



New York Headache Center
Headache Update
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Lecture outline



Headache diagnosis



Migraine pathogenesis – research update



Abortive therapies



Botox and other prophylactic therapies



Magnesium and alternative therapies



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Number of Migraine Sufferers in the U.S.



	1989 (Million)	1999 (Million)
Overall	23.6	27.9
Female	18.0	20.9
Male	5.6	6.9

Lipton et al. 2001.
American Migraine Study II.



Migraine Diagnosis



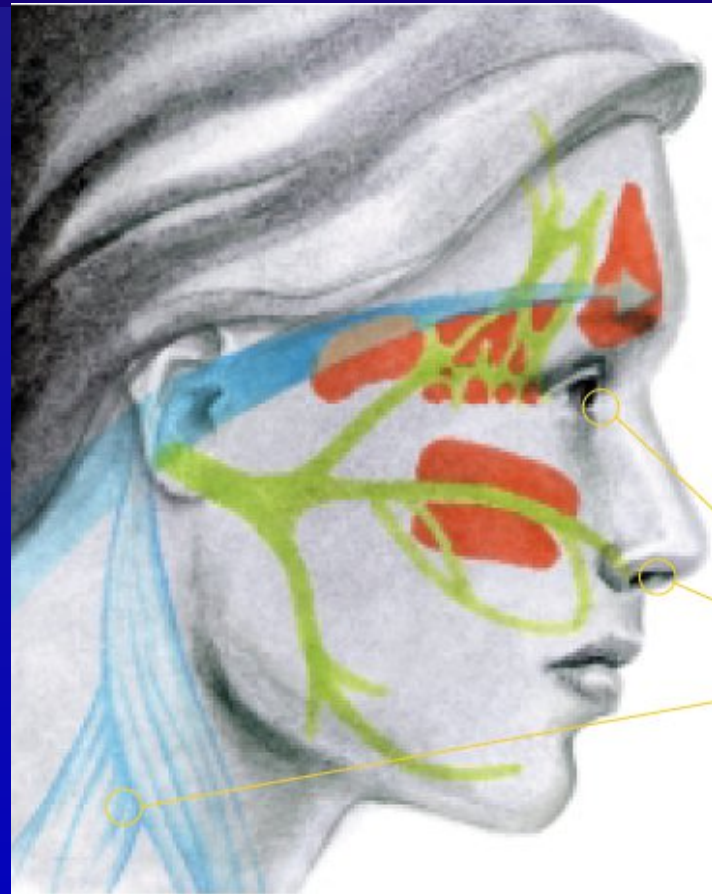
Migraine is under-diagnosed

94% of patients presenting to a PCP with recurrent headache met IHS criteria for migraine or probable migraine

Nearly 90% of “sinus headache” patients met IHS criteria for migraine or probable migraine

Nearly 90% of “tension/stress” headache patients met IHS criteria for migraine or probable migraine

Migraine Is Often Overlooked



Sinus headache is the most common misdiagnosis

Symptoms include:

- Dull ache located near the nose
- Pressure in the sinus cavities
- Thick, colored nasal discharge
- OTCs can sometimes relieve the pain

1.1 Migraine Without Aura

Diagnostic Criteria



At least five attacks fulfilling the following criteria:



Headache lasts 4 to 72 hours (untreated or unsuccessfully treated)



Headache has at least 2 of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe intensity (inhibits or prohibits daily activities)
- Aggravation by walking stairs or similar routine physical activity

During headache at least 1 of the following occurs:



- Nausea and/or vomiting
- Photophobia and phonophobia

Migraine Diagnostic Questionnaire



Has a headache limited your activities for a day or more in the last three months?



Are you nauseated or sick to your stomach when you have a headache?



Does light bother you when you have a headache?

Sensitivity - 0.81 (95% CI, 0.77 to 0.85)

Specificity - 0.75 (95% CI, 0.64 to 0.84)

Positive predictive value - 0.93 (95% CI, 89.9 to 95.8).

Test-retest reliability was good - kappa of 0.68 (95% CI, 0.54 to 0.82).

Hemiplegic migraine is overdiagnosed



The International Classification of Headache Disorders 2nd Edition

"distinction between migraine with aura and hemiparesthetic migraine is probably artificial and therefore not recognized in this classification"

"Common mistakes (in diagnosing typical aura with migraine headache) are...mistaking sensory loss for weakness"

The myth of basilar migraine



M. Kirchmann, L.L. Thomsen, J. Olesen. **Basilar-type migraine: Clinical, epidemiologic, and genetic features.**

Neurology 2006; 66(6):880-886.

Conclusions:

Basilar-type aura seemingly may occur at times in any patient with migraine with typical aura. There is no firm clinical, epidemiologic, or genetic evidence that basilar migraine is an independent disease entity different from migraine with typical aura.

