Challenges in Headache

How to Manage Brain Hyperexcitability in Migraine Pathogenesis

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Epilepsy and Migraine

- Neurological chronic disorders with episodic manifestations are characterized by recurrent attack of nervous system dysfunction with a return to baseline between attacks
- Both disorders can present with headache
- Trigger and hormonal change are the same in both conditions

- Migraine; 6% of men, 17% of women
- Epilepsy; 0.5-1% of population

↓

chance coexistence ?

Comorbidity of Migraine and Epilepsy

- Migraine prevalence was 24% among probands with epilepsy and 26% in the relatives of probands with epilepsy
- Control group was 15% had migraine
- Prevalence of epilepsy in migraine was 5.9%
- Seizures were part of clinical spectrum of FHM-2

Migraine-related seizures in adults with epilepsy, with EEG correlation

David A. Marks, MD, and Bruce L. Ehrenberg, MD

Article abstract—We studied the relationship between migraine and epilepsy in 395 adult seizure patients. Seventy-nine patients (20%) also had migraine syndrome, and 13 of these patients (3%) experienced seizures during or immediately following a migraine aura. Patients with catamenial epilepsy and patients with migraine with aura were at an increased risk for an association between these two disorders. In two patients, we recorded the entire sequence from migraine aura to partial seizure, and in both there were distinctive changes on the EEG during the migraine aura that preceded the onset of an electrographic complex partial seizure. Periodic lateralized epileptiform discharges were recorded in five other patients in close temporal relation to their migraine attacks. There was improved seizure control with combination antimigraine and antiepileptic drugs (AEDs) in six patients who failed to respond to AEDs alone.

NEUROLOGY 1993;43:2476-2485

Comorbidity Migraine and Epilepsy

- MELAS can present symptomatically with migraine, epilepsy, migraine aura progressing into an epileptic attack
- Seizures, originating in occipital cortex, can mimic aura
- Migraine induced epilepsy **"Migralepsy"**

ELSEVIER

Journal of the Neurological Sciences 139 (1996) 106–110

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Interictal cortical hyperexcitability in migraine patients demonstrated with transcranial magnetic stimulation

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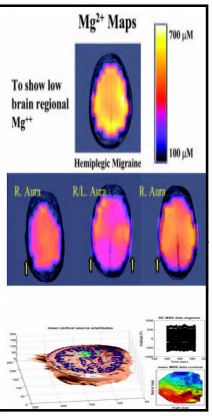
Abstract

Cortical excitability to magnetic stimulation was investigated interictally in 10 patients with migraine with aura, 10 with migraine without aura and in 10 healthy volunteers. Thresholds, latencies and amplitudes of the magnetic-evoked potentials (MEPs) were measured from threshold to 100% stimulus intensity in 10% steps. Compound motor action potentials (CMAPs) evoked with supramaximal electrical stimulation of the ulnar nerve were used to calculate MEP/CMAP amplitude ratios. Thresholds and latencies of MEPs did not differ between patients and controls. MEP/CMAP amplitude ratios were significantly increased at all intensities in patients with migraine with aura (RM-ANOVA, $p < 0.01$) and without aura ($p < 0.05$) compared with controls. In migraine patients, MEP amplitudes and MEP/CMAP amplitude ratios were positively related to the frequency of migraine attacks (Spearman's $r = 0.47$, $p < 0.01$ and $r = 0.56$, $p < 0.002$, respectively). MEP parameters were not related to the side of the headache nor the aura, in either type of migraine, implying that both hemispheres are equally involved in migraine. Migraine with aura and, to a lesser extent, migraine without aura, are associated with increased interictal cortical excitability.

