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# Financial Disclosures

Speakers Bureau: Amgen, Teva, Eli Lilly

When is imaging indicated in the evaluation of headache and what is the imaging study of choice?

# Imaging in Headache

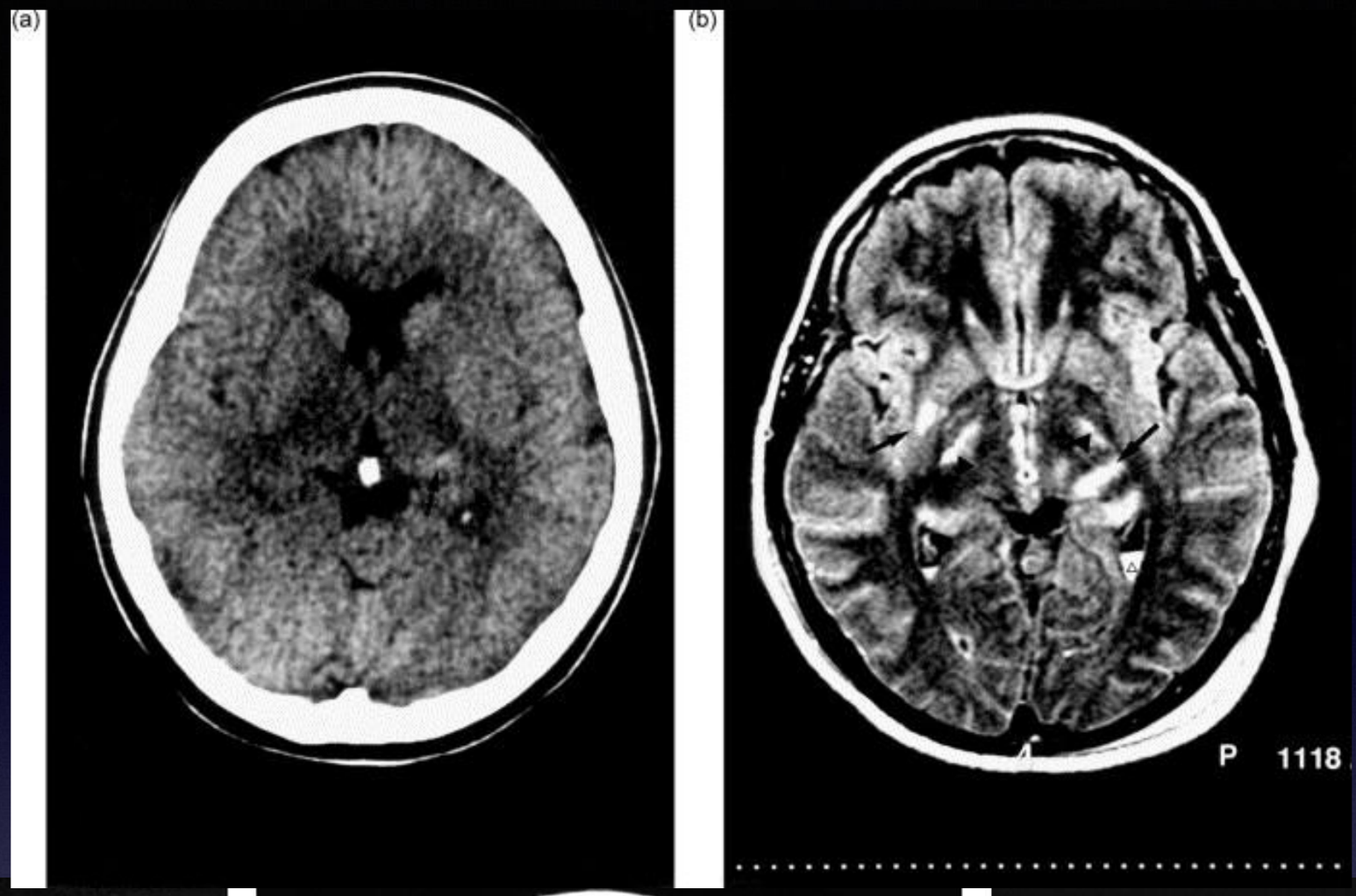
*Most patients do not need imaging*

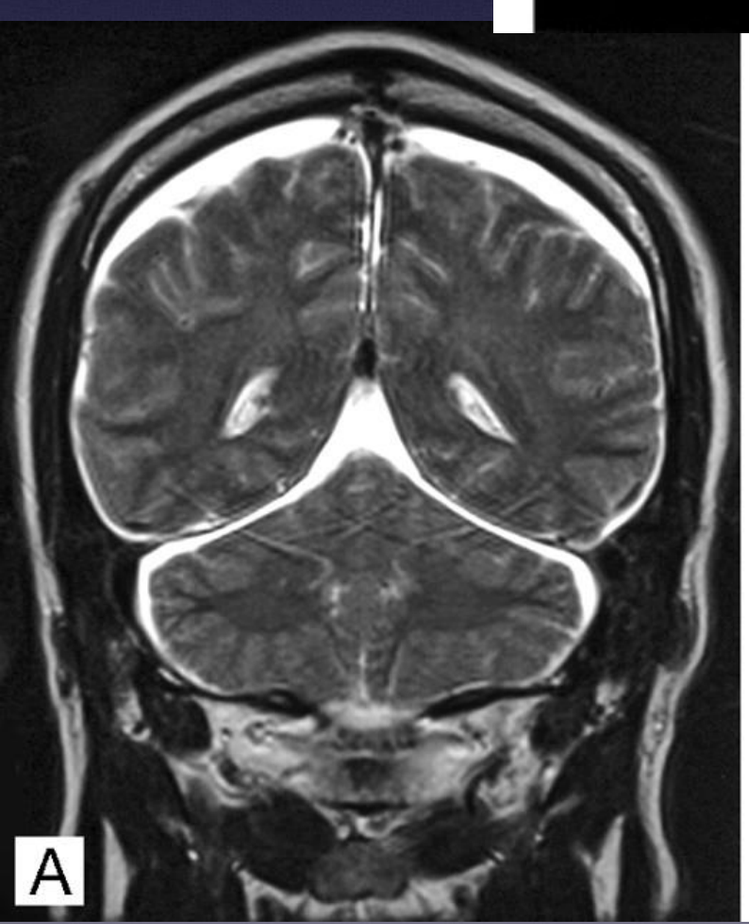