Causes of Migraines



A single gene is responsible for familial hemiplegic migraine



Common migraine is polygenetic, which accounts for its variable expression

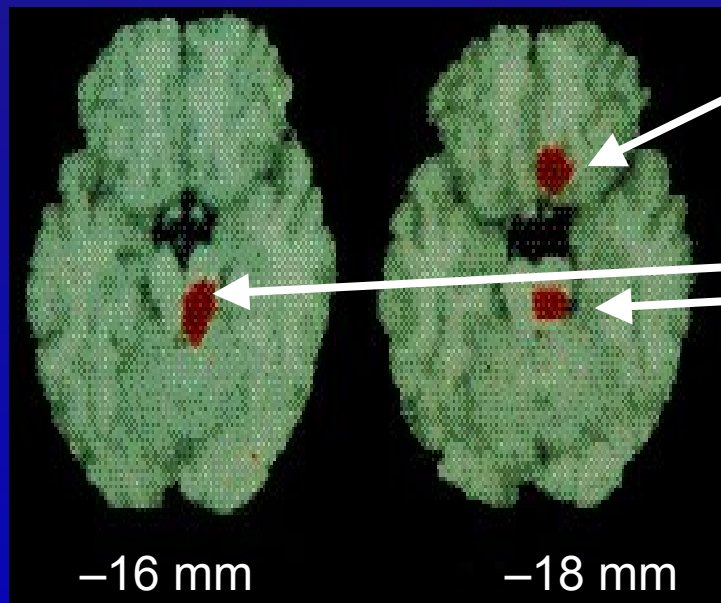


Multiple triggers modify the frequency and the severity of attacks

CNS Activation During Migraine



Dysfunction of brainstem pain and vascular control centers



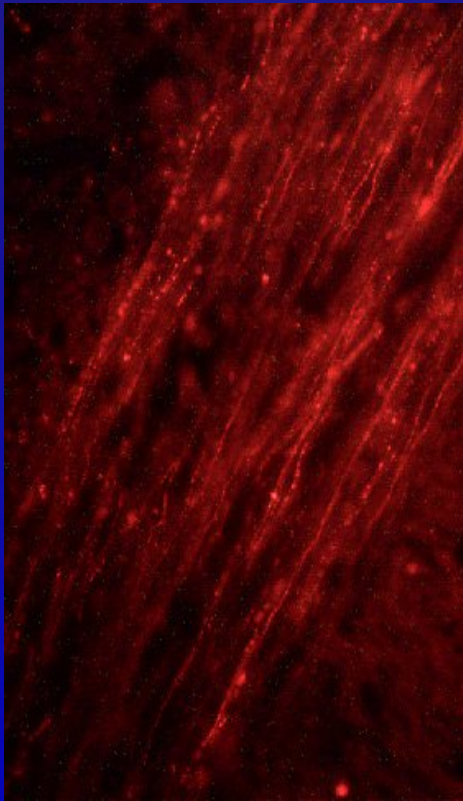
Pain Perception*
Anterior cingulate cortex

Migraine Generator*
Raphe nuclei
Locus coeruleus
Periaqueductal gray

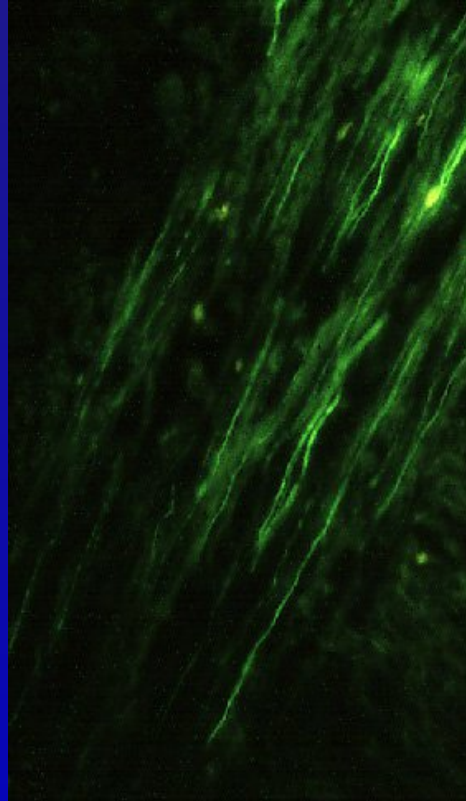
*Areas of red indicate cerebral blood flow increases ($P < 0.001$).

Weiller C et al. *Nat Med*. 1995;1:658–660

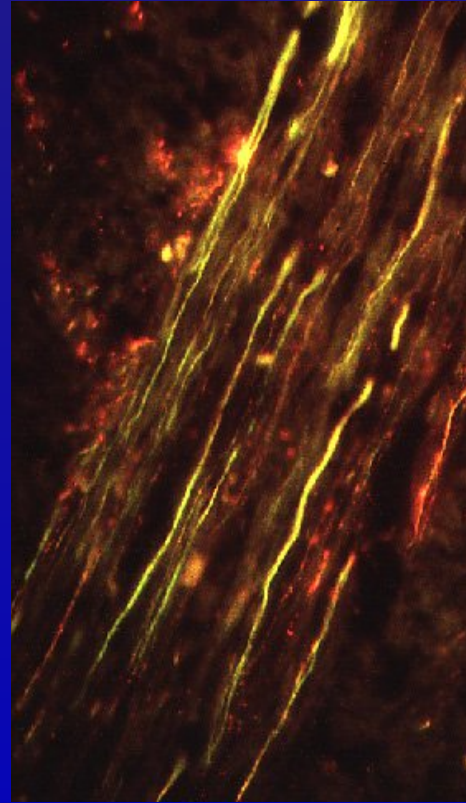
Human Trigeminal Tract: CGRP Fibers Co-express 5-HT_{1D} Receptors



CGRP



5-HT_{1D}



5-HT_{1D} /CGRP

CGRP antagonists in migraine



Calcitonin gene-related peptide receptor antagonist
BIBN 4096 BS for the acute treatment of migraine.

Olesen, Diener, Husstedt et al. *N Engl J Med*. 2004;350:1104-10.

