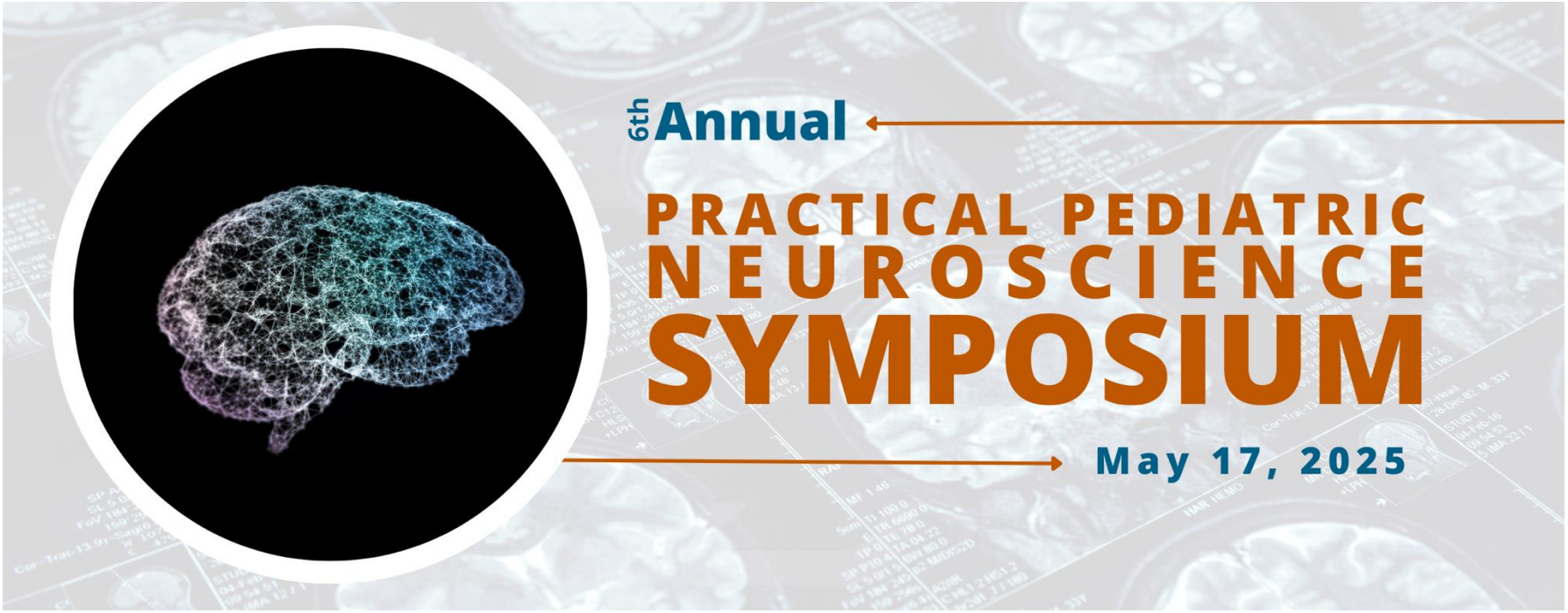


The University of Texas at Austin
Dell Medical School

dell children's
Ascension

The University of Texas at Austin
Dell Medical School

dell children's
Ascension

UPDATE ON PEDIATRIC MIGRAINE: Focus on Neuromodulation

Samantha Irwin, MSc; MB BCh BAO; FRCPC Neurology

Associate Professor of Neurology
UT Health Austin Pediatric Neurosciences at Dell Children's

The University of Texas at Austin
Dell Medical School

dell children's
Ascension

The video of the following presentation has been made available for free by UT Health Austin Pediatric Neurosciences at Dell Children's at:

https://youtu.be/vKwvEDXHCWM?feature=shared

To see all event presentations, please use this link for the 6th Annual Practical Pediatric Neuroscience Symposium presentation playlist:

https://youtube.com/playlist?list=PLPPnZ7QxWdeR-cpRyBnU2C2eEVh1bW1YR& feature=shared

Interprofessional Continuing Education

Disclosure

Samantha Irwin, MBBS

1. Has the following relevant financial relationships with ACCME-defined commercial interests:
    a. ***Consulting Fee-Pfizer (Any division)|Consulting Fee-Merz (Any division)|Consulting Fee-Theranica|Grant or research support-AbbVie (Any division)|Grant or research support-Pfizer (Any division***
2. I will discuss off-label use and/or investigational use in my presentation.
3. All Ascension planners, reviewers and course directors have no relevant financial relationships with ACCME-defined commercial interests

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

IPCE CREDIT™

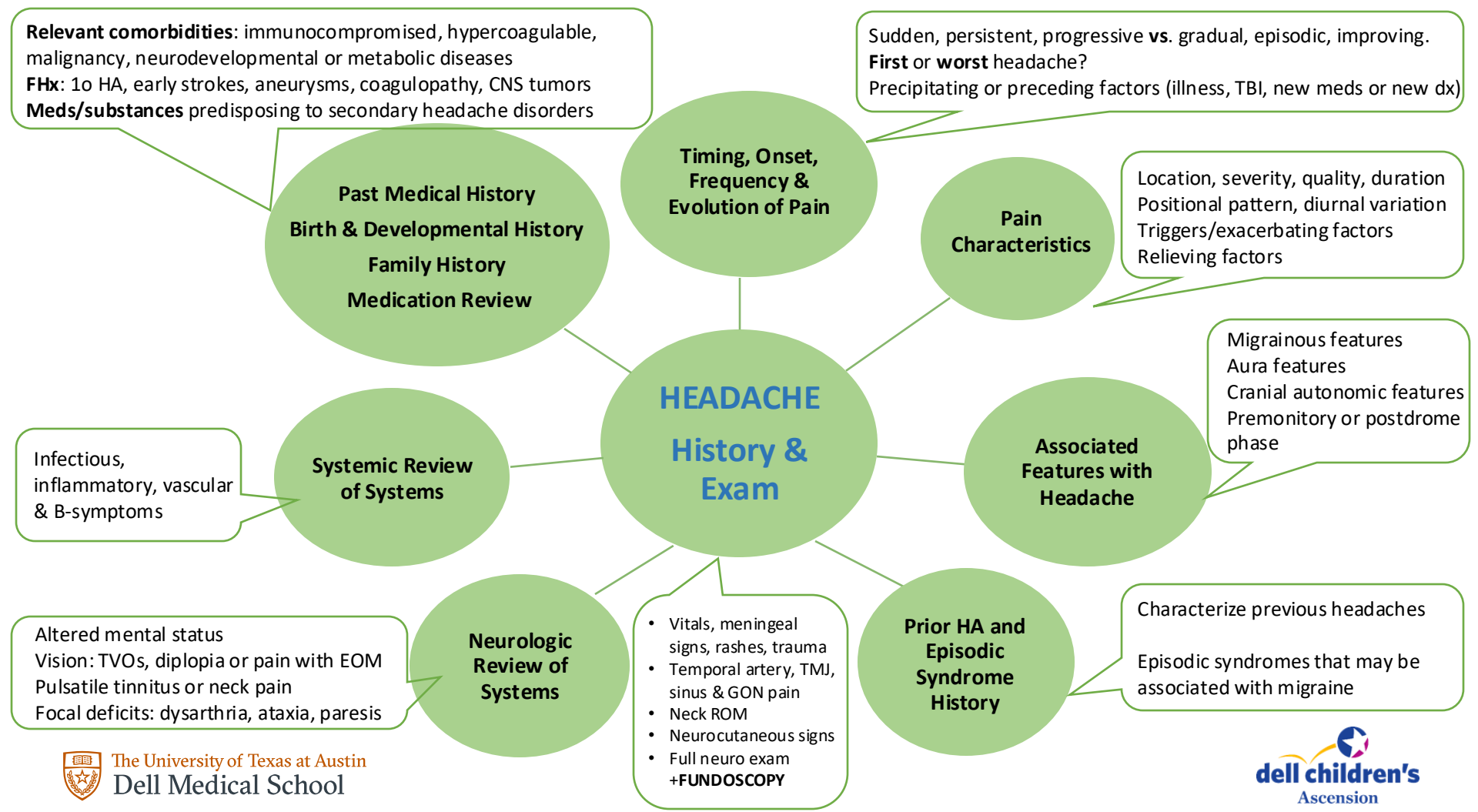
A commercial interest is any entity producing marketing, re-selling, or distributed health care good and services consumed by, or used on, patients.

