New York Headache Center

Complementary and alternative therapies for headaches

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Complementary and alternative therapies

"There is no alternative medicine…

There is only scientifically *proven*, evidence-based medicine supported by solid data or *unproven* medicine, for which scientific evidence is lacking"

Fontanarosa PB, Lundberg GD. Alternative Medicine Meets Science. *JAMA.* 1998;280(18):1618-1619

Physicians tend to use unproven drugs and procedures much more readily than non-drug treatments

Complementary and alternative therapies

- Mind-body techniques
- Physical methods
- Vitamins, minerals, and nutraceuticals
- Botanicals
- Acupuncture
- Music

Mind-body therapy

“Words are, of course, the most powerful drug used by mankind.”

Rudyard Kipling

Mind-body therapy

- Meditation
- Biofeedback / Neurofeedback
- Progressive relaxation, visualization
- Cognitive-behavioral therapy

  Online courses: ThisWayUp.org.au, online-therapy.com
- Feldenkrais Method

Meditation

Alterations in Resting-State Functional Connectivity Link Mindfulness Meditation With Reduced Interleukin-6: A Randomized Controlled Trial

Creswell JD, et al. *Biological Psychiatry* 2016;80(1): 53–61

"…first evidence that mindfulness meditation training, but not relaxation training, "functionally couples the default mode network with a region known to be important in top-down executive control at rest, which, in turn, is associated with improvements in a marker of inflammatory disease risk"

Meditation

Meditation for migraines: a pilot randomized controlled trial. Wells RE, et al. *Headache* 2014; 54(9):1484-95

10 patients with migraine headaches underwent an 8-week course of MBSR and were compared to 9 in the control group

"…this pilot trial did not provide power to detect statistically significant changes in migraine frequency or severity, secondary outcomes demonstrated this intervention had a beneficial effect on headache duration, disability, self-efficacy, and mindfulness"

Meditation

The effect of meditation on brain structure: cortical thickness mapping and diffusion tensor imaging.

Kang D-H, et al. *Soc Cogn Affect Neurosci*. 2013;8(1):27-33

Meditators, compared with controls, showed significantly greater cortical thickness in the anterior regions of the brain, located in frontal and temporal areas, including the medial prefrontal cortex, superior frontal cortex, temporal pole and the middle and interior temporal cortices.

Long-term meditators have structural differences in both gray and white matter.

Exercise and headaches

Physical activity and headache: results from the Nord-Trøndelag Health Study (HUNT). Varkey E, Hagen K, Zwart J-A, Linde M. *Cephalalgia* 2008;28:1292–1297

A study of 46,648 subjects

“Low physical activity was associated with higher prevalence of migraine and non-migraine headache.

In both headache groups, there was a strong linear trend (P< 0.001) of higher prevalence of ‘low physical activity’ with increasing headache frequency”

Exercise and headaches

Exercise as migraine prophylaxis: A randomized study using relaxation and topiramate as controls. Varkey E, Cider Å, J. Carlsson J, Linde M. *Cephalalgia* 2011;31:1428-1438

91 patients divided into 3 groups:

- aerobic exercise (40 minutes three times a week)
- topiramate
- relaxation training

All three treatments equally effective. Only topiramate caused side effects, which occurred in 33% of patients

Magnesium and migraine (Level B evidence)

Low brain magnesium in migraine

N.M. Ramadan, H. Halvorson, A. Vande-Linde et al.

Headache 1989;29:590-593

Phosphorus magnetic resonance spectroscopy:

Magnesium levels were low during a migraine attack

Magnesium and headaches

Deficient energy metabolism is associated with low free magnesium in the brains of patients with migraine and cluster headache

R. Lodi, et al. *Brain Research Bulletin*, 2001;54(4):437–441

Phosphorus magnetic resonance spectroscopy in 78 patients:
7 – migraine stroke, 13 – migraine with prolonged aura, 37 – migraine with typical aura or basilar migraine, 21 – migraine without aura, 13 – cluster headache

In the occipital lobes of all migraine and all cluster headache patients cytosolic free Mg^{2+} as well as the free energy released by the reaction of ATP hydrolysis were significantly reduced.

