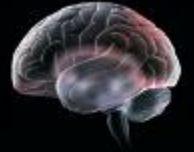


Headache: It's All In Your Head...or Is It???

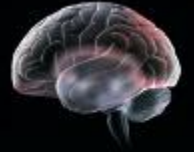


Paul G. Mathew, MD, DNBPAS, FAAN, FAHS
Assistant Professor of Neurology
Harvard Medical School
Headache/Sports Neurology/Concussion Specialist
Mass General Brigham Health Care
Harvard Vanguard Medical Associates



FINANCIAL DISCLOSURES

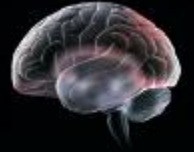
- Consulting
 - Allergan
 - Amgen
 - BioMobie
 - Biohaven
 - ElectroCore
 - Lilly
 - Novartis
 - Revance
 - Satsuma
 - Stealth BioTherapeutics
 - Supernus
 - Takeda
 - Theranica
 - Teva
 - Upsher-Smith



OBJECTIVES:

1. Accurately classify headaches based on International Headache Society Criteria
2. Choose appropriate studies for further evaluation based on patient history and physical findings.
3. Formulate an effective treatment plan including both pharmacological and non-pharmacologic interventions.

HEADACHE = ALARM SYSTEM FOR HEAD



- Headache → Alarm
- Light Sensitivity → Radio
- Sound Sensitivity → Air conditioning
- Nausea/Vomiting → Car going in reverse



HEADACHE TYPES

- Primary Headaches
 - Migraine
 - Cluster
 - Tension
- Secondary Headaches
 - Intracranial Tumors
 - Intracranial Hemorrhages
 - Meningitis
 - Pseudotumor Cerebri
 - Temporal Arteritis...

AZIZI'S SINISTER TRIO

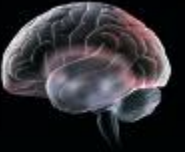


- First
- Worst
- Cursed

THE FRIENDLY TRIO



- Normal History
- Normal Exam
- Family History



IMAGING

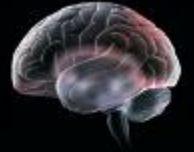
- There are no concerning findings with this patient....When do I perform an imaging study?



AAN GUIDELINES

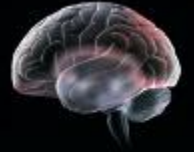
The following symptoms significantly increase the odds of finding a significant abnormality on neuroimaging in patients with non-acute headache:

- Rapidly increasing headache frequency
- History of lack of coordination
- History of localized neurologic signs or a history such as subjective numbness or tingling
- History of headache causing awakening from sleep (although this can occur with migraine and cluster headache)



IMAGING LINE...

- Your headache symptoms sound very consistent with _____.
- Your normal neurologic examination and family history further suggests this diagnosis.
- Let's proceed with x, y, z treatments.
- If your headaches worsen or do not respond to treatment, we can proceed with an MRI scan for further evaluation.



PITFALLS FOR THE LINE

- High Anxiety
- Already Failed Multiple Treatment Plans
- High Frequency/Intensity Headaches



PITFALLS OF IMAGING

- Radiation
- Denials
- Incidental Findings
- Increase health care costs → increase premiums
- Co-Pays

MIGRAINE DIAGNOSTIC CRITERIA

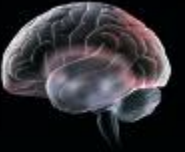


- Migraine Without Aura (Common Migraine)
 - At least 5 attacks
 - Last 4-72 hours
 - Has 2 of the following
 - Unilateral, Pulsating Quality, Mod/Severe Intensity, Aggravated by physical activity
 - Has 1 of the following 3
 - Nausea, Vomiting, or Both Photo AND Phonophobia
 - Not attributed to another disorder

MIGRAINE DIAGNOSTIC CRITERIA



- Migraine With Aura (Classic Migraine)
 - At least 2 attacks
 - Migraine aura fulfils criteria for typical aura
 - Last 4-72 hours
 - Has 2 of the following
 - Unilateral, Pulsating Quality, Mod/Severe Intensity, Aggravated by physical activity
 - Has 1 of the following 3
 - Nausea, Vomiting, or Both Photo AND Phonophobia
 - Not attributed to another disorder

