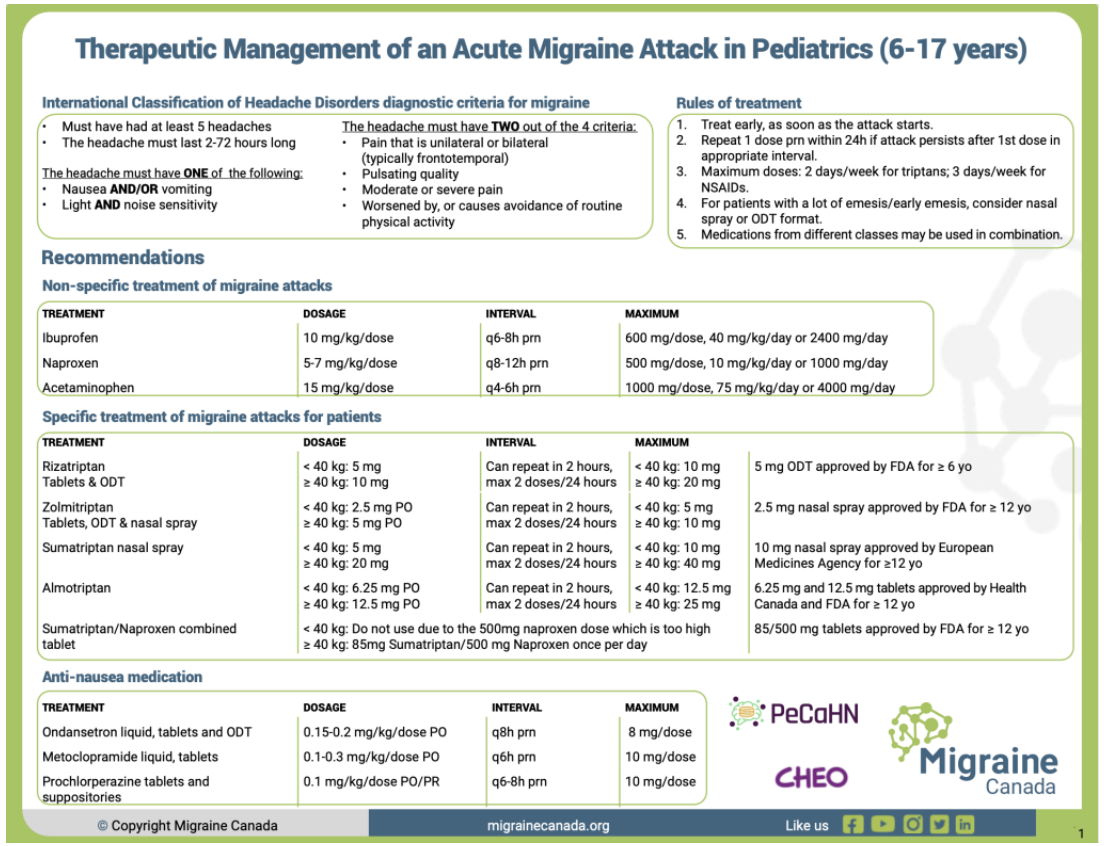
Tools for life

Children and adolescents with headaches need to learn how to manage life with headaches at home, at school and with friends.

Cognitive Behavior Therapy (CBT)	CBT teaches you new ways of thinking about pain and new ways of responding to it by setting goals, pacing activity, and using your brain to turn down your body's pain response. Visit http://www.findcbt.org/FAT/ to learn more about CBT and find a therapist.

Resource

- Therapeutic Management of Acute Migraine in Pediatrics (PeCaHN) - *https://migrainecanada.org/medication-dosing-advice/*



Therapeutic Management of an Acute Migraine Attack in Pediatrics (6-17 years)

International Classification of Headache Disorders diagnostic criteria for migraine

- Must have had at least 5 headaches
- The headache must last 2-72 hours long

The headache must have **ONE** of the following:

- Nausea **AND/OR** vomiting
- Light **AND** noise sensitivity

The headache must have **TWO** out of the 4 criteria:

- Pain that is unilateral or bilateral (typically frontotemporal)
- Pulsating quality
- Moderate or severe pain
- Worsened by, or causes avoidance of routine physical activity

Rules of treatment

1. Treat early, as soon as the attack starts.
2. Repeat 1 dose prn within 24h if attack persists after 1st dose in appropriate interval.
3. Maximum doses: 2 days/week for triptans; 3 days/week for NSAIDs.
4. For patients with a lot of emesis/early emesis, consider nasal spray or ODT format.
5. Medications from different classes may be used in combination.

Recommendations

Non-specific treatment of migraine attacks

TREATMENT	DOSAGE	INTERVAL	MAXIMUM
Ibuprofen	10 mg/kg/dose	q6-8h prn	600 mg/dose, 40 mg/kg/day or 2400 mg/day
Naproxen	5-7 mg/kg/dose	q8-12h prn	500 mg/dose, 10 mg/kg/day or 1000 mg/day
Acetaminophen	15 mg/kg/dose	q4-6h prn	1000 mg/dose, 75 mg/kg/day or 4000 mg/day

Specific treatment of migraine attacks for patients

TREATMENT	DOSAGE	INTERVAL	MAXIMUM	
Rizatriptan Tablets & ODT	< 40 kg: 5 mg ≥ 40 kg: 10 mg	Can repeat in 2 hours, max 2 doses/24 hours	< 40 kg: 10 mg ≥ 40 kg: 20 mg	5 mg ODT approved by FDA for ≥ 6 yo
Zolmitriptan Tablets, ODT & nasal spray	< 40 kg: 2.5 mg PO ≥ 40 kg: 5 mg PO	Can repeat in 2 hours, max 2 doses/24 hours	< 40 kg: 5 mg ≥ 40 kg: 10 mg	2.5 mg nasal spray approved by FDA for ≥ 12 yo
Sumatriptan nasal spray	< 40 kg: 5 mg ≥ 40 kg: 20 mg	Can repeat in 2 hours, max 2 doses/24 hours	< 40 kg: 10 mg ≥ 40 kg: 40 mg	10 mg nasal spray approved by European Medicines Agency for ≥12 yo
Almotriptan	< 40 kg: 6.25 mg PO ≥ 40 kg: 12.5 mg PO	Can repeat in 2 hours, max 2 doses/24 hours	< 40 kg: 12.5 mg ≥ 40 kg: 25 mg	6.25 mg and 12.5 mg tablets approved by Health Canada and FDA for ≥ 12 yo
Sumatriptan/Naproxen combined tablet	< 40 kg: Do not use due to the 500mg naproxen dose which is too high ≥ 40 kg: 85mg Sumatriptan/500 mg Naproxen once per day			85/500 mg tablets approved by FDA for ≥ 12 yo