Lecture Overview & Objectives

- Review how to take a focused headache history and diagnose pediatric migraine.
- Identify red flags and when a diagnostic workup is needed.
- Discuss appropriate management options, including neuromodulation.*

****Many treatments discussed are off-label in pediatrics and adolescents.***

Headache History & Examination


Relevant comorbidities: immunocompromised, hypercoagulable, malignancy, neurodevelopmental or metabolic diseases
FHx: 1o HA, early strokes, aneurysms, coagulopathy, CNS tumors
Meds/substances predisposing to secondary headache disorders
Past Medical History
Birth & Developmental History
Family History
Medication Review
Sudden, persistent, progressive **vs**. gradual, episodic, improving.
First or **worst** headache?
Precipitating or preceding factors (illness, TBI, new meds or new dx)
Timing, Onset, Frequency & Evolution of Pain
Pain Characteristics
Location, severity, quality, duration
Positional pattern, diurnal variation
Triggers/exacerbating factors
Relieving factors
HEADACHE
History & Exam
Migrainous features
Aura features
Cranial autonomic features
Premonitory or postdrome phase
Associated Features with Headache
Infectious, inflammatory, vascular & B-symptoms
Systemic Review of Systems
Altered mental status
Vision: TVOs, diplopia or pain with EOM
Pulsatile tinnitus or neck pain
Focal deficits: dysarthria, ataxia, paresis
Neurologic Review of Systems
• Vitals, meningeal signs, rashes, trauma
• Temporal artery, TMJ, sinus & GON pain
• Neck ROM
• Neurocutaneous signs
• Full neuro exam +**FUNDOSCOPY**
Prior HA and Episodic Syndrome History
Characterize previous headaches
Episodic syndromes that may be associated with migraine
The University of Texas at Austin
Dell Medical School
dell children's
Ascension

CASE

Case Example

- 12-year-old female.
- History of mild and intermittent headaches since she was **7 years old.**
- Headache became **troublesome six months ago, at age 11 years**. Menstruation started 3 months ago.
- **Frequency**:
  - 4 headaches per week = ***16/30 headache days a month.***
  - 8 days are severe and have associated features.
- **Duration**: 2 hours.
- **Location**: Bitemporal. **Quality**: Throbbing.
- **Associated symptoms**: Nausea & osmophobia (smell sensitivity).
- No aura. No cranial autonomic features. Denies premonitory or postdromal symptoms.
- **Family history:** Migraine present in her mother and maternal grandmother. No aura in the family.
- **"Episodic syndromes that may be associated with migraine"**: + Infantile colic.
- **Pediatric "migraine markers"**: + Motion sickness.
- **Past medical history**: Unremarkable.
- **Examination**, including fundoscopy: Normal.

Diagnostic Pearls for Pediatric Migraine

- **Case dx: chronic migraine without aura** *(>15 HA days a month, >8 severe HA/migraine, for 3 months)*
- **Duration**: **2 hours** – accepted in ICHD-3 dx criteria for pediatric migraine (vs. 4-72 hours in adults)
- **Location**: **BITEMPORAL** – accepted in ICHD-3 dx criteria for pediatric migraine (vs. unilateral in adults)
- **Associated symptoms:**
  - **Only need** 1 of nausea and/or vomiting per the criteria for diagnosis
  - Not necessary to have photophobia (light) or phonophobia (sound) to make diagnosis (if using, need both, can infer)
  - **Osmophobia** (smell sensitivity) is helpful for differentiating migraine vs. tension-type headache
- The **peri-menarcheal** period is a common period for onset/worsening.
- **Other supportive features:**
  - **Episodic syndromes that may be associated with migraine:** infantile colic, benign paroxysmal torticollis (BPT), benign paroxysmal vertigo of childhood (BPVC), recurrent GI disturbance
  - **Pediatric "migraine markers"**: motion sickness, periodic limb pain/growing pains, and "brain freeze" (cold-stimulus HA)
- **Family history:** Migraine heritability is ~35-60% (42%), typically polygenic. **Aura** often runs in families.

Gelfand et al., Neurology 2013
Raieli et al., J Child Neurol 2014
Irwin et al., Curr Pain & Headache 2018
Il et al., Headache 2011

Bear J et al., Neurology 2017
Eidlitz-Marcus et al., Pediatr Neurol 2014
Lewis, Neurology 2012
Alexiou et al., Pediatr Radiol 2013

Pediatric Migraine Diagnosis by ICHD-3 Criteria

Must have at least 5 attacks to make the diagnosis.

Each attack lasts 2-72 hours.

