Migraine A-Z

Gary W. Jay, MD, FAAPM, FACFEI

Disclosure

- Nothing to disclose

Learning Objectives

- Identify the pathophysiology of migraine headache
- Describe the various forms of migraine headache
- Differentiate the various migraine headache treatment alternatives

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Epidemiology

- In adults 18-65 YOA throughout the world, 50% to 75% globally have had a headache at least once over the last year
- In the USA, >30 M people have 1 or more migraine headaches/year
  - 18% of women and 6% of men
- Migraine accounts for 64% of severe headaches in women and 43% in men
- Approximately 75% of all people who experience migraine are women
  - 1 in 6 American women has migraine

Lipton et al. *Neurology*. 2002.

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Epidemiology (cont'd)

- Incidence of migraine with aura peaks in boys at about 5 YOA, and in girls about 12-13 YOA
  - Incidence of migraine without aura peaks in boys at age 10-11, in girls at age 14-17
- Prior to puberty, both prevalence and incidence of migraine are higher in boys than girls
  - After 12 YOA, prevalence increases in both men and women, peaking at 30-40 YOA
- Female to male ratio increases from 2.5:1 at puberty to 3.5:1 at 40 YOA

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1. Stewart et al, Am J Epidem, 1991
2. Hsu et al, Cephalalgia, 2011

Epidemiology (cont'd)

- Decreased attack severity and frequency after menopause in 2/3 of women
- Onset post 50 YOA is rare, but can begin after 60

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ICHD III

- This talk has been changed to use the terminology of the International Classification of Headache Disorders, 3rd Edition (ICHD III), published in *Cephalalgia* in 2018.
  - Many nosological and other changes
- There are 4 primary headaches: migraine, cluster headache, hemicrania continua, and tension-type headache
- There are an additional 10 other primary headaches
- Particularly when considering a "probable migraine" headache, one must be more concerned about possible secondary headaches

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Red Flags for Secondary Headache

- Using the SSNOOPP mnemonic for red flags
  - Systemic symptoms (weight loss or fever)
  - Secondary risk factors (underlying disease: cancer, HIV, autoimmune disease)
  - Neurological symptoms or abnormal signs (confusion, impaired alertness or consciousness, focal exam)
  - Onset: sudden, abrupt, or split second (first, worst)
  - Older age onset (new-onset and progressive headache, esp. at age >50 (giant cell arteritis, cancer)
  - Pattern change (first headache or different, change from routine headache)
  - Previous headache history changes (attack frequency, severity or clinical features)

- Dodick D W. Advanced Studies in Medicine, 2003

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Migraine Classification

1. Migraine
    - 1.1 Migraine without aura
    - 1.2 Migraine with aura
        - 1.2.1 Migraine with typical aura
            - 1.2.1.1 Typical aura with headache
            - 1.2.1.2 Typical aura without headache
        - 1.2.2 Migraine with brainstem aura

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ICHD-III. *Cephalalgia* 2018; 3(1) 1-211

Migraine Classification (cont'd)

- 1.2.3 Hemiplegic migraine
    - 1.2.3.1 Familial hemiplegic migraine (FHM)
        - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
        - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
        - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
        - 1.2.3.1.4 Familial hemiplegic migraine, other loci
    - 1.2.3.2 Sporadic hemiplegic migraine
- 1.2.4 Retinal migraine
- 1.3 Chronic migraine

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Migraine Classification (cont'd)

1.4 Complications of migraine
- 1.4.1 Status migrainosus
- 1.4.2 Persistent aura without infarction
- 1.4.3 Migrainous infarction
- 1.4.4 Migraine aura-triggered seizure

1.5 Probable migraine
- 1.5.1 Probable migraine without aura
- 1.5.2 Probable migraine with aura

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Migraine Classification (cont'd)

1.6 Episodic syndromes that may be associated with migraine
- 1.6.1 Recurrent gastrointestinal disturbance
  - 1.6.1.1 Cyclical vomiting syndrome
  - 1.6.1.2 Abdominal migraine
- 1.6.2 Benign paroxysmal vertigo
- 1.6.3 Benign paroxysmal torticollis

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ICHD III 1.1 Migraine Without Aura

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnoses

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ICHD-III. Cephalalgia 2018; 3(1) 1-211

Diagnosing Migraine WO Aura

- Associations:
  - Menstrual trigger
  - Red wine trigger
  - Weather trigger
  - Stress trigger
- Location, Location, Location!
  - Bilateral in at least 40% of migraine
  - Cervical pain is common in migraine
- Response to triptans and ergots not diagnostic of migraine
- Many migraine patients have either a family history of “headaches” or personal histories of motion sickness, esp. in childhood, or both
  - Tepper SJ, Tepper DE; Cleveland Clinical Manual, HA Therapy, 2014

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Diagnosing Migraine WO Aura (cont'd)

- Migraine effects daily abilities (increased pain on activity: climbing stairs, etc)
- "Sinus headache" is a nonspecific symptom
  - Does triptan/ergot stop headache?
  - Migraine is variable in both inter- and intrapatient over time
    - Severity of migraine can be moderate, it can be nonthrobbing, no nausea or aura
  - Meningitis and subarachnoid hemorrhage can transiently respond to migraine medications

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Probably Migraine—With/Without Aura

- Diagnosis secondary (in the ICHD-III) for migraine missing one criterion
- ICHD-III diagnosis is to be the one based on the highest complete set of criteria
- If a "probable" diagnosis is made, the clinician should be more likely to look for a secondary headache (may be "sinister" in nature!)