Anti-nausea medication

TREATMENT	DOSAGE	INTERVAL	MAXIMUM
Ondansetron liquid, tablets and ODT	0.15-0.2 mg/kg/dose PO	q8h prn	8 mg/dose
Metoclopramide liquid, tablets	0.1-0.3 mg/kg/dose PO	q6h prn	10 mg/dose
Prochlorperazine tablets and suppositories	0.1 mg/kg/dose PO/PR	q6-8h prn	10 mg/dose

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Back to CASE 1: Jorge

6 months later:

- *Migraine attacks:* no change over the past 6 months, persist at frequency of 3-4 days a month and can last up to a full day
- +++ severe and nausea within 10-15 mins from headache onset
- *Medications*: sumatriptan and zolmitriptan NS, almotriptan, rizatriptan, naproxen (no response, persistent vomiting with attacks)
- *Exam*: unremarkable

Q: What would you offer for acute therapy?

A. Lidocaine nasal spray

B. CGRP antagonists (oral gepants)

C. Neuromodulation device

D. Nerve block

E. None of the above *(I am not comfortable trying any of these options)*

The landscape is changing

- Rethinking known targets
- Evaluating new targets
- Advancing technology

Paediatrics & Child Health, 2022, XX, 1–6
https://doi.org/10.1093/pch/pxac054
Original Article

OXFORD

Original Article

A randomized controlled pilot study of intranasal lidocaine in acute management of paediatric migraine and migraine-like headache

Kate Maki MD[1], Quynh Doan MDCM[1,2], Kendra Sih PharmD[1], Karly Stillwell BSc[2], Alaina Chun BSc[2], Garth Meckler MDS[1,2]

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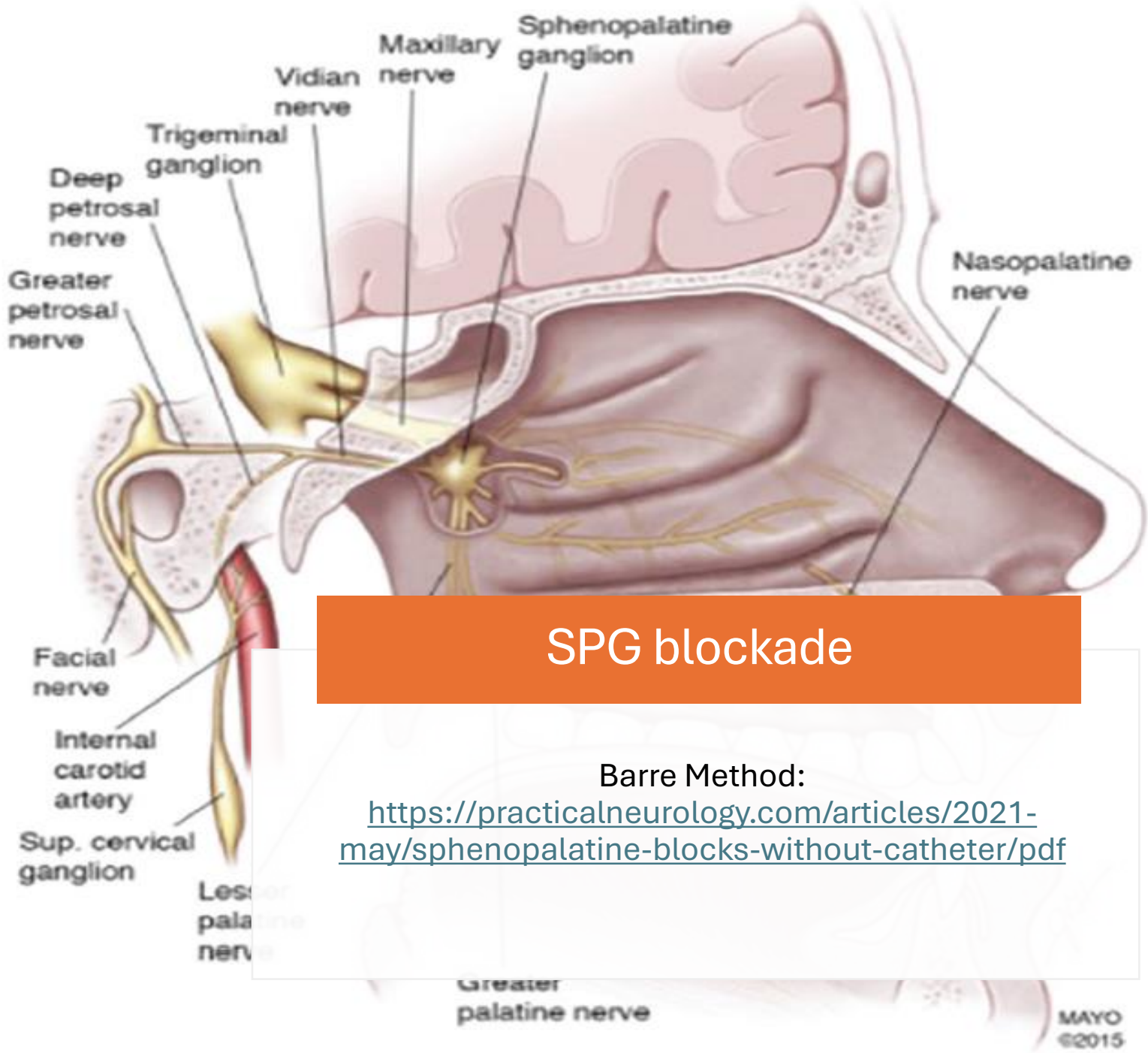


SPG blockade

Barre Method:
https://practicalneurology.com/articles/2021-may/sphenopalatine-blocks-without-catheter/pdf

