What's New in Pediatric Migraine?

DATE: October 25, 2024
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Disclosures

Role	Organization
Grant Support	International Headache Academy/American Headache Society
Site PI (no personal compensation)	Upsher-Smith: Topiramate XR (Qudexy®) for prevention of migraine in children age 6-11 Amgen: Erenumab for the prevention of episodic and chronic migraine in adolescents 12-17 Eli Lilly: Lasmitidan for the acute treatment of migraine in adolescents 12-17
Speaker Engagements	American Headache Society
Advisory Board	Theranica (manufacturer of “Nerivio” device)

I will discuss off-label treatments for migraine in children and adolescents!

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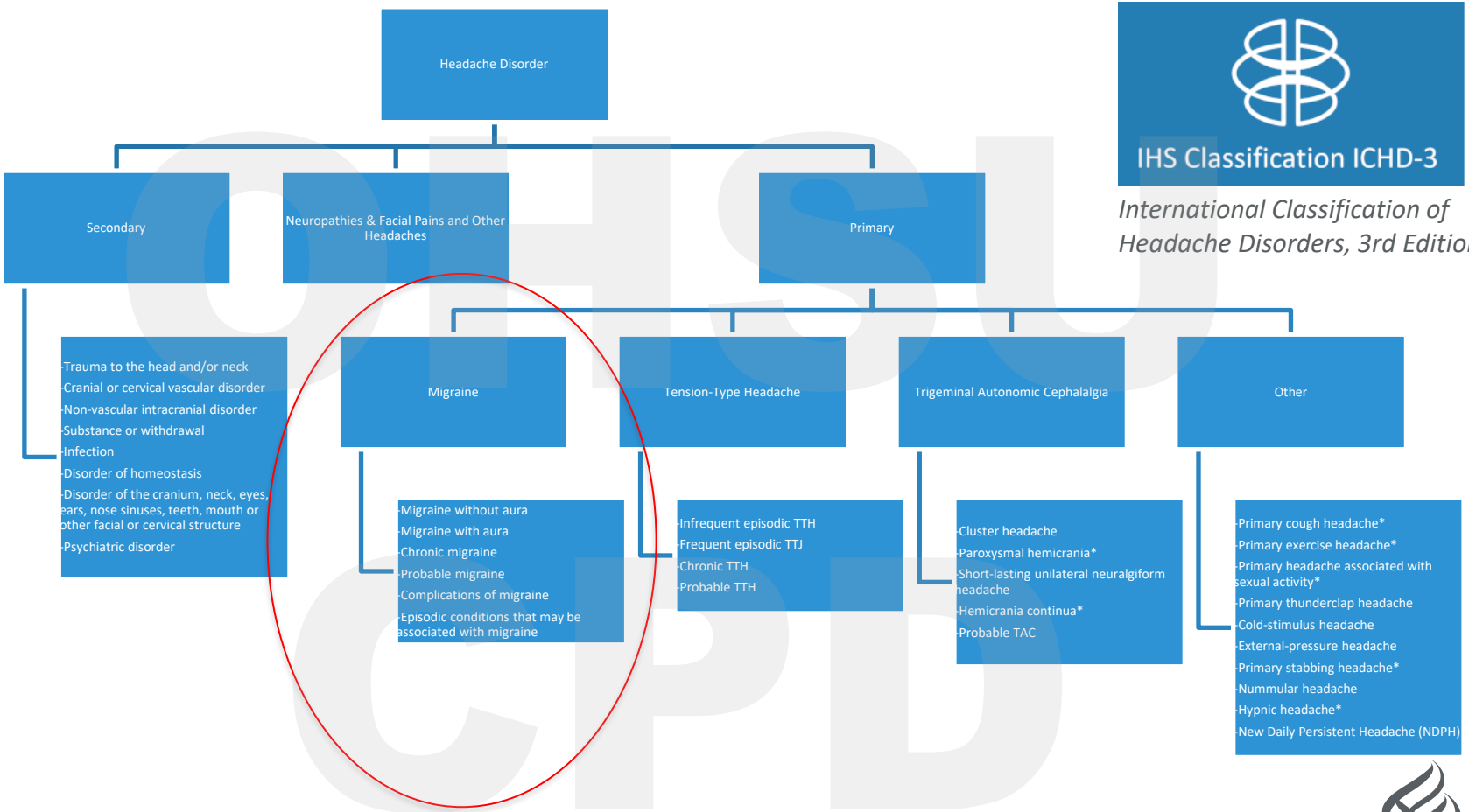


IHS Classification ICHD-3

International Classification of Headache Disorders, 3rd Edition[1]

[1]ICHD-3 *Cephalalgia* 2018

Goals!

- Review definitions of migraine, migraine epidemiology and functional impact of migraine
- Provide overview of anatomy and pathophysiology of migraine
- Discuss current approach to treatment – and its challenges!
- Describe novel migraine therapeutics coming soon(ish) to a pediatrics office near you….

Imagine….

- 16 yo young woman you have been following since childhood for migraine

- How can we help her along the way?

What is “migraine”?

Migraine without aura (*ICHD-3*):

A. ≥5 attacks fulfilling criteria B-D

B. Headache attacks lasting 2-72 hours (untreated or successfully treated)

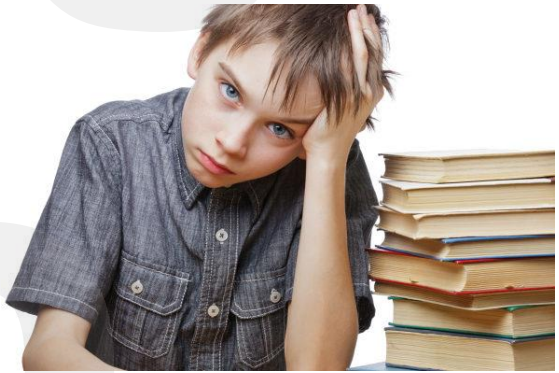
C. Headache has at least two of the following four characteristics

1. Unilateral location (More often bilateral in children[2])
2. Pulsating quality
3. Moderate or severe intensity
4. Aggravation by or causing avoidance of routine physical activity

D. During headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia AND phonophobia (Can be inferred from behavior)

E. Not better accounted for by another diagnosis



Chronic migraine: Headache on ≥15 days per month with ≥8 meeting criteria for migraine for ≥3 months

[1]ICHD-3 *Cephalalgia* 2018; [2]deGrauw *et al.*, *Headache* 1999

What is “migraine”?

	 Migraine 	 Tension-Type 
Duration	**2 hours** – 72 hours	30 min – 7 days
Characteristics		
Photophobia/ phonophobia	BOTH	Either
Nausea/vomiting	**YES**	No
Cranial autonomic symptoms	Maybe (usually bilateral)	?
Restlessness/agitation	No (see motion sensitivity)	No

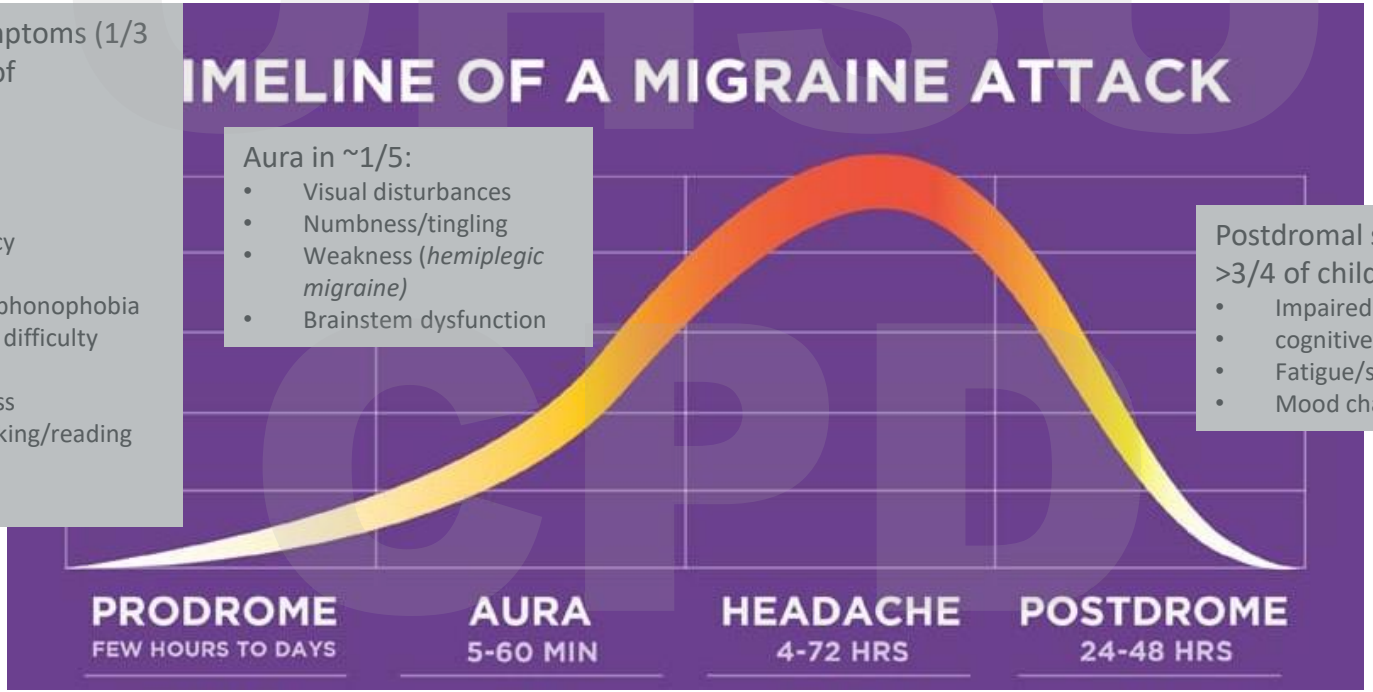
- Among patients presenting to primary care with episodic he
  - 94% migraine
  - 3% TTH
  - 3% unclassified

“If it’s disabling enough to come to the doctor, it’s probably mi

Migraine…NOT “just a bad headache”

Premonitory symptoms (1/3 of children, 2/3 of adolescents):

- Irritability
- Depression
- Yawning
- Urinary urgency
- Food craving
- Photophobia, phonophobia
- Concentration difficulty
- Fatigue
- Muscle stiffness
- Difficulty speaking/reading
- Nausea
- Insomnia



Aura in ~1/5:

- Visual disturbances
- Numbness/tingling
- Weakness (*hemiplegic migraine)*
- Brainstem dysfunction

Postdromal symptoms >3/4 of children):

- Impaired concentration/
- cognitive difficulty
- Fatigue/somnolence
- Mood changes

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Who has migraine in childhood and adolescence?