Keywords: Migraine; Magnetic stimulation; Cortical hyperexcitability; Stimulus–response relationship



Potential Mechanisms of Migraine

- Neuronal hyperexcitabiltiy
- Mitochondrial dysfunction
- Channelopathy
- Reduced Mg level

- Factors that increase or decrease brain excitability may trigger migraine attacks
- **AEDs that decrease neuronal excitability for the prevention of migraine attack is a logical approach to the management of severe and frequent migraine**

- AEDs, topiramate, valproate are effective for both migraine and epilepsy prevention
- Epilepsy and migraine arise from a common brain state wherein patients have abnormal increased neuronal excitability

	Antimigraine dose	Antiepileptic dose
Valproate *+	500 – 1500 mg	750 – 4000 mg
Gabapentin *	300 – 3000 mg	600 – 3600 mg
Levetiracetam	1500 – 4500 mg	1000 – 3000 mg
Topiramate *+	50 – 100 mg	50 – 400 mg
Zonisamide	100 – 400 mg	100 – 400 mg

*Evidence for moderate efficacy from at least two well designed placebo-controlled trials
+Approved by the Food and Drug Administration for treatment.

Table : Antiepileptic drugs used for migraine

Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches

A Mauskop
State University of New York, Downstate Medical Center, Brooklyn and New York Headache Center, New York, USA

Cephalalgia

Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia 2005; 25:82–86. London. ISSN 0333-1024

Anticonvulsant and antidepressant medications have demonstrated efficacy in migraine treatment. Vagus nerve stimulation (VNS) is an effective treatment for drug-refractory epilepsy and possibly depression and it also has documented analgesic effects. These observations suggested a possible role for VNS in treating severe refractory headaches, and led to a trial of VNS in patients with such headaches. VNS was implanted in four men and two women with disabling chronic cluster and migraine headaches. In one man and one woman with chronic migraines VNS produced dramatic improvement with restoration of ability to work. Two patients with chronic cluster headaches had significant improvement of their headaches. VNS was well tolerated in five patients, while one developed nausea even at the lowest current strength. In conclusion, VNS may be an effective therapy for intractable chronic migraine and cluster headaches and deserves further trials. ☐*Migraine, cluster headache, vagus nerve stimulation, epilepsy*

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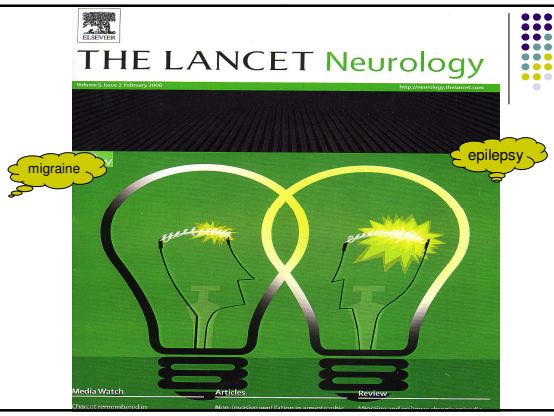


Brain Hyperexcitability: The Basis for Antiepileptic Drugs in Migraine Prevention

K. Michael Welch, MB, ChB, FRCP

Abnormal brain excitability may provide the susceptibility for triggering migraine attacks. Antiepileptic drugs may diminish neuronal excitability and consequently reduce the frequency of migraine. Because migraine aura is predominantly visual, hyperexcitability of the occipital cortex has been the focus of investigations. Functional magnetic resonance imaging of the brain and magnetoencephalography provide the most consistent evidence for the role of brain hyperexcitability in migraine and confirm that triggering an abnormal electric and metabolic event consistent with the cortical spreading depression (CSD) of Leao is anatomically and functionally linked with migraine aura symptoms. Future drug discovery should focus on the interface between the excitable cell and the earliest events of CSD.

