Migraine: Practical Approaches to Maximizing Therapeutic Yield

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Objectives

- Recognize the various presentations of migraine and appreciate the limitations of the diagnostic criteria for migraine headache as set forth by the IHS
- Identify common triggers of migraine and counsel patients on behavioral strategies to reduce migraines

Objectives (cont.)

- Prescribe the appropriate acute and prophylactic therapy for individuals suffering from migraine headache
- Maximize the therapeutic yield and minimize potential side effects of abortive medications through their early use

Migraine - Epidemiology

- Affects 18% of women, 6% of men
- Highest incidence in ♀ occur bt age 25-55
- Migraine most frequent disabling condition in middle-aged women (WHO)
- Familial disorder - Up to 90% of patients have a family history
- Most common neurological disorder w/ estimated cost to U.S. employers of $13 billion a year

Migraine Pathophysiology

- Idiopathic, recurrent neurovascular disorder
  - Disturbance in the excitatory and inhibitory mechanisms of the nervous system
    - Initiated by neuronal activity rather than vascular Δ
    - Genetically mediated and environmentally modifiable
  - Excessive trigeminal system discharge
  - Interaction between the brain stem & cranial blood vessels ⇒ release of neuropeptides that cause vasodilation and headache
  - Sets up a sterile inflammatory response in the arteries of the scalp and possibly within the dura

Migraine Pathogenesis

- Threshold for headache appears to be determined, in part, by genetics
  - Monozygotic twin studies suggest that up to 50% of the contribution to the common migraine variants is genetically based
- Attack occurrence and frequency are governed by the sensitivity of the CNS to migraine-specific triggers
- Activity within the trigeminovascular system may be regulated in part by noradrenergic and, most important, serotonergic neurons within the brain stem.
- Thus the pathogenesis of migraine may be related to an imbalance in the activity of serotonin-containing neurons and/or noradrenergic pathways in brain stem nuclei that modulate cerebral vascular tone and nociception.
Migraine

Clinical Presentation

• Prodrome
• Migraine without aura (common migraine)
  – 85% of migraines
• Migraine with aura (classic migraine)
  – 15% of migraines
  – Up to 30% of pts experience aura w/ at least some attacks
• Headache
• Postdrome

Migraines without Aura:
International Headache Society Criteria

• At least 5 attacks
• Episodic attacks that last 4-72 hrs (when untreated or unsuccessfully treated)
• Headache has at least 2 of the following
  – Unilateral pain (only 60% of time)
  – Throbbing or pulsating quality (only 50% of time)
  – Pain of mod to severe intensity (prohibits daily activities)
  – Aggravation by movement or routine physical activity
• Headache has at least one of following sx
  – Nausea &/or vomiting
  – Photophobia
  – Phonophobia
• There is no evidence of related organic disease

Adapted from the Headache Classification Committee of the International Headache Society.

Common Expression of Aura in Migraines

• Visual aura (most common)
  – Fortification spectra (Zigzag lines)
  – Photopsia (Flashing lights)
  – Other visual distortion
• Sensory paresthesias
  – Hemiparesis that travels (cheiroaural)
• Speech disturbance
• Develops over 5-20 minutes
  – Usually lasts < 1 hour (approx. 20 min)
  – Gradual, evolving (vs. maximal & simultaneous at onset in TIA)
  – Provides warning of impending migraine
  – Full neurological recovery afterwards

Diagnostic pitfalls: Atypical Features of Migraine

• Only ½ migraines are correctly diagnosed
• Spreading depression of Leao
  – Electrical event that travels over surface of brain can include any neurologic function of cortex
• Some only experience the aura without headache pain (e.g., retinal migraine; acephalgic migraine)
• True characteristics of migraine
  – Pain severity ranges from mild to severe (47% of patients do NOT require bedrest)
  – Headaches can begin in back of neck and lateralize (in one study, 76% of patients reported neck pain with migraine)
  – Sinus symptoms can develop in association with migraine: many patients with migraine report sinus symptoms, including stuffiness and drainage

