Pediatric Migraine: An Update
PROJECT ECHO
October 27, 2023

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DECLARATION OF DISCLOSURE

Dr. Barmherzig

- *Speakers Bureau/honoraria:* Miravo, TEVA

Dr. Lagman

- *Advisory Board:* TEVA, Pfizer, Lundbeck, Miravo
- *Research/Unrestricted Educational Grant*: Amgen, Lundbeck, TEVA, Abbvie (submitted to WCH Centre for Headache & HSC)
- *Royalties as author*: Canadian Pharmacists Association

- We will only present the published data on any medications from these companies
- None of these companies contributed to the content of this presentation
- The off-label use of some therapies in the management of pediatric migraine will be discussed

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LEARNING OBJECTIVES

1. Recognize the scope, distribution, and burden of diagnosed and undiagnosed headache disorders and migraine in children and youth

2. Review updates on acute and preventive therapies in the treatment of pediatric migraine

3. Apply evidence-based strategies for managing and preventing disability related to migraine in children and adolescents

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I am comfortable managing children and youth with headache.

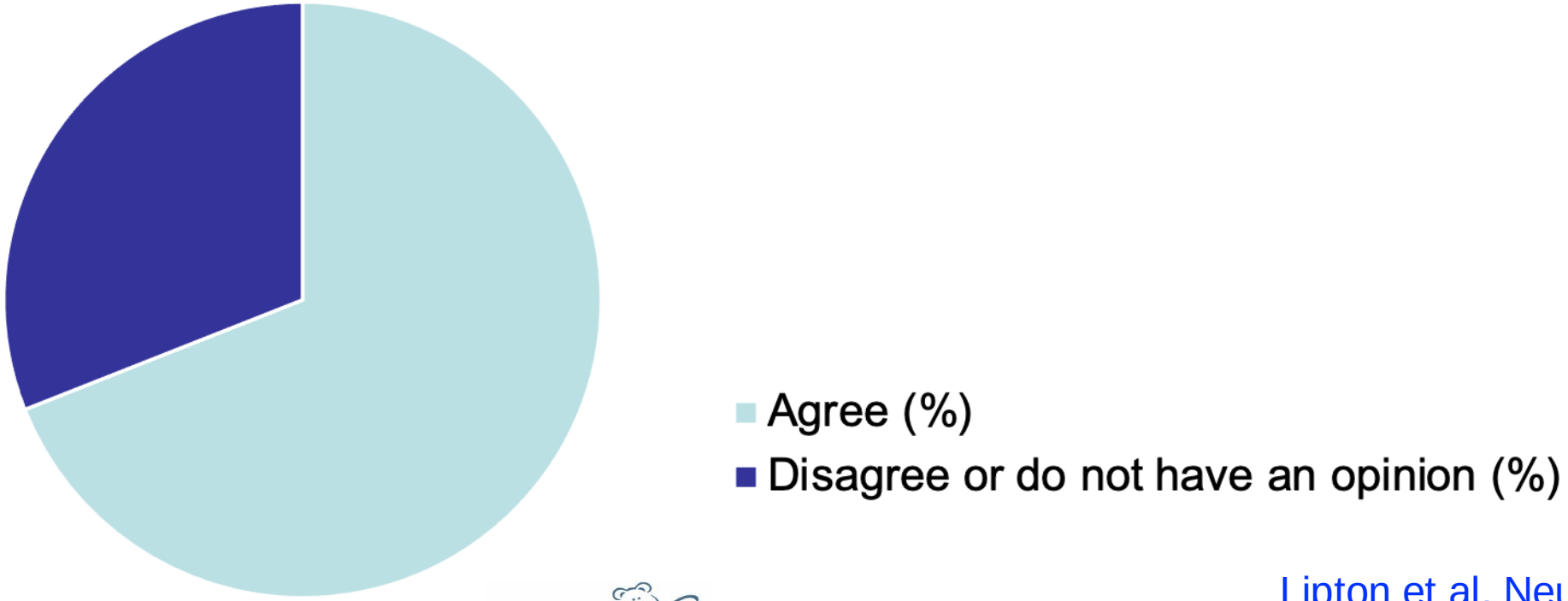
A. Yes, I usually feel confident managing these patients

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

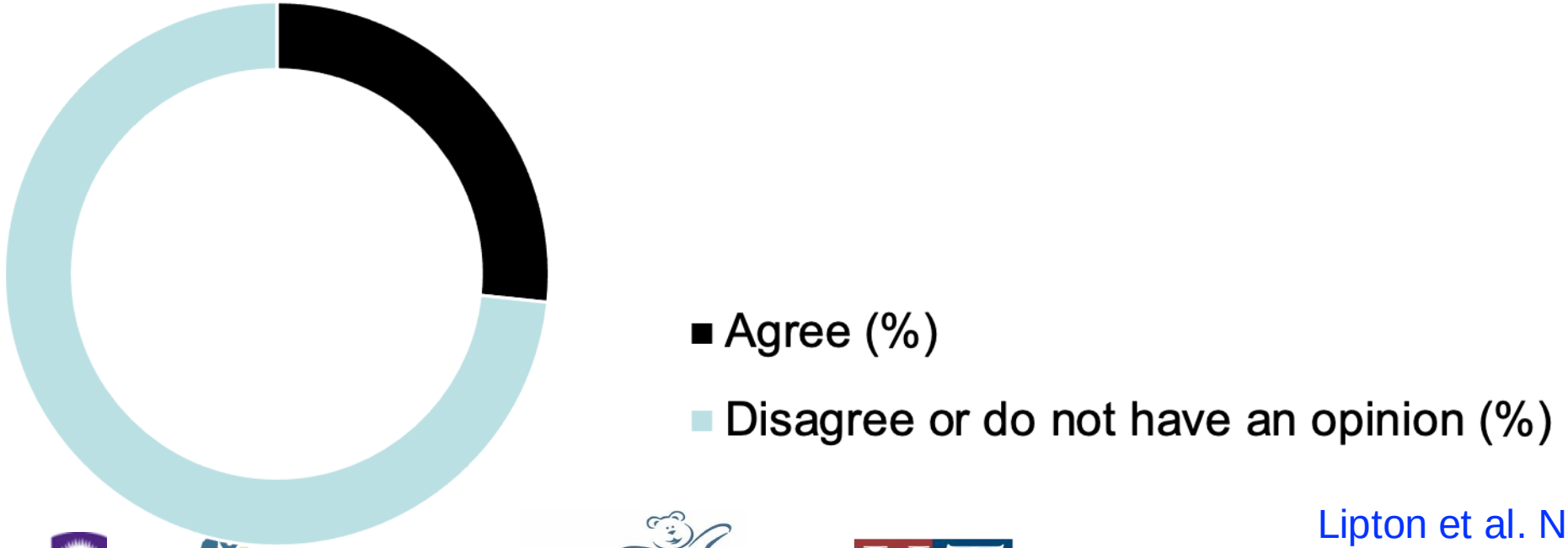
Migraine is a legitimate brain disease



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)