Response rate:

2.5 mg - 66%

placebo - 27%

$P=0.001$

CGRP antagonists in migraine



MK-0974

		Pain relief at 2 hours	Pain free
300 mg	n=38	68.1%	45.2%
400 mg	n=45	48.2%	24.3%
600 mg	n=40	67.5%	32.1%
rizatriptan	n=34	69.5%	33.4%
placebo	n=115.	46.3%	14.3%

Prescription Drugs



Non-triptans



Cafergot, Wigraine



Migranol



Midrin



Fioricet, Fiorinal, Esgic



NSAIDs, COX-2



codeine, hydrocodone



Stadol NS

Medication-Overuse Headache (MOH) New to IHS Classification



Common cause of headaches 🕒 15 days/month



Headache has developed or is markedly worse with regular overuse of opioids or caffeine-containing drugs



Diagnosis important: patients often do not respond to preventive Rx until the overused medication is withdrawn



Discontinuation of acute medication usually results in

- Withdrawal symptoms (increased headache)
- Later improvement

Previously used terms: rebound headache, drug-induced headache, medication-misuse headache



Migralex



A rapidly dissolving
combination of:



Aspirin – 500 mg



Magnesium oxide – 75 mg

Prescription Drugs



Triptans



Imitrex (Treximet) – sumatriptan (+naproxen)



Zomig - zolmitriptan



Maxalt - rizatriptan



Amerge - naratriptan



Axert - almotriptan



Frova - frovatriptan



Relpax - eletriptan

Triptans



Contraindications

- ▶ Ischemic heart disease
- ▶ Coronary vasospasm
- ▶ Multiple risk factors for CAD
- ▶ Hemiplegic or basilar migraine
- ▶ Uncontrolled hypertension
- ▶ Use within 24 hours of ergot or another triptan
- ▶ Pregnancy: Category C

Consider Prevention When:



- ▶ Migraine significantly interferes with patient's daily routine despite acute treatment
- ▶ Frequency attacks >2 /week with risk of acute medication overuse
- ▶ Contraindication to, failure, adverse events, or acute medication overuse
- ▶ Patient preference

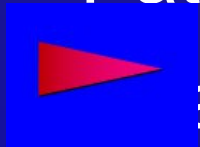


Preventive Treatment

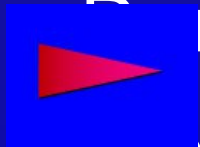


Choice is based on:

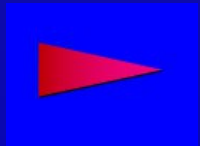
Patient's preferences



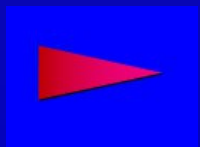
Migraine type



Drug side effects



Presence of coexisting conditions



Principles of Preventive Drug Treatment



- ▶ Start with low dose and increase slowly
- ▶ Need adequate trial (1 to 2 months)
- ▶ Avoid drug overuse and interfering drugs
- ▶ Evaluate therapy
 - Use calendar
 - Taper (and stop?) if headaches well controlled

Currently Used Preventive Drugs



High efficacy

- -blockers: propranolol, timolol
- TCAs: amitriptyline
- Divalproex
- Topiramate

Moderate efficacy



- -blockers: atenolol, metoprolol, nadolol
- ARBs: candesartan
- Some NSAIDs
- SNRIs: duloxetine
- Gabapentin

History of BTX-A Use in Migraine



Anecdotal reports of reduced migraines from patients receiving BTX-A treatment for other indications