Triptan/ NSAID Combination

- **Sumatriptan + naproxen 85/500 mg**
  - Approved by FDA in 2008
  - Approved by Health Canada in September 2020
  - For acute migraine treatment in adults and adolescents (ages 12-17)
    - Pain free at 2h: 24% vs 10% (37 % vs 18%, adolescents)
    - Significant improvement of nausea, photophobia, phonophobia at 2h

Derosier et al. Pediatrics (2012)

CASE 2: Nina

17y F athlete with infrequent migraine without aura since age 12

- Jan 2024: gradual increase in headache frequency to 5 days a week (duration: 4-12 hours)
- Headache **RED** flags: none
- Recent diagnosis of depression

- **Previous trialed headache medications:** ibuprofen, naproxen, almotriptan, zolmitriptan, sumatriptan, rizatriptan

- **Current medications:** sumatriptan-naproxen
- Exam: unremarkable

When do you start migraine preventive treatment?

- **Consider and discuss preventive treatment in pediatric migraine patients with the following:**
  - frequent headache (>4 headache days a month or 3-4 migraine attacks a month for ≥3 months) and migraine-related disability (PedMIDAS score ≥30) or both **(Level B)**
  - medication overuse (taking triptans, ergot, opioids and combination analgesics > 9 days/months or taking OTC analgesics >14 days/month for ≥3 months **(Level B)**

Oskoui et al. Neurology (2019)

How do we counsel about preventive medications?

Shared decision making

Inform patients and caregivers: Majority of preventive meds are NOT superior to placebo in all comers **(Level B)**[1]

Setting expectations:

1. Treatment trials are typically for minimum of 2 months **(Level B)**
2. Goal is to **decrease headache burden**

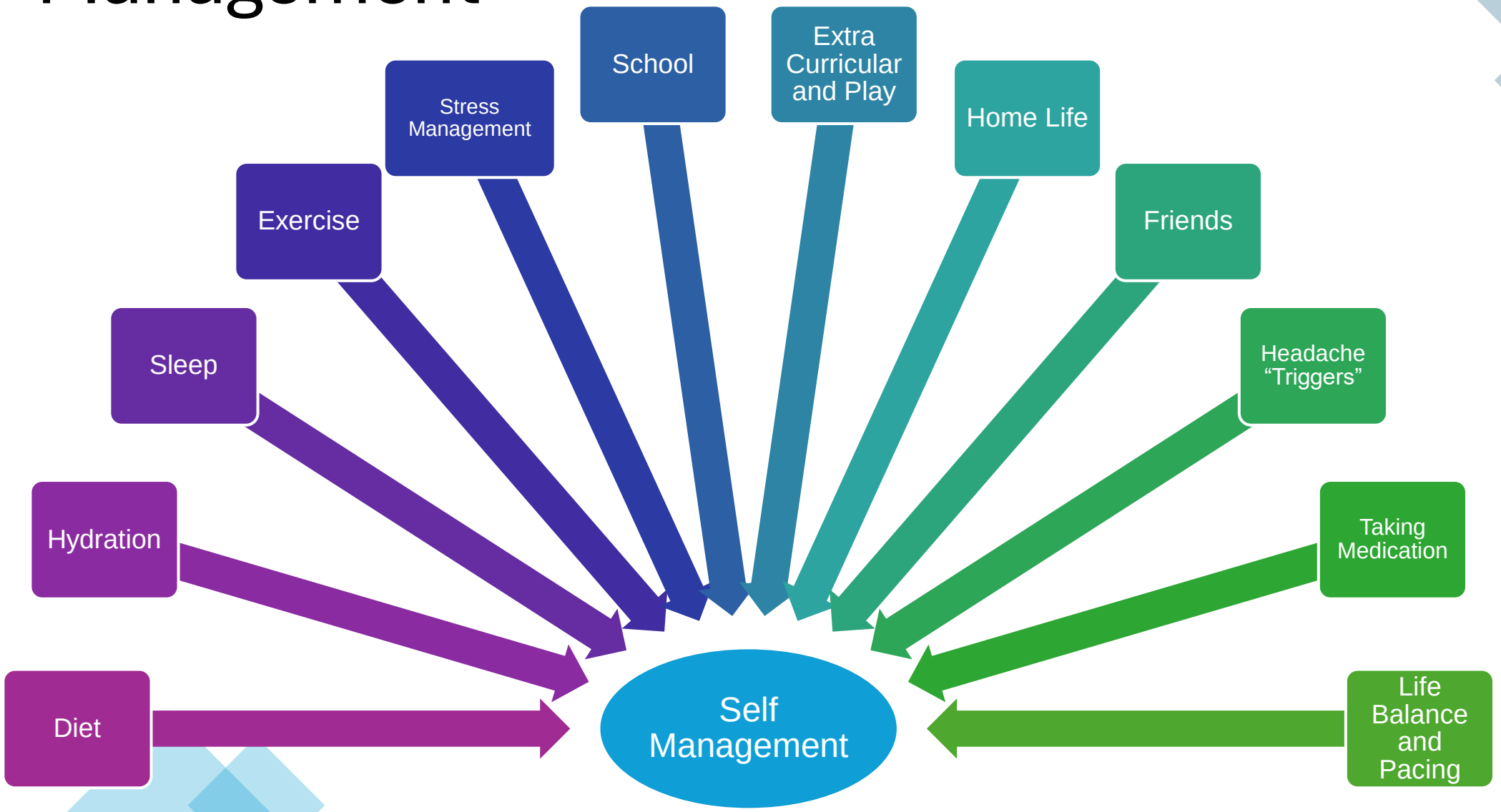
Nina is asking if we can start with non-prescription therapies

Nutraceutical	Recommendation	Strength	Level of evidence
Coenzyme Q10	Use	Weak	Low
Magnesium	Use	Weak	Low
Butterbur	Do not use	Strong	Low
Other petasites formulations	Do not use	Strong	Low
Polyunsaturated fats	Do not use	Weak	Low
Ginkgolide B	Do not use	Weak	Low
Riboflavin (Vitamin B2)	Do not use	Weak	Low

