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 alternative
Epidemiology-1

- 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

Epidemiology-2

- 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\(^1\)
- 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\(^2\)

2. Hsu et al, Cephalalgia, 2011
Epidemiology-3

- Decreased attack severity and frequency after menopause
- Onset post 50 YOA is rare, but can begin after 60
Migraine Classification-1

- Migraine without aura (common migraine)
- Probably migraine without aura
- Migraine with aura (classic migraine)
- Probably migraine with aura
- Chronic migraine
- Chronic migraine associated with analgesic overuse
Migraine Classification (Cont.)

- Childhood periodic syndrome that may not be precursors to or associated with migraine
- Complications of migraine
- Migrainous disorder not fulfilling above criteria (probable migraine)
- Hemicrania continua

1. International Classification of Headache Disorders, 2nd Ed, Cephalalgia, 2004
1.1 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated)

C. Headache has $\geq 2$ of the following 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, climbing stairs)

D. During headache $\geq 1$ of the following
   1. Nausea and/or vomiting
   2. Photophobia or phonophobia

E. Not attributed to another disorder

ICHD-II. Cephalalgia 2004; 24 (Suppl 1)
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Migraine without aura (about 75%-80% of migraine) is formally diagnosed:
1.2 Migraine With Aura
Subtypes New to Classification

1.2.1 Typical aura with migraine headache
   — Most migraine auras are associated with headache fulfilling criteria 1.1 *Migraine without aura*

1.2.2 Typical aura with non-migraine headache

1.2.3 Typical aura without headache
   — Migraine aura is sometimes associated with a headache that does not fulfil these criteria
   — Or occurs without headache

ICHD-II. *Cephalalgia* 2004; 24 (Suppl 1)
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- 15%-20% of migraine attacks
- Different from migraine without aura by the presence of
  - Period of local neurological symptoms preceding the headache, including:
    - Visual, sensory or speech symptoms
    - Visual symptoms may include scotoma or seeing zig-zag lines
    - Sensory auras may be numbness or tingling in the face or fingers
    - There may also be speech difficulties
Chronic Migraine

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

B. Occurring in a patient who has had at least 5 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:
   — Criteria C and D for 1.1 migraine without aura
   — Criteria B and C for 1.2 migraine with aura
   — 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

- Headache (tension-type or migraine) on 15 or more days/month for at least 3 months
- Headache occurring in a patient who has had at least 5 IHS migraine attacks
- On 8 or more days/months, if the headache have fulfilled
  - IHS criteria for migraine or are
  - Treated and relieved by triptan/ergot before the expected development of symptoms fulfilling IHS migraine criteria
  - No medication overuse headache (MOH) as defined by IHS 8.2
Chronic Migraine and MOH-1

- 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 months, in women > men
  - Triptans: migraine progression seen in patients with high frequency of migraine at baseline (10-14 days/month)\(^1\)

Chronic Migraine and MOH-2

- Effect of NSAIDs varied with headache frequency, induced migraine progression in patients with a high baseline frequency of headaches.
- 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%.

New Appendix Criteria for MOH (IHS, 2004)

- Headache present on 15 or more days/months
- Regular overuse for 3 months of more of acute medication as defined in IHS 8.2
- Headache has developed or markedly worsened during medication overuse
- MOH duration definition:
  - Intake on a regular basis for 3 months or more
  - On 10 or more days/months, the patient takes:
    - Opiates
    - Combination analgesics
    - Triptans
    - Ergots
  - On 15 or more days/month, the patient takes simple analgesics
Chronic Migraine and MOH-3

- 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 the Raskin protocol in an interdisciplinary headache center is appropriate\(^2\)

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1. Diener, 53rd Annual Scientific Meeting, AHS, 2011
2. Jay, HEADACHE HANDBOOK, CRC Press, 1999
1.6 Probable Migraine

1.6.1 Probable migraine without aura
1.6.2 Probable migraine with aura
1.6.5 Probable chronic migraine
1.6 Probable Migraine

1.6.1 Probable migraine without aura
A. Attacks fulfilling all but one of criteria A-D for 1.1 Migraine without aura
B. Not attributed to another disorder

1.6.2 Probable migraine with aura
A. Attacks fulfilling all but one of criteria A-D for 1.2 Migraine with aura
B. Not attributed to another disorder

ICHD-II. Cephalalgia 2004; 24 (Suppl 1)
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Migraine Variants

- Acephalgic migraine
- Hemiplegic migraine
- Basilar migraine (Bickerstaff’s)
- Childhood periodic syndromes
- Retinal migraine (ophthalmic, ocular)
- Ophthalmoplegic migraine
- Complicated migraine
- Migralepsy
- Acute confusional migraine (transient global amnesia)
- Vertiginous migraine
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