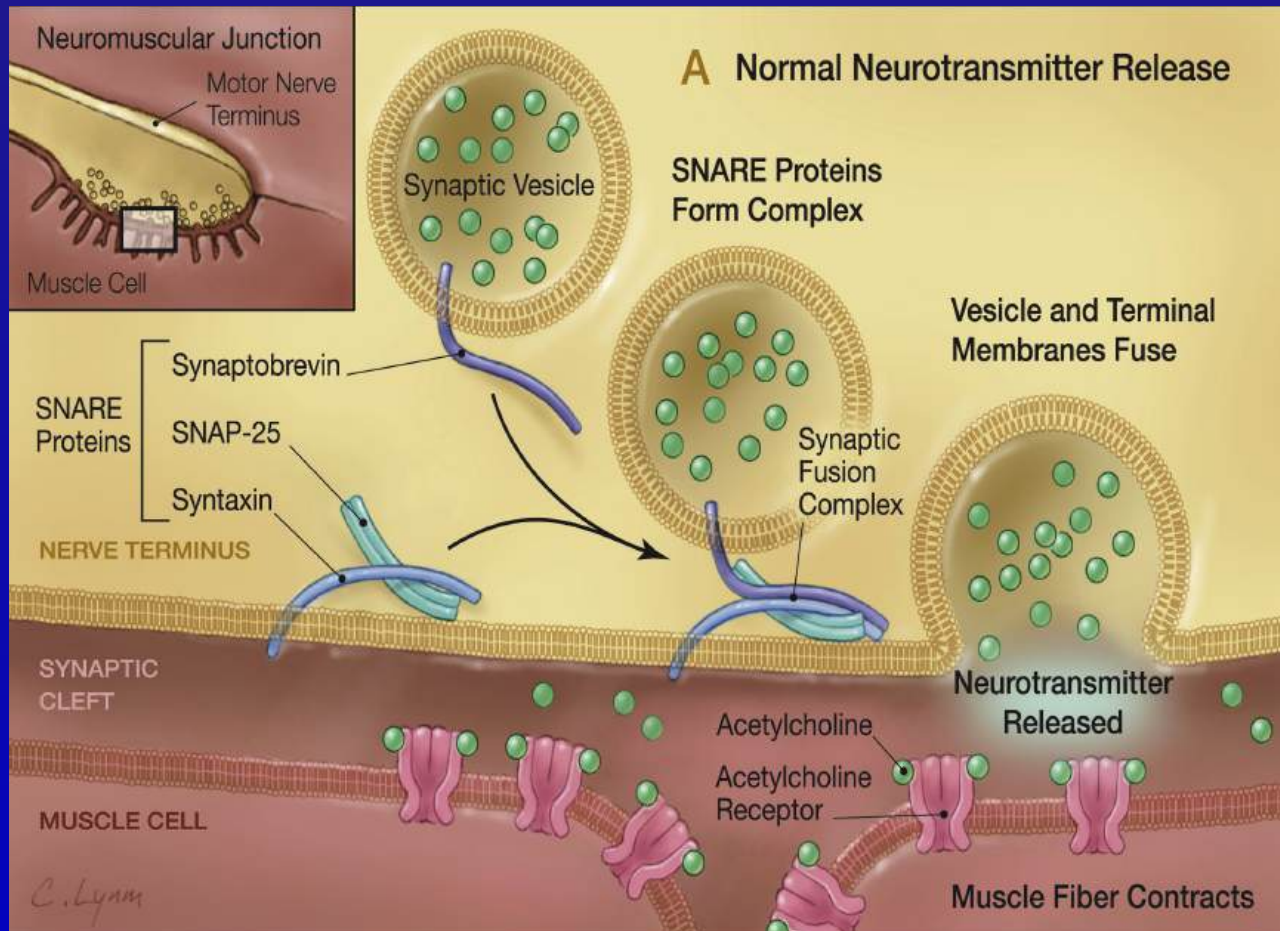


A retrospective review of patient charts suggested migraine relief was associated with certain injection sites

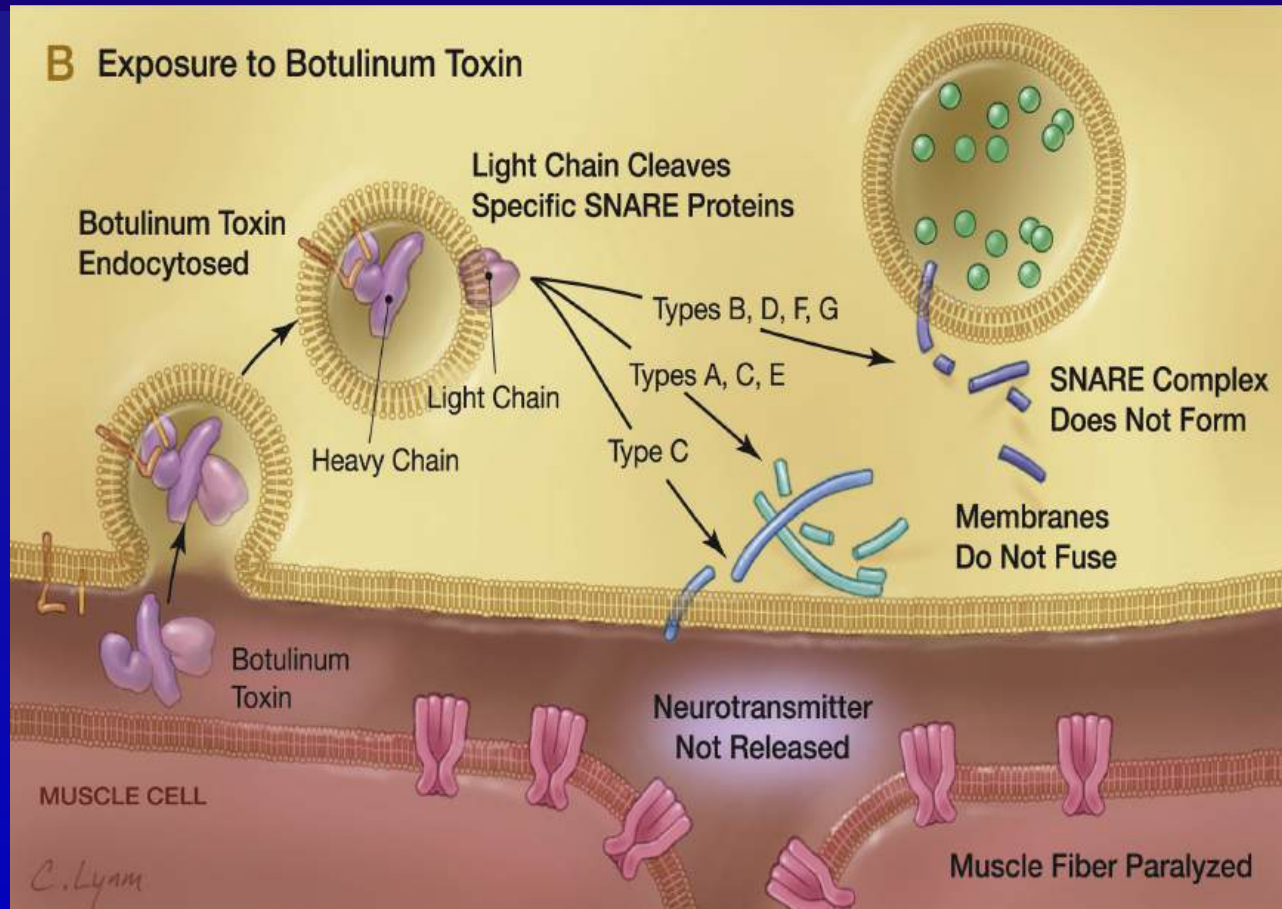


This information was used in designing early clinical studies

The Neuromuscular Junction



Botulinum Toxin Type A Mechanism of Action



CGRP and Botulinum Toxin



Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential.