Key words: migraine, hyperexcitability, brain, imaging, aura, visual, spreading depression

Abbreviations: CSD cortical spreading depression, AEDs antiepileptic drugs, FHM familial hemiplegic migraine, fMRI functional magnetic resonance imaging, MEG magnetoencephalography, TMS transcranial magnetic stimulation, BOLD blood oxygen level dependent, MELAS mitochondrial myopathy-encephalopathy-lactacidosis-stroke, NAA N-acetylaspartate

(*Headache* 2005;45[Suppl 1]:S25-S32)

Migraine Prevention Mechanisms

- Raise threshold to migraine activation
  - Inhibit migraine generator
  - Enhance antinociception
  - Inhibit cortical spreading depression
  - Inhibit sensitization
  - Block neurogenic inflammation
- Stabilize more reactive nervous system
  - Modulate sympathetic or serotonergic tone

Table.—Sites at Which Standard Preventive Drugs Regulate Neuronal Hyperexcitability

Site	Antiserotonin	β-Block	Calcium Block	NSAIDs	Valproate
Sodium channel					+
Calcium channel	?		+		+/?
EAA receptor			+		
GABA REC/Cl^-					+/?
5 HT/NE NT	+	+	+	+	

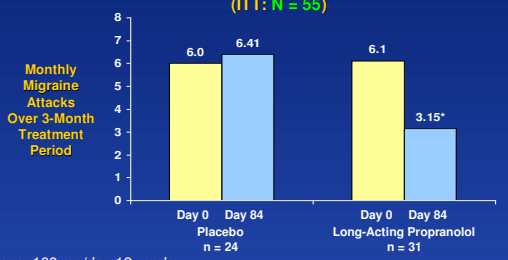
EAA, excitatory amino acid; GABA REC/Cl^-, gamma-aminobutyric acid-gated chloride channel receptor; 5 HT/NE NT, serotonin/norepinephrine neurotransmitter; NSAIDs, nonsteroidal anti-inflammatory drugs.

Current Preventive Medications

- β-blockers*
- Calcium channel antagonists
- Serotonin antagonists
- Neuromodulators*
- Antidepressants
  - TCAs*, MAOIs
- Other
  - Riboflavin (B_2)
  - Magnesium (Mg^{++})
  - Botulinum toxin
  - ACE inhibitors ?
  - Angiotensin receptor blockers ?
  - NSAIDs

* = approved or being reviewed by FDA; TCAs = tricyclic antidepressants; MAOIs = monoamine oxidase inhibitors; ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

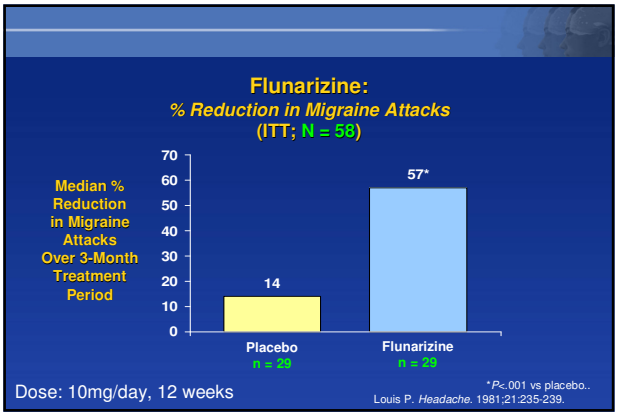
Long-Acting Propranolol: *Migraine Frequency* (ITT: N = 55)

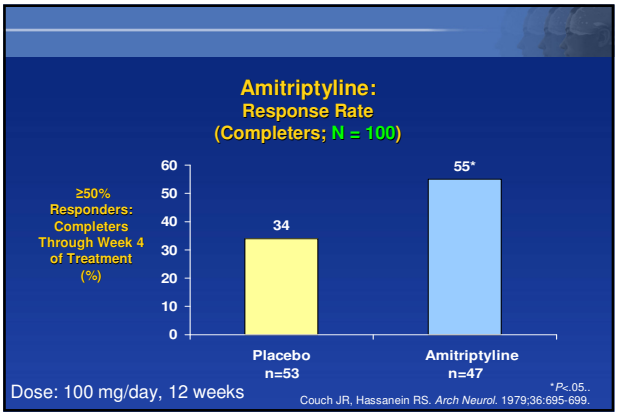


Dose: 160 mg/day,12 weeks

*P<.01.