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

Potential causes of magnesium deficiency

- Stress
- Genetics
- Low dietary intake
- Caffeine, alcohol, calcium
- Gastro-intestinal disorders
- Chronic illness

Practical considerations

Clinical symptoms of hypomagnesemia

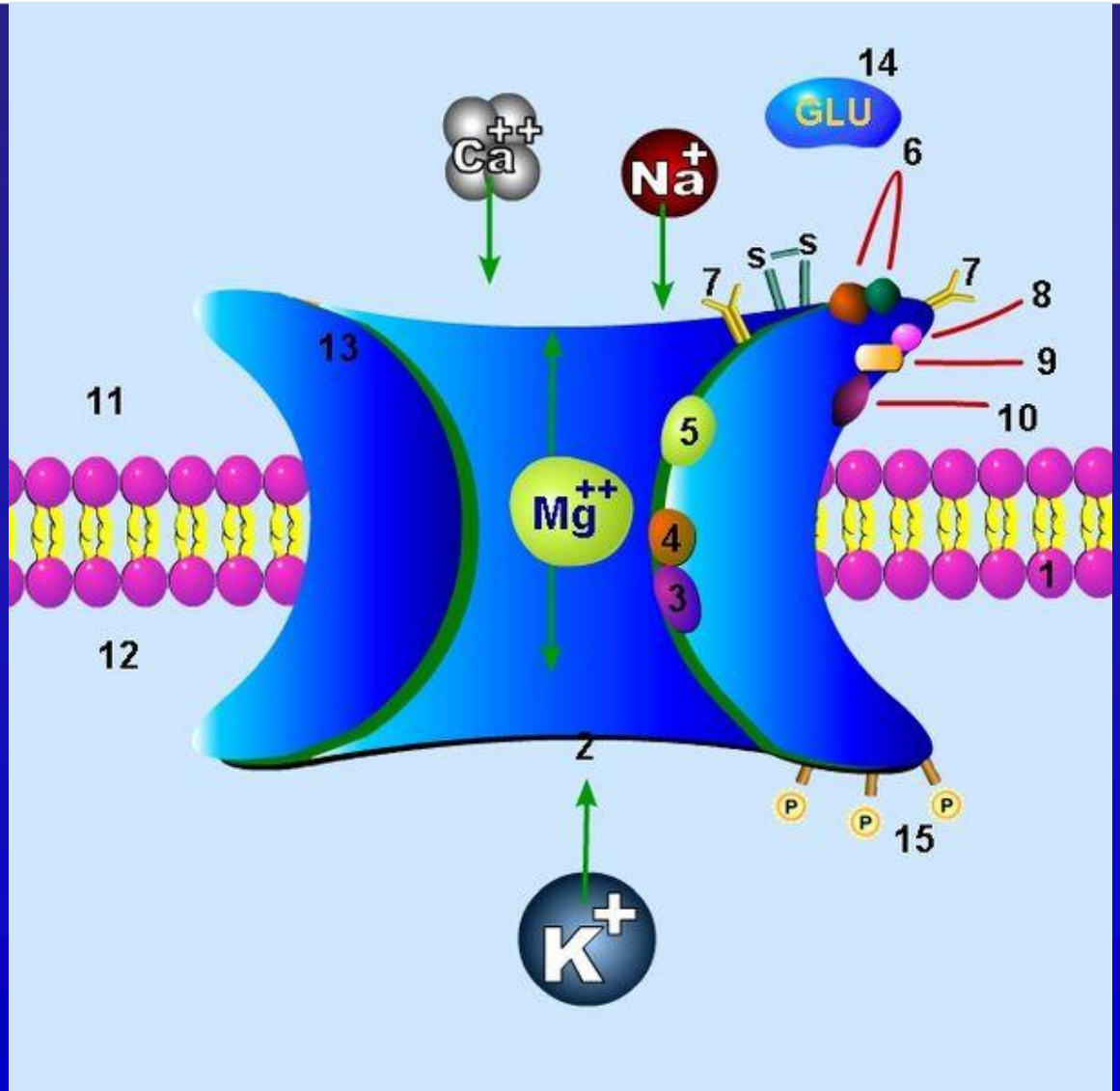
- Headaches
- Leg muscle cramps
- Coldness of extremities or body
- PMS
- Mental fog
- Irritability, depression
- Palpitations