Meng J, Wang J, Lawrence G, Dolly JO. *J Cell Sci.* 2007;120(16):2864-74

Botox for chronic migraine: Phase III trials



Aurora SK, Schim JD, Cutrer FM, et al. Botulinum neurotoxin type A for treatment of chronic migraine: PREEMPT 1 trial double-blind phase. Cephalalgia 2009;29 (suppl 1):29.

Dodick DW, Smith TR, Becker WJ, et al. Botulinum neurotoxin type A for treatment of chronic migraine: PREEMPT 2 trial double-blind phase. Cephalalgia 2009;29 (suppl 1):29.



Caffeine



“Withdrawal syndrome after the double-blind cessation of caffeine consumption.”

- ▶ 52% moderate or severe headache
- ▶ 11% depression
- ▶ 11% low vigor
- ▶ 8% anxiety
- ▶ 8% fatigue

235 mg (2.5 cups) a day

(Silverman et al. *NEJM* 1992)

Magnesium and Migraine



Low brain magnesium in migraine

N.M. Ramadan, H. Halvorson, A. Vande-Linde et al.
Headache 1989;29:590-593.

Magnesium and Migraine



Oral magnesium load test in patients with migraine

Trauninger et al. *Headache* 42:114-119;2002

Conclusions:

Magnesium retention occurs in patients with migraine after oral loading, suggesting a systemic magnesium deficiency

Magnesium and Migraine



Known effects of IMg^{2+}



glutamate



angiotensin II



potassium



serotonin



G proteins



acetylcholine



nitric oxide



norepinephrine

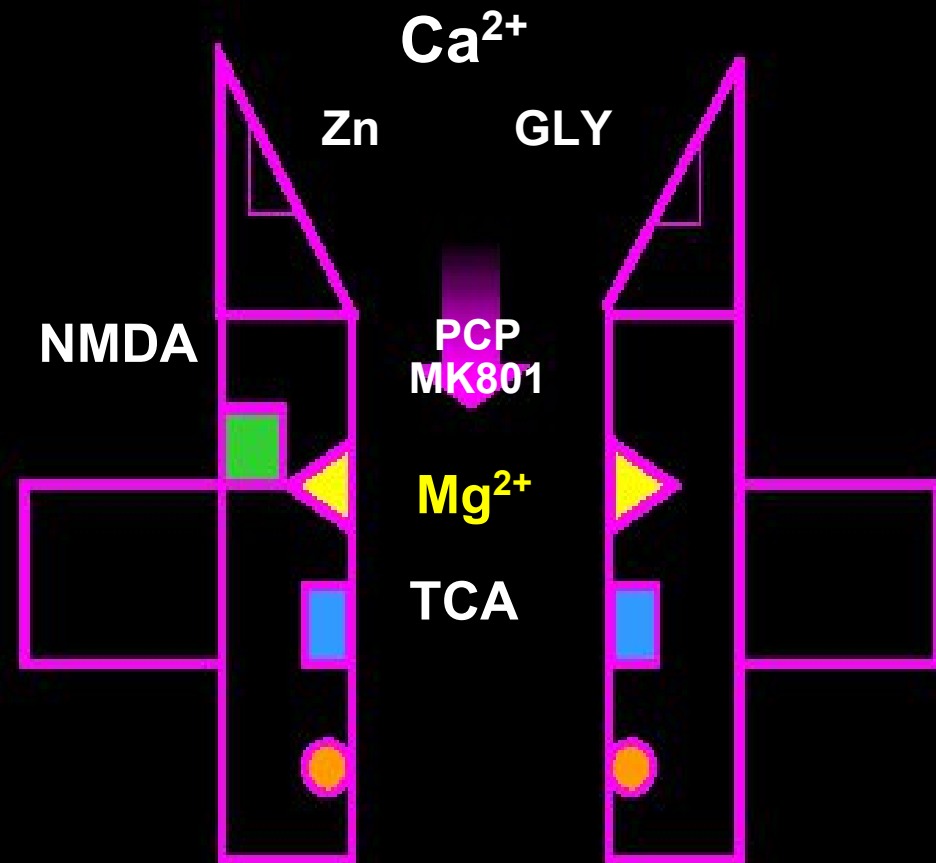
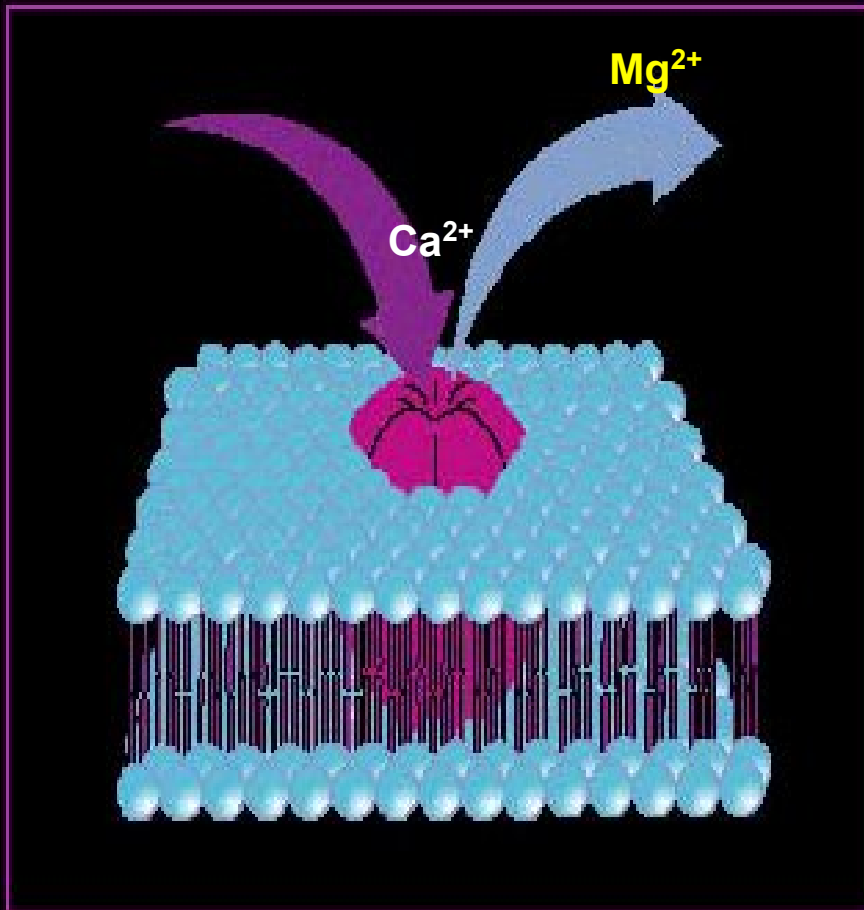