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ICHD III 1.2 Migraine With Aura

1.2 Migraine with aura
- 1.2.1 Migraine with typical aura
  - 1.2.1.1 Typical aura with headache
  - 1.2.1.2 Typical aura without headache
- 1.2.2 Migraine with brainstem aura
- 1.2.3 Hemiplegic migraine
  - 1.2.3.1 Familial hemiplegic migraine (FHM)
    - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

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ICHD III 1.2 Migraine With Aura (cont'd)

- 1.2.3.1.2 Familial hemiplegic migraine type (FHM2)
- 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
- 1.2.3.1.4 Familial hemiplegic migraine, other loci
- 1.2.3.2 Sporadic hemiplegic migraine

1.2.4 Retinal migraine

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IHS Criteria for Migraine Without Aura (2018)

- Migraine without aura (about 75%-80% of migraine) is formally diagnosed
- Migraine with typical aura—approx. 15%-20%

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Migraine With Aura

- ICHD III definition of aura:
  - "Recurrent attacks, lasting minutes of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms"
- Auras now considered visual, sensory, speech and/or language, motor, brainstem, or retinal
  - The first three types of aura are "typical"
  - Motor aura is "hemiplegic"
  - Basilar-type migraine is now "brainstem aura"
  - Migrainous monocular visual change is "retinal"

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ICHD III 1.2.1 Migraine With Typical Aura

A. At least two attacks fulfilling criteria B and C

B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem, or retinal symptoms

C. At least two of the following four characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
2. each individual aura symptom lasts 5-60 minutes
3. at least one aura symptom is unilateral
4. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-III diagnosis, and transient ischemic attack has been excluded

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ICHD-III. Cephalalgia 2018; 3(1) 1-211

Typical Aura

- Visual aura is 5-60 minutes long and not monocular, the diagnosis is typical aura without headache—homonymous in nature
  - Can be positive or negative—hemianopsia and/or disturbances of visual perception that are not typical of aura, but can be seen
    - Blurred vision
    - Kaleidoscopic vision
    - Illusory splitting
    - Metamorphopsia
    - Micropsia/macropsia (Alice in Wonderland Syndrome)
  - They are predominantly unilateral, involving the same half of the visual field or than can involve central vision
    - They often present as fortification spectra (zig-zag lines)

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Typical Aura (cont'd)

- Sensory symptoms can include paresthesias on one side of the body
- Numbness may be the single symptom or occur after paresthesias
- The hand is most often affected, followed by the face
  - The leg and trunk less frequently
- Paresthesias going up the hand, occasionally to the elbow and then to the perioral region of the ipsilateral mouth are called "cheiro-oral" migraine

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Typical Aura (cont'd)

- Speech symptoms include paraphasic errors
  - Impaired language production
  - Errors of comprehension are less common

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Typical Aura (cont'd)

- Other types of cortical symptoms may be seen during the aura phase and may include (in part):
  - Spatial and geographical disorientation
  - Déjà vu, jamais vu
  - Acalculia
  - Agraphia
  - Automatic behavior
  - Extreme anxiety
  - Gustatory hallucinations
  - Transient global amnesia
  - Depersonalization
  - Olfactory hallucinations
    - And more

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ICHD III Diagnostic Criteria for Migraine With Brainstem Aura

A. At least two attacks fulfilling criteria B-D

B. Aura consisting of visual, sensory and/or speech/language symptoms,

each fully reversible, but no motor or retinal symptoms

C. At least two of the following brainstem symptoms:

1. Dysarthria
2. Vertigo
3. Tinnitus
4. Hypoacusis
5. Diplopia
6. Ataxia
7. Decreased level of consciousness

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Migraine With Brainstem Aura

D. At least two of the following four characteristics:

1. At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5-60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied, or followed within 60 minutes, by headache

E. Not better accounted for by another ICHD-III diagnosis, and transient ischemic attack has been excluded

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Migraine With Brainstem Aura (cont'd)

- Migraine with brainstem aura is always, by definition, accompanied by a "typical aura"
  - It is also associated with an attack that included an aura with at least two brainstem posterior fossa symptoms
  - There can be no motor weakness
  - The duration of each aura is 5-60 minutes
  - Headache may occur during the aura or following the aura within an hour
- Typical aura and brainstem aura never include weakness
  - If weakness is seen, it is considered a hemiplegic migraine or not a migraine at all

• Robertson CE, Migraine with Brainstem Aura. UPTODATE, 2015

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ICHD III Diagnostic Criteria for Familial Hemiplegic Migraine

A. At least two attacks fulfilling criteria B and C

B. Aura consisting of both of the following:

1. fully reversible motor weakness
2. fully reversible visual, sensory and/or speech/language symptoms

C. At least two of the following four characteristics:

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ICHD III Diagnostic Criteria for Familial Hemiplegic Migraine (cont'd)

1. At least one aura symptom spreads gradually Over 5 minutes, and/or two or more symptoms occur in succession
2. Each individual non-motor aura symptom lasts 5-60 minutes, and motor symptoms last <72 hours
3. At least one aura symptom is unilateral
4. The aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack and stroke