Magnesium and migraine

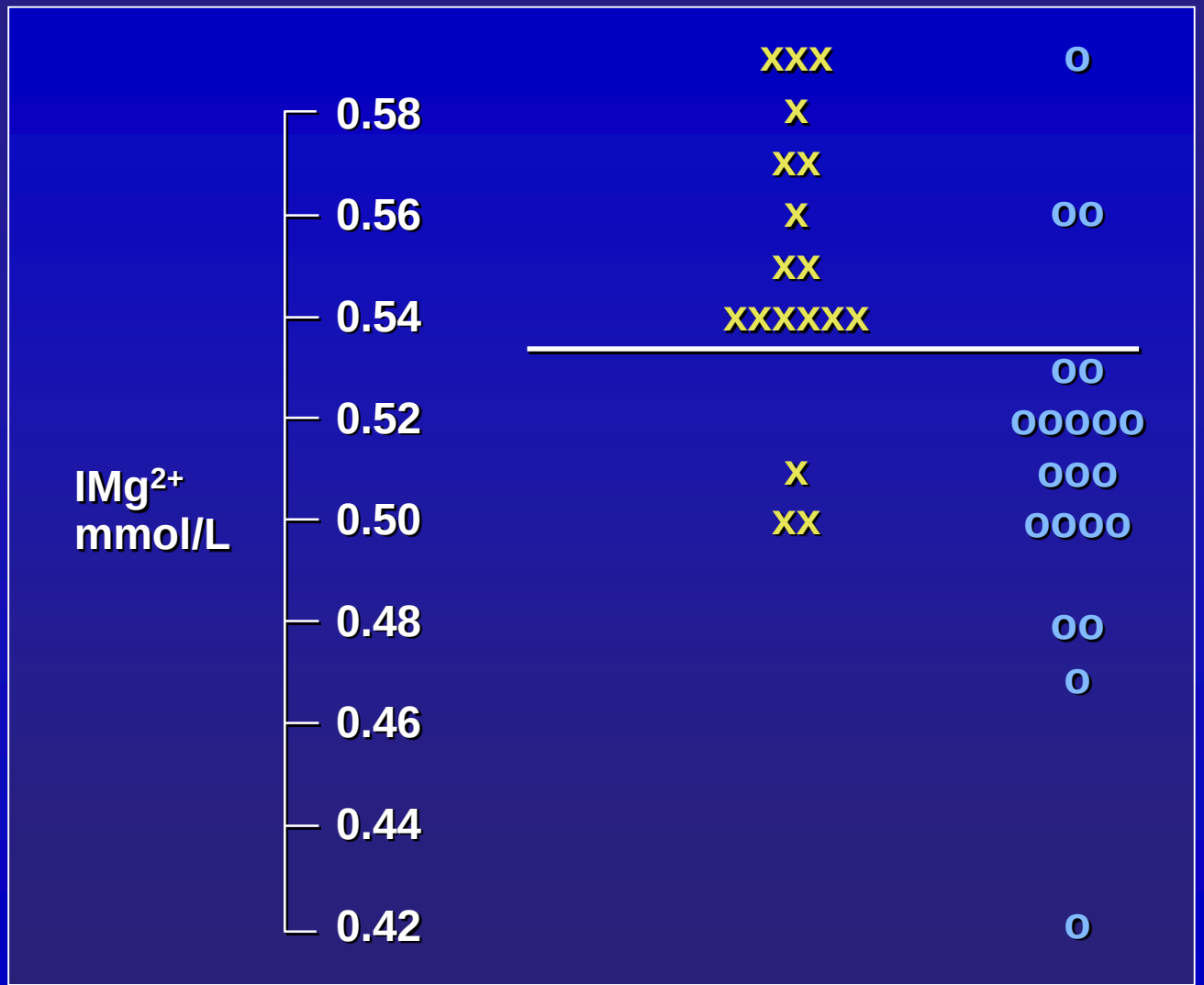
Known effects of IMg^{2+}

- glutamate
- angiotensin II
- potassium
- serotonin
- G proteins
- acetylcholine
- nitric oxide
- norepinephrine
- calcium
- enzyme complexes (325)

NMDA receptor



IV $MgSO_4$ for acute migraine



x = non-responders

o = responders

Mauskop A, et al, *Clin Science* 1995;89:633-6

IV $MgSO_4$ for acute migraine

Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks

Demirkaya S, Vural O, Dora B, et al. *Headache* 2001;41:171-177

1 gram of magnesium sulfate intravenously or placebo

- 13 of 15 patients (87%) receiving magnesium obtained
- complete pain relief
- none of the 15 patients in the placebo group

Magnesium and migraine

Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study

Bigal ME, et al. *Cephalalgia* 002 Jun;22(5):345-53

60 patients; 1 gram of MgSo4 – IV push

Relief of all symptoms in MA, relief of photo, phonophobia in MWA; all trends in favor of magnesium