Attacks must have the following:

2 + 1

ANY 2:

- ❑ **Bilateral or unilateral pain** (unilateral often starts as teen).
- ❑ **Throbbing/pulsating quality of the pain.**
- ❑ Worsened/aggravated by **activity** (or causes avoidance).
- ❑ Moderate or **severe pain intensity.**

ANY 1:

- ❑ NAUSEA **AND/OR** VOMITING.
- ❑ PHOTOPHOBIA **AND** PHONOPHOBIA

(can be inferred in pediatrics).

Not better accounted for by another ICHD-3 diagnosis

The University of Texas at Austin
Dell Medical School

dell children's
Ascension

ICHD 3, Cephalalgia 2018

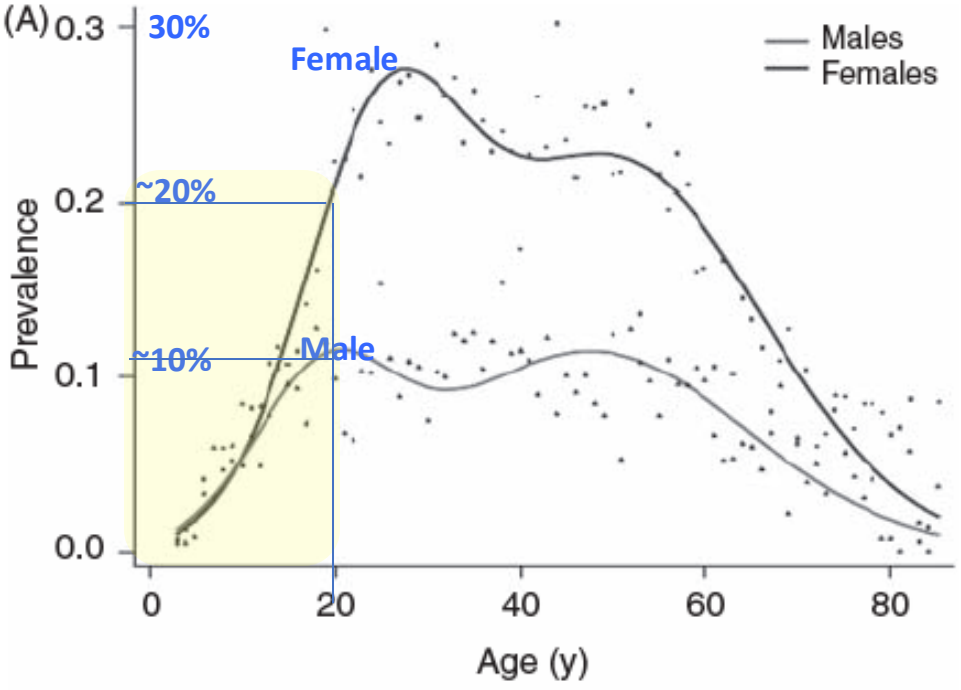
MIGRAINE

Epidemiology & Pathophysiology

Migraine Epidemiology

- **Migraine is common:**
  - **>1 billion people worldwide** with migraine.
  - Leading cause of "years lost to disability."[1]
  - School absences[2] and impaired performance.[3]
- **Overall prevalence:**
  - **~12% overall, 7% (males), 17% (females)**[4,5,9]
    - Pre-puberty: 1:1 female:male ratio.
    - Post-puberty: 3:1 female:male ratio.
- **Chronic migraine**[2,7-8]
  - **0.6%** of 5-12-year-olds.
  - **0.8-1.8%** of 12-17-year-olds (*range= ± MOH).*
  - 1-2% of adults (1.3% women, 0.5% men).
- **Evolution EM to CM:** ~2.5%/yr.[9]

One-year period prevalence of migraine[4]



The University of Texas at Austin
Dell Medical School

[1] GBD, The Lancet 2018
[2] Smanack et al., Curr Pain Headache Rep 2011
[3] Arruda et al., Neurology 2012
[4] Lipton et al., Headache 2007
[5] Victor et al., Cephalalgia 2010
[5] Lipton & Silberstein, Headache 2015
[7] Lipton RB et al., Neurology 2015
[8] Cohen et al., Headache 2024
[9] Buse et al., Headache 2012

dell children's
Ascension

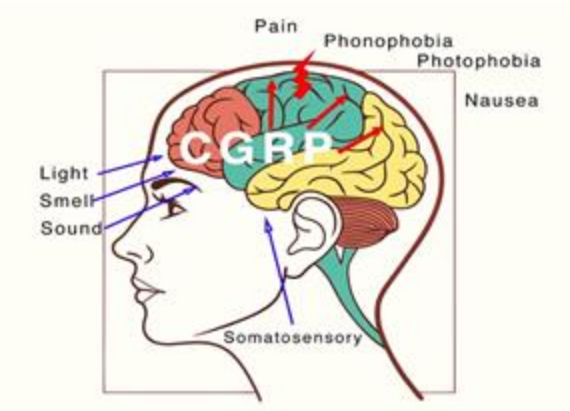
Migraine Pathophysiology

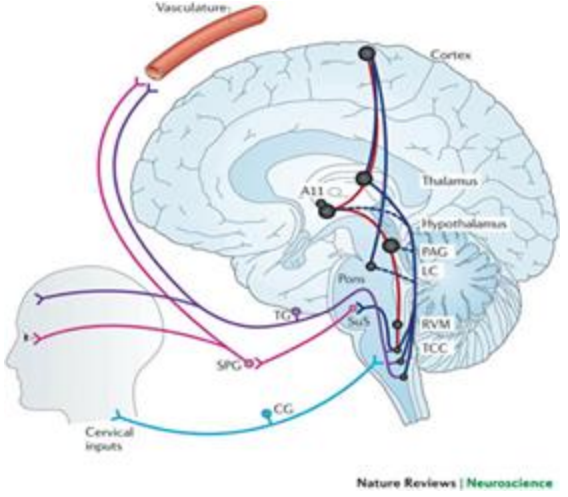
- Migraine is a complex **genetic** sensory processing disorder of the brain.
  - **~180 risk loci (SNPs) in GWAS.[6]**
- Involves **calcitonin gene-related peptide** (**CGRP**), among other proteins.[1]
- **Vascular theory** is now considered neither "sufficient nor necessary."[2]
- Interestingly, ~40% of pediatric migraine patients are misdiagnosed as "**sinus HA**."[3]
- Migraine is **not psychologic** in origin:
  - Behavioral trial in middle schoolers (*n*=69)[4]:
    - Patients with migraine had an **equal number** of friends vs. non-migraine peers.
    - Not described as "more sensitive," but rather described as **"leaders" or "popular."**
  - Study of youths with chronic daily headache (*n*=169, age 10-17 yo)[5]:
    - **Not more likely to have a comorbid psychiatric diagnosis** than their peers.
    - **But those with comorbid psychiatric illness do seem to have higher HA-related **disability** & **poorer QOL.**