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Hemiplegic Migraine

- As with brainstem aura, a hemiplegic migraine patient must have at least 2 attacks with typical aura as well as motor weakness.
- The typical aura will last, as usual, 5-60 minutes
- The motor weakness can last <72 hours, with no residual
- Familial hemiplegic migraine indicates that the patient must have at least one first- or second-degree relative to attain the diagnosis
  - If no relatives, the diagnosis becomes sporadic hemiplegic migraine
- ICHD-III lists 3 known and validated gene mutations triggering hemiplegic migraine (CACNA-IA (FHM-1); ATPIA (FHM-2): SCN1A (FHM-3)
- All gene mutations induce excel glutamate in the synapse, which increases neuronal excitability postsynaptically, probably by activating NMDA glutamate receptors

• Robertson CE. Hemiplegic Migraine. UpToDate, 2015

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ICHD III Diagnostic Criteria for Retinal Migraine

A. At least two attacks fulfilling criteria B and C

B. Aura consisting of fully reversible monocular positive and/or negative visual phenomena (eg, scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:

1. clinical visual field examination
2. the patient's drawing (made after clear instruction) of a monocular field defect

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ICHD III Diagnostic Criteria for Retinal Migraine (cont'd)

C. At least two of the following three characteristics

1. the aura spreads gradually over >/- 5 minutes
2. aura symptoms last 5-60 minutes
3. the aura is accompanied, or followed within 6 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded

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Retinal Migraine

- Was called ophthalmic and ocular migraine. No more!
- Retinal migraine, per the ICHD-III, is defined as "repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache"
- This monocular activity may be secondary to neuronal activation in the retina or to vascular changes
- Monocular positive or negative visual changes are required to make the diagnosis, and they must meet the criteria for migraine aura with clinical confirmation
  - Doyle E et al. Br J Ophthalmol. 2004 Feb; 88(2): 301–302.

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Complications of Migraine

- Per the ICHD-III:
  - Status migrainosus (>72 hours)
  - Persistent aura without infarction
  - Migrainous infarction (CVA must occur in a patient with a previously established aura, and in the same distribution of that aura)
  - Migraine aura-triggered seizure (migralepsy) (seizure occurs during or within one hour after a migraine aura)

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Menstrual Migraine—ICHD-3 appendix definitions

- 2 forms, both as migraine without aura
  - Menstrually related migraine without aura: headaches occur on days -2 to +3 of menstruation in more than 2/3 of menstrual cycles and also at other times of the cycle
  - Pure menstrual migraine: attacks occur exclusively on days -2 to +3 of menstruation in at least 2/3 of the menstrual cycles and at no other time of the cycle

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Periodic/Episodic Syndromes

- Episodic syndromes that may be associated with migraine, were called childhood period syndromes that are commonly precursors of migraine
  - Recurrent gastrointestinal disturbance
  - Cyclic vomiting syndrome
  - Abdominal migraine
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis

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ICHD III 1.3 Diagnostic Criteria for Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on ≥15 days/month for >3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≥8 days per month for >3 months, fulfilling any of the following:
   1. criteria C and D for 1.1 Migraine without aura
   2. criteria B and C for 1.2 Migraine with aura
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-III diagnosis

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ICHD-3 Diagnostic Criteria for MOH

A. Headache occurring on >/-15 days per month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

C. Not better accounted for by another ICHD-3 diagnosis

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Chronic Migraine and MOH

- Contradiction in definition, as some define development of chronic migraine by the intake of analgesic or vasoconstrictor medications
- Overuse of symptomatic medication is considered one of the most important risk factors for migraine progression:
  - Opiates: critical dose of exposure is around 8 days per month, in men>women
  - Barbiturates: critical dose of exposure is around 5 days per month, in women>men
  - Triptans: migraine progression seen in patients with high frequency of migraine at baseline (10-14 days/month)[1]

Bigal, Neurology, 2008

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Chronic Migraine and MOH (cont'd)

- Effect of NSAIDs varied with headache frequency, induced migraine progression in patients with a high baseline frequency of headaches[1]
- It was noted that medications containing barbiturates or opioids are associated with a 2-fold increased risk for progression to transformed migraine
- In patients with episodic migraine, the annual incidence of transformed migraine was 2.5%

Bigal, Neurology, 2008

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Chronic Migraine and MOH (cont'd)

- Treating chronic migraine: Diener suggested counseling followed by topiramate or onabotulinumtoxinA, and then admission to a detoxification program if necessary[1]
  - He felt that counseling would be sufficient in 50% of patients
- Jay notes treatment with a modified Raskin protocol in an interdisciplinary headache center is appropriate[2]

Diener, 53rd Annual Scientific Meeting, AHS, 2011
Jay, HEADACHE HANDBOOK, CRC Press, 1999

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Migraine Variants—NO MORE!!!

- Acephalgic migraine
- Basilar migraine (Bickerstaff's)
- Childhood periodic syndromes
- Ophthalmic, ocular migraine
- Ophthalmoplegic migraine
- Complicated migraine
- Acute confusional migraine

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Not in the IHS Information

- Children who experience physical and emotional abuse or neglect are more likely to have migraines and headaches as adults
  - "Dose response relationship between abuse and headache"
  - Growing evidence that genes are involved in either increased vulnerability or resilience in response to early stressful experiences

Buse, 4th Annual Headache Cooperative of the Pacific, 2011;
Tietjen GE et al, Headache, 2010.