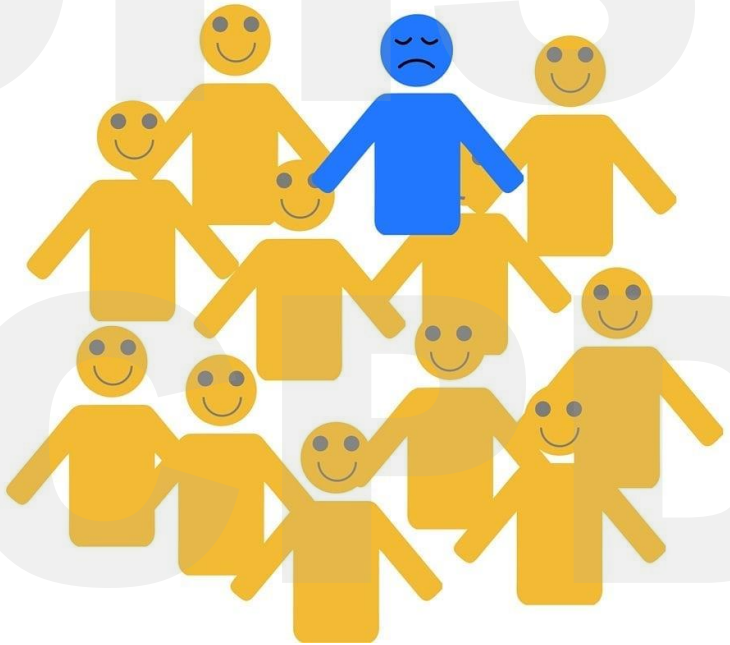


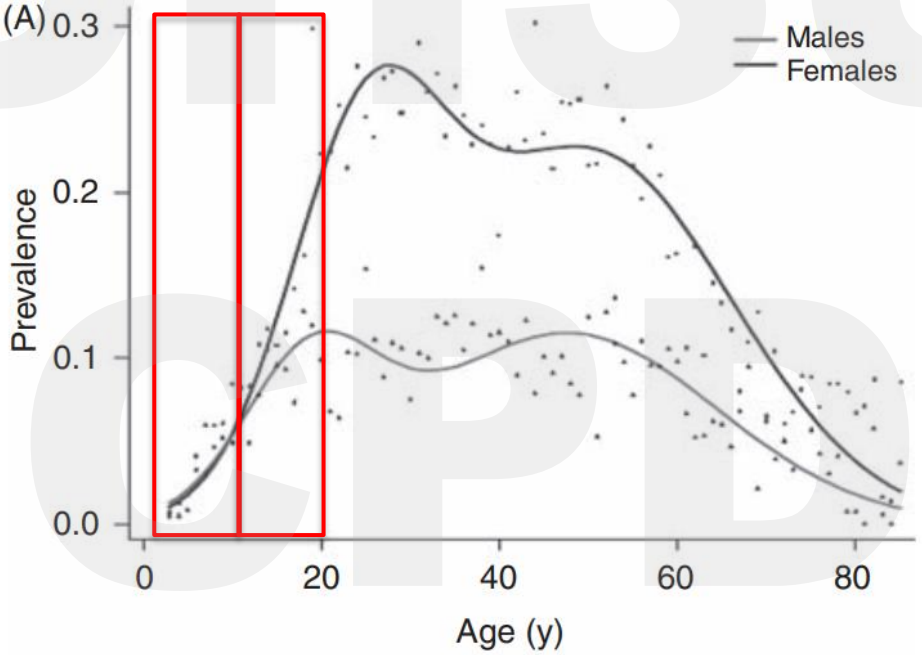
Photo: migraineresearchfoundation.org

Who has migraine in childhood and adolescence?

5-10 yo: 5-10%

♂=♀

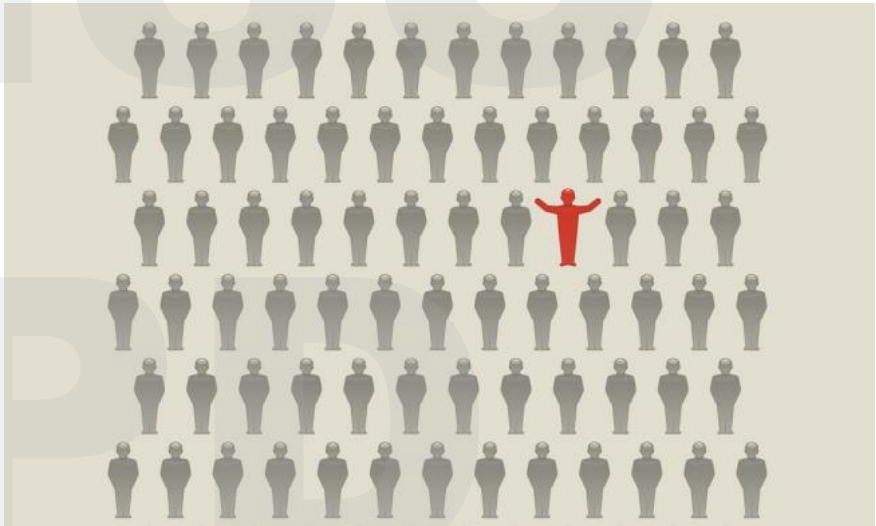
Teens: 15%



[1]Victor *et. al.*, *Cephalalgia* 2010; [2]Abu-Arefeh et al, *Dev Med Child Neurol* 2010

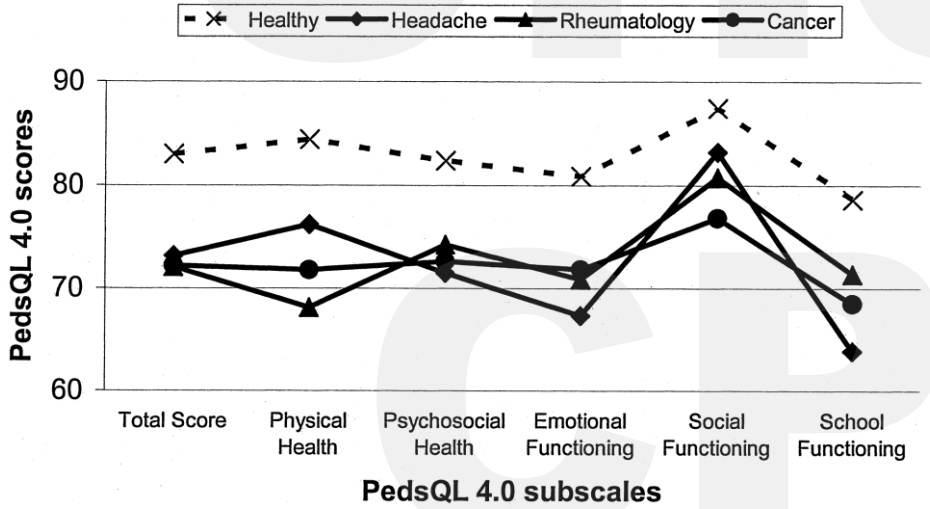
Who has chronic migraine?

- **Chronic migraine**: Headache ≥15 days per month, with ≥8 “migraine” days
- Affects 0.8-1.8% of children and adolescents[1]
- Headache frequency in this population is high!
  - ~**25** days per month on average[3]
  - 2 in 3 have *daily* headache [4]
  - 1 in 5 have *daily and continuous* headache [4]



1 Lipton et al, *Headache* 2011; 2 Fuh et al *Neurology* 2006; 3 Bigal et al *Neurology* 2004 ; 5 Hershey et al *Neurology* 2001

Why do we care about migraine?