[1] Goadsby et al., Physiol Rev 2017
[2] Amin et al., The Lancet Neurology 2013
[3] Senbil et. al., J Headache Pain 2008
[4] Vannatta et al., Cephalalgia 2008
[5] Slater et al., Cephalalgia 2012
[6] Grangeon et al., J Headache Pain 2023

Migraine Pathophysiology

Change in homeostasis (migraine trigger) ➡ alters dural **vasculature** ➡ leads to the release of **neuroinflammatory peptides** (including CGRP) in the **trigeminovascular nucleus (TVN)/trigeminocervical complex (TCC)** ➡ interacts with the hypothalamus/thalamus/cortex ➡ to produce the **symptoms of migraine (pain + sensitivity symptoms + nausea/vomiting).**



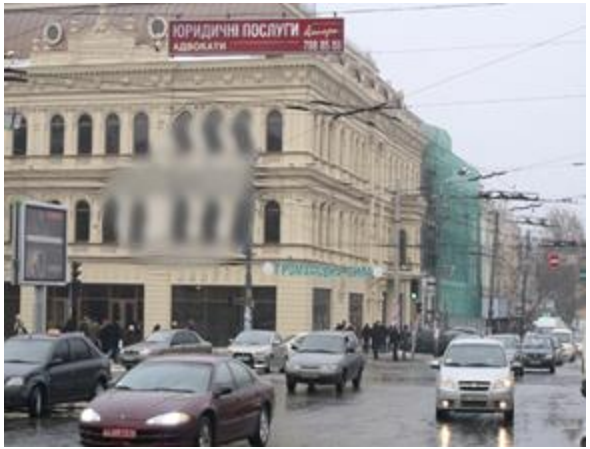


Goadsby et al., Physiol Rev 2017

Migraine Aura

- **Aura** is present in the minority of patients (~25%).[1]
- Clinical presentation of aura can help you differentiate from **TIA or seizure**.[2]
  - **Slowly spreads/progresses/evolves** over 5 mins, and/or symptoms occur in **succession**.
  - **Duration** 5-60 mins.
  - **Positive** symptoms, not negative, often ascending (hand → face → tongue).
  - Headache can occur **before, during, or after** aura (in 73% headache is already present during aura).[3]
  - ***vs. negative, abrupt onset without a stereotyped pattern, static/fixed post-onset.***
- **Visual** aura > **sensory** > **language** > motor (hemiplegic) > brainstem (2/7) > retinal (monocular vision).
- Consider the **premonitory phase** if the symptoms occurring "pre-headache" are not consistent with aura.
- **Importance of aura:**[4,5,6]
  - Migraine with **aura** = ~**2x** increased ischemic stroke and MI risk (absolute risk is low – 0.03% vs. 1% HTN and DM).
    - Further increased risk in women **<45 yrs**, using **estrogen contraception (6x)**, and/or **smoking *(10x).***
  - ***WHO/ACOG:*** *Women with migraine and aura (focal neurologic symptoms) should* ***not*** *use estrogen OCPs.*
  - ***OPERATIONALLY****: 20mcg estrogen is* ***likely safe*** *in an otherwise healthy woman without CV risks or changes in aura.*
  - ***TRIPTANS****: Contraindicated in hemiplegic migraine or brainstem aura. Use with caution in retinal aura.*

[1] Viana et al., Cephalalgia 2016
[2] Hansen et al., Cephalalgia 2016
[3] Hansen et al., Neurology 2012
[4] Kurth et al., BMJ 2018
[5] Schurks et al., BMJ 2009
[6] Kurth et al., JAMA 2006 and 2020



Scotoma

Scintillating scotoma

Fortification spectra

https://en.wikipedia.org/wiki/Aura_(symptom)
http://www.raynersmale.com/blog/2016/11/4/pathophysiology-symptomology-of-migraine-headaches

DIAGNOSTIC WORKUP

Migraine Workup

- **Typically, no diagnostic workup is needed beyond H&P.**
  - **Child with normal exam, recurrent HA, & no risk factors = <3% neuropathology**
    - 2002 practice parameter[1]: **3%** of all children imaged for HA had concerning results (n=1,275) - **all** with abnormal exams.
    - 2013 systematic review[2]: **2.5%** of all children imaged for HA had concerning results (n=3,260)- **>95%** with abnormal exams
    - **~1%** of children <18 yo presenting to the ED with nontraumatic HA had emergent intracranial abnormalities (Rossi 2017[3] n=1833, 33% imaged, Tsze 2018[7] n=224, 8.8% imaged).
  - **Predictive**:
    - Abnormal neuro exam (CN nerve palsies, papilledema, or gait abnormalities), extreme intensity, thunderclap or subacute HA (<1mo), absent FHx migraine, seizures, <3 yo.
  - **Occipital headache** in children, in and of itself, is no longer considered a red flag.[4,5]
  - **Cranial autonomic symptoms** COMMON in peds (62% have one, often bilateral).[6]

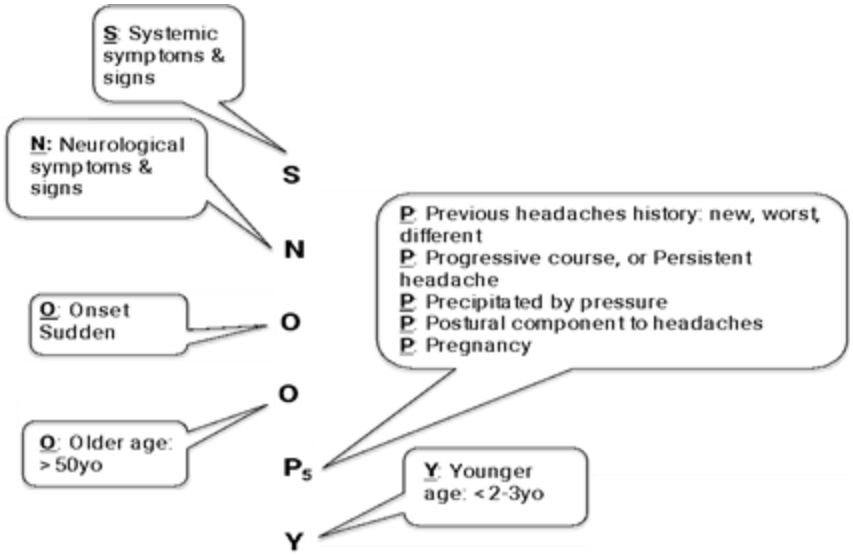
[1] Lewis et al., Neurology 2002
[2] Alexiou et al., Pediatr Radiol 2013
[3] Rossi et al., Cephalalgia 2017
[4] Genizi et al., J Child Neurol 2017
[5] Irwin et al., Headache 2018
[6] Gelfand et al., Neurology 2013
[7] Tsze et al., Cephalalgia 2018