Migraine can be felt in various locations along the trigeminal nerve and its branches

Mediscapes www.mediscapes.com

Undiagnosed Migraine Sufferers Often Receive a Diagnosis of Sinus or Tension Headache

28 MM Migraineurs
13.4 MM Diagnosed Migraineurs
14.6 MM Undiagnosed Migraineurs

26%
32%
42%
Other 26%
Tension Headache 32%
Sinus Headache 42%

Adapted from a study in Arch Neurol 2001;58:2145.
Atypical Features of Migraine: Sinusitis or Migraine Headache?

- 47 subjects self-described “sinus” headache
- Inclusion Criteria
  - No prior migraine diagnosis
  - Absence of purulent nasal discharge and fever
  - Had > 6 attacks over past 6 months
  - 98% of subjects met IHS criteria for migraine-type headache
  - Most experienced high level of headache related disability
  - Two hours after tx with sumatriptan 50mg
    - 34% of attacks had pain free response
    - 66% of attacks had pain relief
    - 62% reported satisfaction with sumatriptan tx

SUMMIT Study Objectives

- Primary Objective
  - Determine proportion of subjects with hx of self-described or physician-diagnosed “sinus” headaches that meet IHS criteria for migraine
- Secondary Objective
  - Determine the efficacy of sumatriptan 50 mg tab in the tx of migraine in said subjects that meet IHS diagnostic criteria for migraine

SUMMIT Study Design

- Prospective, open-label, multi-center observational (n=3038)
- Pts w self-described or physician-diagnosed “sinus” headache
- Inclusion criteria
  - Age 18 to 65 yrs
  - > 6 attacks “sinus” headache in past 6 months
- Exclusion criteria
  - Prior diagnosis of migraine
  - Prior use of a triptan med
  - Fever, purulent or discolored nasal discharge, radiographic evidence of sinus infection in past 6 mth
- Subjects fulfilling IHS criteria for migraine randomized to sumatriptan 50 or placebo arm

SUMMIT Study Results & Conclusions

- 88% of subjects met IHS diagnostic criteria for migraine headache
- Sinus pressure, pain and other nasal symptoms or ocular symptoms are common during migraine
- “Sinus” headaches commonly associated w sig disability & subjects often dissatisfied w OTC & Rx med used for “Sinus” headache
- Greater pain relief w sumatriptan (69% vs. 43% P<0.001) and greater pain free (33% vs. 21 P<0.05) at 2 hrs
- IHS defined migraine that manifests as pt self-described “sinus” headache responds well to sumatriptan (including sinus area pain)

Atypical Features of Migraine: Sinusitis or Migraine Headache?

- Most complaining of sinus headache (esp. unilateral) have migraine headache
- Migraine frequently accompanied by sinus symptoms, when acute sinusitis and sinus pathology ruled out, migraine first on differential diagnosis
- Switching on trigeminal nucleus (migraine generator) also activates parasympathetic nervous system, causing tearing and nasal congestion
- These “sinus” headaches are effectively managed w triptans
Mild Migraine vs. Tension-Type Headache
- Continuum from tension-type headache to migraine with aura; few patients present with textbook diagnosis
  - Patients can transition from tension-type headache to migraine
  - Impact-based recognition
- In population-based study
  - 32% of patients thought to have tension headache actually had migraine
  - 75% of those with headache and neck pain had migraine (after excluding those with head and neck trauma)
    - Neck pain relieved by triptans in 73% of patients

Common Migraine Triggers
- Identify & reduce common triggers of migraine
  - Skipping meals
  - Erratic sleep patterns disturbance
    - e.g., waking up 1 hour late or early
    - Exposure to high altitude
    - Change in weather
    - Lack of exercise
    - Food containing MSG, caffeine, red wine, nitrates
    - Bright lights & loud noises
    - Physiologic or psychological stress
    - Hormonal changes associated with menstrual cycle