Magnesium and migraine

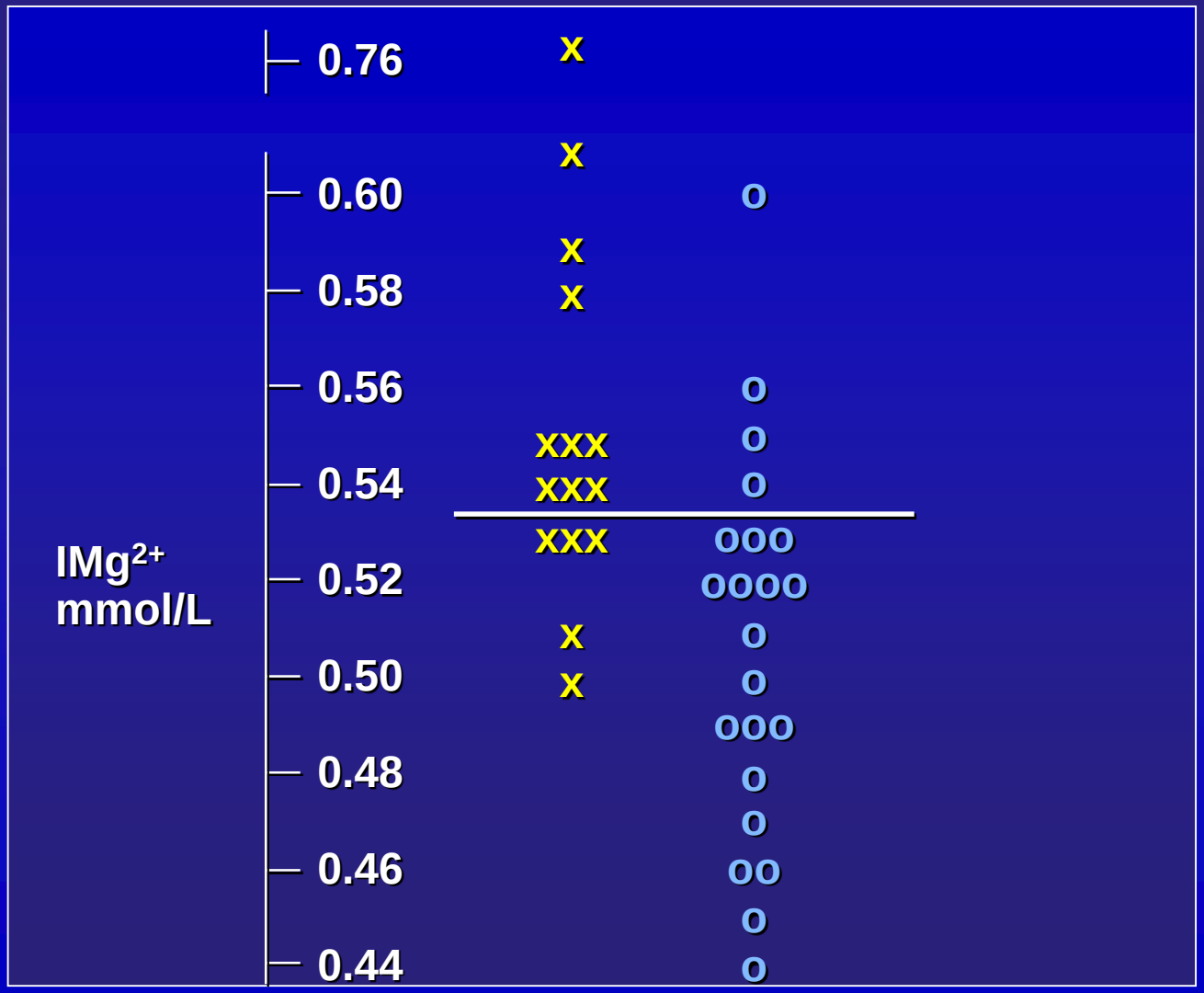
Remission of migraine-associated allodynia after intravenous magnesium. Xu F, Cesar P-H, Sahai-Srivastava S.

Presented at the 59th Annual American Headache Society Meeting, Boston, 2017

63-year-old woman with chronic migraine and severe scalp allodynia of 5 years in duration. She was afraid to wash and comb her hair and slept poorly as she was afraid to put her head on a pillow.

A single infusion of 2 grams of magnesium sulfate stopped allodynia for several months. She required several infusions a year to keep allodynia under control.

IV $MgSO_4$ for cluster headaches



x = non-responders

o = responders

Mauskop A, et al,
Headache
1995;35:597-600

Magnesium and migraine

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

Peikert A, et al. *Cephalagia* 1996; 16:257-263

Trimagnesium dicitrate – 600 mg vs placebo
81 patients

- 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 prophylaxis of menstrual migraine: Effects on intracellular magnesium

F. Facchinetti, G. Sances, A.R. Genazzani, G. Nappi.
Headache; 1991;31:298-310

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

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

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

Pfaffenrath V, 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

Oral magnesium absorption issues:

Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection.
Schuette SA et al. *J Parenter Enter Nutr* 1994;18:430-435

Equal absorption, diglycinate better tolerated (fewer stools).