Migraine Workup: Reasons to Image/Risks

- **Thunderclap** onset, **first** or **worst** headache (HA)
- Progressive **change** in HA character, freq, severity
- **New** headache <6 years of age (esp. <3 yo)

- **Positional** HA (different than movement sensitivity)
- **Nocturnal** or **morning** vomiting or headache
- Pain that worsens with **Valsalva**
- **Site- or side-locked** HA or "unable to describe pain"

- High-risk populations (e.g., immunosuppressed)
- Developmental delay and/or neurocutaneous signs
- Meds/substances increasing risk of secondary HA
- Seizures occurring with onset of HA
- Change in mental status or focal neurologic deficits
- Persistently abnormal vitals (esp. Cushing's triad)
- Nuchal rigidity, petechial rash, or meningismus



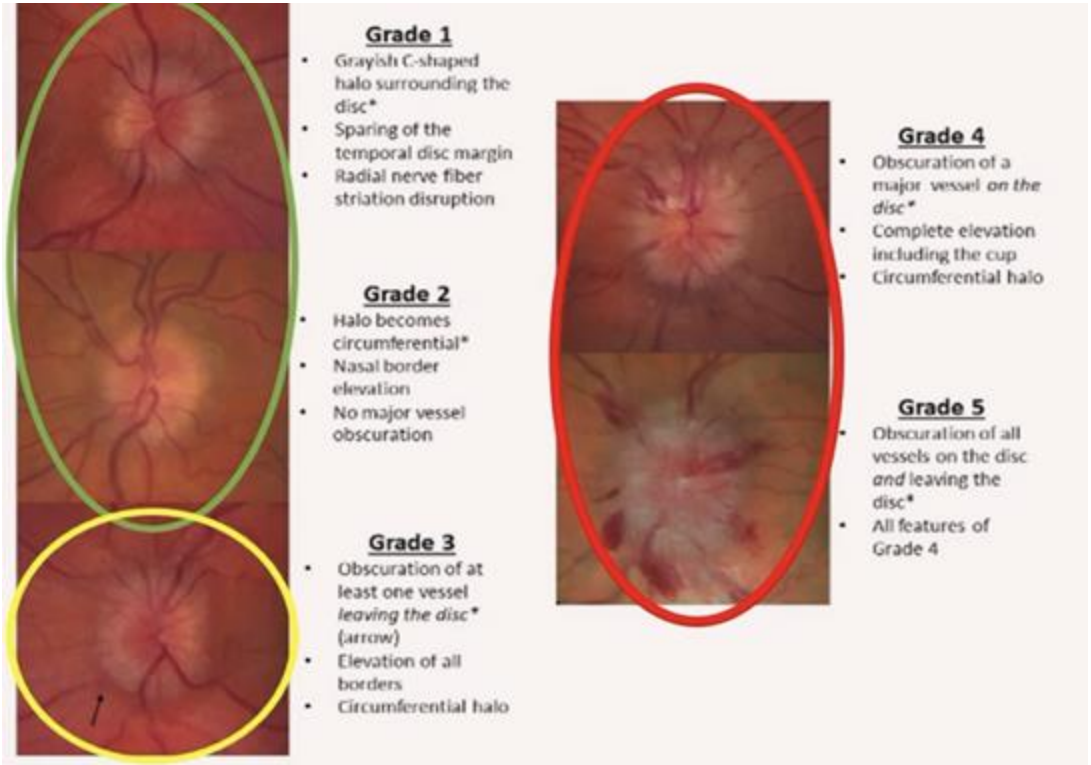
Irwin et al., Curr Pain Headache Rep 2018

Lewis et al., Neurology 2002
Alexiou et al., Pediatr Radiol 2013
Alfonzo et al., Pediatr Emerg Care 2015
Rossi et al., Cephalalgia 2017
Tsze et al., Cephalalgia 2018

Fundoscopy with EVERY HA exam

Normal optic nerve

https://www.eyedolatryblog.com/2014/04/whats-that-in-my-retinal-photograph.html



Slide courtesy of E. Steve Roach

TREATMENT

Migraine Treatment: General Principles

- Try to identify triggers to possibly **preempt** a migraine (menses, travel, etc.).
- Investigate **contributing factors**: contraceptives, stimulants (ADHD), caffeine, or MOH.
- **Acute**:
  - Treat acute pain when **mild**:
    - 53% effective if treated when early/mild vs. 38% if late/severe.[1]
    - Treating when the pain starts is more effective/safe than treating during the aura phase.[2, 3,4]
  - **Maximize dose** and try acute treatments for **2-3 migraine attacks** before assessing response.
- **Prevention**: Education is key. **Start low & go slow** to avoid med failure due to side effects.
  - Consider starting a preventive if **>4-6** HA days/month (any severity), or **3+** severe days.[5]
  - Try preventive treatments for at least **~8 weeks** before assessing the response.[5]
- Set **realistic goals** for treatment endpoints[5]:
  - **Prevention*: ~50% reduction of headaches in 50% of patients*** by ~3 months.
  - **Acute treatments**: ***~2/3 experience pain relief and 1/3 are pain-free*** by 2 hrs.

[1] Worthington et al., Can J Neurol Sci 2013
[2] Bates et al., Neurology 194
[3] Olesen et al., Eur J Neurol 2004
[4] Dowson et al., Eur J Neurol 1996
[3] Oskoui et al., Neurology 2019

ACUTE TREATMENT OF MIGRAINE

Acute Treatment Categories for Migraine

- **4 categories of acute treatments**, as per new AAN pediatric guidelines, 2019:
  1) ***Analgesic***: preferably **NSAIDs** (ibuprofen, level A 2004).
  2) ***Migraine-specific medications:*** **triptans, gepants, ditans, acute neuromodulation.**
     - Use intranasal forms if migraine rapidly peaks (IN sumatriptan, level A 2004).
     - Failure of one triptan doesn't mean failure in all.
     - The second triptan dose within 24 hrs doesn't increase initial efficacy (but might help with recurrence).
     - **Adding naproxen** to a triptan increases 2-hr pain-free rate and lowers the 24-hr recurrence rate.
     - Be aware of triptan **contraindications** – vascular disease, HTN, hepatic disease, hemiplegic migraine, and brainstem aura. Caution retinal aura. Category C in pregnancy. Not to be combined with ergots/DHE/gepants or MAOIs within 2 weeks.
  3) ***Nausea-specific medication***: **5HT-3 antagonists** (ondansetron or granisetron).
  4) ***Bridge treatments and/or rescue options***: **dopamine (D2) receptor antagonist** (prochlorperazine).