calcium

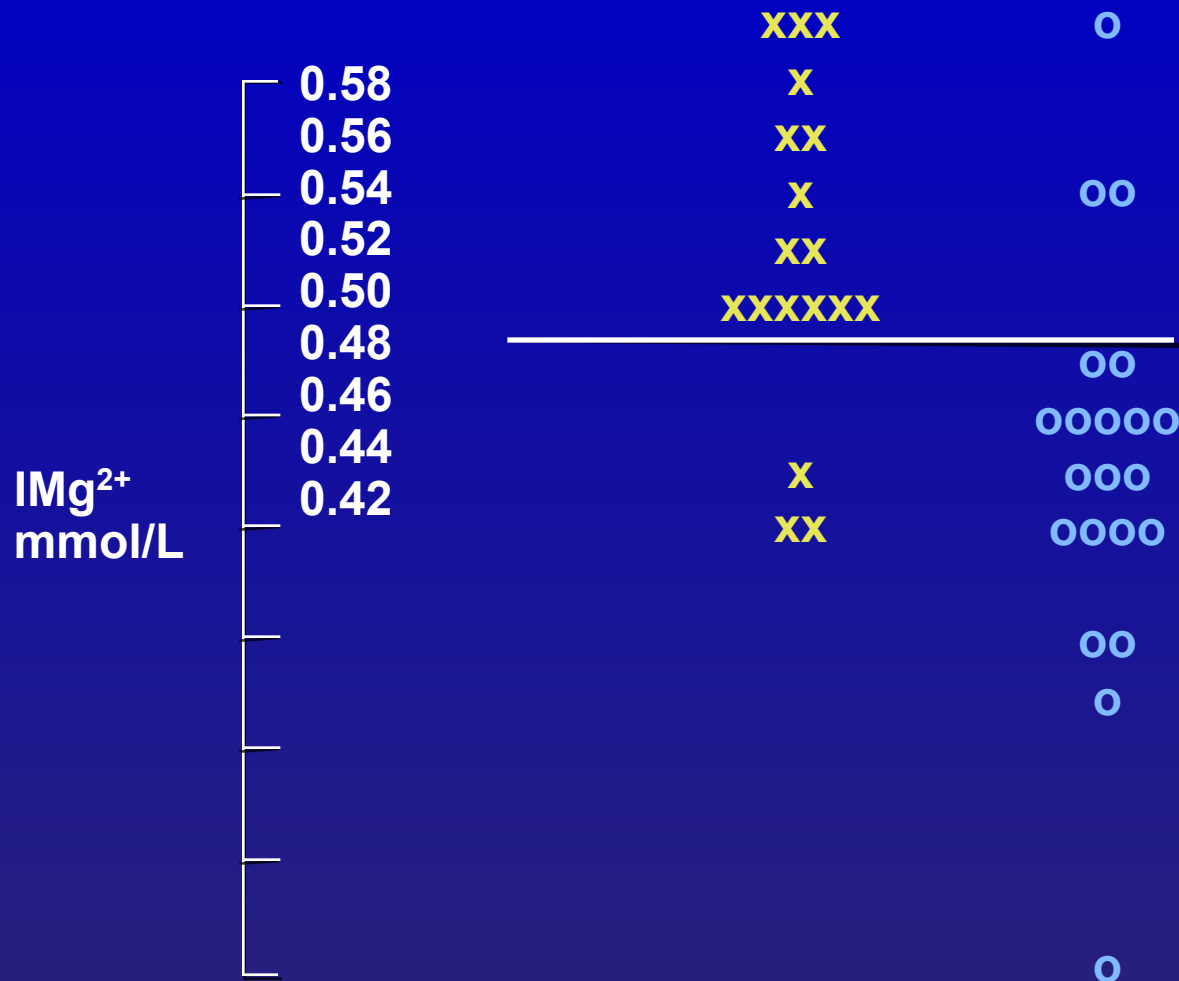


enzyme complexes (325)