Blood and urinary magnesium kinetics after oral magnesium supplements. White et al. *Clin Ther* 1992:14(5)678-687

No difference in total serum Mg AUC:
chloride solution, slow release chloride tabs, gluconate tabs

Magnesium and migraine: Practical considerations

Oral supplementation

- Start with 400 mg of chelated magnesium (glycinate, aspartate, etc.)
- If not tolerated, try a different salt of magnesium (oxide, chloride, etc.)
- If tolerated but ineffective, consider increasing the dose to 400 mg BID – TID; always with food

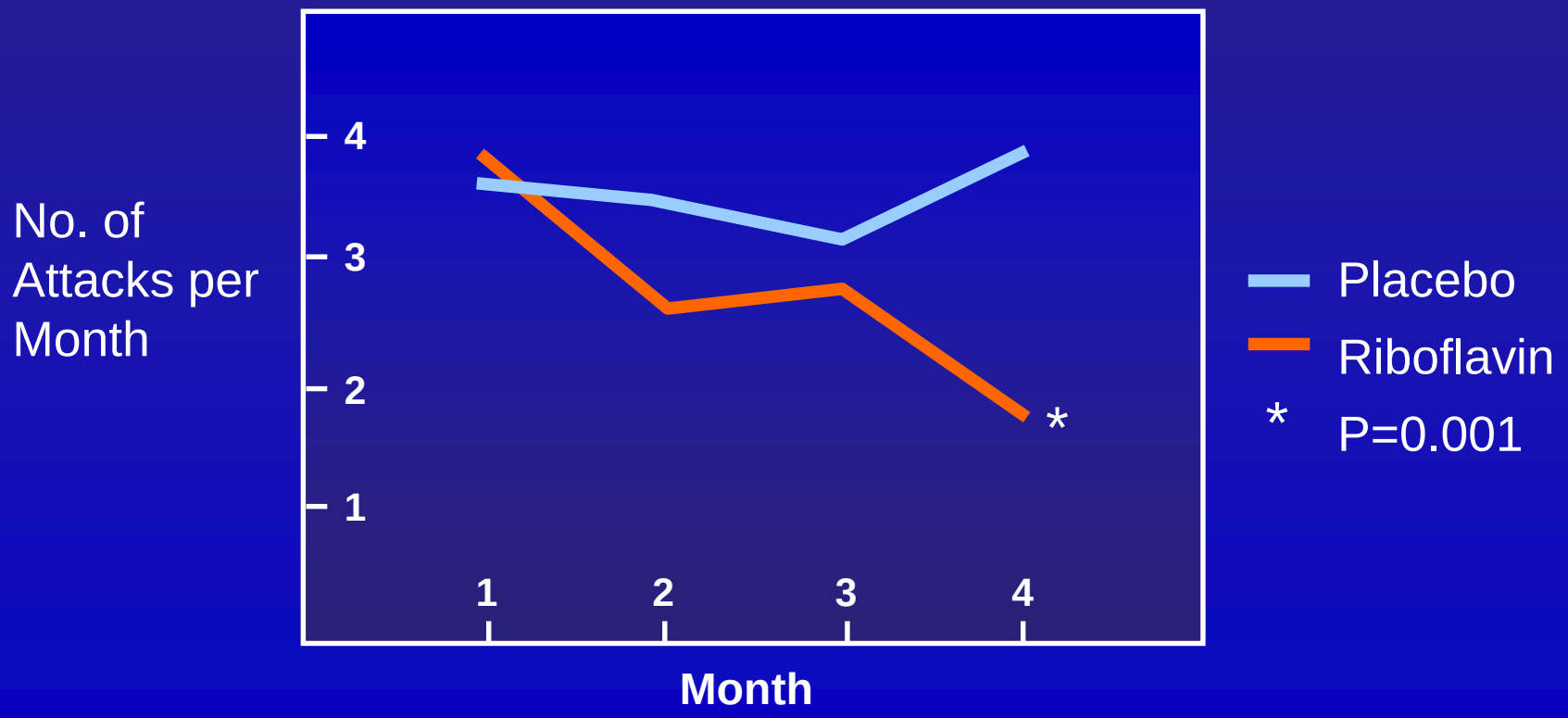
Magnesium and migraine: Practical considerations

Intravenous magnesium

- If oral magnesium is not tolerated or not absorbed
- Give 1 gram of magnesium sulfate in 10 cc's of normal saline by slow push over 5 minutes with patient in a reclined position
- Typically, infusion is repeated every month (before menstruations for menstrual migraines and/or PMS)
- More frequent infusions are sometimes needed and are safe, except in patients with renal insufficiency

Riboflavin (Level B evidence)

Effectiveness of High-dose Riboflavin in Migraine Prophylaxis



Shoenen J. et al. *Neurology* 1998; 50:466-440

Headache genetics

MTHFR gene variant C677T has been implicated as a genetic risk factor in susceptibility to migraine with aura.