- Counsel about **medication overuse risk**.
  - Acetaminophen or ibuprofen – limit to **<15 days/month.**
  - Triptans, opioids, combo meds – limit to **<10 days/month.**

Oskoui et al., Neurology 2019
ICHD3, 2018

Practical Acute Treatment Step Approach

What should I give an otherwise healthy teen for acute migraine home treatment?

- ***Mild to moderate HA:*** **analgesic** (limit **<15 days a month**).
  - Ibuprofen 10 mg/kg tab, chewable, or liquid q6-8hrs PRN *(level A, pediatrics, 2004)*.
  - Naproxen 10 mg/kg tab or liquid q12hrs PRN.
- ***Moderate to severe HA***: Add a **triptan** (limit **<9 days a month**): **4 FDA approved for pediatrics**.
  - **Almotriptan:** 6.25mg if 20-40 kg and 12.5mg if >40kg. PO. Approved for ages 12-17 (2009).
  - **Rizatriptan:** 5mg if 20-40 kg and 10mg if >40kg (6-18 yo). PO or **MLT (dissolving melt)**. Approved for ages **6**-17 (2012).
  - **Zolmitriptan:** 2.5mg if 20-40 kg and 5mg if >40kg. PO, **NS, and MLT**. Approved for ages 12-17 (2015).
  - **Sumatriptan** 25mg if <30kg, 50mg if >40kg, 100mg if >60kg. PO, **NS, SC.** *Suma/naproxen; IN suma.*
- Add ***anti-nausea therapy*** if required: **5HT-3 antagonists**
  - Ondansetron 0.15mg/kg q8hrs (max 8mg).
- Add ***rescue therapy*** if required: **dopamine (D2) antagonist**
  - Prochlorperazine 0.15mg/kg q8hrs (max 10mg) with Benadryl after normal ECG (limit **3 doses/week**).
- Consider ***"bridge"***: **naproxen** BID used short term (1-4 weeks) during periods of worsening migraine (see next slide).
- Consider ***"new" migraine-specific therapies – gepants, ditans, or neuromodulation***.
  - ***Ubrogepant, rimegepant, zavegepant, lasmiditan, REN (8+), niVNS (12+), TMS (12+).***

PREVENTIVE TREATMENT OF MIGRAINE

Pillars of Prevention

- Lifestyle regulation
- Cognitive Behavioral Therapy (CBT)
- Medications: nutraceuticals/pharmaceuticals
- Devices
- Injections/infusions

Prevention: Lifestyle Regularity

- **Regular sleep:**
  - Changes in sleep (too much or too little) can lead to migraine: Mondays and post vacations.
  - Children 6-12 years: 9 to 12 hours per night; teens 13-18 years: 8 to 10 hours per night.
  - AAP/CDC advocates for an 8:30 a.m. start time for school.
- **Regular exercise:** 20-30 mins a day, 3-5 days a week.
  - Equivalent to **topiramate** in 18-65-year-olds with episodic migraine (40 min exercise 3x/week).[1]
  - Non-inferior/additive to 25mg **amitriptyline** in 18-50-year-olds with chronic migraine.[2]
- **Regular meals:**
  - Breakfast, ideally protein-rich (anecdotal), within 30 mins of waking up.
  - Nitrates, artificial sweeteners, MSG, dyes, alcohol/caffeine, and tyramine-rich foods can be triggers.
- **Adequate hydration:**
  - General guide of **1 ounce/kg** up to 1.5-2.5L/day (~65 ounces).
  - Adult study, 2005: reduction in HA with an increase in hydration by 1L/day (if baseline <2.5L/day).[3]
  - Up to 55% of children 6-18 yo were dehydrated on urine tests.[4]
- **Headachereliefguide.com**

[1] Varkey et al., Cephalalgia 2011
[2] Santiago et al., Arq Neuropsiquitar 2014
[3] Spigt et al., Eur J Neurol 2005
[4] Kenney EL, AM J Public Health 2015

Prevention: CBT

Goals of cognitive behavioral therapy (CBT):

- Recognize errors in patient's thought process and encourage more helpful and realistic responses.
- Reduce emotional distress and improve treatment adherence.

- **Research:**
  - **Pivotal trial (JAMA 2013)**:
    - Amitriptyline + CBT = **fewer HA days and disability** vs. amitriptyline + HA education group in pediatric CM.[1]
    - **1-year follow-up: 72%** of the CBT + amitriptyline group had ≤4 HA days/mo. vs. **52%** of the education group.[2]
  - ***2017 metanalysis***: **"significant improvement"** with CBT in pedi migraine vs. wait-list controls, placebo, or standard-of-care.[3]
  - ***2019 pediatric guidelines:*** CBT & amitriptyline combined is only therapy with level A evidence.[4]

- **Bottom Line**: **CBT is effective, may augment meds and works long-term.**

[1] Powers et al., JAMA 2013
[2] Kroner et al., Headache 2016
[3] Ng et al., Headache 2017
[4] Oskoul et al., Neurology 2019

Preventive Treatments

Expert opinion and extrapolation from adult guidelines informs use in pediatrics (AHS/AAH 2012):

38.8% of patients need a preventive[4] but **only ~15% use a preventive.**[5]

- **CHAMP study** (NIH-funded trial, 2017)[2]:
  - **Amitriptyline vs. topiramate vs. placebo** for migraine prevention in pediatrics.
  - **8-17 yo patients (n=328),** with at least **4 HA days/month. Randomized 2:2:1.**
  - Stopped early for futility: 1º outcome of *">50% decrease in HA days*" seen in **61% of placebo**, 55% of TPM, and 52% of amitriptyline.
  - **Post-CHAMP era:** "*Provide preventive treatment with evidence for efficacy, but with a favorable side effect profile.*"
- **"New" pediatric guidelines**, September 2019[1] (prior guidelines – AAN 2004):
  - The only "**high-quality evidence**" was for **amitriptyline** 1mg/kg/day + **CBT**.[2]
  - "Cognitive behavioral therapy (**CBT**) should be considered **1st line** in pediatric migraine."[3]
- **No "level A" preventive medications for kids.** Nothing is labeled <12 years.
- **Topiramate** is FDA labeled for migraine prevention in adolescents 12-17 years.
- **Adult consensus statement** (2024): "CGRP-targeting therapies should be considered as a first-line for migraine prevention along with previous first-line treatments **without a requirement for prior failure** of other classes of migraine preventives."[6]