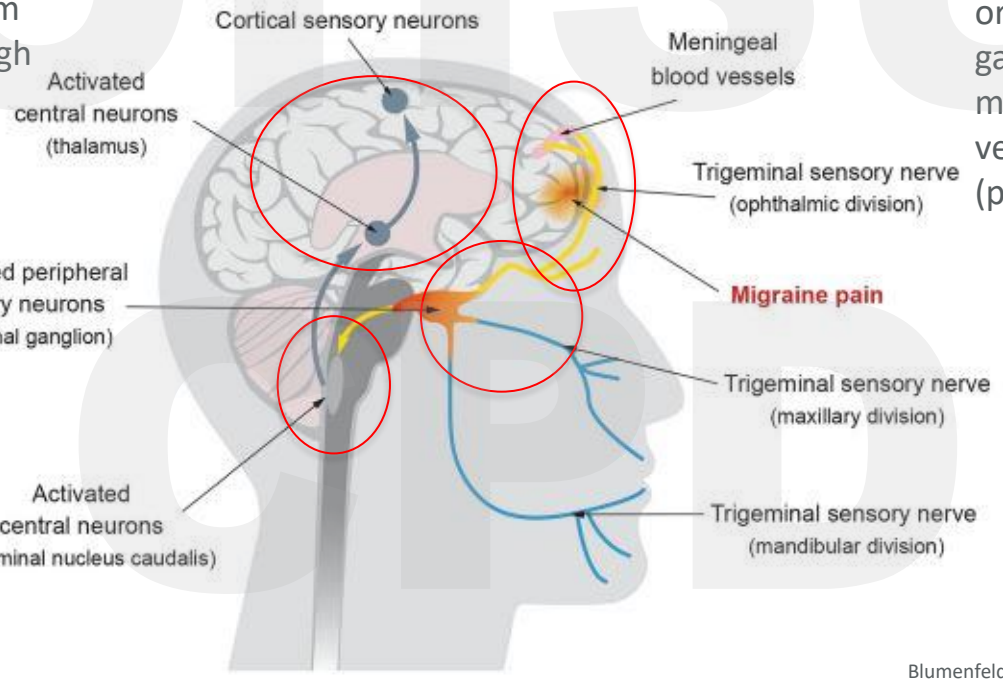
Powers et al, *Pediatrics* 2003;

- Compared to their peers without migraine, children with migraine miss more school and perform more poorly in school[1]
  - Higher headache frequency predicts worse school performance[1]
- "..over **130,000 school days** are missed **every 2 weeks** due to pediatric migraine"[2]

[1]Arruda *et al*., *Neurology* 2012; [2]Hershey *et. al*., *Headache 2013;* Powers et al, *Pediatrics* 2003

How does migraine happen? The trigeminovascular system

3. Sensory input from TCC is relayed through the thalamus to cortical sensory neurons



1. Pain-sensing fibers originate in trigeminal ganglion and innervate meninges and blood vessels via V1 (peripheral)

2. Afferent fibers from trigeminal ganglion terminate in the "trigeminocervical complex" (TCC) in the brainstem

4. Signaling mediated by nociceptive neuropeptides: Substance P, neurokinin A AND…CGRP!

Blumenfeld et al, *Neurol Ther* 2021

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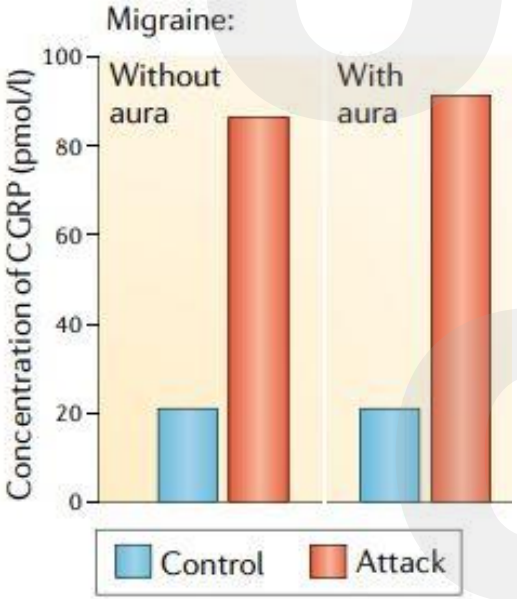
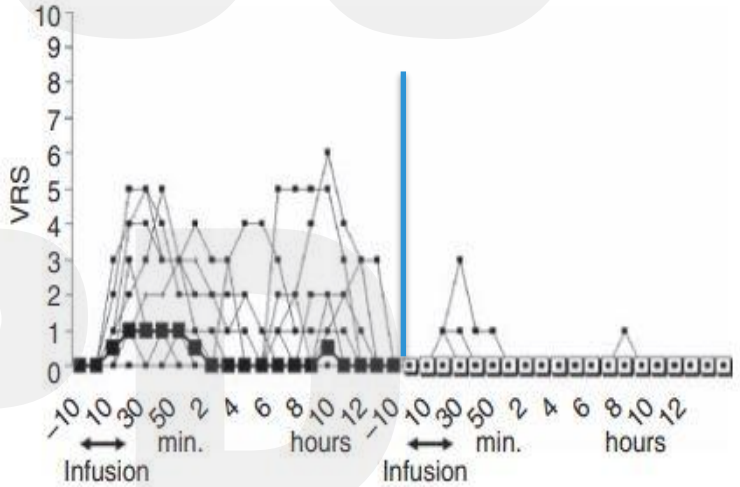
So what is CGRP and what does it do?

- Nociceptive neuropeptide present throughout the trigeminovascular system, potent vasodilator of cerebral arteries, and seems to be involved in pathophysiology of migraine!



Goadsby and Edvinsson, *Ann Neurol* 1993; Fig: Edvinsson Nature Neurol 2018



Hansen et al, *Cephalalgia* 2010

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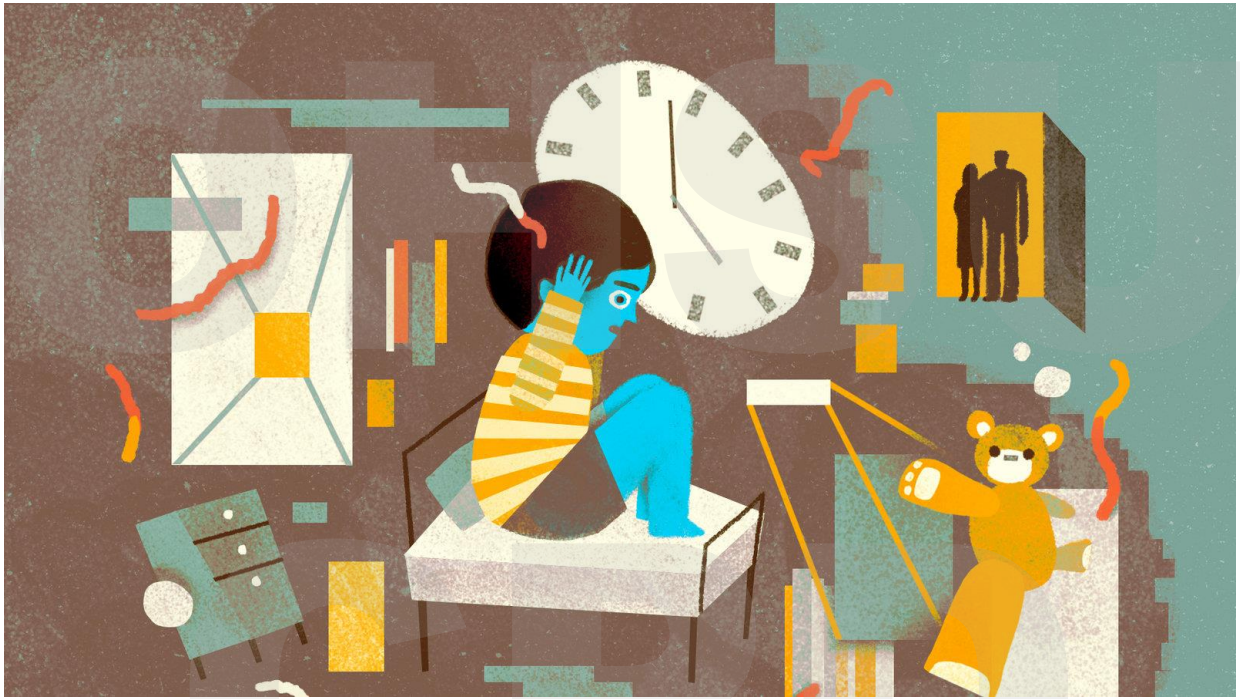

Photo: nytimes.com

Pediatric Migraine Treatment: Current Approach

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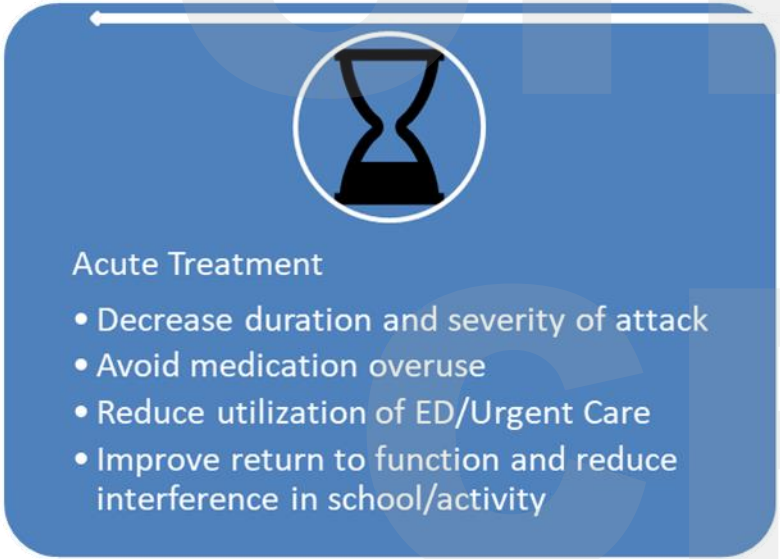
Imagine….