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Migraine With Aura

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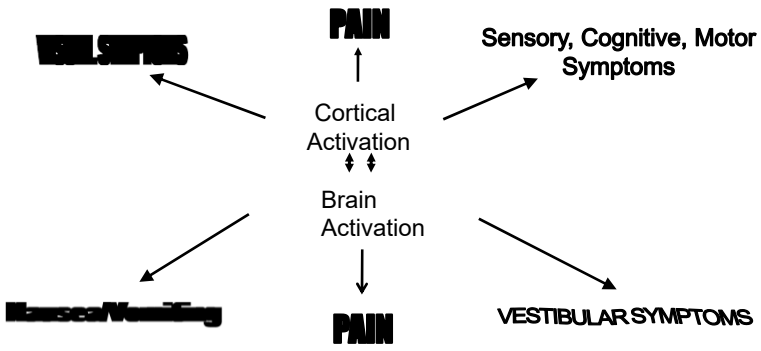
Migraine—A Multisymptom Complex



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Different Clinical Features of Migraine With vs Without Aura

- Different patterns of inheritance
- Different occurrence relative to menstrual cycle
- Higher incidence of allodynia in patients with aura

Vibeke et al., Evidence of a genetic factor in migraine with aura: A population-based Danish twin study. Annals of Neurology. 1999;45:242-6.
MacGregor E. Oestrogen and attacks of migraine with and without aura. The Lancet Neurology. 2004;3:354-61.
Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. Ann Neurol. 2008;63:148-58.

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Migraine With Aura Has Greater Association With:

- Stroke
- Patent foramen ovale
- Cardiovascular disease in women
- Depression
- Anxiety, panic, phobias, suicidal ideation

Schwedt TJ, Demaerschalk BM, Dodick DW. Cephalalgia. 2008;28:531-40.
Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Jama. 2006;296:283-91.
Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, et al. Neurology. 2005;64:1020-6.
Samaan Z, Farmer A, Craddock N, Jones L, Korszun A, Owen M, McGuffin P. The British Journal of Psychiatry. 2009;194:350-4.

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However….

- Very few migraine with aura patients have aura with 100% of their attacks
- Many patients classified as having migraine without aura have had 1 or 2 episodes with typical aura
- Clinical symptoms may not meet definition of aura (eg, cognitive symptoms, timing relative to headache)

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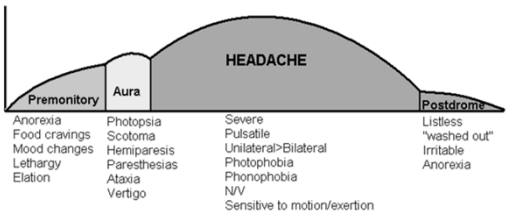
Phases of Migraine
Migraines Are More Than Just Pain



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Migraine Phases

- Premonitory symptoms (prodrome)—autonomic
- Aura
- Headache
- Resolution
- Postdrome
  - Not every attack has or every patient has all phases

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Postdrome

- Postheadache, many patients experience “hang-over” type symptoms: cognitive difficulties, dizziness, fatigue, and concern that the headache may recur
- The postdrome may last 24-48 hours

Burstein et al. Brain, 2000

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Pathophysiology

- 1944 Leão: theory of cortical spreading depression (CSD) (*J Neurophys*)
  - Well defined wave of neuronal excitation in the cortical gray matter spreading from site of origin at ave. 4 mm/min (2-6 mm/min)
  - Ensuing cellular depolarization causes the primary cortical phenomenon (aura phase)
    - Basis is release of potassium or glutamate from neural tissue, which depolarizes adjacent tissue,
      which releases more neurotransmitters, propagating the CSD

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Pathophysiology (cont'd)

- Activation of the trigeminovascular system from CSD stimulates nociceptive neurons on dural blood vessels to release plasma proteins and algetic substances including CGRP, SP, VIP, and NKA
  - This yields a sterile inflammatory state accompanied by continued vasodilation, increasing pain
  - Initial cortical hyperperfusion in CSD is partly mediated by release of trigeminal and parasympathetic neurotransmitters from perivascular nerve fibers, while delayed meningeal blood flow increase is mediated by a trigeminal-parasympathetic brainstem connection
  - Altered descending modulation in the brainstem may contribute to the headache phase of migraine, leading to a loss of inhibition or enhanced facilitation, resulting in trigeminovascular neuron hyperexcitability[1]

1. Moulton et al, PLoS One, 2008

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Pathophysiology

- Aura
  - Cortical spreading depression
  - Initially decreased and then increased blood flow
  - May be related to initiation of migraine

Image courtesy of http://migraine.co.nz/

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Migraine with Typical Aura

- 15%-20% of migraineurs have aura, with the classical “slow march” of symptoms seen in migraine with aura (MWA)
  - A patient may experience several distinct auras in a row, one after the other
  - The symptoms can be spectacular and frightening
- The rate of expansion or movement of a visual scotoma is about 4 mm/min
- Initial hyperemia followed by oligemia spreads from the occipital cortex at a rate of 2-6 mm/min
- A PET study of spontaneous migraine demonstrated a spreading bilateral oligemia, establishing the phenomenon exists in migraine patients
- Headache usually begins while cerebral blood flow is diminished
- Note: the HA begins when blood flow is still reduced, making it unlikely that at least initially vasodilatation is the cause of pain

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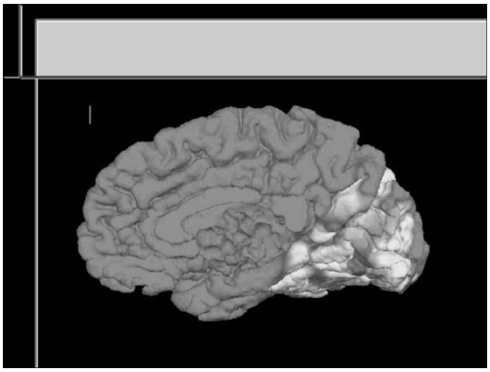
Woods RP et al N Engl J Med 1994; Olesen J et al, Ann Neurol 1990; Lauritzen M, Brain, 1994