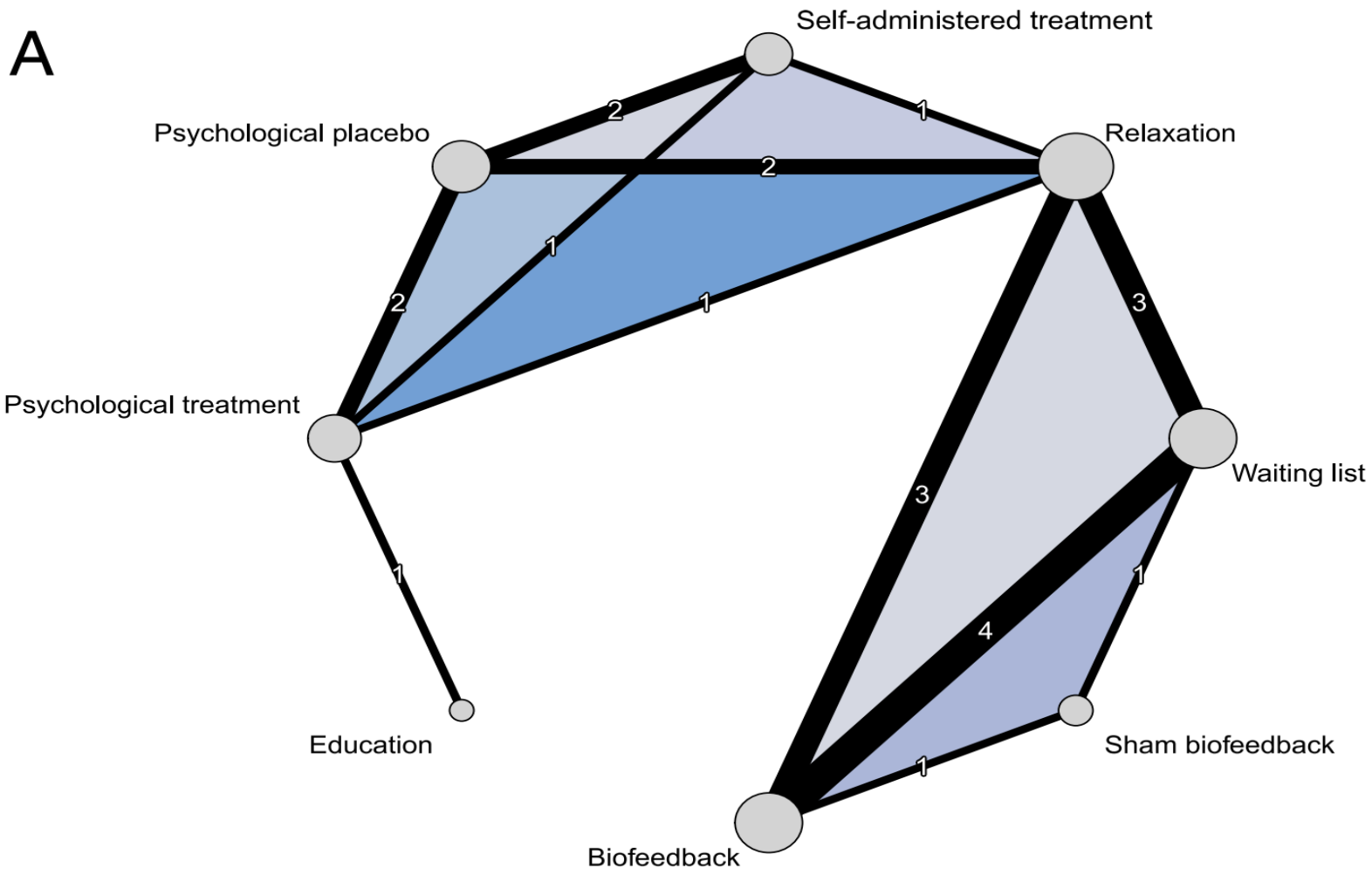
New kids on the block: Melatonin, Vitamin D, Palmitoylethanolamide (PEA)

Orr . Curr Pain Headache Rep (2018)

Self-Management



Psychological Interventions



N=12 RCTs of children and adolescents with migraine comparing non-pharm intervention to control/another non-pharm intervention

Koechlin et al. Pediatrics (2021)

Mind-body therapies and their potential application in migraine in paediatric age.

	Biofeedback	Cognitive Behavioural Therapy	Mindfullness
Mechanism of action	Pain management, improving self-regulation and the development of coping strategies	Dysfunction of multiple brain areas (prefrontal cortex, midcingulate cortex, thalamus, amygdala) or enhanced behavioural reactions to stimuli including pain or stress.	Reduction of pro-inflammatory cytokines and interleukin, augmentation in telomerase activity and downregulation of inflammatory response genes
Efficacy in the management of migraine	Significant decrease in headache attacks frequency and medications assumption	Attacks frequency decrease; disability and life quality improvement; depression and anxiety symptoms reduction	Management of primary headache and chronic pain

Baglioni et al. Journal of Clin Med (2024)

Back to CASE 2: Nina

- Trialed Magnesium citrate and Coenzyme Q10 for 3 months. Completed a block of CBT
- Partial response: 15 days a month (less disabling) + some improvement in mood

What is your next step?

Goals for preventive treatment

≥ 50% ↓ in frequency

AND/OR

≤ 4 days/month

2019 AAN/AHS Pediatric Migraine Treatment [1]

Level B recommendation

Propranolol
Topiramate
Amitriptyline + CBT

Off label treatment[2]:

Onabotulinum toxin A
Venlafaxine
Duloxetine
Candesartan
Cinnarizine
Valproic acid
Gabapentin
Flunarizine
Cyproheptadine
Nadolol/Metoprolol

Oskoui et al. AAN/AHS Guideline Neurology (2019)
Szperka . Headache. Continuum (2021)

Q: What preventive therapy would you consider?