Nonpharmacologic treatment (Dietary triggers)
- Highly restrictive diet not recommended
- Skipping meals - one of most common reasons cited as cause of migraine
  - 2/3 of migraines occur after 5 hr of fasting

Impact of Fasting on Migraines
- Yom Kippur headache study in Israel (n=370)
  - During 25-hr religious fast among hospital workers, headache occurred in
    - 39% of fasters
      - 66% of headache sufferer who fasted
      - 29% of non-headache sufferers who fasted
    - Only 7% of non-fasters during same period
  - Migraine occurs most frequently 12-15 hrs after last meal when serum glucose & liver glycogen depleted & activation of SNS occurs to stimulate gluconeogenesis

Impact of Fasting on Migraines
- Brain 100% dependent on glucose for energy ($\approx$10g/hr)
- Dietary carbohydrate main source of glucose and stored as glycogen in liver
- Glucose supply to brain—serum glucose (up to 20 g; $\approx$2 hr); liver (up to 100 g; $\approx$10 hr)
- Gluconeogenesis (glucose production from fat and protein) requires activation of sympathetic nervous system (SNS); i.e., stress response which triggers migraine in susceptible individuals


Neurology
Dietary Guidelines for Avoiding Migraine Attacks

- Carbohydrates with high glycemic index (GI) cause rapid surges and drops in serum glucose 
  → causes intracranial epinephrine and prostaglandin release and triggers migraines
- Eat low-GI foods (release glucose at even rate)
  - e.g., oatmeal; yogurt; milk; many fruits (apples, banana); pasta
- Avoid High-GI foods
  - e.g., glucose; doughnuts; corn flakes; potatoes

Behavioral Strategies to Prevent Migraine

- For patients with frequent migraines
  - Do not go more than 4 to 5 hrs without eating while awake
  - Eat breakfast with 4 to 5 hr dose of carbohydrates (40-50 g)
  - Eat snacks providing 2 to 4 hr dose (20-40 g) of carbohydrate as bridge between meals
  - Eat small carbohydrate bedtime snack (e.g., yogurt, 1 apple, 1 slice sourdough bread)
  - Avoid high-GI foods; eat foods that give gradual rise in glucose, causing less stress on brain

Abortive Therapy

- Treatment goals: patient headache-free within 2 hr of taking drug; restoration of full function; elimination of associated symptoms
- Abortive
  - Nonspecific medications
    - e.g., NSAIDs, combo, opioids
  - Migraine-specific medications
    - e.g., Triptans, DHE
- Adjunctive anti-emetic

Abortive Agents

- Ergot-Alkaloids
- “Triptans” (5-HT1b/d agonists)
- Aspirin/NSAIDS
- Midrin
- Excedrin Migraine
- Stadol NS & other opioids
- Corticosteroids

Migraine-Abortive Therapy

General considerations in selection
“Stratified Care”
- Drug selection is based on severity of pt’s level of disability
- Triptans & DHE are 1st-line for pts w/
  - Moderate to severe Migraine
  - Mild to moderate headache that respond poorly to nonspecific analgesics
- More effective than “stepped care”
  - Migraine is initially treated w/ an analgesic, then “stepped up” to a triptan or DHE if response is inadequate

Migraine-Abortive Therapy

General considerations in selection
- Impact-based recognition vs IHS criteria
- Routes of administration
  - If significant N&V
    - Use non-oral products (IM, IV, NS, PR, SC)
  - Consider onset & duration of symptom relief
    - Select medications with onset and duration of analgesia that appropriately match symptoms
- Coexisting conditions (CHD, pregnancy, uncontrolled HTN)
- An antiemetic (e.g., metoclopramide) may be added for sig N & V
Abortive Therapy- NSAIDs
Available Agents
• Use NSAIDs w/ rapid onset of action in anti-inflammatory (high end) dose
  – Ibuprofen
    • Ibuprofen 600-1200mg PO at onset, then 600mg q4-6hr prn (max per day = 2400mg)
  – Naproxen Na (Anaprox, Aleve OTC)
    • Addition of Na confers rapid onset (1/2 hr vs. 2hr for EC form)
    • 550-825 mg, then 220-550mg bid prn
    • Longer duration of action (than ibuprofen) for longer lasting HA
  – Ketorolac
    • 30-60mg IM/IV; No more than 3 x per week due to risk of nephrotoxicity
    • 15.75mg/nasal spray
    • Ideal for migraines w/ sig vomiting