- Additional history:
  - Headaches are infrequent but can last 6 hours or sometimes 2 days
  - Vomiting with at least half the headaches, often starts within 30 minutes of the headache so doesn't always help
- How can we help?

Approach to Migraine Treatment



*Consider when bothersome headaches are occurring >1 day per week or causing significant functional impact

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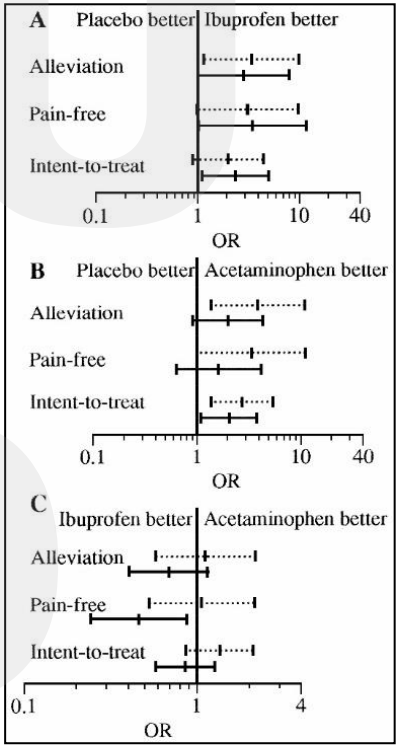
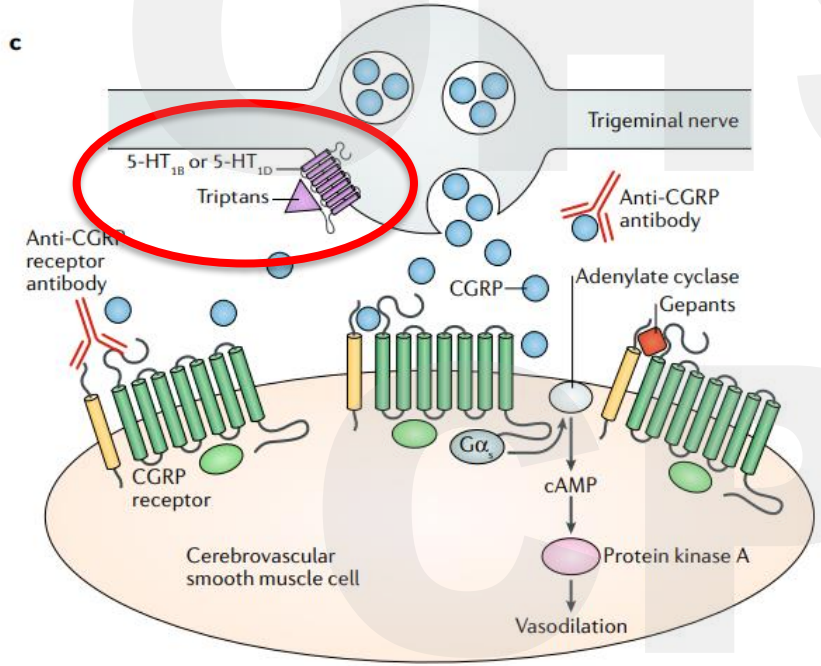
Pediatric Migraine: Acute Treatment

- First line: Effective OTC options:
  - Acetaminophen 15 mg/kg OR ibuprofen 10 mg/kg
  - Both superior to placebo; ibuprofen maybe more helpful



1 Hamalainen *et. al., Neurology* 1997;2 Lewis *et. al., Headache*, 2002; 3 Lipton Neurology 2015; 4 Cady Headache 2014

Pediatric Migraine: Acute Treatment



Second line: Triptans (5-$HT_{1b/1d}$ agonists)

- Side effects: nausea, malaise, flushing, chest/neck "tightness"
- Contraindications: Cerebrovascular disease, cardiovascular disease, uncontrolled hypertension, hemiplegic migraine/brainstem aura

➢ Generally safe in children with young healthy vessels!

Edvinsson Nature Neurol 2018

Pediatric Migraine: Acute Treatment

Triptan	Forms	Dose <40 kg	Dose >40 kg	Ped Approval
Almotriptan	PO	6.25 mg	12.5 mg	12-17 yo (2009)
Rizatriptan	**MLT,** tab	5 mg	10 mg	**6**-17 yo (2011) - MLT
Sumatriptan	PO (sumatriptan also NS and SQ)	10/60 mg – 85/500 mg (Sumatriptan alone: 25 mg (<40 kg) – 50 mg (>40 mg)		12-17 yo (2015) as PO sumatriptan / naproxen combo
Zolmitriptan	N**S**	2.5 mg	5 mg	12-17 yo (2015) - NS

Triptan	Forms	Dose	Ped Approval
Frovatriptan	PO	2.5 mg	N/A (≥ 18)
Naratriptan	PO	1 mg, 2.5 mg	N/A (≥ 18)
Eletriptan	PO	20 mg, 40 mg, 80 mg	N/A (≥ 18)

 Adapted from Dr. Amy Gelfand

FDA.gov; Lewis *et al. Pediatrics* 2007; Ho *et al, Cephalalgia* 2012; Hewitt *et. al Headache* 2013; Linder *et al Headache* 2008

Pediatric Migraine: Acute Treatment Guidelines

1. Establish specific headache diagnosis!
2. Treat early, with ibuprofen and/or triptan (*unless* contraindication)
3. Counsel about "**trial and error**" and "risks and benefits"; try a second triptan if the first doesn't work; consider **non-oral routes** if nausea/vomiting or rapid onset
4. Offer **[NSAID] PLUS triptan** to improve efficacy and duration
5. Offer **anti-emetics** if nausea and vomiting are bothersome
6. Discuss lifestyle factors and triggers, collaborate on goals, track response with headache diary and monitor for medication overuse

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Acute treatment of migraine in children and adolescents

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

Maryam Oskoui, MD, MSc, Tamara Pringsheim, MD, Yolanda Holler-Managan, MD, Sonja Potrebic, MD, PhD, Lori Billinghurst, MD, MSc, David Gloss, MD, MPH&TM, Andrew D. Hershey, MD, PhD, Nicole Licking, DO, Michael Sowell, MD, M. Cristina Victorio, MD, Elaine M. Gersz, Emily Leininger, Heather Zanitsch, Marcy Yonker, MD, and Kenneth Mack, MD, PhD

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Neurology® 2019;93:487-499. doi:10.1212/WNL.0000000000008095

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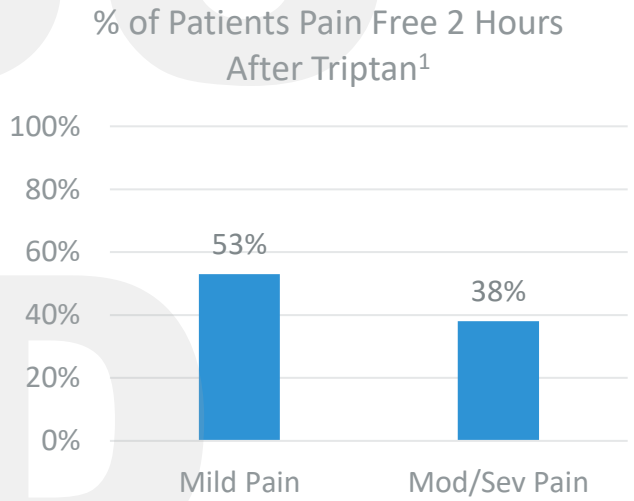
Oskoui et al, *Neurology* 2019; 1 Goadsby, *Cephalalgia*, 2008; 2 Brandes *et. al.,* JAMA 2007; 3 De Felice Ann Neurol 2010

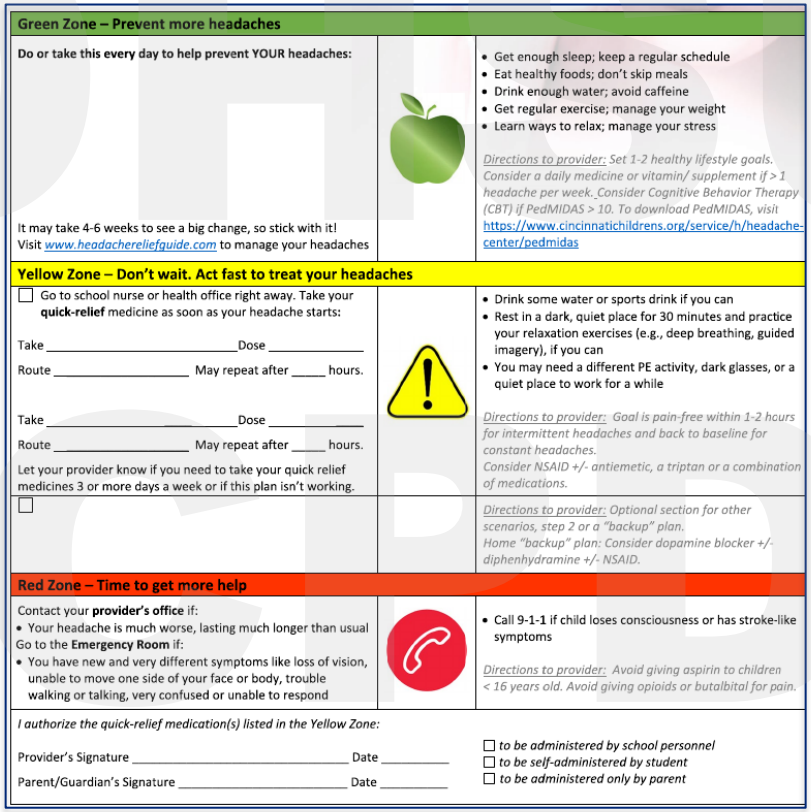
Pediatric Migraine: Acute Treatment

- Triptan Pearls
  - Better to take early when pain is MILD (53% pain free at 2h)[1]
    - BUT okay to take when mod/sev (38% pain free at 2h)
  - Choose formulation based on speed of action and mode of administration
  - Take with NSAID!
    - Higher 2h pain-free rate, lower 24h recurrence (adults)[2]
  - Safe to re-dose but no strong evidence for better efficacy
    - Better to dose adequately at the onset and make sure dosing is appropriate
  - Limit to <10 days per month to decrease risk of medication overuse[3]



1 Goadsby, *Cephalalgia*, 2008; 2 Brandes *et. al.,* JAMA 2007; 3 De Felice Ann Neurol 2010

Pediatric Migraine: Acute Treatment



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.