A. Amitriptyline

B. Propranolol

C. Topiramate

D. Onabotulinum toxin A

E. None of the above *(I am not comfortable starting any of the above medications for this patient)*

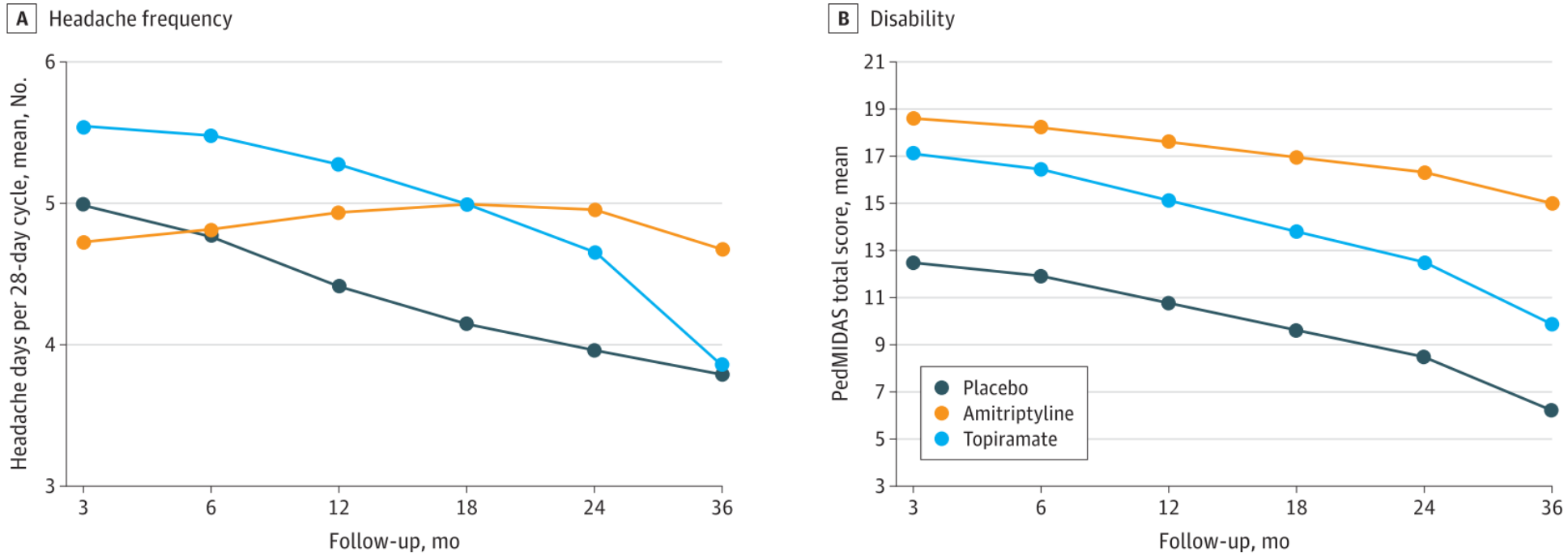
Depression	Venlafaxine*, Sertraline*, Duloxetine*	B-blockers, Topiramate, Amitriptyline (? increased suicidal risk in adolescents)
Anxiety	Amitriptyline, Venlafaxine*, Propranolol, Gabapentin*	Sertraline* (lower doses may worsen anxiety)
Sleep disturbance	Amitriptyline, Gabapentin*, Melatonin, Cyproheptadine*	Topiramate
Obesity	Topiramate, Candesartan*	Amitriptyline, Valproate, Cyproheptadine*
Epilepsy	Topiramate, Valproate*, Gabapentin*	

*Off-label use

Tips on how to choose the “right” preventative treatment for your patient

1. D'Amico D, Tepper SJ. *Neuropsychiatr Dis Treat*. 2008;4(6):1155-67 2. Pary R, et al. Managing bipolar depression. *Psychiatry* (Edgmont). 2006;3(2):30-41 3. Engmann B. Case Rep Med. 2012;2012:389851. 4. Cascade E, et al. *Psychiatry* (Edgmont). 2008;5(10):20-2 5. UpToDate. Headache, migraine, and stroke. Available at: https://www.uptodate.com/contents/headache-migraine-and-stroke. Accessed August 28, 2017. 6. National Headache Foundation. Aspirin and Migraine. Available at: http://www.headaches.org/2007/10/25/aspirin-and-migraine/. Accessed August 28, 2017. 7. Antonaci F, et al. Springerplus. 2016;5:637 8. Evans RW, et al. Headache. 2012;52(4):663-71
9. Bigal ME, et al. Epilepsy Behav. 2003;4 Suppl 2:S13-24

Figure. Results From Longitudinal Growth Curve Analyses at 3, 6, 12, 18, 24, and 36 Months for Headache Days and Disability



Prognosis with Pill-Based Rx

Powers SW. JAMA Netw Open 2021;4(7):e2114712

When do you taper off a preventive medication?

Monitor for medication effectiveness and side effects

Stop once good migraine control is established for 6-12 months[2] (Level B)[1]

1. Oskoui et al. AAN/AHS Guideline Neurology (2019)
2. Powers. JAMA Netw Open (2021)

CASE 2: Nina

1-year later

- Headache frequency: daily and constant
- 70% ++ migraine features
- No headache RED flags

Previous trialed headache medications:

- ACUTE: ibuprofen, naproxen, diclofenac, almotriptan, zolmitriptan, sumatriptan, rizatriptan
- PREVENTIVE: topiramate and amitriptyline (worsened depression), gabapentin, nadolol, flunarizine

Current medications:

- ACUTE: sumatriptan-naproxen, lidocaine NS, Cefaly (partial response)
- PREVENTIVE: venlafaxine 150 mg/day

Exam: unremarkable

Q: What else can be trialed?