Abortive Therapy- Triptans
Available Triptans
• All available triptans are more similar (in efficacy, tolerability & safety) than dissimilar
  – Differences are in onset, duration, and formulations
• Sumatriptan (Imitrex) Naratriptan (Amerge)
  – SC (Pen device), PO, NS PO
• Rizatriptan (Maxalt) Almotriptan (Axert)
  – PO, DIS PO
• Zolmitriptan (Zomig)
  – PO, NS, DIS PO
• Eletriptan (Replax)
• 7 triptans available; 5 short-acting & 2 long-acting
  – Long-acting triptans are frovatriptan [Frova] and naratriptan [Amerge]

Abortive Therapy- Triptans
Sumatriptan (Imitrex)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Onset</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>6mg</td>
<td>10-15 min</td>
</tr>
<tr>
<td></td>
<td>6mg x2</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>5-20mg</td>
<td>15-20 min</td>
</tr>
<tr>
<td></td>
<td>40mg</td>
<td></td>
</tr>
<tr>
<td>PO</td>
<td>50-100mg</td>
<td>30-60 min</td>
</tr>
<tr>
<td></td>
<td>200mg</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic gain of 51% w/ SC and 16-42% w PO
Therapeutic gain = % of pts responding to the triptans minus % responding to placebo

Triptans
• All triptans work as 5-HT1B and 5-HT1D receptor agonists in the trigeminal ganglia
  – 5-HT1B post-synaptic causes vasoconstriction
  – 5-HT1D pre-synaptic prevent release of vasoactive neuropeptides → decrease in neurogenic inflammation → preventing sensitization of sensory afferents
  – Contraindicated in patients with (or with risk factors for) coronary artery disease
• 7 triptans available; differences include formulations and half-lives (5 short-acting; 2 long-acting
  • Long-acting triptans are frovatriptan [Frova] and naratriptan [Amerge]

Factors in Choosing Triptan
• Time of onset, time to peak pain intensity
• Non-oral route (injectable therapy or nasal spray) best for migraineurs who present with nausea and vomiting or rapidly escalating headache
  – Sumatriptan injection works fastest (adult dose 6 mg; onset of action 5-10 min)
  – Nasal sprays take approximately 15 min to act and have slightly unpleasant taste

Millionaire Question
• Which formulation of Imitrex is ideal for a 45 y/o diabetic male w/ predictably slow onset migraine that follows aura lasting ≈30min. He is not prone to vomiting & migraines last for at least 8 hrs
  • A) PO
  • B) NS
  • C) SC
Abortive Therapy - Triptans

**Sumatriptan (Imitrex)**

<table>
<thead>
<tr>
<th>SC</th>
<th>NS</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best for pt w/</td>
<td>Disadvantage</td>
<td></td>
</tr>
<tr>
<td>Speed onset of</td>
<td>- Rapid onset</td>
<td>- Slow onset</td>
</tr>
<tr>
<td>symptom &amp; sig. NA &amp; V</td>
<td>at site of injection</td>
<td>w/ SC</td>
</tr>
<tr>
<td>often helps</td>
<td>- Bitter taste</td>
<td>- Markedly slower</td>
</tr>
<tr>
<td>under observation</td>
<td>(- by cutaneous</td>
<td>onset vs SC, NS, DHE, NS</td>
</tr>
<tr>
<td>- risk of coronary</td>
<td>adm technique)</td>
<td></td>
</tr>
<tr>
<td>vasospasm:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abortive Therapy - Triptans Adverse Effects**