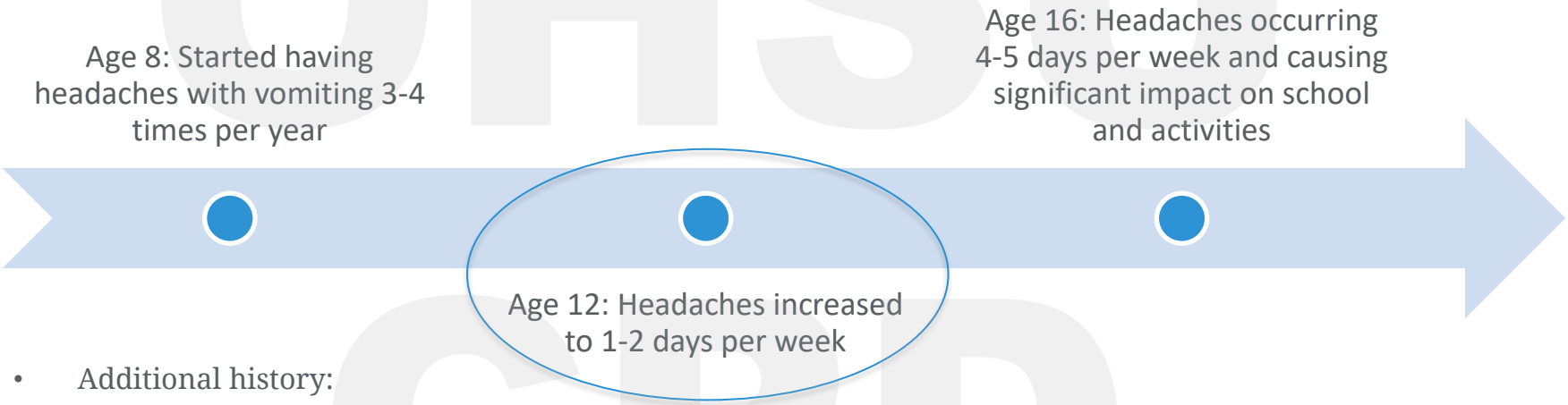
I authorize the quick-relief medication(s) listed in the Yellow Zone:

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*

Turner et al, Headache 2019

Imagine….



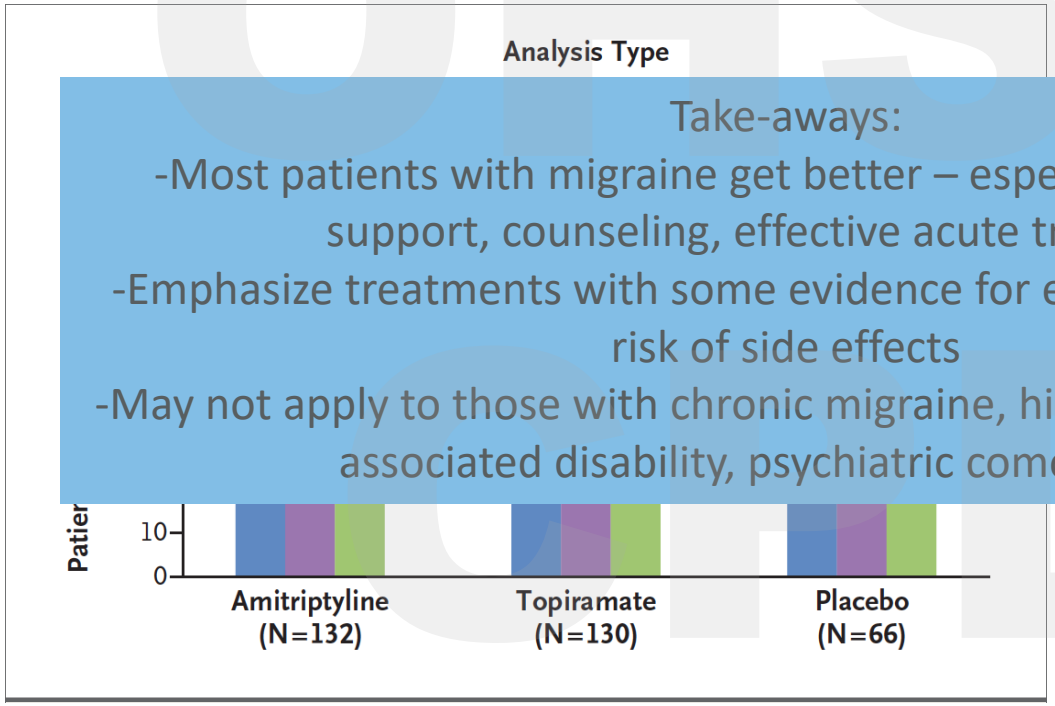
- Additional history:
  - Started ibuprofen +/- sumatriptan nasal spray +/- ondansetron for as-needed treatment, very effective when headaches occur!
  - BUT headaches seem to be happening more and more often and are interfering more with dance class
- How can we help?

Pediatric Migraine: Preventive Treatment

- Topiramate is the only FDA-labeled *medication* for migraine prevention in adolescents 12-17
  - No migraine preventive labeled for <12 yo's
- Principles of treatment:
  - Try one treatment at a time for minimum of 8 weeks
    - Goal: 50% reduction in headache frequency over 2-3 months
  - Choice of medication depends on evidence for effectiveness, co-morbidities, patient preferences

Pediatric Migraine: The "CHAMP" Trial

Child and Adolescent Migraine Prevention Study



Take-aways:

-Most patients with migraine get better – especially with lifestyle support, counseling, effective acute treatment!

-Emphasize treatments with some evidence for effectiveness and low risk of side effects

-May not apply to those with chronic migraine, high rates of headache-associated disability, psychiatric comorbidities

- 1 syncope with amitriptyline
- 1 suicide attempt with topiramate

*75% with episodic migraine

Powers *et al, NEJM* 2016

What are our current treatment options for migraine prevention in Peds?

SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

Maryam Oskoui, MD, MSc, Tamara Pringsheim, MD, Lori Billinghurst, MD, MSc, Sonja Potrebic, MD, PhD, Elaine M. Gersz, David Gloss, MD, MPH&TM, Yolanda Holler-Managan, MD, Emily Leininger, Nicole Licking, DO, Kenneth Mack, MD, PhD, Scott W. Powers, PhD, ABPP, Michael Sowell, MD, M. Cristina Victorio, MD, Marcy Yonker, MD, Heather Zanitsch, and Andrew D. Hershey, MD, PhD

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Neurology® 2019;93:500-509. doi:10.1212/WNL.0000000000008105

What are our current treatment options for migraine prevention in Peds?

- Recommend discussing lifestyle modification and discussion of modifiable risk factors (Level B)
- Recommend discussion of role or preventive treatments in those with frequent headaches, migraine-related disability and medication overuse (Level B)
- Recommend informing families of placebo response rates in trials and that majority of preventives are not superior to placebo, with shared decision making about pros/cons of short-term treatment trials (Level B)

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Oskoui et al, *Neurology* 2019

Pediatric Migraine: Prevention

- Try to eat a healthy diet and avoid prolonged fasting
- Stay hydrated and limit caffeine
- Stay active with aerobic exercise
- Maintain a consistent sleep schedule with adequate sleep

Headachereliefguide.com

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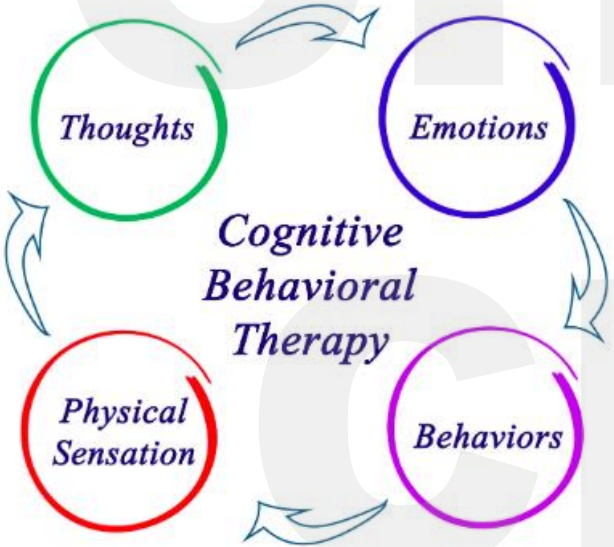
Pediatric Migraine: Prevention