C677T polymorphism reduces enzymatic capability and causes elevated homocysteine levels.

Disruption of neurovascular endothelium by elevated homocysteine levels is a possible trigger for migraine with aura. It is also a possible cause of white matter lesions and strokes seen in patients with migraine with aura.

Headache genetics

The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability

Lea R, Colson N, Quinlan S, Macmillan J, Griffiths L. *Pharmacogenet Genomics.* 2009 Jun;19(6):422-8

Daily supplementation for 6 months with 2 mg of folic acid, 25 mg vitamin B6, and 400 mcg of vitamin B12 vs placebo.

1. Homocysteine – ↓ by 39%, p=0.001
2. Prevalence of disability – ↓ from 60% to 30%, p=0.01
3. Headache frequency and pain severity ↓, p<0.05

   1 and 2 were associated with MTHFRC677T genotype

Headache genetics

MTHFR and ACE Polymorphisms Do Not Increase Susceptibility to Migraine Neither Alone Nor in Combination

Essmeister R, Kress H-G, Zierz S, Griffith L, Lea R, Wieser T. *Headache* 2016;56(8):1267–1273

It is still important to correct vitamin deficiencies and an elevated homocysteine level

Coenzyme Q_{10} (Level C evidence)

Efficacy of coenzyme Q_{10} in migraine prophylaxis: A randomized controlled trial

P. S. Sándor, et al., *Neurology* 2005;64:713-715

Double-blind, randomized, placebo-controlled trial

42 patients;

CoQ_{10} 100 mg TID vs placebo

50% responder rate for attack frequency

14.4% for placebo and 47.6% for CoQ_{10}

Coenzyme Q_{10}

Coenzyme Q_{10} 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
- CoQ_{10} 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

α-lipoic acid

A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis

Magis D et al. *Headache* 2007;47:52-57

- 44 patients: α-lipoic acid 600 mg (n=26) vs placebo (n=18)
- 50% responder rate for attack frequency – no difference
- Improved: attack frequency, p=.005, headache days, p=.009, severity, p=.03
- No adverse effects reported

Botanicals

"Your condition is serious, Mr. Reynolds, but fortunately I recently scored some excellent weed that should alleviate your symptoms."

Curcumin

Turmeric (*Curcuma*)

Photo credit: IshaPur

Curcumin

Memory and brain amyloid and tau effects of curcumin in non-demented adults: A double-blind, placebo-controlled 18-month trial. Small GW, et al. *Alzheimer's & Dementia*. 2017;13(7)Supplement:1264

40 patients, mean age 63

Curcumin, 90 mg BID vs placebo:

- Improved verbal and visual memory tests
- Curcumin prevented brain deposits of amyloid plaques and tau tangles
- AEs: stomach pain & nausea in 4 on curcumin and 2 on placebo

Curcumin

The synergistic effects of ω-3 fatty acids and nano-curcumin supplementation on tumor necrosis factor (TNF)-α gene expression and serum level in migraine patients. Abdolahi, M., et al. *Immunogenetics,* 2017; 69: 371-378

Two-month trial in 74 patients with episodic migraines

4 groups – placebo, curcumin, omega-3, and combination of omega-3 and curcumin

The combination produced:

- Reduction in TNF-α levels
- Fewer migraine attacks than in the other 3 groups

Feverfew (*Tanacetum parthenium*) (Level B evidence)

Photo credit: Natural remedies

Feverfew (*Tanacetum parthenium*)

Efficacy and safety of 6.25 mg t.i.d. feverfew CO_2-extract (MIG-99) in migraine prevention – a randomized, double-blind, multicenter, placebo-controlled study. Diener HC, et al. *Cephalalgia* 2005;25:1031-1041

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

Feverfew (*Tanacetum parthenium*)

Results (Diener H-C, et al.)