Pradalier A et al. *Cephalalgia*. 1989;9:247-253.





Migraine prophylaxis with AEDs since 1970

- CBZ was the first drug used
- Sodium valproate
- Lamotrigine
- Gabapentin
- Topiramate
- Zonisamide
- Vigabatrin
- Oxcarbazepine
- Levetiracetam

Comparison of mechanism-related actions of anticonvulsants

	Na+ channel blockade	GABA potentiation	Glutamate antagonism
Topiramate	X	X	X
Phenytoin	X		
Carbamazepine	X		
Valproate	X	X	
Barbiturates		X	
Benzodiazepines		X	
Vigabatrin		X	
Tiagabine		X	
Lamotrigine	X		
Gabapentin		X	

Lamotrigine

- First report was published in 1997
- RCT
- 37 were placebo, 40 lamotrigine
- 200 mg/day
- Ineffective for prophylaxis

Lamotrigine

- Lampl, 1999
- 15 pt, with or without aura
- Slowly titrated up to 100 mg/day
- Aura were significantly reduced
- Increase after cessation of treatment

Lamotrigine

- D' Andrea, 1999
- 24 pt, with or without aura
- 100 mg/day
- 13 pt were pain free
- Side effect : skin rash, paresthesia, dizziness, sleep disturbances

zonisamide

- 2 open-label studies, 2001
- ZNS as add-on therapy, 34 pt
- 40% reduced headache severity
- 25% reduced headache frequency
- 50% reduced headache duration

Vigabatrin

- Double-blind, cross-over RCT
- 23 pt migraine with or without aura
- 12 week, 2000 mg/day
- Severity, duration were slightly but significantly reduced

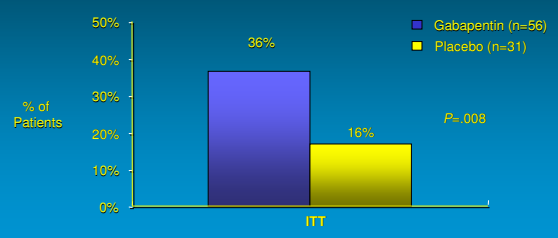
Levetiracetam

- 3 open-label trial
- 50% reduction in frequency, severity
- 1000-3000 mg/day
- Significant reduced headache at a dosage of > 1500 mg/day
- Intravenous for acute intractable migraine
- 77.2% pt reduction of pain

Oxcarbazepine

- Open-label trial
- 30 refractory migraine
- 1800 mg/day
- 7 pt reported early success, and significant value

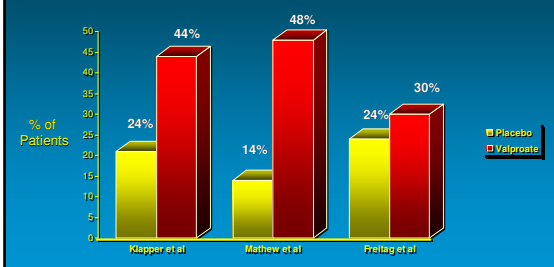
Gabapentin: ≥50% Reduction in 4-Week Migraine Rate



Dose: 900- 2400/3600 mg/day

Mathew et al. Headache 2001

Responder Rates for Valproate Klapper, Mathew, Freitag



Dose: 500-3000 mg/day

Topiramate Multiple Mechanisms of Action

Site	Action
Voltage-activated Na^+ channels	Limits sustained repetitive firing via state-dependent blockade of Na^+ channels
$GABA_A$ receptor subtypes	Potentiates GABA -neuro inhibition at $GABA_A$ site not modulated by benzodiazepines or barbituates
Glutamate receptor subtype (kainate & AMPA)	Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity
Ca^{2+} channel subtypes	Mild reduction of amplitude of high voltage-activated Ca^{2+} currents Weak Inhibits Type II and IV CA
Carbonic anhydrase	

White SH; Mid-Winter 2000 Epilepsy Educator's Conference.