Migraine Aura is Neuronal



Hadjikhana N Et al, Proc Natl Acad Sci USA 2001

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Migraine Aura

- Hadjikhana et al recorded induced and spontaneous migraine aura
  - They concluded that migraine aura is not evoked by ischemia, but by aberrant firing of neurons and related cellular elements characteristic of cortical spreading depression (CSD)
  - During the visual aura, vascular changes follow changes in neuronal activity
    - In these patients, the neurophysiological events of the aura, be it visual or sensory, also result from activation of the trigeminal/cervical nociceptive neurons
  - Shown in the last slide: aura related changes are first evident in the extra-striate cortex
    - The spread of the aura begins and is most systematic in the representation of the lower visual field and becomes less regular as it progresses into the representation of the upper visual field

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Migraine Aura

- The trigeminal nerve innervates the meninges
  - Events intrinsic to the cerebral cortex are capable of affecting the pain sensitive dural vascular structures
- Bolay et al found that, in animals, there is a connection between CSD and activation of trigeminal nerve afferents
  - Activation of V evokes a series of meningeal and brainstem events that appear to be consistent with that seen during a migraine
  - Triggering CSD leads to a long-lasting blood flow increase within the middle meningeal artery
    - This increase in blood flow is dependent on both trigeminal and parasympathetic activation
    - At the same time, plasma protein leakage occurs in the dura—the first study to demonstrate that vasodilatation during headache is possibly linked to a series of neurometabolic events, including pain transmission by the trigeminal nerve

Bolay et al, Nat Med 2002; Iadecola C, et al, Nat Med, 2002

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Issues With Classical Cortical Spreading Depression in Migraine

- Classic EEG findings of cortical spreading depression have not been observed in migraine patients
- Most patients do not have the profound neurological impairment one would expect with classical CSD
- *Migraine may involve cortical waves that are related to, but not identical to, CSD observed in animal models*
- *Different types of cortical waves may involve distinct cellular mechanisms*

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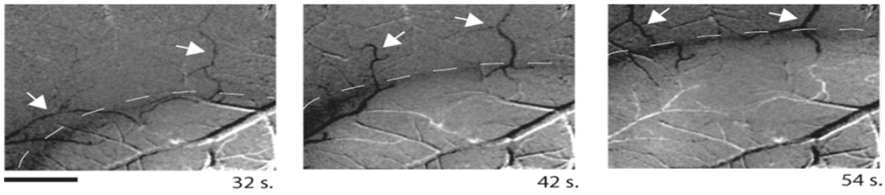

Arteriolar dilation propagates ahead
of parenchymal changes of CSD

Could vascular signaling play an active role in cortical waves?

"It seems well to consider, therefore, that, however brought about, vascular changes may precede and condition the cortical depression".
Leão, J Neurophys. 1945

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Propensity for CSD Is Increased By:

- GENES—Transgenic mice expressing FHM1genes show increased propensity for CSD
- GENDER—Female mice have a reduced threshold for CSD
- HORMONES—Ovarian hormones reduce the threshold for CSD

van den Maagdenberg AMJM, Pietrobon D, Pizzorusso T, Kaja S, Broos LAM, Cesetti T, et al. Neuron. 2004;41:701-10
Brennan KC, Romero-Reyes M, López Valdés HE, Arnold AP, Charles AC. Annals of Neurology. 2007;61:603-6
Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ, et al. J Clin Invest. 2009;119:99-109

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Medications that Inhibit Cortical Excitability Prevent Migraine *With and Without* Aura

- Ayata et al, *Annals of Neurology* 2006
  - Diverse pharmacological agents that are effective for migraine prevention suppress cortical spreading depression in rats
- Memantine for migraine prevention?
  - Identified as an inhibitor of CSD
  - Initial clinical results encouraging (Charles et al, *Journal of Headache and Pain*, 2007)
- Specific neuronal, astrocytic, and vascular cortical mechanisms may represent individual distinct targets for new acute and preventive therapies

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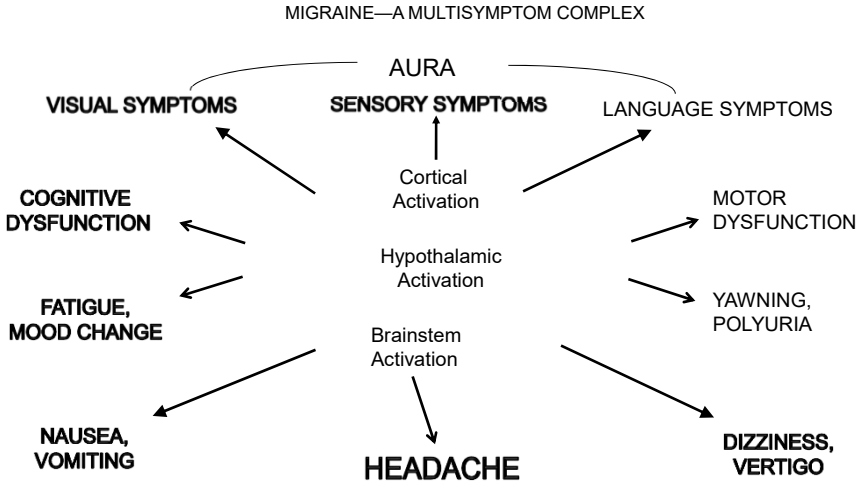