- 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 averse events (25.2% active, 26.6% – placebo)
- No effect on duration of attacks

Butterbur (*Petasites hybridus*) (Level A evidence)

Photo credit: Ntural Remedies Facts

Butterbur (*Petasites hybridus*)

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

Butterbur (*Petasites hybridus*)

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

Attack frequency reduced by:

- 48% in 150 mg group (p=0.0012)
- 36% in 100 mg group (p=0.127)
- 26% in placebo

Butterbur (*Petasites hybridus*)

Use caution with butterbur:

WebMD: "*Some butterbur products may contain pyrrolizidine alkaloids (PAs), and that's the major safety concern. PAs can damage the liver, lungs, and blood circulation, and possibly cause cancer . Butterbur products that contain PAs are* ***UNSAFE*** *when taken by mouth or applied to broken skin. Do not use butterbur products unless they are certified and labeled as free of PAs*

Pregnancy and breast-feeding: Taking butterbur by mouth is **LIKELY UNSAFE**."

Petadolex is a brand that was proven to be safe and initially approved for sale in Germany, but is no longer sold there because the manufacturer changed the extraction method and did not repeat safety studies. All forms of butterbur are banned in Switzerland and the UK

Indian frankincense
(Boswellia Serrata)

Photo credit: The Herbal Resource

Indian frankincense
(Boswellia Serrata)

Long-term efficacy of Boswellia serrata in four patients with chronic cluster headache. Lampl C, et al. *Cephalalgia* 2012;32(9):719-22

The Efficacy of Gliacin, a Derivative of Boswellia Serrata Extract, on Indomethacin Responsive Headache Syndromes. Eross E. Presented at the Annual AHS Meeting, 2011
Gliacin relieved indomethacin-responsive headaches in 21 of 27 patients

A case of Hemicrania Continua Responsive to Gliacin. Karashi J, et al. Presented at the 59th Annual AHS Meeting. Boston, 2017

Headache Bush
(*Capparis cynophallophora*)

Many herbals have no evidence at all

Marijuana *(Cannabis sativa, Cannabis indica)*

Photo credit: Foothill Wellness

Marijuana *(Cannabis sativa, Cannabis indica)*

Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: relation with serotonin levels Rossi C., et al. *Eur J Clin Pharmacol* 2008;64:1-8

- Level of two main endocannabinoids, 2-acylglycerol (2-AG) and anandamide (AEA) were significantly lower in MOH patients (n=20) and CM patients (n=20) than in the control subjects (n=20), without significant differences between the two patient groups
- Serotonin levels were also strongly reduced in the two patient groups and were correlated with 2-AG levels

Marijuana *(Cannabis sativa, Cannabis indica)*

Anti-migraine effect of Δ^9-tetrahydrocannabinol in the female rat

Kandasamy R, et al. *Eur J Pharmacol* 2018; 818:271-277

- THC reduces migraine-like pain when induced by AITC
- THC's anti-migraine effect is mediated by CB_1 receptors
- Wheel running is an effective method to assess migraine treatments because only treatments producing antinociception without disruptive side effects will restore normal activity
- These findings support anecdotal evidence for the use of cannabinoids as a treatment for migraine in humans and implicate the CB_1 receptor as a therapeutic target for migraine

THC - Δ^9-tetrahydrocannabinol, AITC - allyl isothiocyanate (TRPA1 agonist)

Marijuana *(Cannabis sativa, Cannabis indica)*

Endocannabinoids in Chronic Migraine: CSF Findings Suggest a System Failure

Sarchielli P, et al. *Neuropsychopharmacology*, 2007;32:1384–1390

- Reduced levels of anandamide (AEA) in the CSF of CM patients may reflect an impairment of the endocannabinoid system, which may contribute to chronic head pain and seem to be related to increased CGRP and NO production

Marijuana *(Cannabis sativa, Cannabis indica)*

Anandamide Is Able to Inhibit Trigeminal Neurons Using an in Vivo Model of Trigeminovascular-Mediated Nociception Akerman S, et al. *J Pharmacol Exp Ther* 2004:309 (1):56-63

Anandamide or the CB_1 receptor site represents a potential therapeutic target for migraine, given anandamide's ability to attenuate neurogenic, CGRP, and NO-induced dural vessel dilation

Marijuana *(Cannabis sativa, Cannabis indica)*

Cluster Attacks Responsive to Recreational Cannabis and Dronabinol

Robbins MS, et al. *Headache* 2009; 49(6):914–916

- A patient with cluster headaches refractory to multiple acute and preventive medications but attacks successfully aborted with recreational marijuana and subsequently with dronabinol
- The beneficial effect may be related to the high concentration of cannabinoid receptors in the hypothalamus, which has been implicated as a site of dysfunction in neuroimaging studies of patients with cluster headache.