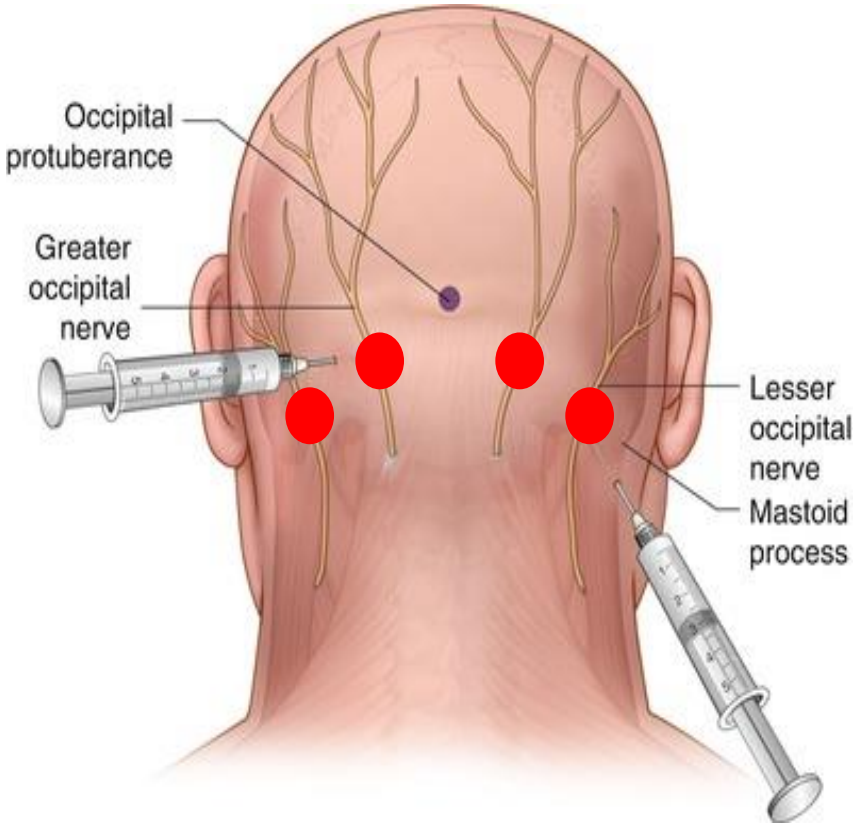
A. CGRP targeted therapy

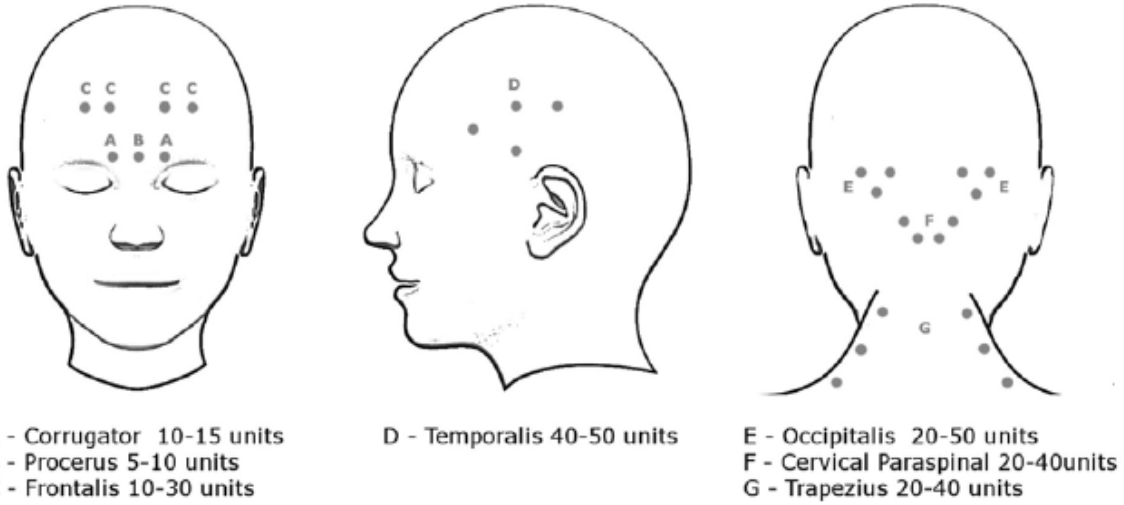
B. Neuromodulation therapy

C. Onabotulinum toxin A

D. Monthly pericranial nerve blocks

E. None of the above *(I am not comfortable starting this patient with any of the above options)*





A - Corrugator 10-15 units
B - Procerus 5-10 units
C - Frontalis 10-30 units

D - Temporalis 40-50 units

E - Occipitalis 20-50 units
F - Cervical Paraspinal 20-40units
G - Trapezius 20-40 units

What is the role of interventional headache procedures in pediatric migraine treatment?

Procedural Interventions

Intervention	Pediatric data	Level of pediatric evidence	Approvals
Onabotulinum toxin A (chronic migraine)	✓	• Open-label case series • Parallel-group RCT of one injection series (N=125) **Negative trial* • Cross-over RCT of one injection series (N=15)	N/A
Nerve blocks	✓	• Open-label case series only (4 with ONB; 1 with other)	N/A

Winner. Headache (2020)
Shah et al. Reg Anesth Pain Med (2021)
Dubrovsky. Curr Opin Pediatr (2018)
Esparham et al. J Child Neurol (2021)

What is the role of emerging therapies in pediatric migraine management?

Emerging Preventive Treatments

Intervention	Pediatric Data	Level of evidence	Approvals/ clearances
Gepants	✓	• Retrospective chart review: N=13 (ubrogepant, rimegepant) • Phase III trials underway for ubrogepant, rimegepant & atogepant	✗
CGRP mAbs	✓	• Retrospective observational studies (N=112 with mixed Ab and N=9 with eptinezumab) • Phase III trials underway for all 4 antibodies	✗
Remote electrical neuromodulation (Nerivio)	✓ (acute)	• Prospective open-label acute study (N=71)	US ≥12yo
Electrical trigeminal nerve stimulation (Cefaly)	✓ (acute)	• Retrospective study (N=154 visits): reduce intensity	✗
Non-invasive vagal nerve stimulation (GammaCore)	✓ (acute)	• Prospective observational open-label acute study (N=9)	US + CA ≥12yo
Single pulse transcranial magnetic stimulation (sTMS mini)	✓	• Prospective open-label study (N=21)	US ≥12yo