NMDA (N-Methyl-D-Aspartate) Receptor Complex



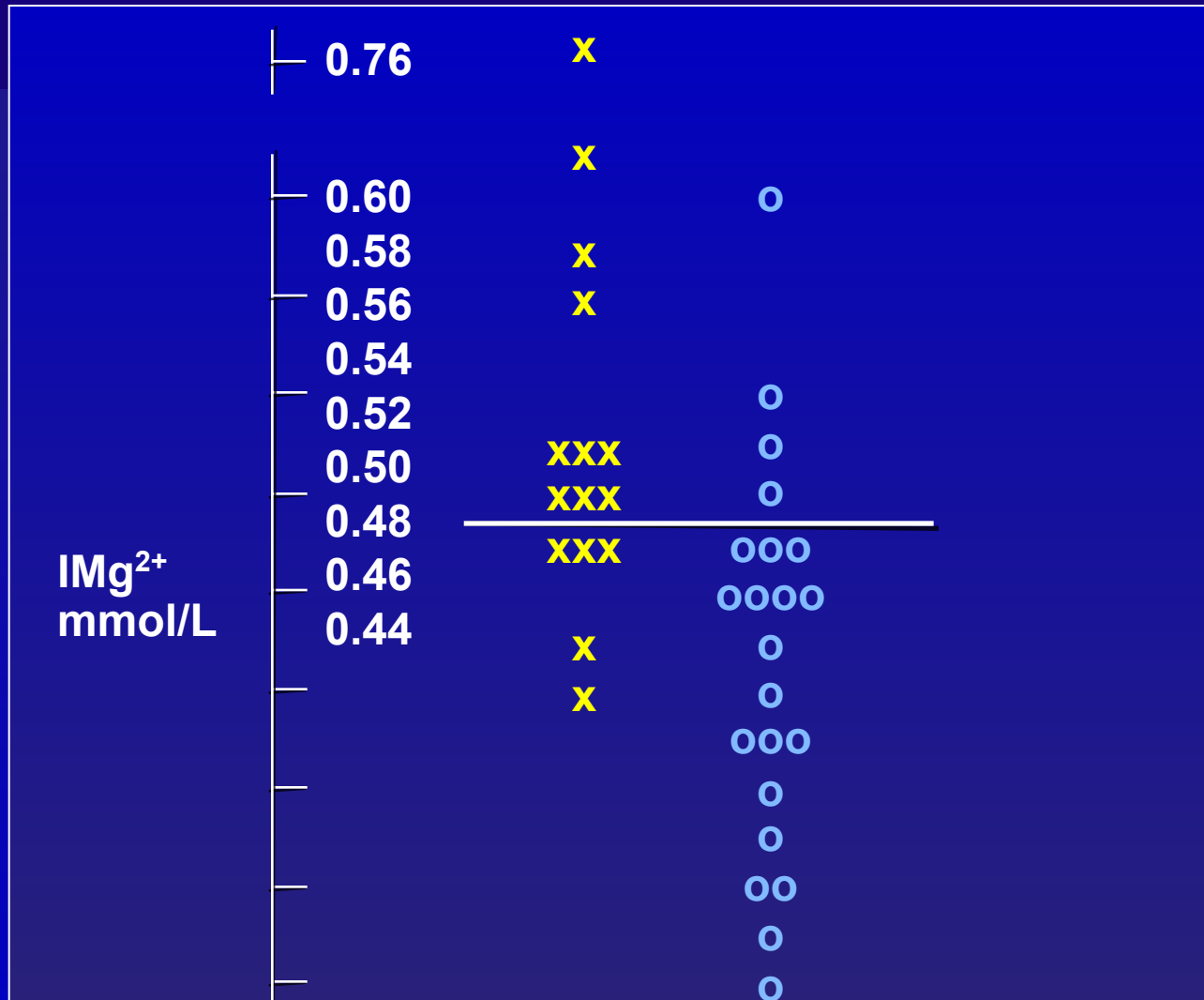
IV MgSO₄ for Acute Migraine



x = non-responders

o = responders

IV MgSO_4 for Cluster Headaches



x = non-responders

o = responders

Mauskop et al,
Headache 1995;35:59

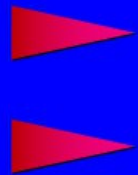
Magnesium and Migraine



Magnesium prophylaxis of menstrual migraine:
Effects on intracellular magnesium.

F. Facchinetti, G. Sances, A.R. Genazzani, G. Nappi.
Cephalagia 1996; 16:257-263.

Magnesium pyrrolidone carboxylic acid – 360 mg



Days with migraine reduced 4.7 to 2.4 ($p < 0.01$)
Significant reduction in MDQ scores ($p < 0.05$)

Magnesium and Migraine



Prophylaxis of migraine with oral magnesium: results from a prospective, multicenter, placebo-controlled and double-blind randomized study.