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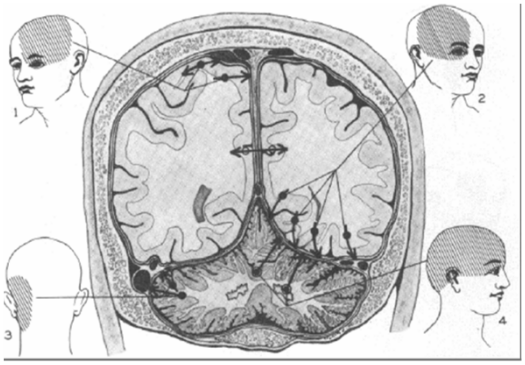
Pain Producing Intracranial Structures



Ray BS, Wolfe HG, Arch Surgery, 1940

PAINWEEK

A Migraine Generator?

- Thought to be the trigeminal nucleus caudalis
- In animal models of migraine, a number of receptor systems mediating c-fos expression are within the trigeminal nucleus caudalis
- Intracranial, unmyelinated c- and A delta-fibers of the of the trigeminal nerve transmit pain stimuli from the meninges to the trigeminal nucleus caudalis (Sp5C)
- Peripheral nerve endings surround meningeal vessels (the trigeminovascular system) and contain neuroactive neuropeptides (CGRP, SP, NKA)
- Activation of the trigeminovascular system promotes a meningeal sterile inflammatory response via the release of neuropeptides by peripheral endings

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A Migraine Generator? (cont'd)

- Orthodromic conduction along trigeminovascular fibers transmits information centrally with induction of immediate early c-fos genes within postsynaptic Sp5C neurons as a marker of stimulation of the TG
- At least 10 receptors modulate c-fos expression in the Sp5C: 5-HT(1B), 5-HT(1D), 5-HT(1F), 5-HT(2B), NK-1, GABA(A), NMDA, AMPA, class III metabotropic glutamate receptors and opioid mu receptors
- C-fos expression is a marker of cephalgic nociception

Mitsikostas, et al. Brain Res Brain Res Rev, 2001

PAINWEEK

A Migraine Generator? (cont'd)

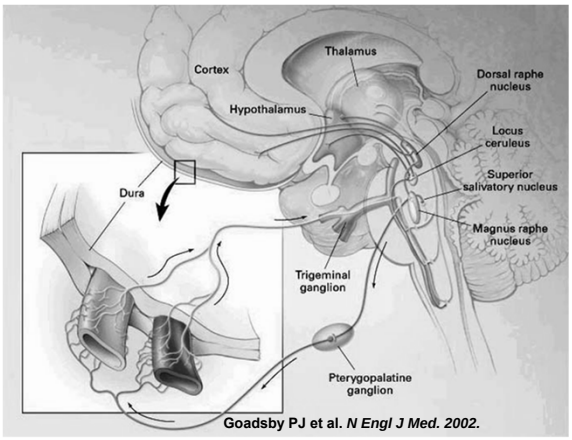
- CGRP, in animals and humans, shows the trigeminal ganglion and the trigeminal nucleus caudalis are likely to be sites of action of CGRP in migraine[1-3]
- Immunohistochemical studies have detected 5-HT(1D) receptors in trigeminal sensory neurons, including peripheral projections to the dura and within the trigeminal nucleus caudalis and solitary tract while 5-HT(IB) receptors are present on smooth muscle cells in meningeal vessels
- These findings indicate that triptans (selective 5-HT(1)) agonists decrease headache by abolishing neuropeptide release in the periphery and blocking neurotransmission by acting on second-order neurons in the trigeminocervical complex

1. Lassen et al, Cephalalgia, 2002
2. Sexton et al, Neuroscience, 1986
3. Ma et al, Neuroscience, 2003

PAINWEEK

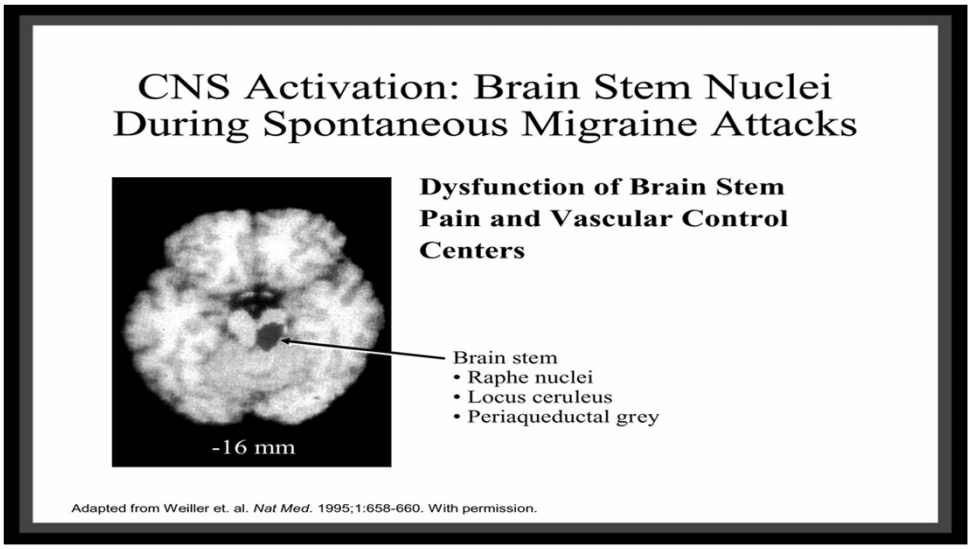
Migraine Pathophysiology

- Migraines are triggered by internal (dehydration, lack of sleep, stress) or external (smell, light, food) stimuli
- Deep nuclei in the brainstem begin to malfunction (trigeminal nucleus and magnus raphe nucleus)
- Energy failure allows the nerves surrounding vascular structures in the brain (which are part of the trigeminal nerve) to propagate the problem and malfunction (throbbing pain)
- These malfunctioning nerves trigger thalamic dysfunction (nausea, severe pain)