- Usually well tolerated
- Most commonly documented AE include:
  - N & V
    - likely due to migraine itself & often helped by use of triptans
  - Bitter unpleasant taste (w/ intranasal triptans)
  - Mild pain or redness at site of injection (w/ SC Imitrex)
    - Occurs in 40% but usually resolve w/in 60 min
  - Chest pressure, tightness or pain (Up to 15%)
    - Rarely serious & also occur in young health pts
    - Mild & usually resolves w/in 2 hrs & are usually unrelated to cardiac ischemia but evaluation for CV cause recommended
    - More common with SC than w/ PO administration

**Abortive Therapy - Triptans Contraindications**

- Contraindications
  - Said chest symptoms are rarely serious but rare coronary artery constriction resulting in heart attack, arrhythmia, and death may be possible
  - These AE usually occur in pts w/ CAD
    - Coronary vasculature also contains 5-HT1B receptors
    - Because of potential vasoconstrictive effects, triptans should NOT be used in pts w/:
      - Uncontrolled HTN
      - Peripheral or cerebral vascular dx (e.g. stroke)
      - CAD, Previous MI, Prinzmetal’s angina

**Strategies to ↑ Efficacy Abortive Agents**

- Early use of Abortive agents to optimize response
  - When pain is tx before Central Sensitization occurs, pts receive greatest benefit from abortive medications
  - Triptans originally said to be effective at any point; however, when sumatriptan taken early
    - Pain-free response (therapeutic gain) rate roughly doubled at both 2 and 4 hrs compared to those who waited till migraine was moderate-to-severe
    - Other abortive agents seem to have similar benefits when taken early
      - 60% of headaches prevented when naratriptan taken during prodrome; of headaches that did occur, 44% mild (vs 5% when not treated during prodrome)

**Combining Triptan with an NSAID**

- Method
  - A randomized, db, pc, multicenter study was performed to assess the efficacy of sumatriptan and naproxen sodium versus a combination of the two agents (n= 965)
  - Each participant treated one migraine attack of moderate or severe intensity with one of four treatment options: sumatriptan 50 mg and naproxen sodium 500 mg, sumatriptan 50 mg, naproxen sodium 500 mg or placebo
- Results
  - The side effect incidence was similar with both sumatriptan monotherapy (24%) and combination therapy (23%)
  - But both were higher than naproxen only (17%) and placebo (15%). The most common effects were dizziness and somnolence.
Combining a Triptan and an NSAID

- **Results**
  - **Response at the 2 hour time point**
    - 65% of the sumatriptan/naproxen sodium group
    - 49% in the sumatriptan only
    - 46% of the naproxen only
    - 27% of the placebo group
  - “Sustained pain response” was achieved in
    - 46% of the sumatriptan/naproxen sodium group (p<0.001)
    - 29% in the sumatriptan only
    - 25% of the naproxen only
    - 17% of the placebo group
  - “Sustained pain response” was defined as having no pain greater than mild at 2 hours, taking no rescue medication for 24 hours after dosing, and having no recurrence of moderate or severe pain within the 24 hour window

**Reference:** Headache 2005;45:874, 983

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Does the Use of SSRI Preclude Use of Triptan?

- **In July 2006, the FDA issued an alert concerning serotonin syndrome associated with use of triptans with SSRIs or SNRIs**
  - Thought to carry risk for serotonin syndrome (fever, restlessness, sweating, poor coordination, confusion, hallucinations); subsequent research found syndrome rarely occurs
  - Triptan w/ SSRI commonly used together
    - Higher incidence of depression and anxiety disorders among migraineurs
    - The triptans are agonists at 5-HT1b/d receptors
    - Sporadic case reports suggestive of the serotonin syndrome when these drugs are combined


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Serotonin Syndrome: Triptan & SSRIs