FLASHING LIGHTS
TENSION
FATIGUE
DIAGNOSE YOUR HEADACHES
STRESS
VISUAL DISTURBANCES
THROBBING
ALL IN YOUR HEAD

WHO Global Burden of Disease

1st

Most expensive brain disorder

2nd

Leading cause of medical disability worldwide

3rd

Most common medical condition worldwide

GBD 2019 Diseases and Injuries Collaborators.Lancet (2020)

Prevalence

- **Pediatric migraine**: 7.7%
- **Chronic migraine**: 0.8% -1.8% among children (12 -17)

Abu-Arafeh I, et al. Deve Med Child Neurol. (2010)

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 F, et al, The Journal of Headache and Pain (2014)

Disability of migraine and TTH by age

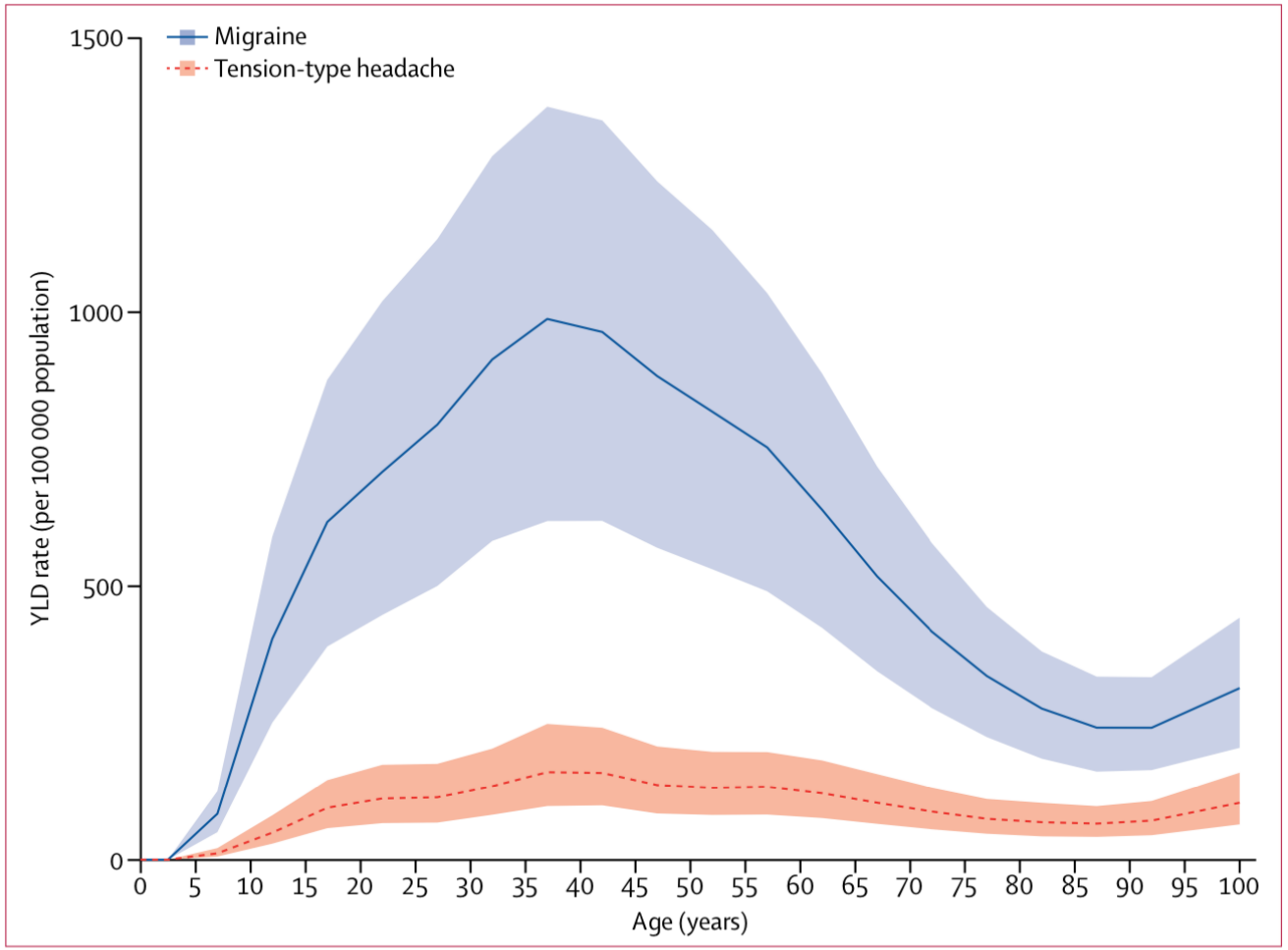


Figure 4: **Global years of life lived with disability (YLD) rate per 100 000 population due to migraine and tension-type headache by age, 2016**

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

Lancet Neurology (2017)

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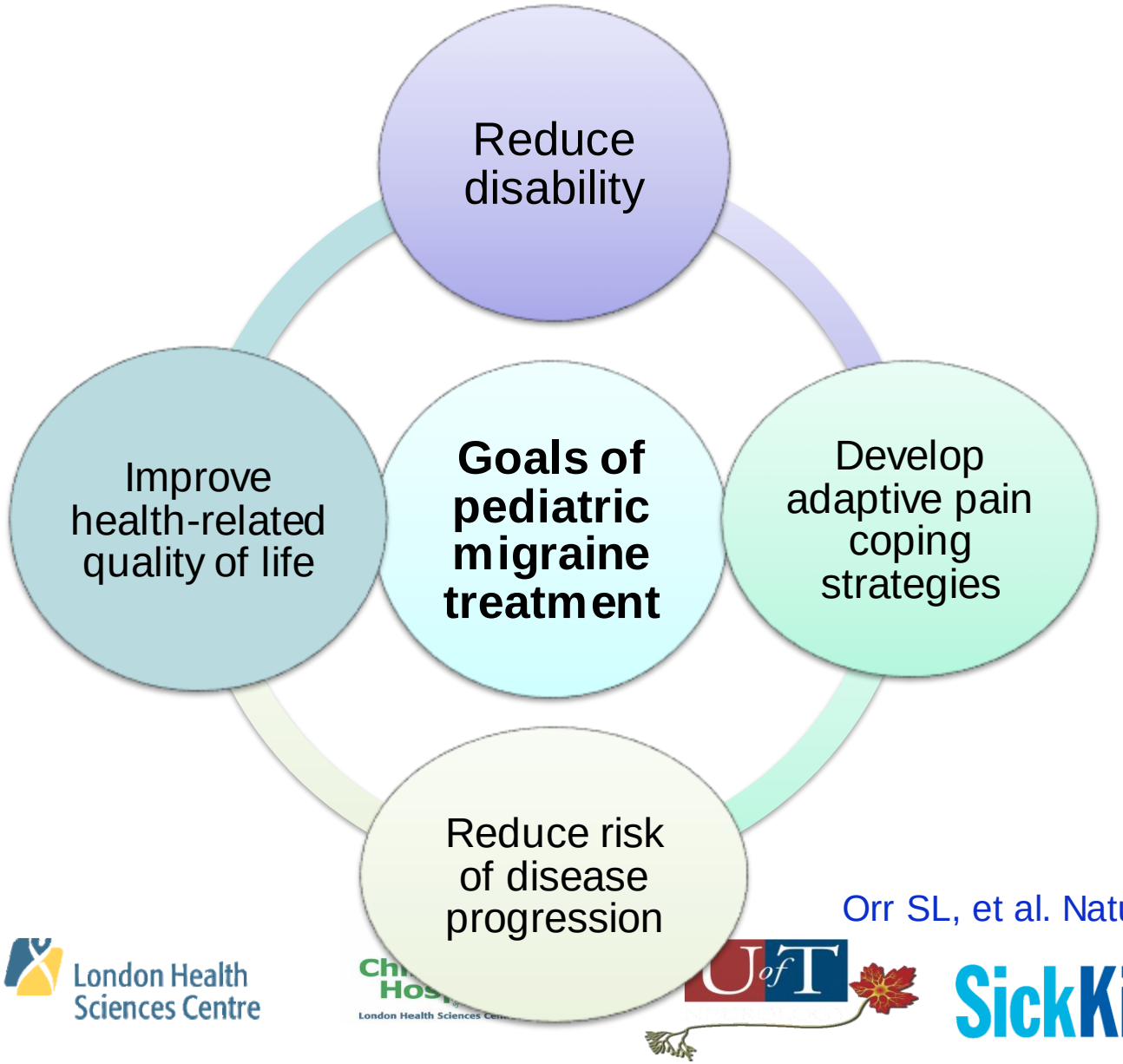
Goals for pediatric migraine treatment