- Emphasis on multi-disciplinary approach!
- Cognitive Behavioral Therapy
  - Children and adolescents (10-17) who received CBT + amitriptyline had greater reduction in headache and headache-related disability (Headache Education ("placebo") + amitriptyline)
  - Also supported by systematic review and meta-analysis[2,3]
- Other behavioral interventions – mindfulness, biofeedback – may have benefit as well

1 Powers et al, JAMA 2013; 2 Fisher et al, Cochrane Reviews 2018; 3 Ng et al Headache 2017

Pediatric Migraine: Prevention

- Over-the-counter medications/supplements
  - Riboflavin 100-200 mg BID
  - Coenzyme Q10 50-100 mg BID (1-3 mg/kg/d)
  - Melatonin 1-3 mg QHS
  - Magnesium 200-400 mg QD
- May choose based on side effects, ability to take PO, comorbidities

[1]Bruijn et al Cephalalgia 2010;[2]MacLennan J Child Neurol 2009;[3]Talebian Nutrients 2018;[4]Miano Neural Sci 2008; [5]Fallah Curr Drug Saf 2015; [6]Hershey Headache 2007; [7]Slater Cephalalgia 2011

Pediatric Migraine: Prevention

Table Outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Decreased frequency of migraine or headache days	Amitriptyline (1 mg/kg/d) combined with CBT	Topiramate (100 mg/d or 2–3 mg/kg/d) Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) Flunarizine (5 mg/d) Nimodipine (10–20 mg, 3 times a day) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased headache severity		Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				
At least a 50% reduction in headache frequency	Amitriptyline (1 mg/kg/d) combined with CBT		Propranolol (20–40 mg, 3 times a day) Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)			Topiramate (100 mg/d or 2–3 mg/kg/d) DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased migraine-related disability		Amitriptyline (1 mg/kg/d) combined with CBT			Topiramate (100 mg/d or 2–3 mg/kg/d)	Amitriptyline (1 mg/kg/d)

Abbreviations: CBT = cognitive behavioral therapy; DVPX ER = extended-release divalproex sodium.

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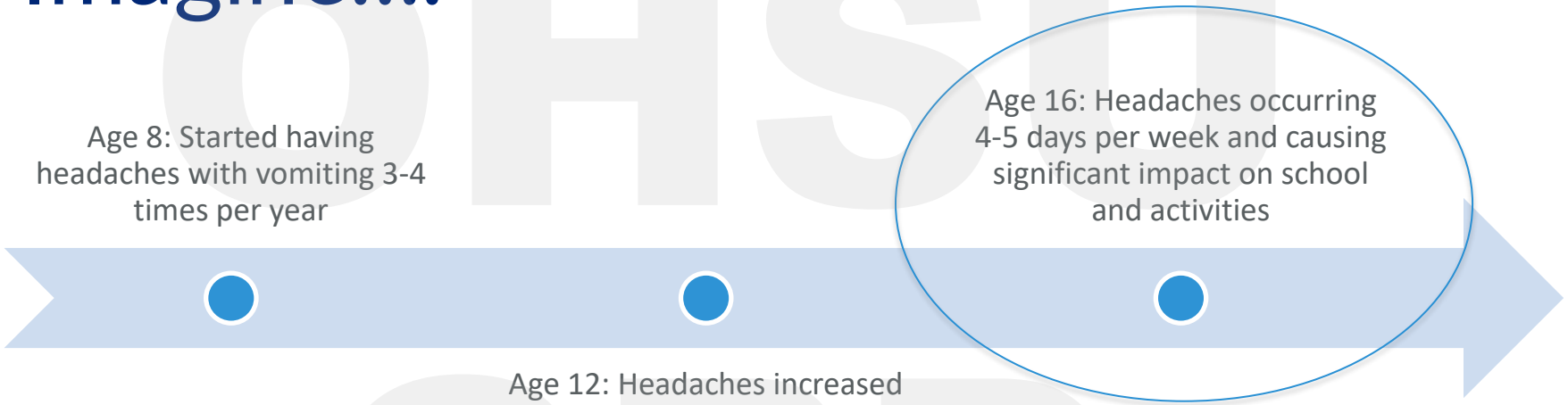
Oskoui et al, *Neurology* 2019

Pediatric Migraine: Prevention

Prescription Preventive Medications

- Amitriptyline 1-2 mg/kg/d
  - Consider if: Sleep is also a problem, sometimes can help mood (though also risk of suicidality)
- Topiramate ~2 mg/kg/d (generally 50-100 mg daily)
  - *Only FDA-approved med
  - Consider if: Overweight, on other anti-depressants, other contraindications to TCAs/beta-blockers
- Propranolol 1-2 mg/kg/d
  - Consider if: Tremor, POTs, anxiety; NOT for asthma, DM, serious athletes
- (Cyproheptadine 0.2-0.4 mg/kg/d)
  - Consider if: younger kid, appetite/sleep are also problems, episodic syndromes
- Other pill-based preventives: Candesartan, memantine, venlafaxine, valproic acid

Imagine….



- Additional history:
  - Has been really consistent with sleep, exercise, hydration and diet
  - Established with a therapist which has been helpful for sleep, anxiety AND headaches
  - Started riboflavin – helped some, but not enough
  - Tried topiramate – caused side effects
  - Saw a neurologist -> tried amitriptyline – helped some, but not enough, also has asthma – beta-blockers not ideal
- Is there anything else we can do??

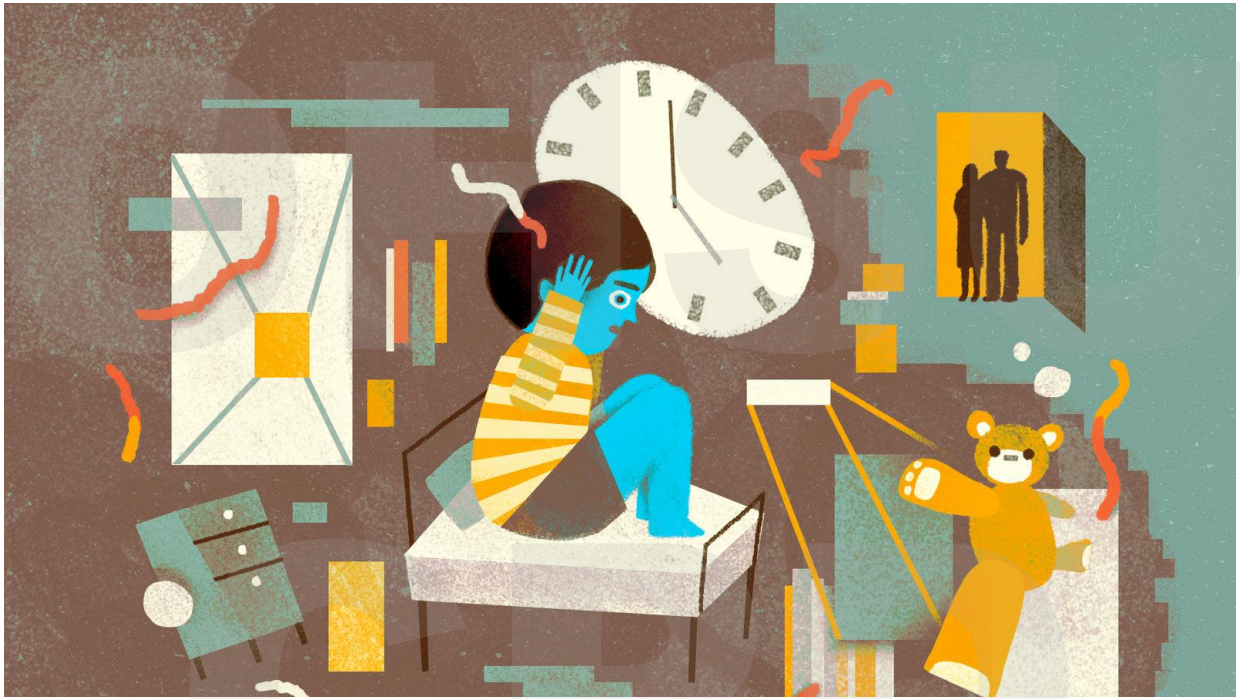


Photo: nytimes.com

Pediatric Migraine Treatment: Beyond Pills and The Future!

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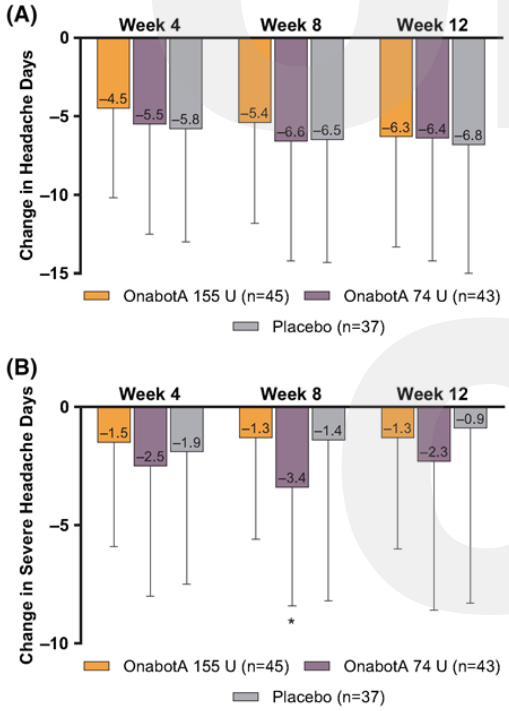
Pediatric Migraine: Prevention



- What about Botox?
  - Retrospective studies and case series suggest efficacy in chronic migraine and/or chronic daily headache[1-6]
  - One placebo-controlled, double-blind RCT in *n*=125 patients with chronic migraine[7]
    - ONE treatment cycle with onabot 155U (*n* = 45), onabot 74U (*n*=43) or placebo (*n* = 37)
    - Did not meet primary endpoint (reduction in headache by 4 days)
    - No serious adverse effects; neck pain and musculoskeletal pain reported more often in onabot group (6% vs 0% and 5% vs 0%)
- More placebo-controlled studies are needed but may be helpful for some patients

1 Kabbouche et al, *Curr Neurol Neurosci Rep* 2012;2 Ahmed *Pediatr Neurol* 2010; 3 Havat et al, *Pediatr Neurol* 2014; 4 Chan et al, *J Neurosci* Nurs 2009; 5 Yonker et al, *Headache* 2016; 6 Pezzuto et al, *Ann Neurol* 2016; 7 Winner et al, *Headache 2020* ;

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Migraine Treatment: What else is there?