- Putnam et al. (1999) prospectively followed 12,339 patients with migraine headaches
  - Of these, a total of 1,784 also received an SSRI.
  - Authors concluded that there appeared to be no difference with respect to the development of symptoms suggestive of serotonin syndrome when the combination was used in comparison to sumatriptan alone
  - They concluded that the safety profile of sumatriptan was not affected by the addition of SSRIs
  - The case reports, however, should not be ignored
  - Overall Risk appeared to be very low
  - Use with Caution & careful patient monitoring


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Medication Overuse Headache (MOH)

- Use of most abortive agents for > 2 days/week over 2-3 months may ↑ HA frequency
  - Seen w/ all abortive agents except DHE & possibly NSAIDs
  - Can cause daily (or near daily) dull headache
  - Triptan overuse can cause migraine-like daily headache or ↑ migraine headache frequency
  - Particularly problematic with medications that contain either caffeine or barbiturates
  - Tx requires starting prophylactic medication, stopping overused analgesic agent causing the MOH, and treating acute headache using an abortive agent with low risk for MOH such as DHE

**Reference:** Neurology 2002;59:1011

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Does Failure to One Triptan Predict Failure to Another?

- Response idiosyncratic
  - May have robust response to one triptan and poor response to another
  - Similar variation noted in side-effects to triptans
  - 75% to 80% of patients failing to respond to one sumatriptan responded to another triptan
  - Therefore, trials of multiple triptans often necessary before finding an effective triptan

**Reference:** Headache 42:1, 2002

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MIGRAINE HEADACHE

Prophylactic Therapy

- Daily use of prophylactic agents can reduce frequency and severity of migraine attacks
  - ≈ 50% reduction of frequency in 2/3 of all patients
  - Increase responsiveness to abortive migraine therapies
  - Adequate trial of 2-6 months to determine efficacy
  - Consider use for at least 3-6 month after the frequency and severity of headaches have diminished then taper over 1 month → may break headache cycle
  - Realistic goal is to better control (not eradicate) migraines; complete elimination of headache is rarely achieved and unrealistic

**Reference:**
Migraine Headache
Prophylactic Therapy
• Usual criteria for migraine prophylaxis:
  – Consistent use of abortive medication >2/ wk
  – Disabling HA that occur less frequently but are severe & unresponsive to usual abortive measures
  – Pts in whom abortive agents are contraindicated
• Selection of agent should be based on its side-effect profile, comorbid conditions of pt, and on convenience of drug formulations

Prophylactic Therapy
Beta Blockers
• Generally regarded as tx of choice
  – ↓ frequency of attacks by 50% in 60-80% of pts
  – Propranolol, metoprolol, or timolol have the best evidence
  – B-blockers with ISA are ineffective
  – MOA: ?? Raise migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical or subcortical pathway

Prophylactic Therapy
Calcium Channel Blockers
• Verapamil
  – Most effective among CCB but still has only modest benefits in ↓ frequency of attack & has little effect on the severity of migraine attacks
  – Less effective than B-blockers
  – Effective in 50% with recurrent headache vs. 60-70% efficacy w/ b-blockers
  – Reserved for pts who have not benefited from DOC (e.g. B-blockers, topiramate and valproate )
  – Adverse effect: constipation, bradycardia, worsening of systolic CHF
  – Aside: Most effective prophylactic therapy for Cluster Headaches

MIGRAINE HEADACHE
Prophylactic Therapy
(Evidence-based guideline from Neurology 2012;78:1337-45)
• Beta-Blockers, topiramate, or valproate are 1st-line
  – Venlafaxine or duloxetine are second-line
    – Venlafaxine (SNRI) is a rational choice for pts w/ depression and/or certain subtypes of anxiety disorders
    – Low-dose amitriptyline if the patient is already doing well on an SSRI.
  – Lisinopril, candesartan, cyproheptadine, or NSAIDs have less evidence and are reserved for when other prophylactic tx aren’t helpful
  – SSRI, gabapentin, or CCB have unreliable or conflicting evidence
  – Likely safe and effective CAM
    – Riboflavin (Vitamin B2)
    – Butterbur
    – Magnesium
    – Feverfew