Orr SL, et al. Nature Reviews Neurology (2018)

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CASE 1: Ethan

15y M with episodic migraine without aura since age 10

- Migraine attacks: moderate to severe, bilateral frontal pressure headache
- Frequency/duration: 2-3 days a month/ lasting 7-10 hours
- Associated features:
  - light and sound bothersome
  - prefers to rest during attacks when severe
  - nausea within 10-15 mins from headache onset
- Medications: acetaminophen and ibuprofen (no longer working)
- Past medical history: asthma, motion sickness, infant colic
- Exam: unremarkable

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What would you offer him 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?

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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*

1. Bigal ME, et al. Headache (2008)
2. Lipton RB, et al. Neurology (2015)

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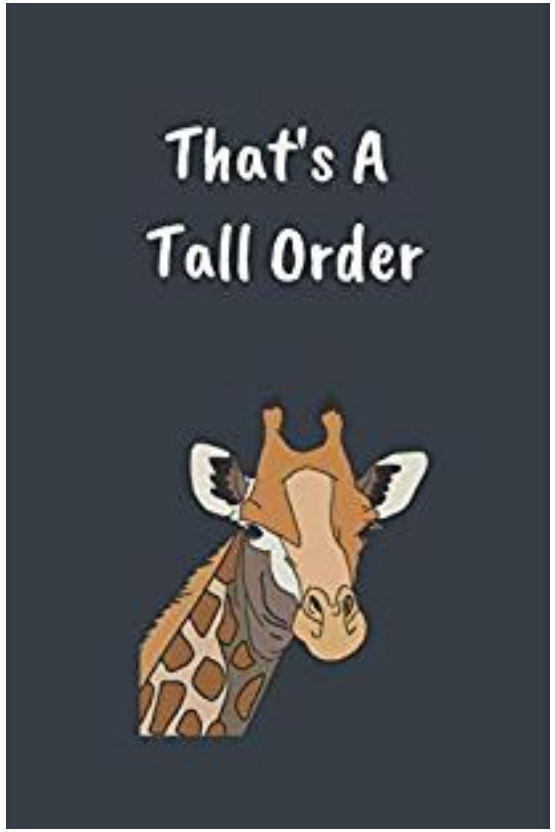
Effective acute treatment

1. Rapid and consistent freedom from pain and most bothersome symptoms (MBS) without recurrence
2. Restored ability to function
3. Minimal need for repeat dosing or rescue medications
4. Optimal self-care and reduced subsequent use of resources (e.g. ED visits)
5. 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

Challenges in children

- Heterogeneous population
- Difficulty with case definitions
- Outcome measures
- Confounders, confounders, confounders
- Placebo/ nocebo effects – **as high as 65%**

Patterson-Gentile C, Szperka CL. JAMA Neurology (2018)

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

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Headache
doi: 10.1111/head.13428
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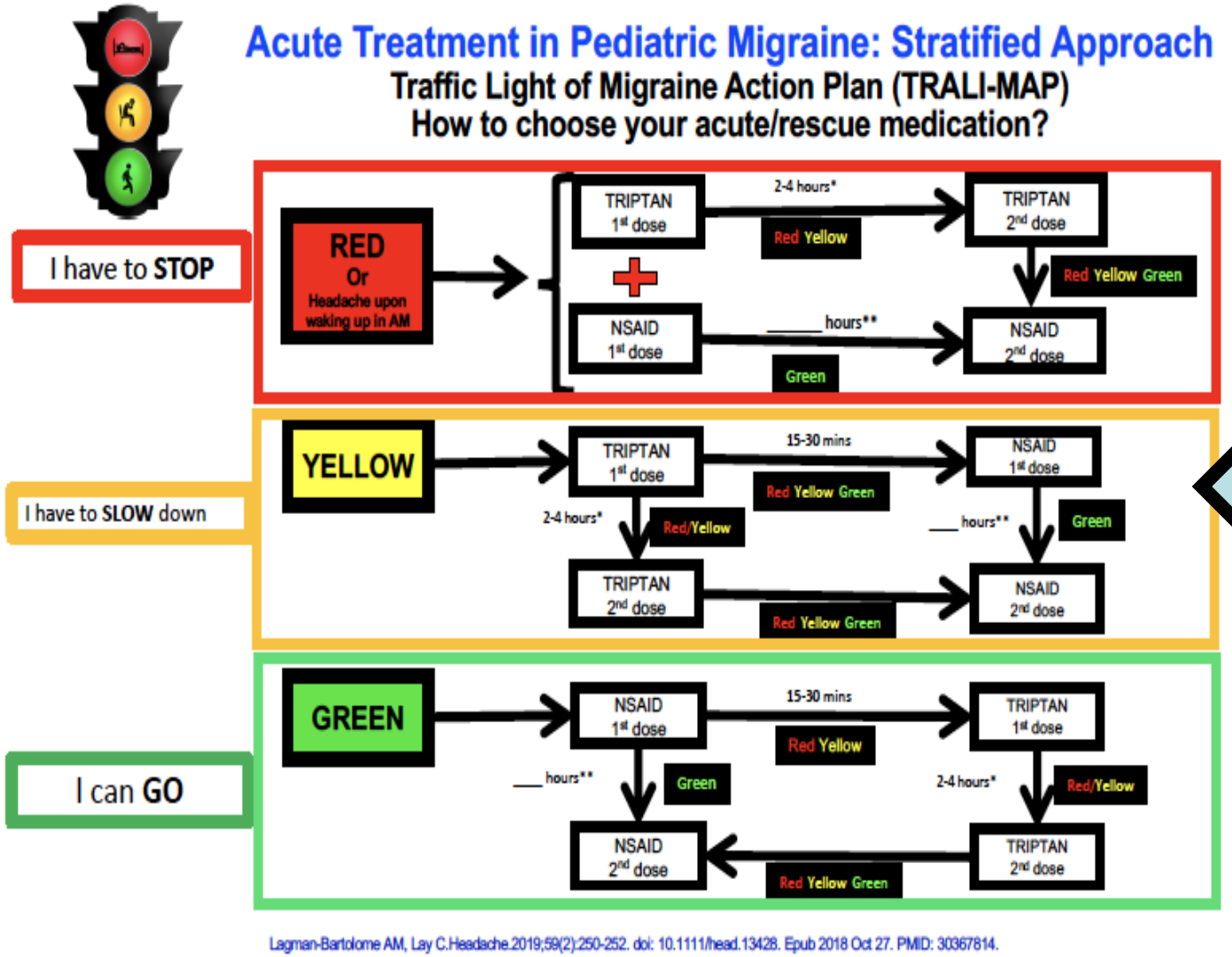
Views and Perspectives