Goadsby PJ et al. *N Engl J Med. 2002.*

PAINWEEK



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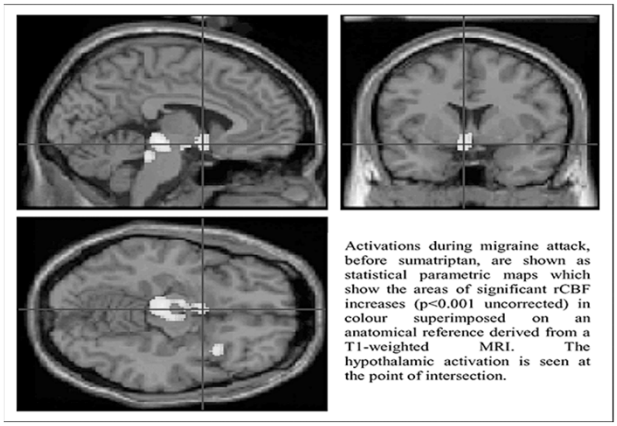

Hypothalamic Activation in Migraine (Denuelle et al., Headache, 2007)

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Migraine Headache and Allodynia

- Migraine lasts 4-72 hours in adults
- Pain can begin mild, diffuse, and become moderate to severe
- Associated symptoms—nausea, vomiting, sonophobia, and photophobia
- BEGIN TREATMENT EARLY

1. Schoenen, Biomed Pharmacother, 1996
2. Lipton et al, Neurology, 2002

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Migraine Headache and Allodynia (cont'd)

- When the migraine becomes severe, some patients may develop allodynia—cephalgic (hair hurts) and/or extracephalgic
  - The allodynia comes soon after the onset of headache
- The chest, extremities, and back muscles may become tender
- This suggest central sensitization—a physiological state in which central neurons transmit noxious sensory signal independent of sensory signals from the periphery[1]

1. Aurora et al, Headache, 2007

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Five Principles of Migraine Management

- Treat occipital neuralgia and trigeminal nerve dysfunction
- Avoid rebound headache
- Abortive therapy
- Preventative therapy
- Lifestyle issues

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Avoid Rebound Headache (Medication Overuse Headache)

- In general if acute meds are used more then 3 days/week they will cause rebound headache
- This HA is usually a dull constant HA
- Treatment: tough love—stop taking meds completely
- Things might get worse for two weeks but then will improve
- The worst offenders: narcotics, Excedrin®, Fioricet®, butalbital containing meds
- This may also keep headache preventive medications from working well

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Rational Polytherapy

- NSAID plus triptan
- Antiemetic (metoclopramide 10 mg) plus NSAID (naproxen sodium 550 mg)
- Antiemetic plus triptan
- Antiemetic plus NSAID plus triptan

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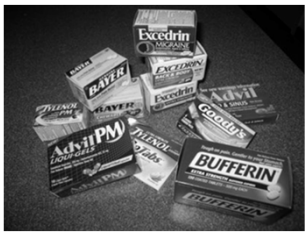
Treatment

- One of Jay's Laws—
  the more treatments you have for a specific medical problem, the less likely any are very successful



Images from migraine support blogs

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Medications That May Make Migraines Worse

- Oral contraceptives
- Hormone replacement
- SSRI antidepressants
- Steroids (tapering)
- Decongestants
- Short-acting sedatives (eg, Ambien®?)
- Bone density medications (?)
- Botox

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The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies

Marmura, MJ, Silberstein SD, Schwedt TJ. Headache, 2015; 55: 3-20

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Level A—Medications are established as effective for acute migraine treatment based on available evidence

- Analgesic—acetaminophen 1000 mg (for non-incapacitating attacks)
- Ergots—DHE-IN 2 mg or pulmonary inhaler 1 mg
- NSAIDS—ASA-500 mg; diclofenac 50, 100 mg; ibuprofen 200, 400 mg; naproxen 500, 550 mg
- Opioids—butorphanol nasal spray 1 mg
- Triptans—almotryptan 12.5 mg; eletryptan 20, 40, 80 mgs; frovatriptan 2.5 mg; naratripatn 1, 2.5 mg; rizatriptan 5, 10 mg; sumatriptan: oral 25, 50, 100 mg, IN 10, 20 mg, patch 6.5 mg; SC 4, 6 mg; zolmitriptan IN 2.5, 5 mg, oral 2.5, 5 mg
- Combinations—acetaminophen/ASA/caffeine 500/500/130 mg; sumatriptan/naproxen 85/500 mg

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Level B—Medications are probably effective for acute migraine treatment based on available evidence

- Antiemetics—chlorpromazine IV 12.5 mg; droperidol IV 2.75 mg; metaclopramide IV 10 mg; prochlorperazine IV/IM 10, PR 25 mg
- Ergots—DHE-IV, IM, SC 1 mg; ergotamine/caffeine 1/100 mg
- NSAIDs—flurbiprofen 100 mg; ketoprofen 100 mg; ketorolac IV/IM 30-60 mg
- Others—$MgSO_4$ IV (migraine with aura) 1-2 grm; isometheptene 65 mgs
- Combinations—codeine/acetaminophen 25/400 mg; tramadol/acetaminophen 75/650 mg