Prophylactic Therapy
Tricyclic Antidepressant
• Effective for reducing frequency & severity of both migraine & tension-type HA
• MOA:
  – 5-HT-NE reuptake inhibition
  – Possibly related to antagonism of 5-HT2 receptors on cerebral vessels or suppression of serotonergic neuronal activity in the brainstem??
  – Efficacy most extensively demonstrated with amitriptyline (but high anticholinergic SE)
# Prophylactic Therapy

## Tricyclic Antidepressant

- Nortriptyline & desipramine are better tolerated – 2nd generation active metabolite of 1st generation TCA and has less anticholinergic effect; limited data on efficacy
- **Adverse effects:**
  - Sedation & weight gain are common
  - Prolongation of QT interval
  - Anticholinergic effect
- But can get therapeutic effect at <50% dose need for antidepressant effect (e.g., 25 to 75 mg/day for most TCAs)
- **TCAs are ideals for:**
  - Mixed migraine & tension-type HA
  - Pts with comorbid depression or insomnia
  - Pts w/ comorbid neuropathic pain (e.g., diabetic neuropathy or postherpetic neuralgia)

## Valproic Acid & Derivatives (e.g., Depakote)

- An antiepileptic drug also approved for prevention of migraine HA
  - May be as effective as propranolol
- Proposed MOA
  - Reduces high-frequency neuronal firing and sodium-dependent action potentials and enhances GABA effects??
- **Adverse Effects**
  - Sig. wt gain is common
  - POS, hyperinsulinemia, lipid abnormalities seen
  - N&V, drowsiness, tremor, hair loss, hepatotoxicity (rare)
- **Pregnancy Cat. D**
  - Risk of neural tube defect is increased from 1 in 1500 babies to 1 in 20 exposed to valproate; also associated w lower IQ
  - AVOID in women considering pregnancy
- Effective in doses < required for seizure prophylaxis
  - 1000 mg/day effective in most migraineurs
- Good choice in pts w/ epilepsy or bipolar dx

## Prophylactic therapy: Topiramate (Topamax)

- Approved by FDA in August 2006
- 50% decrease in migraine frequency in 50% of patients
- Significant efficacy in prevention within first month of treatment
- **Recommendations**—start low, go slow; 15 to 25 mg daily; increase weekly to 100-200 mg daily
- **Wt loss** (wt gain seen w/ the AED valproate)
  - Data show weight loss of 3.3% to 4.1%

## Additional Prophylactic Therapy

- Riboflavin (vitamin B2)
  - Safe for all pts including patients during pregnancy
  - Reduction in HA after 2 months w/ 400 mg qd
  - In randomized, PC trial of 55 pts ≥ 50% decrease in number of attacks seen in 59% of pts who took riboflavin compared to 15% of those taking placebo (1)
- Migrelief®
  - Combination product, which contains riboflavin, feverfew and magnesium

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1. Neurology 1998; 50:466;
### Summary of Migraine management

- Migraine is often misdiagnosed as sinus headache
- Skipping meals is one of the most common reasons cited as cause of migraine; do not go >4 to 5 hr without eating while awake and choose low-GI foods to reduce stress on brain
- Overall risk of serotonin syndrome appeared to be low when triptans are combined with SSRIs but use with caution & careful patient monitoring
- MOH is most common with opioids, butalbital and caffeine
- All abortive medications are more effective if taken early in an attack when the pain is in the mild phase

### Summary of Migraine management

- Combining a triptan and an NSAID is more effective than either drug alone for treating migraines
- About 30% more patients get relief from sumatriptan PLUS naproxen compared to triptan alone
- Limit the use of abortive medications to no more than 2 days per week to avoid med-overuse HA
- Give sufficient time before evaluating efficacy of preventative drugs
- Most consistently effective prophylactic therapy are β-blockers, valproic acid and topiramate
- Consider patient-specific coexisting condition when choosing the most appropriate abortive or prophylactic medications