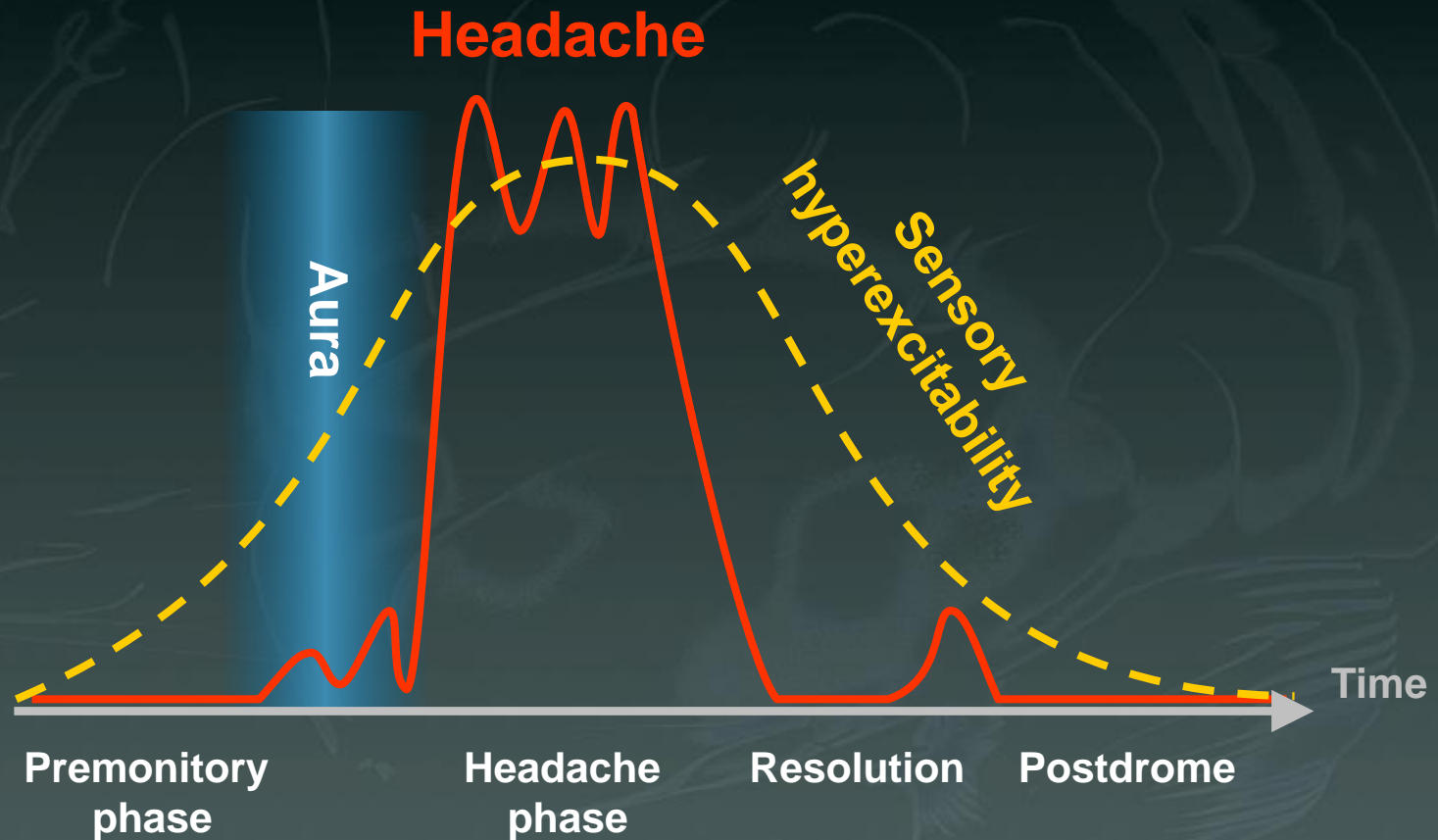


CLASSIC VS. COMMON?