The Traffic Light of Headache: Simplifying Acute Migraine Management for Physicians and Patients Using the Canadian Headache Society Guidelines

Ana Marissa Lagman-Bartolome, MD, FRCPC; Christine Lay, MD, FRCPC

Lagman-Bartolome AM, Lay C. Headache (2019)



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

2019 AAN/AHS Pediatric Migraine Treatment

TRIPTANS: (level B)

For ≥ 6 yo

- Rizatriptan ODT

For ≥ 12 yo

- Almotriptan tablet
- Rizatriptan
- Sumatriptan-Naproxen tablet
- Sumatriptan nasal spray
- Zolmitriptan nasal spray

NSAIDs

- Ibuprofen

Anti-emetics

1. Lagman-Bartolome AM, Lay C. Headache (2019).
2. Oskoui M, et al. AAN/AHS Guideline. Neurology (2019)

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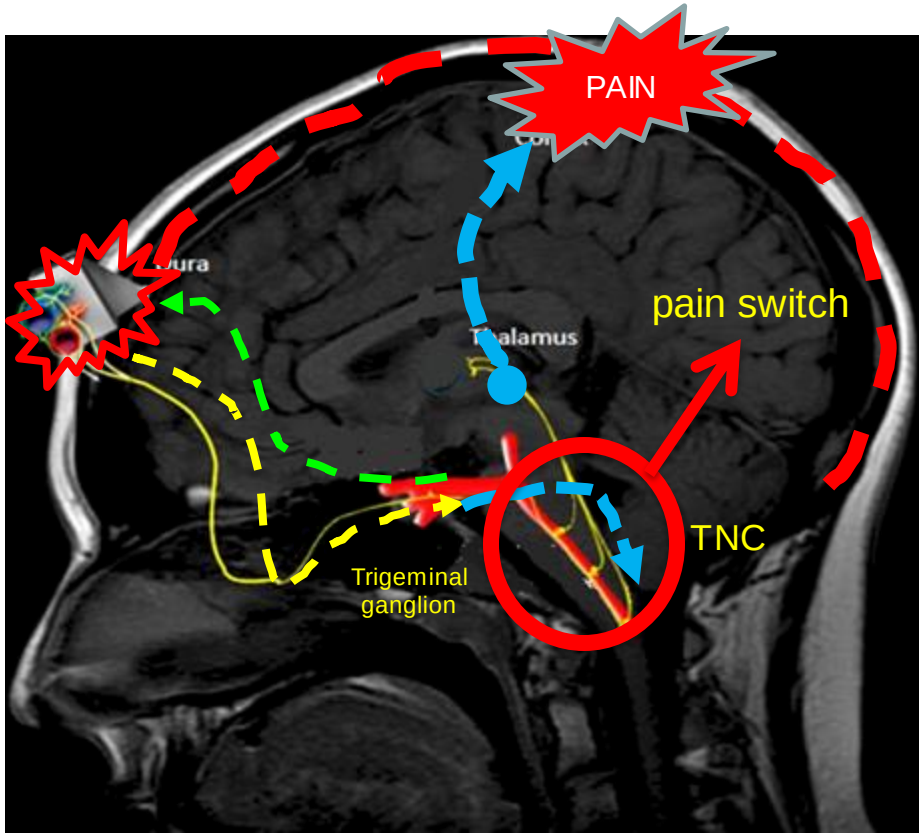
It is important to treat early!!:

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;4:386–398.
2. Goadsby, Headache.2005; 45:S24-44.
3. Cady RK. Diagnosis and treatment of migraine. Clinical Cornerstone. 1999;1:21-32.

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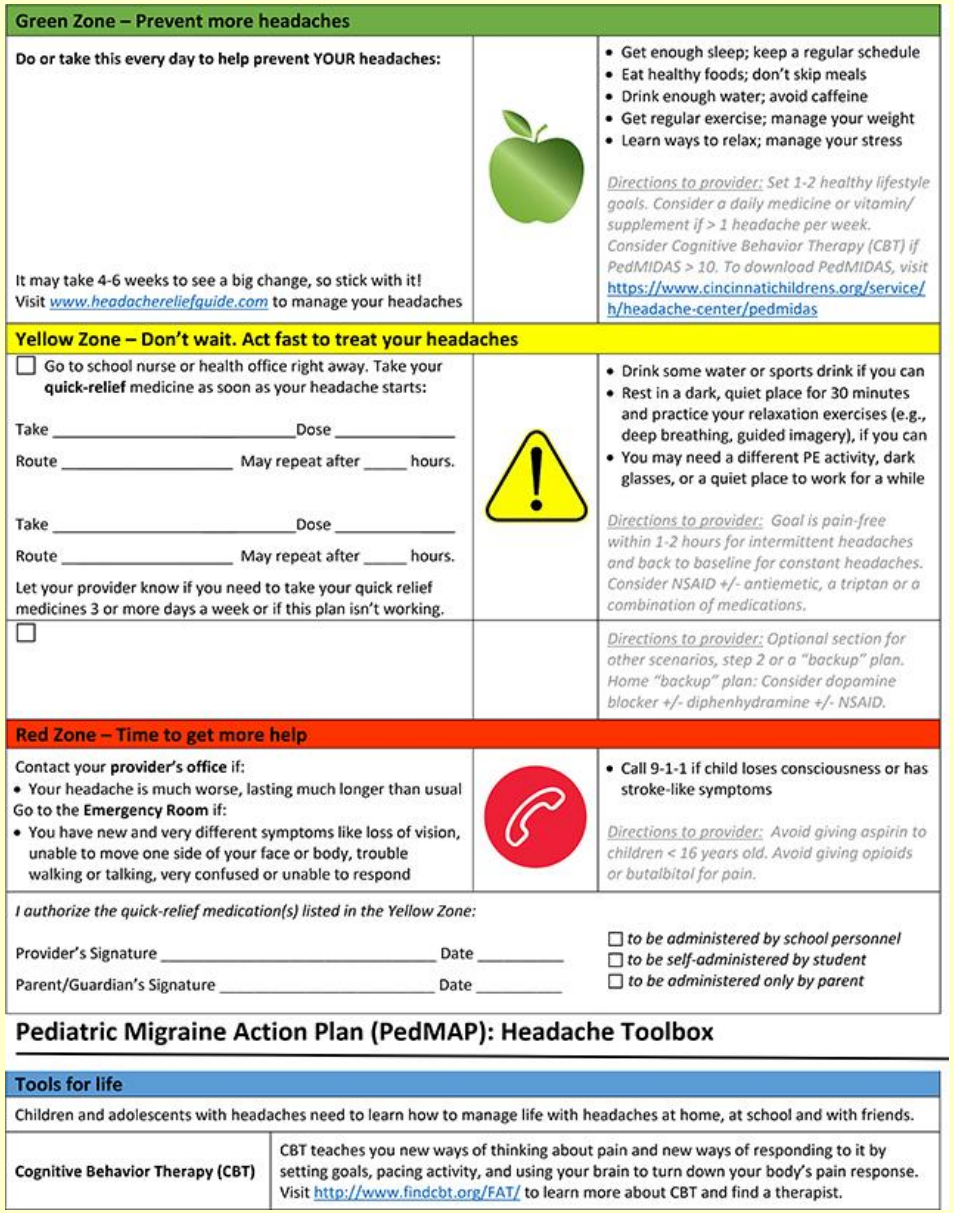
Resource