Comparison of mechanism-related actions of anticonvulsants

	Na+ channel blockade	GABA potentiation	Glutamate antagonism
Topiramate	X	X	X
Phenytoin	X		
Carbamazepine	X		
Valproate	X	X	
Barbiturates		X	
Benzodiazepines		X	
Vigabatrin		X	
Tiagabine		X	
Lamotrigine	X		
Gabapentin		X	

Pharmacokinetics

- Bioavailability ≥80%
- T_{max}≈ 1.5 hours
- $t_{1/2}$≈ 20 hours
- Low protein binding (~15%)
- Majority excreted unchanged in urine

Shank RP et al. *Epilepsia.* 2000;41(suppl 1):S3-S9; Garnett WR. *Epilepsia.* 2000;41(suppl 1):S61-S65.

Topiramate Migraine Prophylaxis Clinical Program

- Pivotal efficacy trials
  - MIGR-001 - US
  - MIGR-002 - US and Canada
  - MIGR-003 – Europe, Asia, Africa
- Children: 1 clinical study (ongoing)
- Chronic daily headache: 1 clinical study (ongoing)

Evaluating Migraine Prevention Trials: Topiramate: Largest clinical trials

- ***Study Design:*** 26-week, randomized, D-B, parallel group, P-C
  - MIGR 001 and MIGR 002
    - 4 arms: Topiramate (50 /100 /200 mg/d) and placebo
  - MIGR 003
    - 4 arms: Topiramate (100/200 mg/d), propranolol (160 mg/d), and placebo
  - 2-week washout, 4-week baseline, 26-week double-blind period
- ***Study Size:*** N=568 (for largest clinical trial, MIGR-003)
- ***Study Analysis:***
  - ITT/ Evaluated entire D-B phase
- ***Study Duration:*** 26-week treatment period
- ***Primary End Points:*** change in monthly migraine frequency

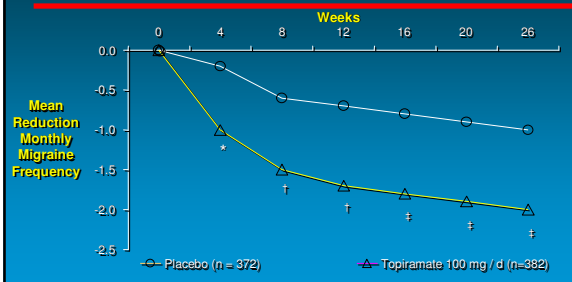
Brandes JL et al. *JAMA.* 2004;291:965-973; Diener HC et al. *J Neurol.* 2004;251:943-950; Silberstein SD et al. *Arch Neurol.* 2004;61:490-495.

Key Inclusion Criteria:
MIGR-001 and MIGR-002

- IHS criteria for migraine with or without aura
- Diagnosis >1 year
- Migraine frequency of 3 to 12 (mean ~5.5) per month during previous 3 months
- Able to recognize migraine headaches and distinguish from other types of head pain
- 12 to 65 years old

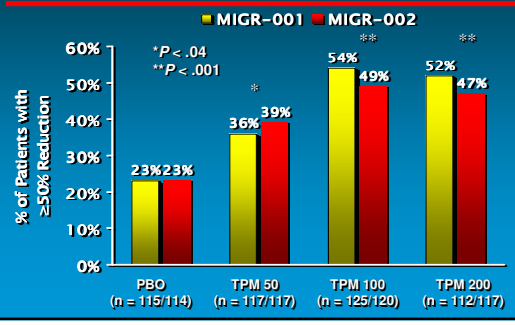
IHS=International Headache Society.
Brandes JL et al. *JAMA*. 2004;291:965-973; Silberstein SD et al. *Arch Neurol*. 2004;61:490-495.