CLASSIC
U
R
A

COMMON
W
I
T
H
O
U
T

The Natural Course of a Typical Migraine Attack





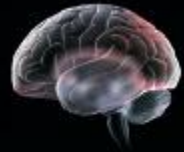
TYPICAL AURAS

- Fully reversible symptom or combination
 - Concern if more than 1 hour
- Homonymous or bilateral visual symptoms including positive or negative features
 - Scintillating Scotomas
 - Fortification spectrum
 - Transient visual loss
- Unilateral +/- sensory symptoms
 - Tingling or numbness w/ no motor weakness
- Speech Symptoms- Aphasia



TYPICAL AURAS

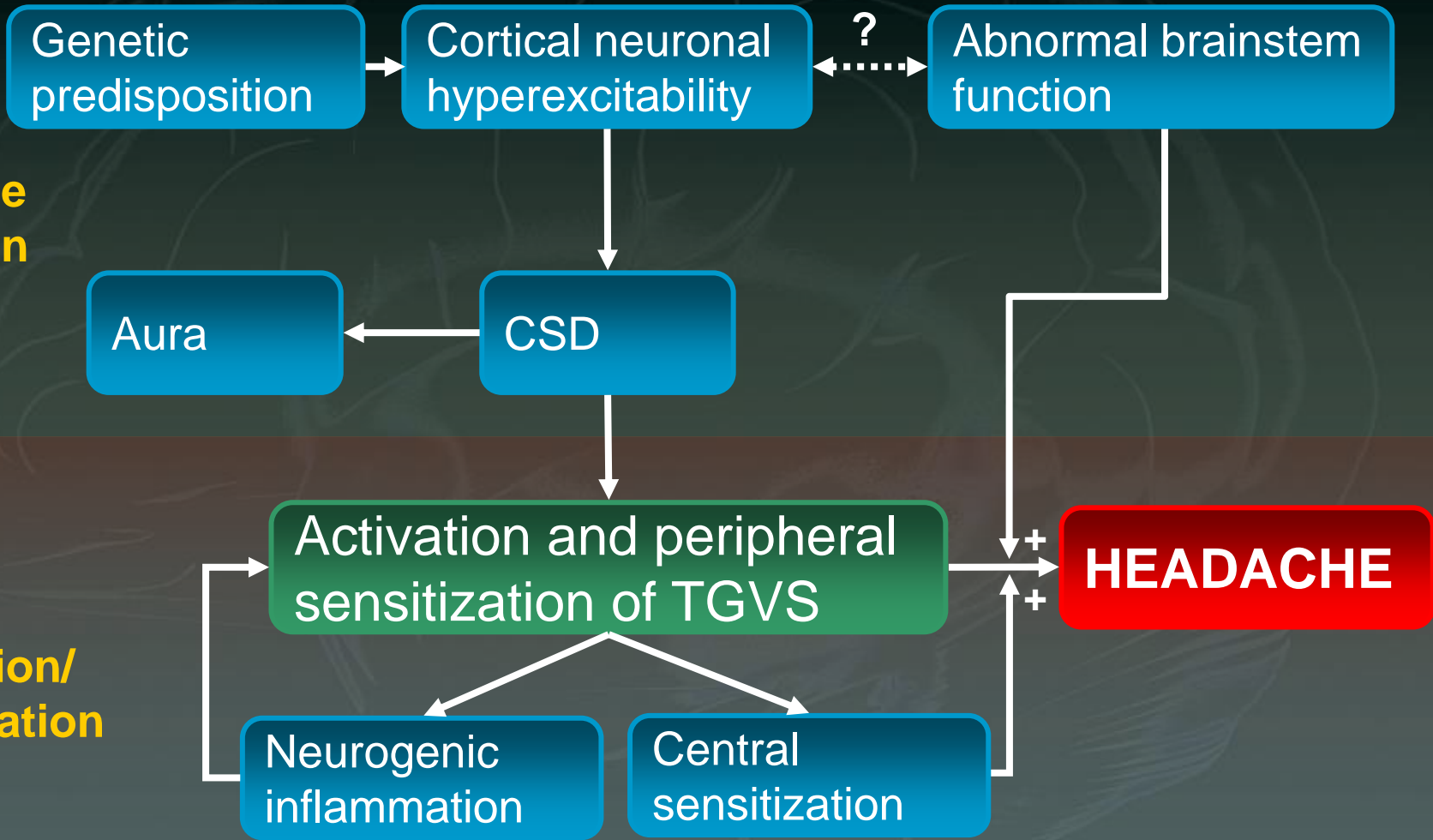
- Symptoms can occur in combinations
- Typically develop gradually over 5 min lasting no greater than 60 min
- Headache can occur during aura, with 60 min following aura, or not at all.