- Neuromodulation!
  - Three devices **approved** in adolescents >12!

Remote electrical nerve stimulation (REN)

(acute and preventive)

External vagal nerve stimulation (eVNS)

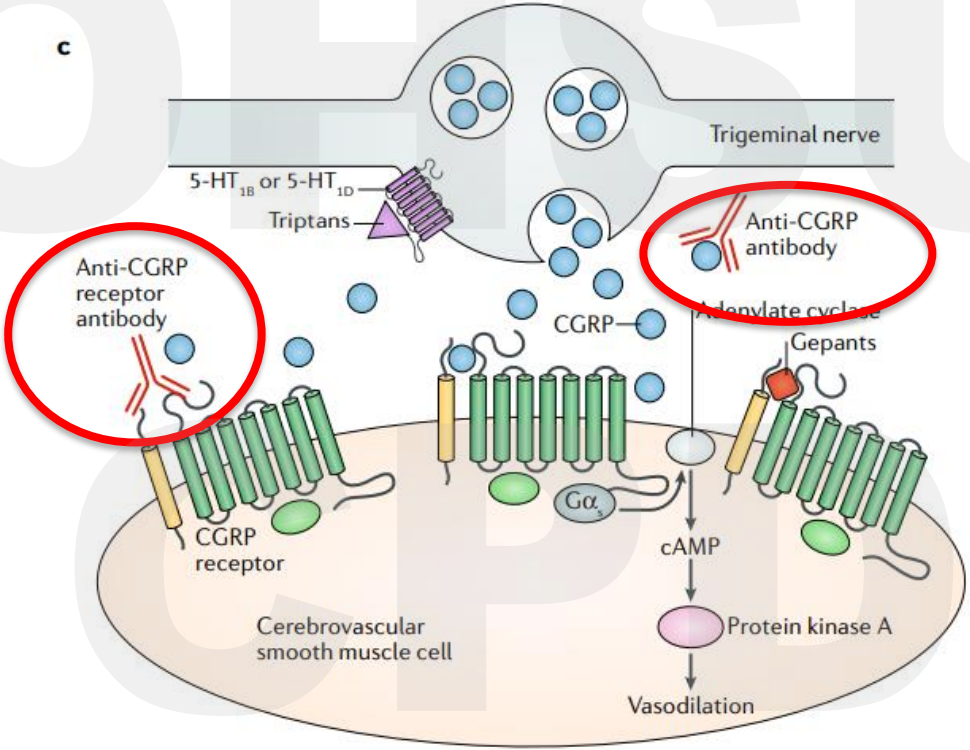
(acute and preventive)

Single pulse transcranial magnetic stimulation (sTMS)

(acute and preventive)

- Plus external trigeminal nerve stimulation (eTNS) (Cefaly) and external combined occipital and trigeminal nerve stimulation (eCOT-NS) (Relivion) in adults

Migraine Treatment: What else is there?



- Note: no anti-CGRP medications have been approved yet in pediatrics!

Edvinsson Nature Neurol 2018

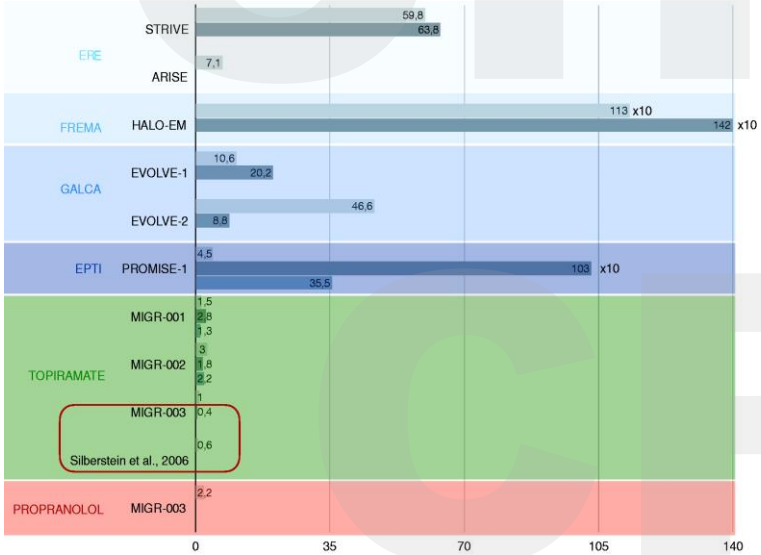
Anti-CGRP monoclonal antibodies

	Target	Dose	Mode
Erenumab (Aimovig)	CGRP Receptor	70 or 140 mg monthly	Subcutaneous
Fremanezumab (Ajovy)	CGRP Molecule	225 mg monthly or 675 mg quarterly	Subcutaneous
Galcanezumab (Emgality)	CGRP Molecule	120 mg or 240 mg monthly	Subcutaneous
Eptinezumab (Vyepti)	CGRP Molecule	100 - 300 mg quarterly	Intravenous

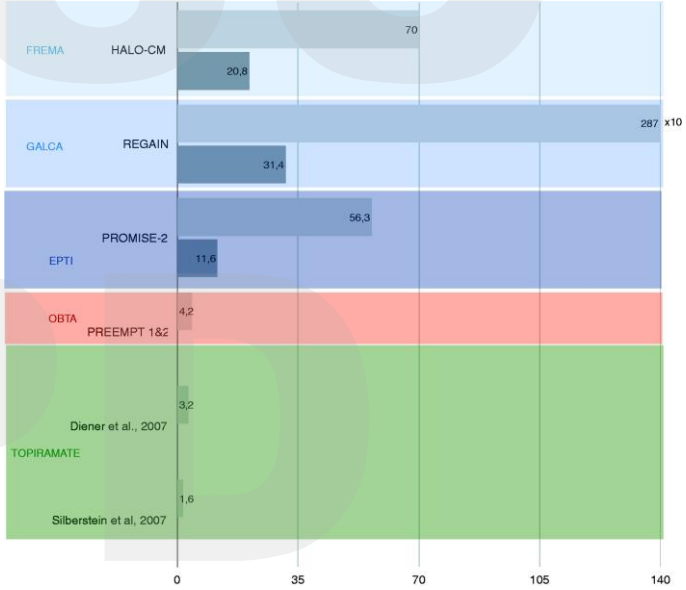
Side effects: Constipation, injection site reaction, hypersensitivity, ?hypertension (erenumab); case reports of Raynaud, RCVS, alopecia

Anti-CGRP mAbs: What's the data?

LHH: Likelihood to help (50% responder rate) vs harm



Episodic migraine



Chronic migraine

Drelia et al, *Cephalagia 2021*

Anti-CGRP mAbs in children and adolescents

TABLE 2.
Efficacy and Functional Status Outcomes After mAb Treatment

Outcome Measure	First Follow-up Mean (S.D.) Time: 2.7 (2.3) Months	Second Follow-up Mean (S.D.) Time: 4.6 (1.9) Months
Prescribed mAb *n* (%)	*n* = 112	*n* = 74
Erenumab	97 (86.6%)	65 (87.8%)
Galcanezumab	8 (7.7%)	4 (5.4%)
Fremanezumab	7 (6.2%)	5 (6.8%)
Missing data	0	38
Headache frequency (days/month)	*n* = 110	*n* = 66
Mean (S.D.)	24.6 (9.0)	25.3 (8.2)
Median (IQR)	30 (20-30)	30 (24-30)
Mean difference from baseline (95% CI)	−2.0 (−0.8 to −3.2)* *P* = 0.001*	−1.4 (−0.03 to −2.8) *P* = 0.045*
Reported benefit	*n* = 112	*n* = 73
Significant benefit	33 (29.5%)	22 (30.1%)
Some benefit	47 (42.0%)	29 (39.7%)
No benefit	27 (24.1%)	17 (23.3%)
Worsened	5 (4.5%)	5 (6.8%)
Not documented in chart or missing data	0	1
Reported functional status	*n* = 94	*n* = 67
Significant improvement	31 (33.0%)	15 (22.4%)
Some improvement	27 (28.7%)	21 (31.3%)
No improvement	31 (33.0%)	22 (32.8%)
Worsened	5 (5.3%)	9 (13.4%)
Not documented in chart or missing data	18	7
Pediatric Migraine Disability Assessment score	*n* = 19	*n* = 11
Median (IQR); *n*	47 (10-197)	34 (25-126)
Mean difference from baseline (95% CI)	−17 (−21 to 55)	−14 (−61 to 88)
Participants reporting *resolution* of continuous headache after treatment *n* (%)	9/74 (12%)	8/48 (17%)
Most common facet of improvement noted "Less severe" headache *n* (%)	*n* = 57/112 (50.9%)	*n* = 35/74 (47.3%)