Neuromodulation

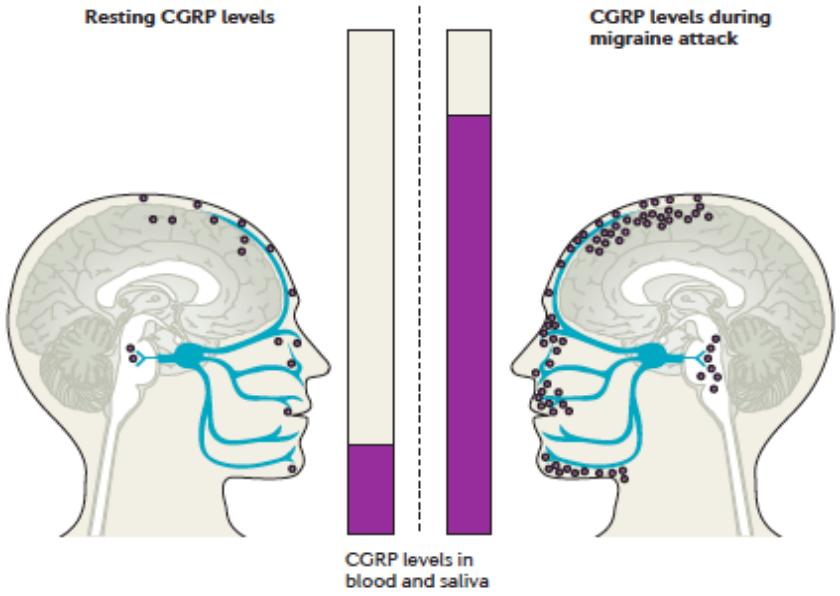
Neuromodulation devices	Pediatric Data	Level of evidence	Approvals/ clearances
Non-invasive vagal nerve stimulation (GammaCore)*	✓ (acute)	• Prospective observational open-label acute study (N=9)	US + CA ≥12yo
Electrical trigeminal nerve stimulation (Cefaly) *	✓	• Retrospective study (N=154 visits): reduce intensity	✗
Remote electrical neuromodulation (Nerivio)	✓ (acute)	• Prospective open-label acute study (N=71)	US ≥12yo
Single pulse transcranial magnetic stimulation (sTMS mini)	✓	• Prospective open-label study (N=21)	US ≥12yo

* Available in Canada

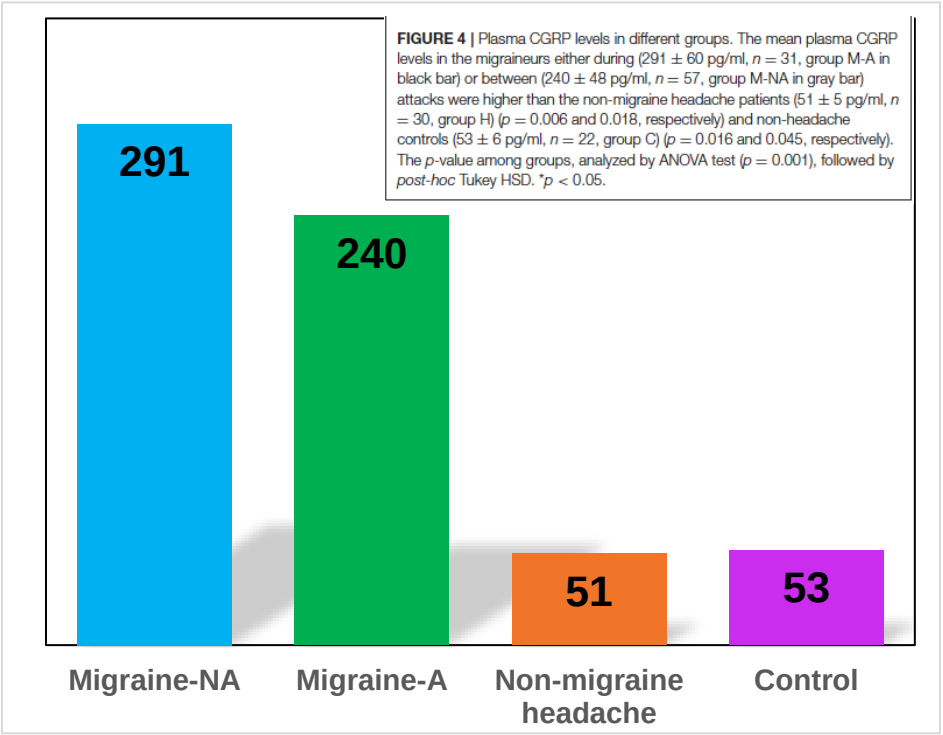
Marshall et al. Current Neurol Neurosci Rep (2022)
Zorrilla et al. Headache (2023)
Esparham et al. J Child Neurology (2022)

Why target CGRP for pediatric migraine treatment?

CGRP levels are elevated in pediatric migraine patients



Plasma CGRP levels (pg/ml) in pediatric patients



1. Edvinsson L et al. Nature (2018)
2. Fan et al. Frontiers of Neurology (2019)

Emerging Pediatric Migraine Therapies

Intervention	Pediatric Data	Level of evidence	Approvals/ clearances
CGRP targeted therapies			
Gepants	✗	• Phase III trials underway for ubrogepant, rimegepant & atogepant	✗
CGRP mAbs	✓	• Retrospective observational studies (N=112 with mixed mAb and N=9 with eptinezumab) • Phase III trials underway for all 4 antibodies	✗

Marshall et al. Current Neurol Neurosci Rep (2022)
Zorrilla et al. Headache. (2023)

CGRP targeted migraine therapies

	Medications	Mechanism	Indication	Route	Adult Dose	Pediatric Trial
Gepants	**Zavegepant**	receptor antagonist	Acute	nasal	prn	✗
	Rimegepant	receptor antagonist	acute and preventive	po	50-100 mg prn/EOD	✓
	Ubrogepant*	receptor antagonist	acute	po	50-100 mg prn	✓
	Atogepant*	receptor antagonist	preventive	po	daily	✓
mAbs	**Erenumab***	mAb (receptor)	preventive	SC	70-140 mg monthly	✓
	Galcanezumab*	mAb (ligand)	preventive	SC	240, 120 mg monthly	✓
	Fremanezumab*	mAb (ligand)	preventive	SC	225/675 mg monthly/quarterly	✓
	Eptinezumab*	mAb (ligand)	preventive	IV	100-300 mg quarterly	✓

*Available in Canada

Suggested indications, contraindications and monitoring for use of CGRP monoclonal antibodies in children and adolescents with migraine