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Level C—Medications are possibly effective for acute migraine treatment based on available evidence

- Antiepileptic—valproate IV 400-1000 mg
- Ergot—ergotamine 1-2 mg
- NSAIDs—phenazone 1000mg
- Opioids—butorphanol IM 2 mg; codeine 30 mg; meperidine IM 75 mg; methadone IM 10 mg; tramadol IV 100 mg
- Steroid—dexamethazone IV 4-16 mg
- Others—butalbital 50 mg; lidocaine IN
- Combinations—butalbital/acetaminophen/caffeine/codeine 50/325/40/30 mg; butalbital/acetaminophen/caffeine 50/325/40 mg

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Level U—Evidence is conflicting or inadequate to support or refute the efficacy of the following medications for acute migraine

- NSAIDs—celecoxib 400 mg
- Others—lidocaine IV; hydrocortisone IV 50 mg

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Others

- Level B negative: other—octreotide SC 100 micrograms
- Level C negative:
  - Antiemetics—chlorpromazine IM 1mg/kg; granisetron IV 40-80 mcg/kg
  - NSAIDs—ketorolac; tromethamine nasal spray
  - Analgesic—acetaminophen IV 1000 mg

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EBM

Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

– Silberstein SD, Holland S, Freitag F, et al Neurology 2012; 78;1337

Note: 284 articles found, 29 classified as Class I or Class II
Studies with completion rates below 80% were downgraded—several studies in the original guideline have been downgraded

PAINWEEK

April 2012 EBM Guidelines from APS and AAN

- Level A—medications with established efficacy (≥ 2 Class 1 Trials)
  - Antiepileptic drugs
    - Divalproex sodium
    - Sodium valproate
    - Topiramate
  - B-Blockers
    - Metaprolol
    - Propranolol
    - Timolol
  - Triptans (MRM)
    - Frovatriptan

PAINWEEK

April 2012 EBM Guidelines from APS and AAN (cont'd)

- Level B—medications are probably effective (1 Class 1 or 2 Class II studies)
  - Antidepressants/SSRIs/SNRIs/TCA
    - Amitriptyline
    - Venlafaxine
  - B-Blockers
    - Atenolol
    - Nadolol
  - Triptans (MRM)
    - Naratriptan
    - Zolmitriptan

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- Level-C—medications are possibly effective (1 Class II study)
  - ACE inhibitors
    - Lisinopril
  - Angiotensin receptor blockers
    - Candesartan
  - A- Agonists
    - Clonidine
    - Guanfacine
  - AEDs
    - Carbamazepine

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- β-Blockers
  - Nebivolol
  - Pindolol
- Antihistamines
  - Cyproheptadine

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- Level U—Inadequate or conflicting data to support or refute medication use
  - Carbonic anhydrase inhibitor
    - Acetazolamide
  - Antithrombotics
    - Acenocoumarol
    - Coumadin
    - Picotamide
  - Antidepressants/SSRIs/SNRIs
    - Flovoxamine
    - Fluoxetine

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- AEDs
  - Gabapentin
- TCAs
  - Protriptyline
- β- Blockers
  - Bisoprolol
- Ca++ Blockers
  - Nicardipine
  - Nifedipine
  - Nimodipine
  - Verapamil

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- Direct vascular smooth muscle relaxants
  - Cyclandelate

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April 2012 EBM Guidelines from APS and AAN (cont'd)

- Other—medications that are established as possibly or probably ineffective
  - Established as not effective
    - AED
      - Lamotrigine
  - Probably not effective
      - Clomipramine
  - Possibly not effective
      - Acebutolol
      - Clonazepam
      - Nabumetone
      - Oxcarbazepine
      - Telmisartan

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QUESTIONS???

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Other Primary Headaches

4. Other primary headache disorders
    4.1 Primary cough headache
        4.1.1 Probable primary cough headache
    4.2 Primary exercise headache
        4.2.1 Probable primary exercise headache
    4.3 Primary headache associated with sexual activity
        4.3.1 Probable primary headache associated with sexual activity
    4.4 Primary thunderclap headache

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ICHD-III. Cephalalgia 2018; 3(1) 1-211

Other Primary Headaches (cont'd)

    4.5 Cold-stimulus headache
        4.5.1 Headache attributed to external application of a cold stimulus
        4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus
        4.5.3 Probable cold-stimulus headache
            4.5.3.1 Headache probably attributed to external application of a cold stimulus
            4.5.3.2 Headache probably attributed to ingestion or inhalation of a cold stimulus

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Other Primary Headaches (cont'd)

- 4.6 External-pressure headache
  - 4.6.1 External-compression headache
  - 4.6.2 External-traction headache
  - 4.6.3 Probable external-pressure headache
    - 4.6.3.1 Probable external-compression headache
    - 4.6.3.2 Probable external-traction headache

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Other Primary Headaches (cont'd)

- 4.7 Primary stabbing headache
  - 4.7.1 Probable primary stabbing headache
- 4.8 Nummular headache
  - 4.8.1 Probable nummular headache
- 4.9 Hypnic headache
  - 4.9.1 Probable hypnic headache
- 4.10 New daily persistent headache (NDPH)
  - 4.10.1 Probable new daily persistent headache

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