1. Buse, 4th Annual Headache Cooperative of the Pacific, 2011;
Migraine With Aura
Migraine—A Multisymptom Complex

**VISUAL SYMPTOMS**
- Nausea/Vomiting

**PAIN**
- Cortical Activation
- Brainstem Activation

**Sensory, Cognitive, Motor Symptoms**

**VESTIBULAR SYMPTOMS**
ICHD Classification of Migraine With Aura

A. At least 2 attacks fulfilling criteria B–D

B. Aura consisting of at least one of the following, but no motor weakness:
   1. fully reversible visual symptoms including positive features (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
   2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
   3. fully reversible dysphasic speech disturbance

C. At least 2 of the following:
   1. homonymous visual symptoms and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
   3. each symptom lasts ≥5 and <60 minutes

D. Headache fulfilling criteria B–D for 1.1 migraine without aura begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder
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

Migraine With Aura Has Greater Association With:

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

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 (e.g., cognitive symptoms, timing relative to headache).
Phases of Migraine

Migraines Are More Than Just Pain

- Anorexia
- Food cravings
- Mood changes
- Lethargy
- Elation
- Photopsia
- Scotoma
- Hemiparesis
- Paresthesias
- Ataxia
- Vertigo
- Severe
- Pulsatile
- Unilateral>Bilateral
- Photophobia
- Phonophobia
- N/V
- Sensitive to motion/exertion
- Listless
- "washed out"
- Irritable
- Anorexia
Migraine Phases

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

Pathophysiology-1

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
Pathophysiology-2

- PET scans show moderately reduced blood flow during a migrainous aura, but the spreading oligemia does not correspond to specific vascular territories
  - The flow is reduced secondary to reduction in metabolism
  - CSD presumably induces clinical manifestation of migraine aura, the spreading oligemia can be clinically silent (migraine without aura: CSD may not be involved in migraine without aura)

Pathophysiology-3

- 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

Molecular Mechanisms of CSD

- CSD up regulates genes: those encoding cyclo-oxygenase 2 (COX-2), tumor necrosis factor alpha and interleukin-1beta, gelatin and metalloproteinases.

- Activation of metalloproteinase causes leakage of the BBB, allowing potassium, nitric oxide, adenosine, and other products released by CSD to reach and sensitize the dural perivascular trigeminal afferent endings.\(^1\)

- Increased activity of matrix metalloproteinase-2 (MMP-2) is found in migraineurs.\(^2\)

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1. Richter et al, Schmertz, 2008;  
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/](http://migraine.co.nz/)
Migraine Aura-1

- 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

Migraine Aura is Neuronal

Hadjikhana N et al, Proc Natl Acad Sci USA 2001
Hadjikhani 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 (CDS)

- 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
Activation of Primary Afferent Neurons May Be Associated With Aura-Related Events in the Cortex

Migraine Aura-3

- 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

Issues With Classical Cortical Spreading Depression in Migraine

- Classic EEG findings of cortical spreading 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.
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
Propensity for CSD Is Increased By:

- **GENES**—Transgenic mice expressing FHM1 genes show increased propensity for CSD
- **GENDER**—Female mice have a reduced threshold for CSD
- **HORMONES**—Ovarian hormones reduce the threshold for CSD

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

- Specific neuronal, astrocytic, and vascular cortical mechanisms may represent individual distinct targets for new acute and preventive therapies
MIGRAINE—A MULTISYMPTOM COMPLEX

AURA

**VISUAL SYMPTOMS**

COGNITIVE DYSFUNCTION

FATIGUE, MOOD CHANGE

NAUSEA, VOMITING

**SENSORY SYMPTOMS**

Cortical Activation

Hypothalamic Activation

Brainstem Activation

**LANGUAGE SYMPTOMS**

MOTOR DYSFUNCTION

YAWNING, POLYURIA

DIZZINESS, VERTIGO

**HEADACHE**
Pain Producing Intracranial Structures

Ray BS, Wolfe HG, Arch Surgery, 1940
Migraine—Simplistic Definition Heard on TV (By TV Physician “Expert”!)

- Migraine is secondary to neurological inflammation of the meninges!

- BUT IT IS A GOOD BIT MORE
A Migraine Generator?-1

- 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 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
A Migraine Generator?-2

- 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 cephalic nociception

A Migraine Generator?-3

- CGRP, in animals and humans, shows the trigeminal ganglion and the trigeminal nucleus caudalis are likely to be sites of action of CGRP in migraine1-3

- 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(1B) 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
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)
CNS Activation: Brain Stem Nuclei During Spontaneous Migraine Attacks

Dysfunction of Brain Stem Pain and Vascular Control Centers

Brain stem
- Raphe nuclei
- Locus ceruleus
- Periaqueductal grey

-16 mm

Activations during migraine attack, before sumatriptan, are shown as statistical parametric maps which show the areas of significant rCBF increases (p<0.001 uncorrected) in colour superimposed on an anatomical reference derived from a T1-weighted MRI. The hypothalamic activation is seen at the point of intersection.
Migraine Headache and Allodynia-1