Migraine Pathophysiology:

Migraine initiation

Pain generation/perpetuation



TVS = trigeminovascular system.
Pietrobon D. *Neuroscientist*. 2005;11:373–386. (Merck)

IS ALLODYNIA PLAYING A ROLE?



- Cutaneous Allodynia
 - Non-noxious skin stimulation causing an unpleasant or painful response
 - Combing/styling hair
 - Shaving your face
 - Wearing eyeglasses, contact lenses
 - Wearing earrings, necklaces, tight clothes
 - Taking a shower with water hitting face
 - Resting face on a pillow on the side of the headache
 - Being exposed to heat (e.g., cooking, placing heating pads on your face)
 - Being exposed to cold (e.g., breathing through your nose on a cold day, placing ice packs on your face)
 - Prevalence estimates of over 90% in chronic migraine patients

TENSION-TYPE HEADACHE DIAGNOSTIC CRITERIA



- DIAGNOSTIC CRITERIA

- Headache lasting from 30 minutes to 7 days
- Headache has at least two of the following characteristics:
 - Bilateral location
 - Bressing/tightening (non-pulsating) quality
 - Mild or moderate intensity
 - Not aggravated by routine physical activity such as walking or climbing stairs
- Both of the following:
 - No nausea or vomiting (anorexia may occur)
 - No more than one of photophobia or phonophobia

- Rarely present with TTH as a chief complaint



CLUSTER DIAGNOSTIC CRITERIA

- Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated
- Headache is accompanied by at least one of the following:
 - Ipsilateral conjunctival injection and/or lacrimation
 - Ipsilateral nasal congestion and/or rhinorrhoea
 - Ipsilateral eyelid edema
 - Ipsilateral forehead and facial sweating
 - Ipsilateral miosis and/or ptosis
 - A sense of restlessness or agitation
- Attacks have a frequency from one every other day to 8 per day



SINUS/ALLERGY HEADACHE

- The great mimicker
 - Pressure in the face
 - Thin liquid nasal discharge
 - Worse with weather changes
 - Seasonal association
 - Responds to steroids
 - Like headaches
 - Responds to antibiotics ???
- Mathew's Sinus Triad
 - Thick purulent discharge
 - Fever
 - Imaging evidence of sinus disease
- Migrainous features?
- The vast majority have migraine in the absence of neurologic and ENT findings



TREATMENT STRATEGIES

- Conservative
 - Avoid triggers ie sleep deprivation, excessive caffeine/alcohol, stress reduction
 - Avoid medication overuse esp narcotics
- Abortive
 - Most effective when taken early during HA
- Preventative

MIGRAINE UNIVERSAL TRIGGERS



- Menstrual cycle
- Stress
- Sleep dysfunction
- Fatigue
- Delayed/skipped meals

MY APPROACH TO SLEEP & HEADACHE...



- Rapid sleep assessment including duration of sleep, interruptions, sleeping in, feeling rested after sleep, daytime drowsiness, daytime naps, snoring, caffeine consumption
 - Pets
 - Partner
 - External Distractions
 - Nocturnal Bruxism

MY APPROACH TO SLEEP & HEADACHE...



- Bathroom awakenings?
 - Chicken or the Egg?
 - Volume restriction?
 - Low output volume?

MY APPROACH TO SLEEP & HEADACHE...



- Discuss sleep dysfunction as a headache trigger
- Avoid naps, sleeping in, and Trazodone (m-chlorophenylpiperazine (mCPP))
- Motivate the patient with other issues
 - Low energy, mood issues, irritability
 - Cognitive/memory issues
 - Risk of stroke, heart attack, and dementia
- Bring partner to appointment

MY APPROACH TO SLEEP & HEADACHE...



- Consider sleep study/sleep referral
- Consider psychological referral for CBT
- Consider pharmacologic interventions
- Consider surgery referral
 - Septoplasty/turbinectomy
 - Bariatric Surgery
 - Enlarged tonsils, tonsilliths, and halitosis



ABORTIVE TREATMENTS

- NSAID's
 - Naproxen Sodium 550mg, Ketoprofen 75mg
- Triptans
- Anti-Emetics
 - Metoclopramide, Compazine, Promethazine
- Combined Analgesics
 - Caffeine and Butalbital containing medications
- Ergot Alkaloids
 - DHE
- Gepants
- Ditants
- Stimulation