[1] Oskoui et al., AAN practice guideline 2019 (replaces 2004 guideline)
[2] Powers et al., JAMA 2013
[3] Ng et al., Headache 2016
[4] Silberstein et al., Headache 2005
[5] Lipton et al., Headache 2005
[6] Charles et al., Headache 2024

Prevention: Peds Medications We Use

- **Nutraceuticals:** Typical dosing >40kg

Supplement	Dose	Mechanism
Riboflavin* (vitamin B2)	200mg BID	*Electron transporter in Krebs cycle.*
Melatonin*	3mg QHS	*Pineal/suprachiasmatic/hypothalamus role + indole structure, anti-inflammatory and anti-nociceptive.*
CoQ10*	100mg BID (1-3mg/kg/day)	*Electron transporter in Krebs cycle. May help cognitive fogginess, esp. in post-traumatic HA.*
Magnesium citrate*	250-500mg QHS (9mg/kg/day)	*Modulates/blocks excitatory glutamate/NMDA receptor and cortical spreading depression. May help sleep, anxiety, and constipation.*

- **Pharmaceuticals:** Data extrapolated from adult consensus guidelines.
  - **LEVEL A**: topiramate*, propranolol*, metoprolol*, timolol, VPA*, CBT + amitriptyline*
  - **LEVEL B**: amitriptyline*, venlafaxine (flunarizine*)
  - **LEVEL C**: candesartan*, memantine*

***Pediatric trials exist**

AAN 2004, Pediatric Guidelines
AAN 2012, Adult Guidelines
Oskoui. Neurology, Sept 2019

My Go-To Prescription Preventives

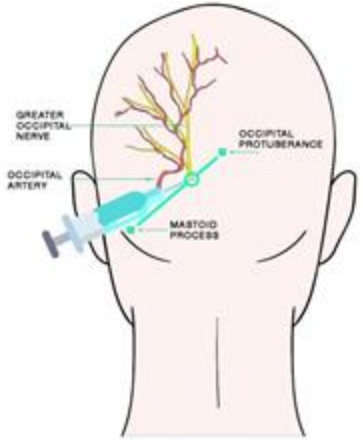
Drug & Class	Pros	Cons/Side Effects	Dose
Amitriptyline (TCA)	May help body pain, sleep, depression	Prolonged QT (get ECG), weight gain, dry mouth, fatigue, constipation, SI	Titrate slowly. Goal 1m/kg/day Max 100mg/day Range 50mg-75mg
Propranolol (BB)	May help anxiety & POTS	Bradycardia, reduced VO2 max, asthma, DM, possible depression	10mg bid, increase to ~1mg/kg/day. Range 30-60mg/day
Memantine (Anti-NMDA)	May help focus	Fatigue	5mg bid, increase to 10mg bid.
Venlafaxine (SNRI)	May help with energy, anxiety, obesity	Insomnia, low appetite, SI	Start 37.5mg, titrate q wk by 37.5mg to max 150mg.

*I may also consider **candesartan or zonisamide or duloextine.***

I tend to avoid TPM and VPA.

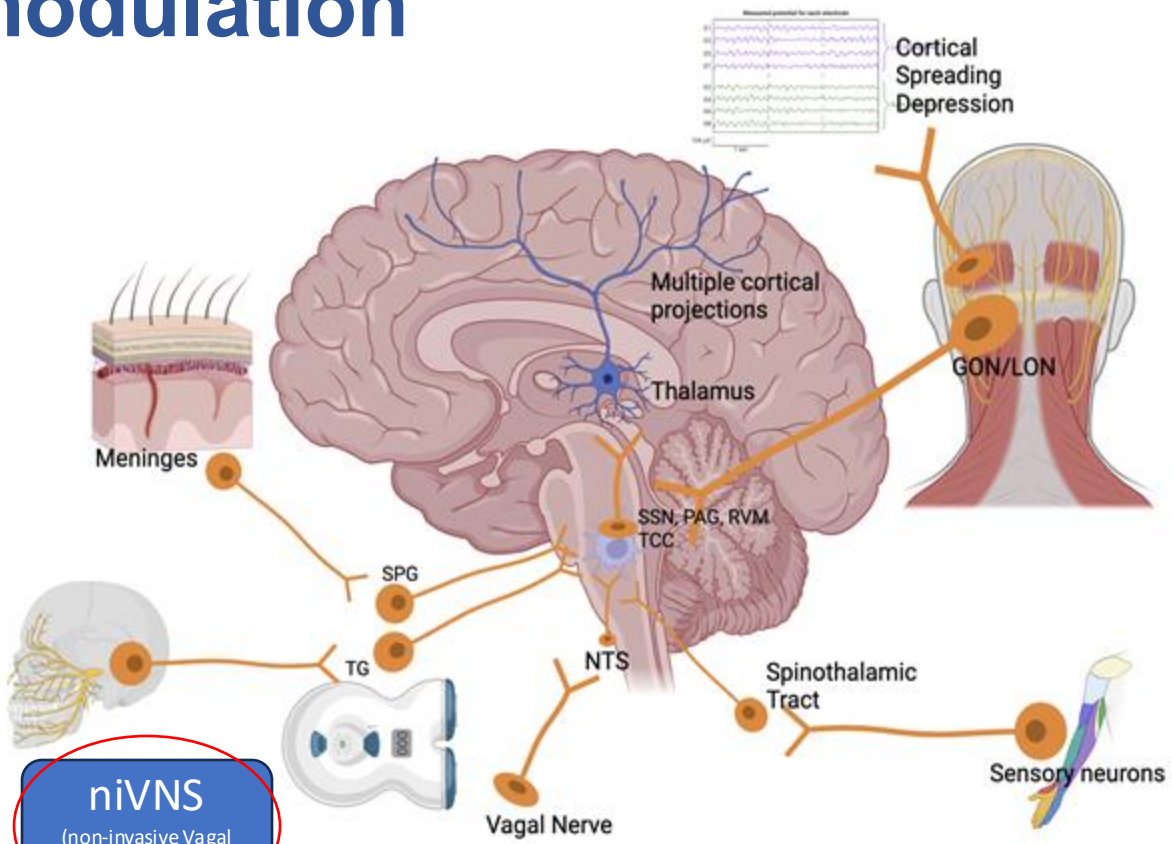
Other Preventive Options

- **Nerve blocks**
- **CGRP monoclonal antibody (mAb) injections**
  - **Erenumab** (SC), **fremanezumab** (SC monthly or quarterly), **galcanezumab** (SC), **epitnezumab** (IV quarterly)
- **CGRP oral antagonists (gepants)**
  - **Atogepant** OD, **rimegepant** QOD
- **OnabotulinumtoxinA (PREEMPT protocol)**
- **Neuromodulation devices**
- ***Admission for infusion treatment if refractory.***



https://www.aptivahealth.com/occipital-nerve-block

Neuromodulation



eTNS
(External Trigeminal Nerve Stimulation)

eCOT-NS
(External Concurrent Occipital and Trigeminal Neurostimulation)

niVNS
(non-invasive Vagal Nerve Stimulation)

eCOT-NS
(External Concurrent Occipital and Trigeminal Neurostimulation)

sTMS
(Single-pulse Transcranial Magnetic Stimulation)