Topiramate: Onset of Action
MIGR-001 / MIGR-002 / MIGR-003(pooled)

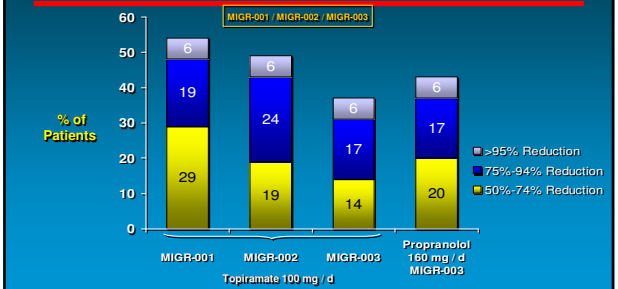


*P<.05, †P<.01, ‡P<.001 vs placebo.
Bussone G et al. Poster at 8th Congress of the European Federation of Neurological Societies; 2004.

Topiramate Responder Rate

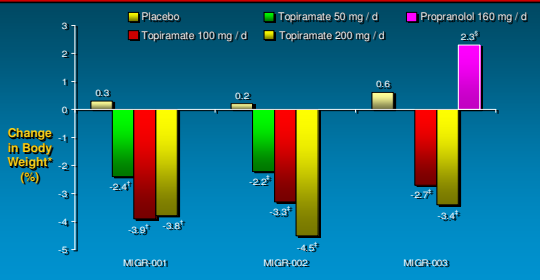


Response to Topiramate Therapy



Silberstein SD et al. *Arch Neurol*. 2004; Brandes JL et al. *JAMA*. 2004; Diener HC et al. *J Neurol*. 2004

Topiramate Migraine Prevention Trials: Body Weight
MIGR-001 / MIGR-002 / MIGR-003 & CAPSS-155



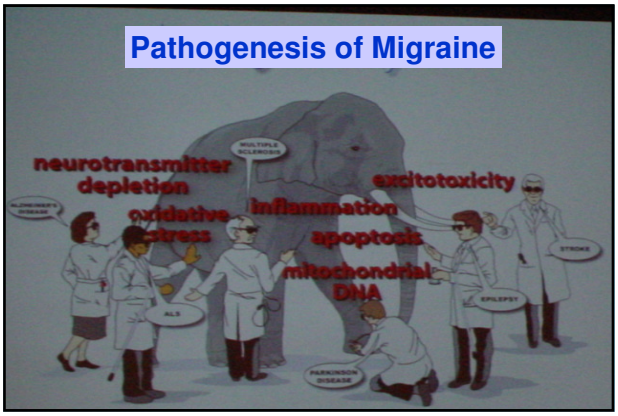
*Least squares mean; †P=.004; ‡P≤.001; §P=.025.
Silberstein SD et al. *Arch Neurol*. 2004; Brandes JL et al. *JAMA*. 2004; Diener HC et al. *J Neurol*. 2004

Topiramate: How to use it

- Start: 15-25 mg HS
- Increase: 15-25mg/week
- Do not increase if AEs: wait until they resolve
  - They usually do
    - If not go up by a lower dose
- Dose: 50-200mg/day given BID (to 600mg/day)
- AEs: weight loss, paresthesias, somnolence, concentration difficulty, kidney stones

AED Efficacy in Migraine: Responder Rate

AED	Drug	Placebo	Difference
Gabapentin	36%	16%	20%
Divalproex			
Mathew	48%	14%	34%
Klapper	44%	21%	23%
Freitag	30%	24%	6%
Jensen	50%	16%	34%
Topiramate			
Silberstein	54%	23%	31%
Migr-002	49%	23%	26%



Conclusions

- No preventive medication has proven more than 60% effective in reducing migraine frequency
- Probably due to uncertainty of precise molecular targets that induce brain hyperexcitabiltiy in patients
- Why do not all AEDs work for migraine?
- Future drugs discovery should focus on the interface between the excitable cell and the earliest events of CSD such as dendritic calcium transients