A. Peikert, C. Wilimzig, R. Kohne-Volland, *Cephalagia* 1996; 16:257-263.

Trimagnesium dicitrate – 600 mg



Attack frequency reduced 41.6% vs 15.8% (p<0.05)



Days with migraine reduced 52.3% vs 19.5% (p<0.05)

Magnesium and Migraine



Magnesium in the prophylaxis of migraine:
A double-blind, placebo-controlled study.

Pfaffenrath V, Wessely P, Meyer C, et al.
Cephalagia 1996; 16:436-440.

Magnesium-u-aspartate-hydrochloride-trihydrate – 20 mmol

No relief of headaches – interim analysis of 69 patients.

Diarrhea: 45.7% on magnesium, 23.5 on placebo

Magnesium and Migraine



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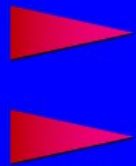
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A. Peikert, C. Wilimzig, R. Kohne-Volland, *Cephalagia* 1996; 16:257-263.

Trimagnesium dicitrate – 600 mg



Attack frequency reduced	41.6% vs 15.8%	($p < 0.05$)
Days with migraine reduced	52.3% vs 19.5%	($p < 0.05$)

Magnesium and Migraine



Oral magnesium oxide prophylaxis of frequent migrainous headache in children: A randomized, double-blind, placebo-controlled trial.

Wang F, Van Den Eeden S, Ackerson L, et al.
Headache 2003;43:601-610.

Magnesium oxide 9 mg/kg

86 of 118 completed;

“statistically significant downward trend in HA frequency over time in MgO but not placebo group”

Magnesium and Migraine



Potential causes of magnesium deficiency

- ▶ Stress
- ▶ Alcohol & caffeine
- ▶ Genetics of absorption and renal excretion
- ▶ Low dietary intake
- ▶ Gastro-intestinal disorders (IBS, colitis, celiac)
- ▶ Chronic illness



Coenzyme Q₁₀



Efficacy of coenzyme Q₁₀ in migraine prophylaxis: A randomized controlled trial

P. S. Sándor, L. Di Clemente, G. Coppola
Neurology 2005;64:713-715

Double-blind, randomized, placebo-controlled trial
42 patients; CoQ₁₀ 100 mg TID vs placebo

50% responder rate for attack frequency
14.4% for placebo and 47.6% for CoQ₁₀

Coenzyme Q₁₀



Coenzyme Q₁₀ deficiency and response to supplementation in pediatric and adolescent migraine

Hershey AD, et al. *Headache*
2007;47:73-80

1550 patients – 32.9% deficient

Supplementation with 1-3 mg/kg/day

CoQ₁₀ levels improved, $p < .0001$

HA frequency improved from 19.2 to 12.5, $p < .001$

HA disability improved from 47.4 to 22.8, $p < .001$

Mind-body therapy



Progressive relaxation



Imagery &
visualization



Behavioral therapy



Cognitive therapy



Social support



Therapeutic touch



Hypnotherapy



Meditation



Biofeedback



Prayer



Reiki

Botanical Remedies



Feverfew

Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂--extract (MIG-99) in migraine prevention – a randomized, double-blind, multicenter, placebo-controlled study.

Diener HC, Pfaffenrath V, Schnitker et al.
Cephalalgia 2005;25:1031-1041

N=170, 89 - feverfew, 81 - placebo, 4 - 6 attacks/month
No prophylactic drugs

Feverfew (Diener)



Results



Reduction in number of attacks in 28 days—
1.9 vs 1.3 ($p < 0.0456$)



Global assessment of efficacy – statistically
significant difference



No difference in adverse events (25.2% active,
26.6% – placebo)



No effect on duration of attacks

Petasites hybridus- butterbur (Petadolex®)



Petasites hybridus root (butterbur) is an effective preventive treatment for migraine.

Lipton RB, Gobel H, Einhaupl KM, Wilks, K and Mauskop A. *Neurology* 2004;63:2240-2244



245 patients



Three groups: placebo, 100 mg and 150 mg



Main outcome measure: attack frequency

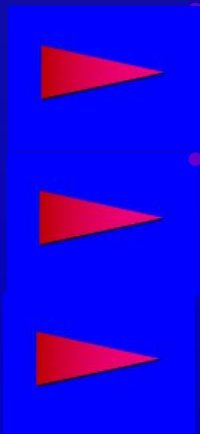
Petasites hybridus- butterbur (Petadolex[®])



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Lipton RB, Gobel H, Einhaupl KM, Wilks, K and Mauskop A. *Neurology* 2004;63:2240-2244

- Attack frequency reduced by:
48% in 150 mg group (p=0.0012)
36% in 100 mg group (p=0.127)
26% in placebo



Approach to migraine patients at the NYHC



- ▶ aerobic exercise, neck exercise
- ▶ biofeedback / meditation / yoga
- ▶ magnesium, riboflavin, feverfew (MigreLief[®])
- ▶ CoQ₁₀, butterbur (Petadolex[®])
- ▶ acupuncture
- ▶ dietary approaches
- ▶ botulinum toxin
- ▶ medications: abortive, prophylactic

Parenteral treatment of acute migraines



Goal: Keep patients out of the ER

- ▶ magnesium sulfate – 1 gram IV
- ▶ sumatriptan – 4-6 mg SC
- ▶ ketorolac – 60 mg IV
- ▶ dexamethasone – 8 mg IV
- ▶ metoclopramide – 10 mg IV
- ▶ dihydroergotamine – 1 mg IV
- ▶ valproate sodium – 500 mg IV
- ▶ droperidol – 2.5-5 mg IV