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.

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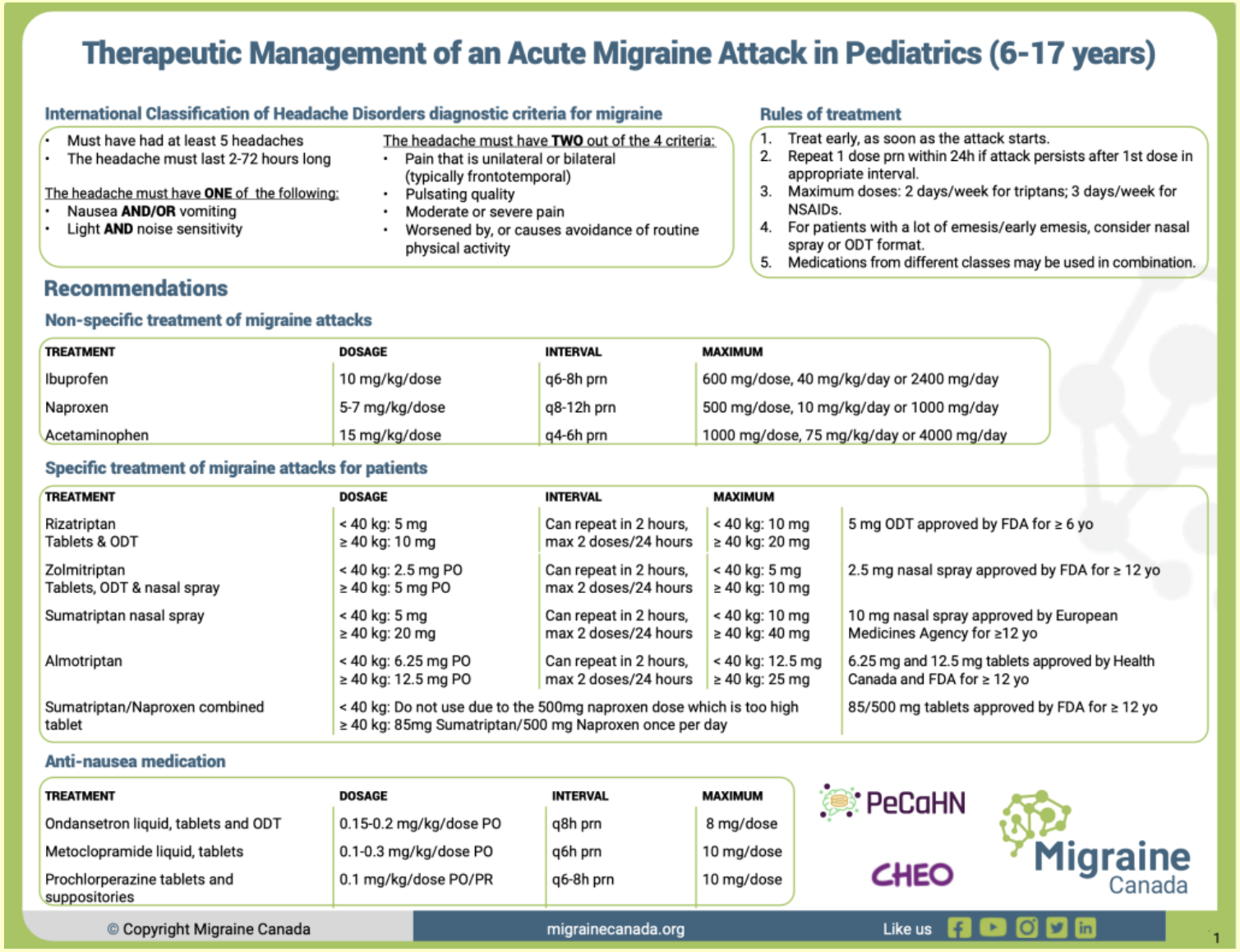
Resource

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

PeCaHN CHEO Migraine Canada

migrainecanada.org Like us

1

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Back to our case…. 6 months later

- Migraine attacks: no change over the past 6 months, persist at frequency of 2-3 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

Which of the following off-label treatments would you recommend next?

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

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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