REN
(Remote Electrical Neuromodulation)

The University of Texas at Austin
Dell Medical School

Illustration created in BioRender.com. Company permission granted for images used.

dell children's
Ascension

Neuromodulation: When to Consider

- Nonpharmacologic option/route is preferred.
- Oral treatments are challenging due to SEs, contraindications, swallowing, and/or other comorbidities.
- Med-med interaction issues are present.
- Pharmacologic options are ineffective or not tolerated.
- Concerns for MOH are present, especially if high HA burden – chronic migraine, new daily persistent headache (NPDH), persistent post-traumatic headache (PPTH).
- Desire to avoid the taper-up/taper-down process.
- Keen to use something in conjunction with preventive meds, or while awaiting preventive meds to work, or concurrently with acute meds.
- Desire for acute/preventive combo treatment.

- Other considerations:
  - *The level of evidence for **FDA clearance** is LOWER than **FDA approval** of meds.
  - *Poor insurance coverage – OOP typically may use FSA/HSA.
  - *Direct shipping from companies/special pharmacies = delays/compliance issues.

Landscape of Neuromodulation

niVNS	REN	sTMS	eTNS	eTNS/ONS (e-COT-NS)
12+ *(8+ Nerivio)*			**18+**	
• Acute: Two 2-min stims, rpt q20min x3 • Px: Two consecutive 2-min stims TID • Needs gel to use. • No charging	• Acute: 45-min Tx • Px: QOD protocol • No charging • Mindfulness app	• Acute: 2-3 clicks q 15 mins x3 PRN • Px: 3-4 clicks bid • 3.2 lb device + base station for charging.	• Acute: up to 1 hour (100Hz) PRN • Px: 20 mins daily (60Hz) • USB charging • Charge lasts several sessions	• **Acute only**: 60-min Tx • Needs to be charged • Charges lasts 5 hours
~$550/month or $950/3 months (subscription).	~$49.00 for 18 Tx, then ~$90 thereafter. **Insurance/subsidies**.	$400/mo, or ~$750.00/3 mo (subscription). **Free for VA**.	~$390–$525 (OTC) + electrodes ($30 for 3). 90-day **return policy**.	~150.00 for 60-day **trial**. Thereafter, $650.00 to buy.
SE: Hoarse, tight neck, dizzy, mouth twitching. **CI**: Metal. Carotid atherosclerosis, cervical vagotomy, BP/HR issues.	**SE**: Warmth, tingle, itch, red, pain in arm (>1%). **CI**: Metal and epilepsy (uncontrolled).	**SE**: Loud, dizzy/tingly, HA, tinnitus. **CI**: Metal and epilepsy (Sz in up to 3.5%).	**SE**: Paresthesia, acne, allodynia, "didn't like" (1.3%), sleepy, skin reaction. **CI:** Metal.	**SE**: Tingling, pain, nausea, sleepy, dizzy, transient skin reactions (irritated/itch/red). **CI:** Metal.

Company permission granted for images used.

Pediatrics

- **niVNS (12+)**: **Prospective acute observational open-label study** (n=9)[1] – safety, tolerability, and efficacy (EM).
  - **46.8%** of treated acute attacks were considered successfully treated (didn't need rescue).
  - No safety concerns.

- **sTMS (12+)**: **Prospective open-label observational preventive study** (n=12)[2] – feasibility, tolerability, acceptability (EM & CM).
  - **-4.5** (+/- 1.7) HA days/mo from baseline run-in to end of 12-week treatment (p=0.019).
  - Reduced MIDAS scores (-36 +/- 14) (p=0.026).
  - No safety concerns.

- **REN (8+)**: **Prospective acute open-label study** (n=35)[3] – vs. standard-of-care meds (EM & CM).
  - Pain-free – **37.1%** vs. 8.6% on meds (p=0.004).
  - Pain relief – **71.4%** vs. 57.1% on meds (p=0.225).
  - No safety concerns.

[1]Grazzi et al., Neurol Sci 2017;197–99
[2]Irwin et al., Headache 2018;724–31
[3]Hershey et al., Pain Med 2022;815–20

TAKE-HOME POINTS

- Migraine is not just a “severe headache.” Migraine is a complex genetic sensory processing disorder of the brain.
- Be familiar with pediatric migraine diagnostic criteria and exceptions.
- Consider the premonitory phase vs. aura.
- Identify red flags and the need for imaging and/or referrals.
- Acute treatment is more effective when taken early/when pain is mild. Maximize the dose and try 2-3 times.
- Consider combining triptans with NSAIDs, using a bridge therapy, or trying newer acute options.
- Address triggers and lifestyle regulation. Consider adding CBT or neuromodulation early.
- Begin with low-risk preventive treatments when HAs are burdensome, ideally with SEs similar to placebo.
- Communicate with the family, health team, and school to optimize care. Evaluate the need for a 504.
- Consider referring to an HA specialist if the pattern is problematic or the symptoms are refractory.

Sara Pavitt, MD
Chief, Pediatric Headache Center

Samantha Irwin, MSc, MB BCh, BAO, FRCPC
Pediatric Neurologist, Headache Center

Lindsay Elliott, PhD
Pediatric Psychologist

Chelsea White, MSN, APRN, CPNP-PC
Neurology Nurse Practitioner

David Heckler, PhD, ABPP
Psychologist

Melissa Wood, PT
Physical Therapist

Abby Glock, LCSW
Social Worker

Zoë [illegible]
Program Coordinator

Dell Children's Specialty Pavilion
4910 Mueller Blvd., Suite 300
Austin, TX 78723
t 512-628-1855 **f** 512-380-7544

The University of Texas at Austin
Dell Medical School

dell children's
Ascension

UT Health Austin Pediatric Neurosciences at Dell Children's