Marijuana *(Cannabis sativa, Cannabis indica)*

Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population

Rhyne DN, et al. *Pharmacotherapy*, 2016;36(5):505–510

- Review of 121 migraine patients who were prescribed medical marijuana
- Migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($p<0.0001$)
- Most patients used more than one form of marijuana & used it daily for prevention
- Positive effects reported by 48 patients (40%),
- Decreased frequency (24, or 20%) and aborted migraine headache (14 or 12%).
- Inhaled marijuana was mostly used for acute migraine treatment.
- Negative effects were more common with edible marijuana: 14 patients (12%) had somnolence and difficulty controlling the effects of marijuana related to timing and intensity of the dose

Peppermint
(*Mentha piperita*)

Photo credit: NCCIH

Peppermint
(*Mentha piperita*)

Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters

Göbel H, Schmidt G, Soyka D. *Cephalagia* 1994;14:228-34

- Double-blind, placebo-controlled, randomized cross-over design
- 32 healthy subjects
- Parameters tested:
  - EMG activity
  - Exteroceptive suppression periods
  - Contingent negative variation
  - Sensitivity to experimental pain
  - Current mood states

Peppermint
(*Mentha piperita*)

Combination of Peppermint Oil and Ethanol

(Göbel H, et al. *Cephalagia* 1994;14:228-34)

- Analgesic effect
- Muscle relaxing effect
- Mentally relaxing effect

Peppermint
(*Mentha piperita*)

Combination of Peppermint and Lavender essential oils

Acupuncture

Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. Melchart D, Linde K, Fischer P, et al. *Cephalalgia* 1999;19:779-786.

Majority of 14 trials comparing true and sham acupuncture showed at least a trend in favor of true acupuncture

Acupuncture

Acupuncture in patients with headache

Jena S, et al. *Cephalalgia* 2008;28(9):969-979

15,056 patients with migraine and tension-type headaches randomized to receive over three months either:

- conventional treatment (1,569) or
- conventional treatment plus up to 15 acupuncture treatments (1,613)
- 11,874 refused to be randomized, received acupuncture and were placed into a third group

Acupuncture

Acupuncture in patients with headache

Jena S, et al. *Cephalalgia* 2008;28(9):969-979

Significant difference in QOL and in headache days per month:

- two acupuncture groups – drop from 8.4 to 4.7 days
- control group – 8.1 to 7.5 days
- Improvement persisted for subsequent 3 months

Acupuncture

Acupuncture for the treatment of headaches: more than sticking needles into humans?

H-C Diener *Cephalalgia* 2008;28:911-913

…acupuncture is as effective as drug therapy, but …sham acupuncture is as effective as 'real' acupuncture.

…acupuncture should be offered to patients who do not respond to prophylactic treatment with drugs, terminate drug treatment because of AEs or have contraindications to drug treatment

Acupuncture

Acupuncture for migraine prophylaxis: a randomized controlled trial. Li Y, et al. *CMAJ* 2011. DOI:10.1503/cmaj.110551

480 patients; 20 treatments over 4 weeks; 3 treatment groups with various types of acupuncture and 1 sham acupuncture group

In all 3 true treatment groups there was significant reduction of days with migraine compared to sham acupuncture for 12 weeks following the treatment

Music therapy

Both happy and sad melodies modulate tonic human heat pain. Zhao H, Chen ACN. *The Journal of Pain.* 2009;10:953-960

20 volunteers subjected to: baseline pain tolerance, pleasant sad music, pleasant happy music and, a lecture

Both happy and sad music resulted in significantly lower pain ratings.

Music therapy

Emotional valence contributes to music-induced analgesia. Roy M, Peretz I, Rainville P. *Pain.* 2008;134:140-147

18 volunteers subjected to pleasant music, unpleasant music and silent period;

thermally-induced pain was reduced only by pleasant music

Music therapy

Butterbur root extract and music therapy in the prevention of childhood migraine: An explorative study

Oelkers-Ax R, Leins A, Parzer P, et al. *European Journal of Pain*. 2008;12(3):301-313

Butterbur (n=19) and music (n=20) groups did better than placebo (n=19) at 6 months follow-up. Only music group did better immediately after 12-week treatment period

CAM for headaches

What to recommend:

- aerobic exercise, neck exercise, weight training
- meditation / biofeedback
- yoga / Tai Chi / Feldenkrais / Alexander
- magnesium, CoQ_{10}
- riboflavin, feverfew, boswellia, butterbur
- methylfolate, cyanocobalamine, vitamin D, omega-3
- acupuncture, massage, reflexology, aromatherapy

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