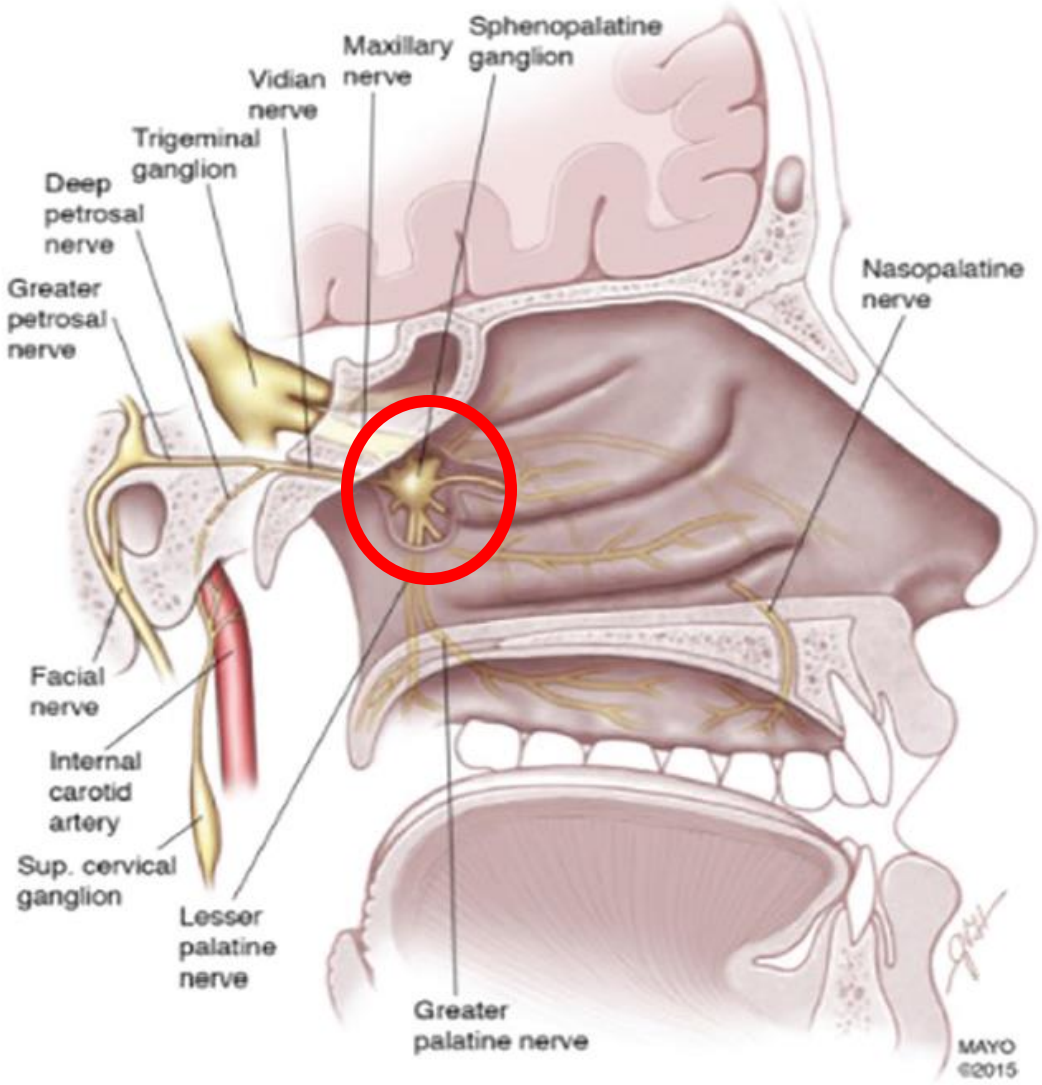
Kate Maki MD[1], Quynh Doan MDCM[1,2], Kendra Sih PharmD[1], Karly Stillwell BSc[2], Alaina Chun BSc[2], Garth Meckler MDS[1,2]

[1]Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada
[2]BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada

SPG blockade

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

SPG



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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 FJ, et al. Pediatrics (2012)

New 5-HT1 target

Lasmiditan- selective 5-HT1**F** agonist

- FDA approved October 2019 in adults

Systematic review and meta-analysis in adults[1]

- 79.2% ≥1 cardiovascular risk factor at baseline
- Significant pain and most bothersome symptom freedom at 2h (200 mg superior efficacy >100 mg)

Safety and tolerability in pediatric migraine patients[2]

- 100 mg (<40 kg) and 200 mg (>40-55kg): no safety or tolerability issues
- Peak at 1.5h and T1/2 is 4h

Precautions: risk of driving impairment, CNS depression (sedation, dizziness)

➢ ***Pediatric phase 3 RCT in progress: ~completion January 2025***
https://clinicaltrials.gov/ct2/show/NCT04396236

1. Bang Y,et al. CNS Drugs (2020)
2. Tsai M, et al. Clin Pharmacokinet. (2021)

CASE 2: Penny

16y F athlete with infrequent migraine without aura since age 13

- Jan 2023: gradual increase in headache frequency to 4-5 days a week (duration: 4-12 hours)
- Headache **RED** flags: none
- Recent diagnosis of severe depression

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

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

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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 M, et al, Neurology, 2019

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How do we counsel parents about preventive medications?

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

- Shared decision making→ use of short-term treatment trials for a minimum of 2 months **(Level B)**[1]

1. *Oskoui M, et al. AAN/AHS Guideline, Neurology, 2019*

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Her mother 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
Butterbu			
Other p			
Polyuns	Do not use	Weak	Low
Ginkgolide B	Do not use	Weak	Low
Riboflavin (Vitamin B2)	Do not use	Weak	Low

Since 2014: Two more reviews, conclusions basically the same – insufficient evidence all around, most promise for prevention is for Coenzyme Q10 and magnesium

Orr SL, Venkateswaran S. Cephalalgia 2014;34(8):568-83; Orr SL. Cephalalgia 2016;36(12):1112-33
Orr SL. Curr Pain Headache Rep 2018;22(5):37.

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Back to our case…

- She took Magnesium citrate and Coenzyme Q10 for 3 months.
- Partial response: 15 days a month (less disabling)

- **What is your next step?**

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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

1. *Oskoui M, et al. AAN/AHS Guideline, Neurology (2019)*
2. *Szperka C. Headache. Continuum (2021)*

QUESTION:

Which prevention therapy would you recommend for Penny?

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)*

Penny is 16 yo

- Jan 2023: 4-5 days a week 4-12 hours
- Recent diagnosis of severe depression
- **Previous failed headache medications:** ibuprofen, naproxen, almotriptan, zolmitriptan, sumatriptan, rizatriptan
- **Current medications:** sumatriptan-naproxen

Tips on how to choose the preventative treatment for your patient

Disorder + Migraine	Consider	Avoid or Caution
Depression	Venlafaxine*, Sertraline*, Duloxetine*	B-blocker, Topiramate, Amitriptyline (increase suicidal risk in adolescents)
Anxiety	Amitriptyline, Venlafaxine*, Propranolol, Gabapentin*	Sertraline (lower doses may worsen anxiety)
Sleep disturbance	Amitriptyline, Gabapentin*, Melatonin	Topiramate
Obesity	Topiramate, Candesartan*	Amitriptyline, Valproate
Epilepsy	Topiramate, Valproate*, Gabapentin*	

*Off-label treatment

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

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Penny is asking how long she has to take her preventive medication?

A. 1-2 months

B. 3 months

C. 4 months

D. 6-12 months

E. I am not comfortable answering herquestion

1. *Oskoui M, et al. AAN/AHS Guideline, Neurology, 2019*
2. *Powers SW. JAMA Netw Open 2021;4(7):e2114712*

When do you taper off her 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 M, et al. AAN/AHS Guideline, Neurology, 2019*
2. *Powers SW. JAMA Netw Open 2021;4(7):e2114712*