- Thunderclap / worst headache of my life
- New headaches in someone over 50
- Change in headache character / pattern
- Headache with exertion (sex, exercise)
- Onset with fever or illness
- Complicated features (weakness, numbness, change in speech, tinnitus, incoordination)

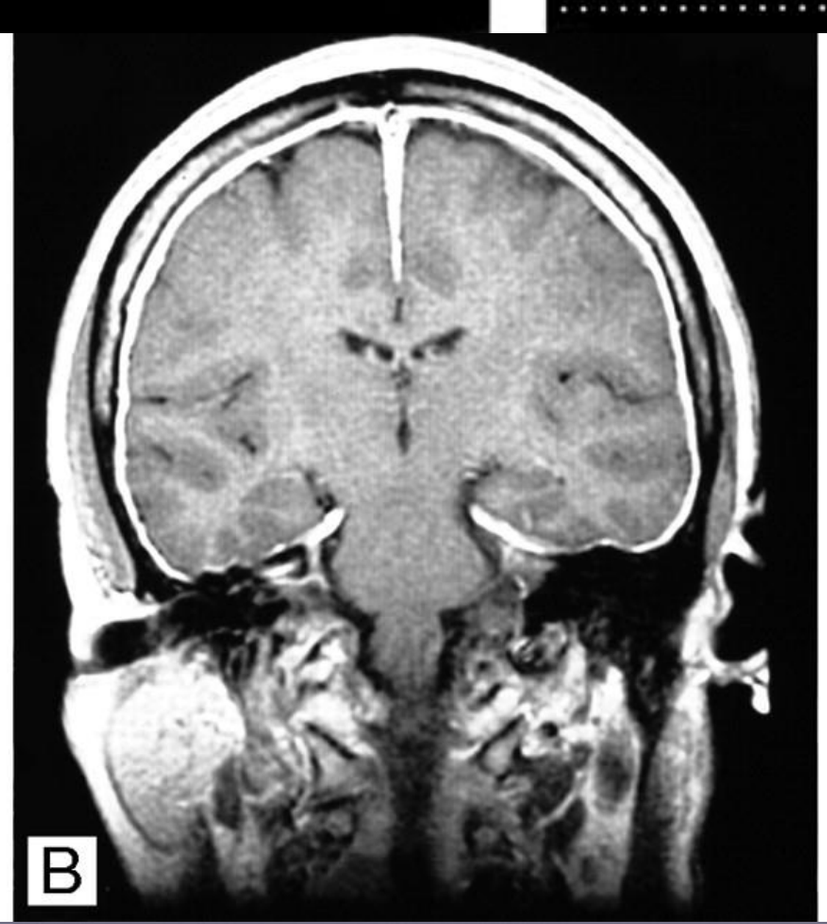
*American Academy of Neurology guidelines 2014*