- 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

2. Lipton et al, Neurology, 2002
Migraine Headache and Allodynia -2

- When the migraine becomes severe, some patients may develop allodynia—cephalalgic (hair hurts) and/or extracephalalgic
  - 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. Aurora et al, Headache, 2007
Migraine Headache and Allodynia-3

- Guy et al (Cephalalgia, 2010) found that modalities of cephalic and extracephalic cutaneous allodynia (CA) were different, with extracephalic CA being mostly thermal, while cephalic CA was mostly mechanical, suggesting different mechanisms for the 2
- Whether a patient shows signs of CA is a predictor of whether or not that patient can become migraine painfree with triptan treatment
  - Need for NSAIDs preceding triptans if CA exists

Treatment of Migraines:

A brief history of natural and homeopathic time-honored therapies
Treatment
Aretaeus AD 81?

For the treatment of headache, Aretaeus recommended inducing sneezing by placing testicle of beaver powder intranasally to "bring off phlegm"
“For the effective treatment of long-standing headache the patient may bind over his head a mole long dead and putrid”
Willis 1685

“The use of Millepedes ought not here to be omitted, or set lightly by, in regard that their express’d Juice, distill’d Water, and also the Powder prepar’d of them, often contribute egregiously to the Cure of ancient and obstinate Head-achs.”
Other “Interesting” Headache Treatments

- Drilling a whole in the skull
- Bloodletting
- Placing a hot iron on the head
- Spinning a patient in a centrifuge
Five Principles of Migraine Management

- Treat occipital neuralgia and trigeminal nerve dysfunction
- Avoid rebound headache
- Abortive therapy
- Preventative therapy
- Lifestyle issues
Avoid Rebound Headache
(Medication Overuse Headache)

- In general if acute meds are used more than 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 2 weeks but then will improve.
- The worst offenders: narcotics, Excedrin®, Fioricet®, butalbital containing meds.
- This may also keep headache preventive medications from working well.
Rational Polytherapy

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

- One of Jay’s Laws—the more treatments you have for a specific medical problem, the less likely any are very successful
Medications that May Make Migraines Worse

- Oral contraceptives
- Hormone replacement
- SSRI antidepressants
- Steroids (tapering)
- Decongestants
- Short-acting sedatives (eg, Ambien®)
- Bone density medications
- Botox
American Headache Society Evidence Assessment—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
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 mgs
- Opioids—butorphanol nasal spray 1 mg
- Triptans—almotriptan 12.5 mg; eletriptan 20, 40, 80 mgs; frovatriptan 2.5 mg; naratriptan 1, 2.5 mg; rizatriptan 5, 10 mgs; 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
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**—MgSO₄ IV (migraine with aura) 1-2 grm; isomethptene 65 mgs
- **Combinations**—codeine/acetaminophen 25/400 mg; tramadol/acetaminophen 75/650 mg
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
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
**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

— 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
April 2012 EBM Guidelines from APS and AAN-1

- Level A—medications with established efficacy (≥ 2 Class 1 Trials)
  - Antiepileptic drugs
    - Divalproex sodium
    - Sodium valproate
    - Topiramate
  - β-Blockers
    - Metaprolol
    - Propranolol
    - Timolol
  - Triptans (MRM)
    - Frovatriptan
April 2012 EBM Guidelines from APS and AAN-2

- Level B—medications are probably effective (1 Class 1 or 2 Class II studies)
  - Antidepressants/SSRIs/SNRIs/TCA
    - Amitriptyline
    - Venlafaxine
  - β-Blockers
    - Atenolol
    - Nadolol
  - Triptans (MRM)
    - Naratriptan
    - Zolmitriptan
April 2012 EBM Guidelines from APS and AAN-3

- Class-C—medications are possibly effective (1 Class II study)
  - ACE inhibitors
    - Lisinopril
  - Angiotensin receptor blockers
    - Candesartan
  - α-Agonists
    - Clonidine
    - Guanfacine
  - AEDs
    - Carbamazepine
April 2012 EBM Guidelines from APS and AAN-3a

- **β-Blockers**
  - Nebivolol
  - Pindolol
- **Antihistamines**
  - Cyproheptadine
April 2012 EBM Guidelines from APS and AAN-4

- 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
April 2012 EBM Guidelines from APS and AAN-4a

- AEDs
  - Gabapentin
- TCAs
  - Protriptyline
- β- Blockers
  - Bisoprolol
- Ca++ Blockers
  - Nicardipine
  - Nifedipine
  - Nimodipine
  - Verapamil
April 2012 EBM Guidelines from APS and AAN-4B

- Direct vascular smooth muscle relaxants
  - Cyclandelate
April 2012 EBM Guidelines from APS and AAN-5

- 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
I DON'T ALWAYS HAVE A MIGRAINE

BUT WHEN I DON'T, I HAVE A MODERATELY PAINFUL HEADACHE.
QUESTIONS???