OVER THE COUNTER DOES NOT MEAN SAFE



- Convenient access does not mean take as much as you want...
 - Acetaminophen → Liver failure
 - Ibuprofen → Ulcers and Kidney failure
- In general, daily preventatives are safer than taking frequent abortive treatments



Abortive Cornerstone: TRIPTANS

- Sumatriptan (Imitrex) **G**
 - Oral 25, 50, 100 mg
 - Intranasal 5, 20 mg
 - Breath Powered Intranasal
 - Autoinjector 6,4, 3 mg
 - Needle Free Injector
- Zolmitriptan (Zomig) **G**
 - Oral 2.5, 5 mg
 - ODT 2.5, 5 mg
 - Nasal 5 mg
- Naratriptan (Amerge) **G**
 - Oral 1, 2.5 mg
- Rizatriptan (Maxalt) **G**
 - Oral 5, 10 mg
 - ODT 5, 10 mg
- Almotriptan (Axert) **G**
 - Oral 6.25, 12.5 mg
- Frovatriptan (Frova) **G**
 - Oral 2.5 mg
- Eletriptan (Relpax) **G**
 - Oral 20, 40 mg

**G= Generic but can
still require a PA**

THE TROUBLE WITH TRIPTANS



- Triptans
 - Inconsistently effective (Timing)
 - Poorly tolerated
 - Contraindicated in CAD, PVD, Stroke



NO FLY LIST

- Abortives to Avoid
 - Narcotics
 - Caffeine Containing Compounds
 - Excess Coffee/Soda
 - Butalbital Containing Compounds
- Medication Overuse Headache
- Sleep Disruption
- Reduces effectiveness of preventative medications



TRIPTAN ALTERNATIVES

- Gepants (Ubrogepant, Rimegepant)
 - CGRP Antagonists
- Ditans (Lasmiditan)
 - 5HT_{1F} agonist
- New Options= Less butalbital/narcotic prescriptions, less medication overuse including OTC's

CALCITONIN GENE-RELATED PEPTIDE (CGRP)



- A neuropeptide heavily involved in migraine pathophysiology
- 2 forms
 - α : PNS and CNS (37 amino acid)
 - β : enteric nervous system (34 amino acid)
- A potent vasodilator
- Peripheral Nervous System
 - Vasodilation and mast cell degranulation
- Central Nervous System
 - Pain modulation, central sensitization



CGRP: LOCATION, LOCATION, LOCATION

- CGRP widely expressed in the:
 - Central nervous system
 - Trigeminovascular system
 - Dura
- Actions:
 - Vasodilation
 - Inflammation
 - Pain transmission



LASMIDITAN

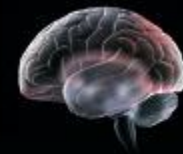
- Ditans differ from triptans
- Triptans:
 - Agonists of 5-HT_{1b}/5-HT_{1d}
 - Some 5-HT_{1f} activity
 - Vasoconstricting effects are caused by activation of 5-HT_{1b}
- Lasmiditan is highly selective for 5-HT_{1f}
 - 5-HT_{1f} receptors expressed on trigeminal neurons (peripherally and centrally)
 - Neuronal, not vasoactive
 - Crosses Blood Brain Barrier = Double Edged Sword
 - Central benefits
 - Not as time sensitive
 - Central side effects
 - 8 hour post dose driving restriction
 - Available in 50mg and 100mg tablets, but approved for a 200mg dose

WHEN TO CONSIDER PREVENTATIVE TREATMENT?



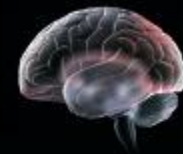
- HA that significantly interfere w/ patient's daily routines
- High Frequency
- Contraindications to, failure of, adverse effects from, or overuse of acute tx.

HOW TO USE PREVENTATIVE TREATMENT?



- Tx w/ best efficacy and fewest adverse events
- Start low and increase slowly until benefit achieved or limited by side effects
- Give drug adequate trial at adequate dose (2-3 months)
- Consider long acting medications for better compliance
- Monitor via headache diary

HOW TO USE PREVENTATIVE TREATMENT?



- Re-evaluate therapy. Taper or discontinue if HA controlled after 6-9 months
- Select drug that treats more than 1 condition
- Make sure treatment is not a contraindication/ exacerbate a co-existent disease
- Make sure a treatment for a co-existing disease is not exacerbating migraine
- Drug interactions
- Pregnancy or Childbearing Age

DIARY USE IS CRITICAL?