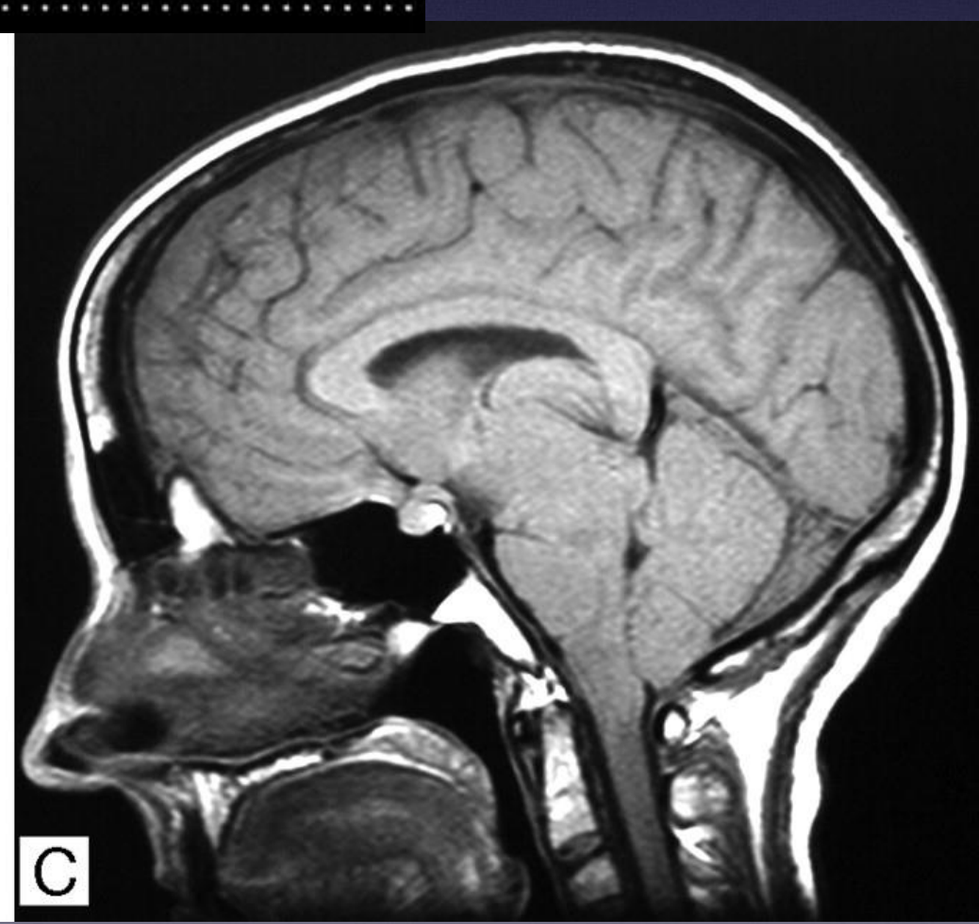
CT

MRI



# CT vs MRI

- CT better for bone or blood, quick, easy
- MRI better for subtle parenchymal changes, I almost always order with and without contrast
- CTA better than MRA for posterior circulation
- MRV may be helpful in some cases
- 4V angiogram is only modality that can identify vascular anomalies smaller than 3mm