Back to our case…. 1 year later

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

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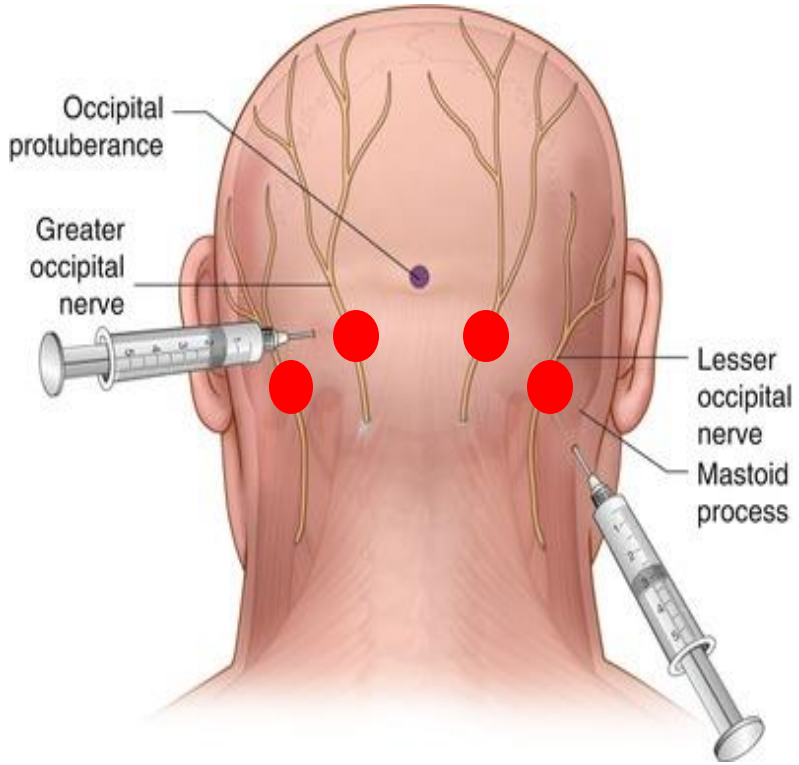
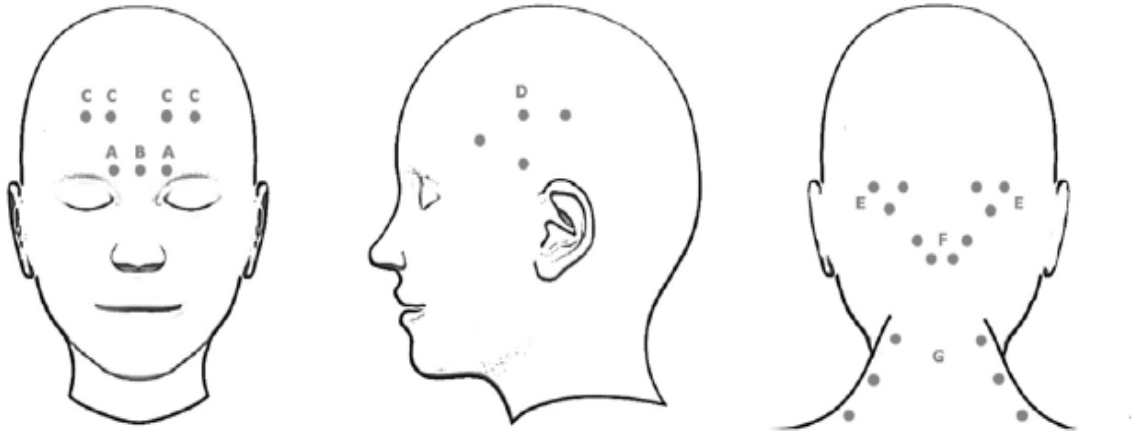
What preventive therapy option would you recommend for this patient next?

A. CGRP targeted therapy
B. Neuromodulation therapy
C. Onabotulinum toxin A
D. Weekly pericranial nerve blocks
E. None of the above *(I am not comfortable starting this patient with any of the above options)*

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





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

Interventional Procedures

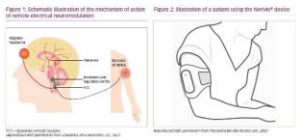
Intervention	Pediatric data	Level of pediatric evidence	Approvals
Onabotulinum toxin A (chronic migraine) [1,2,3]	✓	• Open-label case series • Parallel-group RCT of one injection series (N=125) **Negative trial* • Cross-over RCT of one injection series (N=15) • Several retrospective review/case series: decrease in pain intensity, cumulative benefit, 50% decrease HA frequency	X
Nerve blocks[4,5,6]	✓	• Chronic migraine, status migrainosus, chronic refractory migraine, NDPH using Lidocaine • Open-label case series (4 with ONB; 1 with SPG) • 53-70% improvement (partial to complete) • Reduction in pain scores by 2.4	X

1. *Winner P et al. Headache 2020;60(3):564-575;*
2. *Shah S et al. Reg Anesth Pain Med 2021;46(1):41-48;*
3. Marcelo R, Freund B. J Child Neurol.2020;35(1):844-851
4. *Dubrovsky AS. Curr Opin Pediatr 2018;30(6):780–5;*
5. *Esparham et al. J Child Neurol. 2021;36(1):54–9.*
6. Mousa MA, et al.Pain Physician. 2021.23: E111-116

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

Emerging Pediatric Migraine Therapies

PeCaHN

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) *Marshall et al. Current Neurol Neurosci Rep. 2022* *Zorrilla et al. Headache 2023;63(1):177-82; epub; clinicaltrials.gov.* *Esparham A, et al.J Child Neurology. 2022; 36(1):54-59*	US ≥12yo

* Available in Canada

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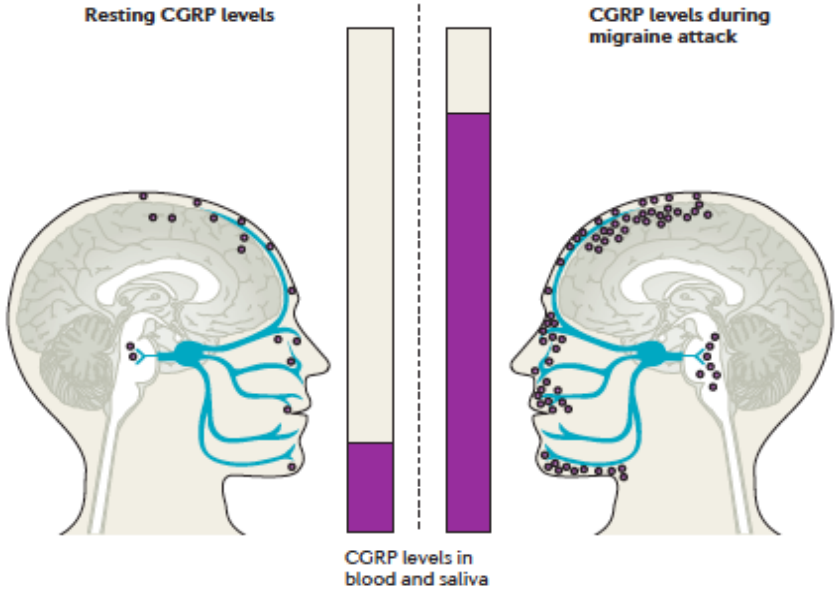
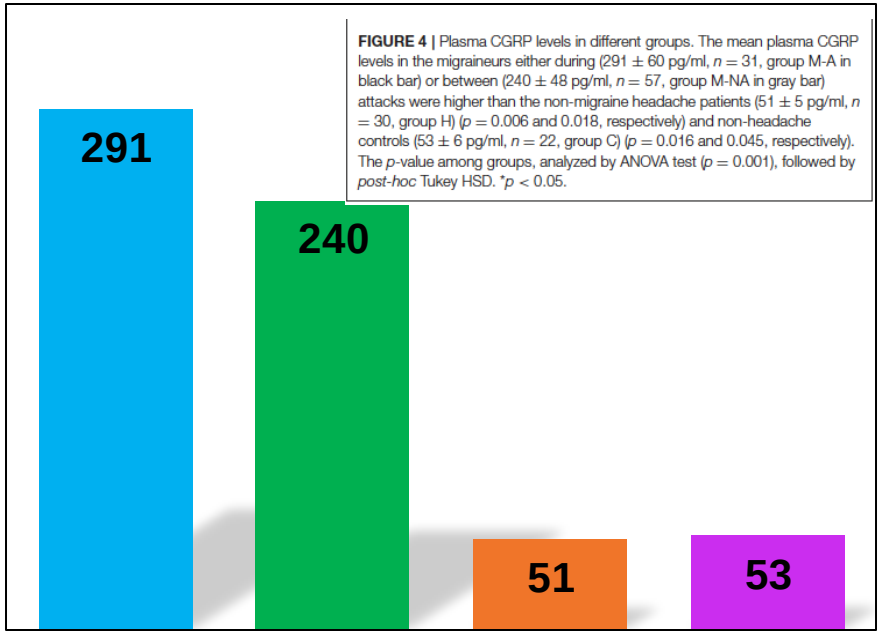
Why target CGRP for pediatric migraine treatment?