PGM HEADACHE CALENDAR

MONTH:

| DAYS | MENSES P | INTENSITY (1-3 Mild, 4-6 Mod, 7-10 Disabling) | | | | | | | | | | ABORTIVE MEDICATION USED N + S |
|------|-------------|---|---|---|---|---|---|---|---|---|----|-----------------------------------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 1 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 2 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 3 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 4 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 5 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 6 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 7 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 8 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 9 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 10 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 11 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 12 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 13 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 14 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 15 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 16 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 17 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 18 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 19 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 20 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 21 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 22 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 23 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 24 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 25 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 26 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 27 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 28 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 29 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 30 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 31 | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |

Use P to indicate days of your menstrual period.

Use abortive medication abbreviations like T for Tylenol.

Combinations of medications like Naproxen and Sumatriptan can be written as N + S

- Establishes baseline
- Establish seasonal, weather associations
- Establish menstrual association
- Steers titrations
- Functional pain scale helps physician and patient agree on quantification of pain

Mathew PG, Mathew T. Taking Care of the Challenging Tension Headache Patient. Curr Pain Headache Rep.2011 Dec;15(6):444-50.



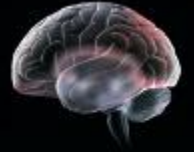
PREVENTATIVE TREATMENT

- Antiepileptic Drugs
 - Topiramate (obesity), Valproate, Gabapentin (neuropathy)
- Calcium Channel Blockers
 - Verapamil (Htn)
- B Blockers
 - Propanolol, Metoprolol, Atenolol, Nadolol, Timolol (Htn)
- Tricyclic Antidepressants
 - Amitriptyline, Nortriptyline (Sleep Dysfunction)
- Botulinum Toxin Injections (Treatment Failure of Above)
 - FDA approved for chronic migraine
- CGRP Monoclonal Antibodies (Mabs)
 - FDA approved for episodic and chronic migraine



SUPPLEMENTS

- Safe and natural?
 - Very little regulation or accountability
 - Toxicity
 - Waste
- Natural weight loss supplement secretly laced with thyroid hormone
- Butterbur, a natural supplement used for decades for migraine
 - Liver toxicity
- For Migraine
 - Magnesium Oxide- Constipation, Muscle Cramps
 - Co Q10- Fatigue (Expensive)
 - Riboflavin- Fatigue
 - Avoid multi-supplement tablets



BOTULINUM TOXIN

- Effective, well tolerated, but q3 month dosing can tie up clinic schedule
 - Become a faster injector

ANTI-CGRP MONOCLONAL ANTIBODIES (MABS)



| | Erenumab (ERN) | Fremanezumab (FRZ) | Galcanezumab (GAZ) | Eptinezumab (EPZ) |
|-----------------------------|-------------------------|---------------------------|--|-----------------------------|
| Approval | Aimovig approved 5/2018 | Ajovy approved 9/2018 | Emgality approved 9/2018 | Eptinezumab approved 2/2020 |
| Target | CGRP receptor | CGRP ligand | CGRP ligand | CGRP ligand |
| Manufacturer | Amgen/Novartis | Teva | Eli Lilly | Alder |
| Route | SC | SC | SC | IV |
| Frequency | Monthly | Monthly or Quarterly | Monthly | Quarterly |
| Indications approved | Migraine prophylaxis | Migraine prophylaxis | Migraine prophylaxis Cluster Headache | Migraine prophylaxis |

ANTI-CGRP MABS: ADMINISTRATION



- Subcutaneous injection
 - Single-dose prefilled autoinjector
 - Erenumab (contains latex), Galcanezumab, Fremanezumab
- IV
 - Eptinezumab
- Adverse effects
 - Injection site reaction most common with pain, redness, induration, etc
 - Constipation
- Contraindications –Pregnancy
 - Wound healing?
- Injection training in office, online, by pharmacist

HOT OFF THE PRESS...



- Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered **atogepant** for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol.* 2020 Sep;19(9):727-737. doi: 10.1016/S1474-4422(20)30234-9.

- 10mg daily to 60mg BID

- Croop R, Lipton RB, Kudrow D, et al. Oral **rimegepant** for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet.* 2021 Jan 2;397(10268):51-60. doi: 10.1016/S0140-6736(20)32544-7. Epub 2020 Dec 15.

- 75mg every other day

QUESTIONS???