- *n*=112 adolescent patients prescribed an anti-CGRP mAB for migraine prevention
  - mean age: 15.9 (10.3-17.8))
  - 81% female
- 84% chronic migraine, 11% NDPH, 5% PPTH
- "Refractory" population
  - Mean # years with headache: 6 (3 years "significant")
  - Mean baseline headache frequency: 27 days/month
  - 68% with continuous headache
  - Mean baseline PedMIDAS score: 120 ("severe disability)
  - Mean number of preventives tried: 9.5 (2-27)

Greene et al, *Pediatric Neurology* 2020

Anti-CGRP mAbs in children and adolescents

Side Effect	Number Reporting a Side Effect *n* (%)
Any side effect	36 (32.1%)
Injection site reaction	19 (17.0%)
Constipation	9 (8.0%)
Fatigue (+ *"sleepiness" x2; "washed out" x1*)	8 (7.1%)
Dizziness or syncope	5 (4.5%)
Nausea	4 (3.6%)
Worsening headache	4 (3.6%)
Other (*each was reported by n = 1, 0.9%*)	Arthralgia, nasopharyngitis, alopecia, decreased appetite, memory/awareness difficulties, flu-like illness, eye twitching, stomachache, sore leg
Discontinued CGRP mAb because of side effects	5 (4.5%)
Reasons for discontinuation cited	Episode of syncope and worsening headache ($n = 1$), worsening constipation ($n = 1$), dizziness and hair loss ($n = 2$), convulsion (undetermined if syncopal or epileptic) ($n = 1$)

Greene et al, *Pediatric Neurology* 2020

Anti-CGRP mAbs in children and adolescents

Statement from the Pediatric Special Interest Group of the American Headache Society:

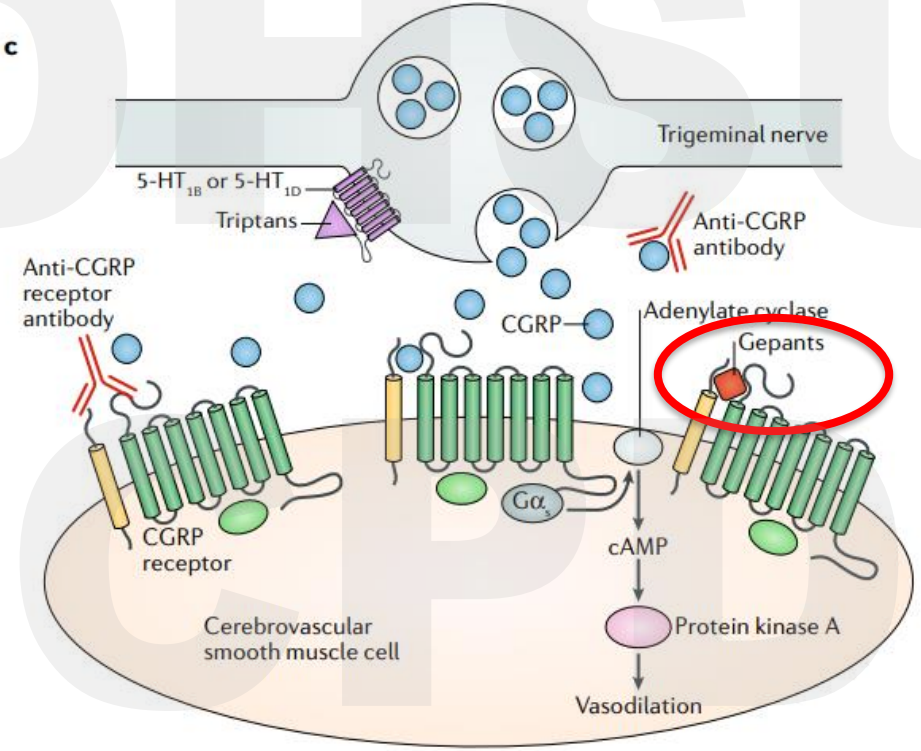
Table 1.—Suggested Indications, Contraindications, and Monitoring for the Use of CGRP mAbs in Children and Adolescents With Migraine

Indications	Contraindications	Monitoring
• ≥8 headache days per month • PedMIDAS score ≥30 • Failure of ≥2 preventive therapies (pharmacologic, nutraceutical, and/or non-pharmacologic) • Post-pubertal adolescent, or pre-pubertal child in selected cases	• Disturbed blood-brain barrier (eg, recent history of meningitis, recent neurosurgery) • Severe cardiovascular disease, stroke • Pregnancy, planned pregnancy or breast-feeding	• Pubertal status • Bone health, consider checking Vitamin D status • Linear growth • Weight/BMI • Infections • Pregnancy status

BMI = body-mass index.

Szperka et al, *Headache* 2018

CGRP-Targeted Therapy



- Note: no anti-CGRP medications have been approved yet in pediatrics!

Edvinsson Nature Neurol 2018

The "gepants"

"Gepants"	Indications	Dose	Side Effects
Atogepant (Qulipta)	Prevention (episodic migraine)	10, 30 or 60 mg tab once daily	Nausea, constipation, decreased appetite, fatigue
Rimegepant (Nurtec)	Acute Prevention (episodic migraine)	75 mg ODT every 24 hours PRN 75 mg ODT every other day	Nausea, abdominal pain/dyspepsia
Ubrogepant (Ubrelvy)	Acute	50 or 100 mg tab PRN; max 200 mg/24h	Nausea, somnolence, dry mouth
Zavegepant (Zavspret)	Acute	10 mg NS every 24 hours PRN	Nausea, dysgeusia

Migraine Prevention: New Recs?

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FEATURE ARTICLE

Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update

Andrew C. Charles MD[1] | Kathleen B. Digre MD[2] | Peter J. Goadsby MD, PhD[1,3] | Matthew S. Robbins MD[4] | Andrew Hershey MD, PhD[5,6] | on behalf of The American Headache Society

TABLE 2 Updated recommendations for migraine prevention.

A Diagnosis of episodic migraine with or without aura (4–14 MMDs) based upon ICHD-3 with at least moderate disability (MIDAS score ≥11 or HIT-6 score >50). Treatments to consider include:

1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
9. Small-molecules targeting the CGRP receptor ("gepants") including atogepant and rimegepant

B Diagnosis of chronic migraine with or without aura (≥15 MHDs) based upon ICHD-3. Treatments to consider include:

1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. OnabotulinumtoxinA
9. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
10. Small-molecules targeting the CGRP receptor ("gepants") including atogepant

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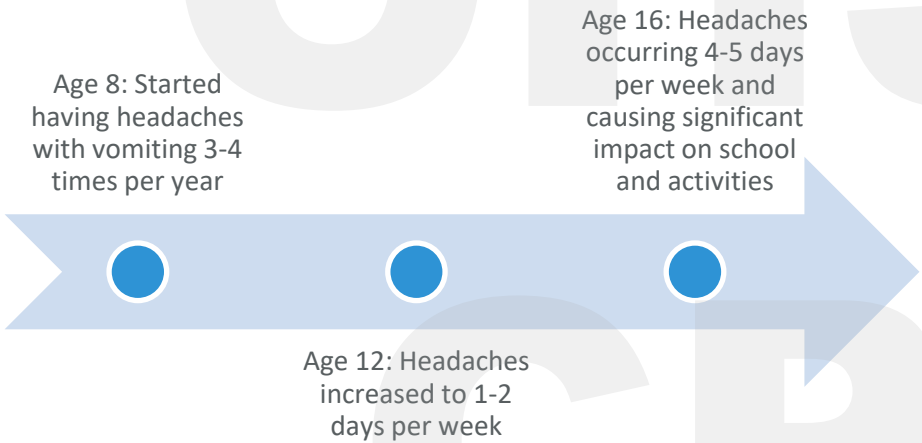
Charles et al, *Headache* 2024

Imagine….



- Engaged in lifestyle treatments including CBT
- Tried several preventives with some improvement but needed more help
- Started on erenumab 70 mg SQ monthly
  - Headache frequency reduced to 14 days per month but only 2 severe headaches per month
- As needed treatments are still working!
  - No longer having as much vomiting with headache, switched to oral sumatriptan
  - Started using the REN device as needed for attacks to help reduce acute medication reliance
- No longer missing school! Back to dance!

Conclusions/Take Away

- Migraine: not “just a headache”
  - Non-headache symptoms can also be problematic
  - Can be a source of significant disability in children and adolescents!
- Migraine is a complex brain disorder of involved disrupted pain signaling in the “trigeminovascular system”
  - Calcitonin gene-related peptide (CGRP) is found throughout the trigeminovascular system and plays a key role in migraine pathogenesis
- Guidelines published for acute and preventive treatment of migraine
  - Acute: NSAIDs, triptans, anti-emetics
  - Preventive: Lifestyle, consider supplements and/or prescription medication in those with frequent headache
  - Role of procedures and devices
- Help is on the way!
  - Anti-CGRP monoclonal antibodies (erenumab/Aimovig, galcanezumab/Emgality, fremanezumab/Ajovy and eptinezumab/Vyepti)
  - “Gepants” (rimegepant/Nurtec, ubrogepant/Ubrelvy, atorgepant/Qutipla

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Thank You