Indications	Contraindications	Monitoring
• ≥8 HA days/month • PedMIDAS score ≥30 • Failure >2 preventive meds • Post-pubertal adolescent, or pre-pubertal child in carefully selected cases	• Disturbed BBB • Severe cardiovascular disease, recent stroke • Pregnancy, planned pregnancy or breast feeding	• BP and HR • Pubertal status • Bone health • Linear growth • Weight/BMI • Infections • Pregnancy status

Szperka et al. Headache. (2018)

Future/Ongoing pediatric migraine trials

ACUTE treatment:

- Intranasal sphenopalatine ganglion block 2% Lidocaine: phase 3 recruiting
- Propofol infusion: open label, recruiting
- Sumatriptan nasal powder: phase 3, recruiting
- Dexamethasone IV: phase 1
- Nitrous oxide
- Occipital nerve blocks
- Prochlorperazine vs Prochlor +Ketorolac
- Intranasal lidocaine
- VPA and DHE
- IV fluids
- IV Ketorolac and Metoclopramide
- Oral Dexamathasone for acute migraine recurrence in ED

Preventive treatment:

- Alpha lipoic acid (ALA) 300 mg VS Flunarizine 5 mg: phase IV, open label, recruiting

Migraine Comorbidities

Psychiatric	General Medical	Neurologic
• Internalizing symptoms/disorders • ADHD • Tourette • Suicidal ideation	• Obesity • Asthma • Atopic dermatitis • Anemia • Sleep disorders	• Epilepsy • Restless legs syndrome

Orr et al. Nat Rev Neurol (2018)

Psychiatric Comorbidities

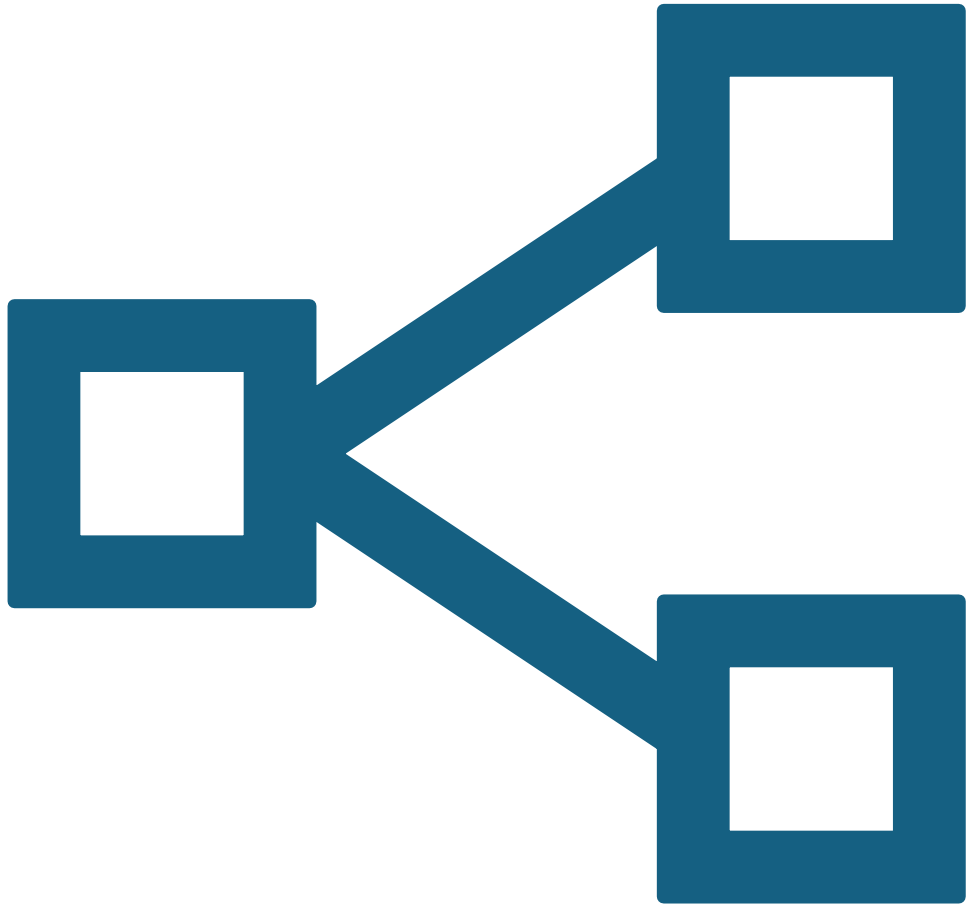
- Youth with migraine have
  - ~2x the odds of anxiety/depressive disorder
  - ~3x the odds of SI

- ACEs are a risk factor for adolescent migraine
  - Dose-response relationship

Falla et al. JAMA Pediatr (2022)
Wang et al. Neurology (2007)

Natural history of pediatric migraine

- Factors with favorable outcome
  - Age of onset after 6 years old
    - Earlier onset < 6y: 4.2 times >> risk of unfavorable outcome
    - Onset 6-10y: 82% good outcome, 12% + prophylaxis
- Male gender is associated with remission
- Early developmental disorders
    - Associated with persistence of migraine



Antonacci et al. Journal Headache and Pain (2014)
Kienbacher et al. Cephalalgia (2006)

The key in migraine management in children of adolescents

Education

Shared-decision making

Individualized treatment

Always review 4 key aspects of treatment

Acute treatment

Preventive treatment

Education and Self-management

Comorbidity management

Key Recommendations

Recognize, diagnose and start migraine treatment early

Counsel that lifestyle factors can influence frequency

Inform re: placebo effect

Discuss evidence for:

- CBT + Amitriptyline (chronic migraine)
- Topiramate
- Propranolol

Monitor effectiveness & counsel re: risks/benefits of stopping preventive medications

Screen and manage comorbidities (i.e., mood and anxiety symptoms & disorders, etc)

© SOrr, Modified

Bottom line

“We are now in an era where we understand what is happening in migraine inside of the brain. Based on our understanding, we’re designing treatment options.”

- Pediatric RCTs and novel trial designs needed *(crossover design, single-blind placebo lead-in)*
- When in doubt: be guided by clinical characteristics, stratify approach

A child’s brain is no place for migraine

https://headaches.org/pediatric-migraine-studies/ (modified)

Useful Resources

Migraine Canada

NATIONAL HEADACHE FOUNDATION™

AMERICAN MIGRAINE FOUNDATION

Any questions?

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