CGRP levels are elevated in pediatric migraine patients



Plasma CGRP levels (pg/ml) in pediatric patients



1. Edvinsson L et al. Nature.2018;14:338- 350
2. Fan PC, et al. Frontiers of Neurology.2019; 10:1-9

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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;63(1):177-82; epub; clinicaltrials.gov.

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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
** Pediatric trials in Children's Hospital. LHSC
** Pediatric trial in Sickkids and Children's Hospital, LHSC

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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 C, et al.. Headache (2018)

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Future/Ongoing pediatric migraine trials[1,2]

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

1. Iannone LF et al, Life. (2022)
2. clinicaltrials.gov

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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 F, et al. Journal Headache and pain.2014;15:11
Kienbacher, et al. Cephalalgia.2006,26:820-830

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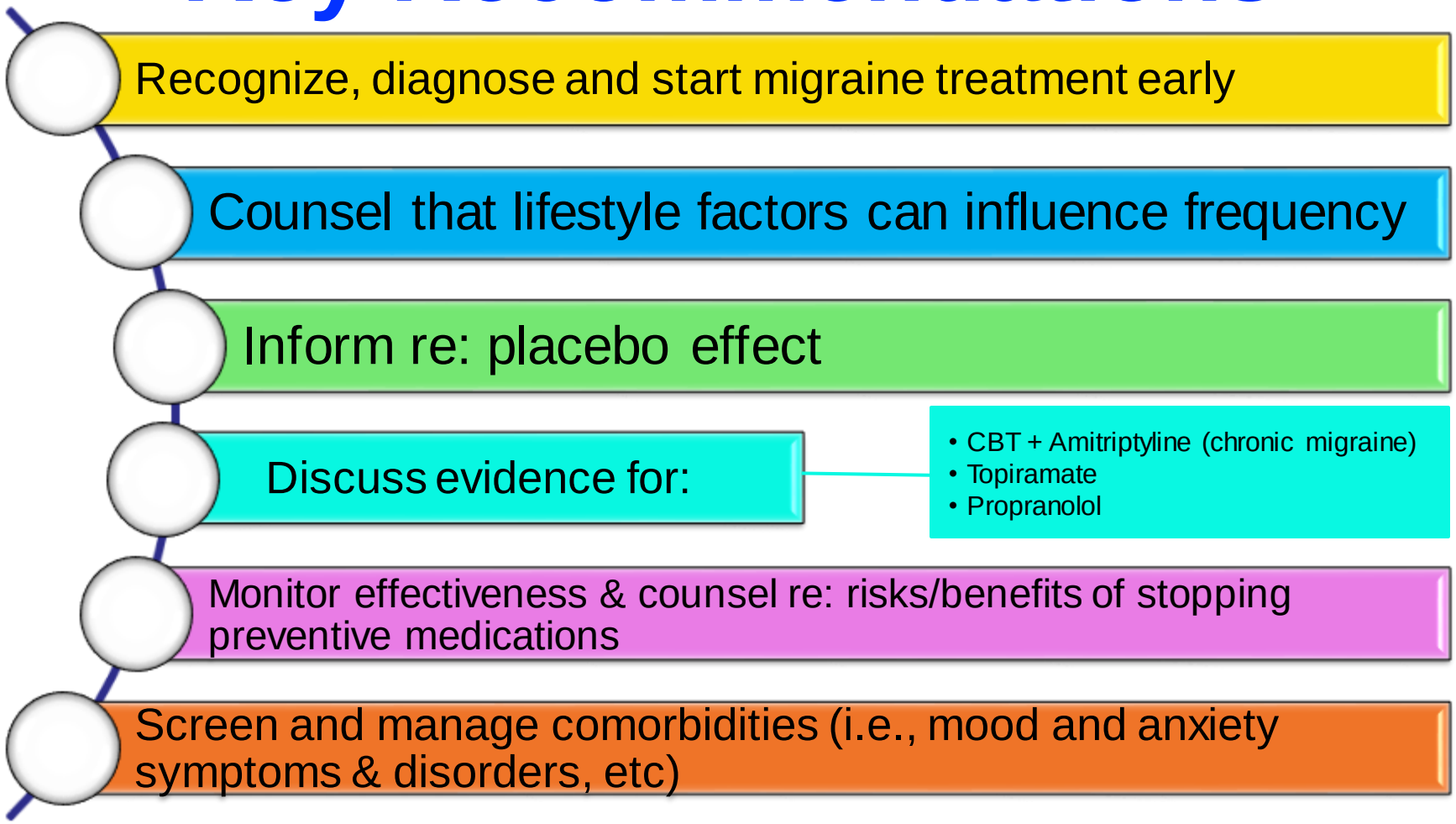
Key Recommendations



Oskoui et al. Neurology 2019. 59(8);1144-1157.

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Key Takeaways

- The  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*

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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

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A child’s brain is no place for migraine

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

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Any questions?

Appendix

SHARED: Lifestyle changes to promote headache health

Headaches in Kids and Teens: SHARED Model of Care	
Supplements **S**creen time	**Magnesium citrate** (9 mg/kg/day): 150-450 mg/day **Coenzyme Q10** (1-3 mg/kg/day): 100-200 mg/day **Screen** exposure (high level >4 hours/day): may trigger migraine, negatively impacts sleep **Screen overuse** >2 hours/day: linked to mood and anxiety symptoms, decreases activity level
Hydration **H**eadache diary	**Increase water**, limit caffeinated drinks, no energy drinks, avoid sugary drinks Use **headache diary** to identify triggers , headache pattern, response to treatment **(Level C)**
Activity and **A**void triggers	Out ev… socialize (face to face)/school, physiotherapy, limit screen/computer act… Ac… Id…
Routine sleep	Re… 3-5… 6-1… 13-…
Eating	NC… foo… aspartame)
Downtime	Stress management and relaxation (**CBT,** mindfulness, biofeedback therapy)

Focus on function >> ~~pain~~

Modified, Monsour D, Lay C, Ansari T, Lagman-Bartolome AM, Curr Neurol Neurosci Rep, 2020; 20:53