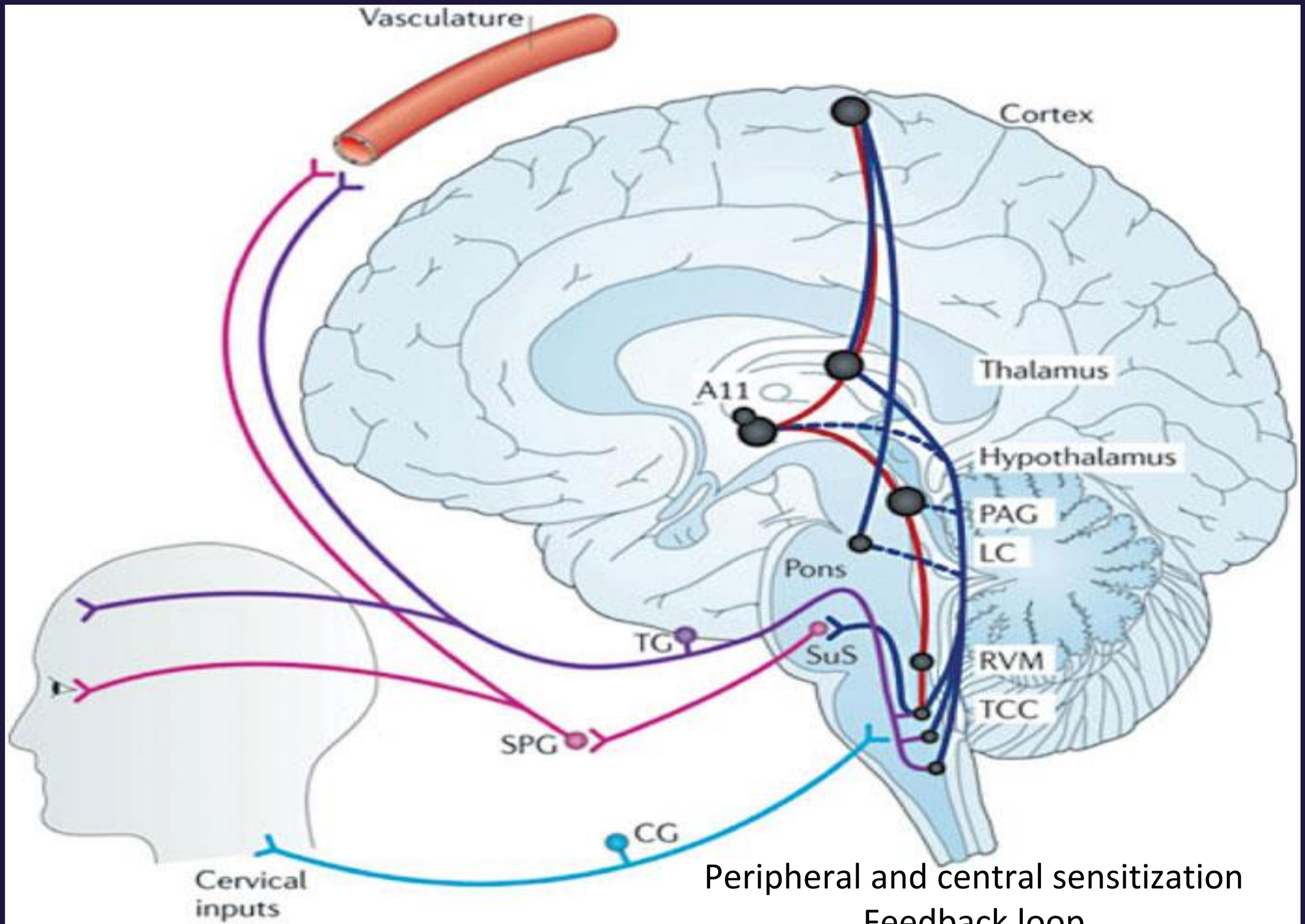
*Practical Neurology 2018; 18 347-347 Published Online First: 17 Sep 2018*

What is the best initial treatment and when should prophylactic treatment be considered for treatment of migraines?

# Pathophysiology of Migraine = Trigemino-Vascular Theory

- Walls of large cerebral arteries, meningeal arteries, & venous sinuses are innervated by trigeminal nerve sensory fibers (nociceptive)
- Trigeminal projections are activated and release vasoactive neuropeptides including CGRP,  substance P, neurokinin A
- Neurons activated in the TNC and upper cervical spinal cord
- Synapse in thalamus which modulates cortical afferents
- Project to somatosensory, visual, and diffuse areas of the cortex
- Sensitization of the brainstem trigemino-cervical complex

*Goadsby et al. Pysiol Rev 2017;  97: 553-622*




Peripheral and central sensitization
Feedback loop

*Pietrobon, Daniela & Striessnig, Jörg. (2003). Neurobiology of migraine. Nat Rev Neurosci. Nature reviews. Neuroscience. 4. 386-98. 10.1038/nrn1102.*

# How I approach headache management

- Set expectations up front
- Patience: 6 weeks to see a change
- Trial and error
- Balance benefits with side effects
- Tailor each treatment plan to the individual

# Preventative Treatment

- More than 6 headache days per month or 4 with disability such as requiring bed rest
- AMPP study demonstrated significant impact of migraine on not only the patient but the family
- Goals are to reduce the number of events as well as the severity
- Benefit of reduced need for abortive meds
- Anti-depressants, anti-hypertensives, anti-epileptics
- Onabotulinum toxin
- CGRP antagonism
- Neuromodulation

Headache. 2016 Sep;56(8):1280-9. doi: 10.1111/head.12878. Epub 2016 Jun 28.

**A Comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study and American Migraine Prevalence and Prevention (AMPP) Study: Demographics and Headache-Related Disability.**

Lipton RB[1,2], Manack Adams A[3], Buse DC[4,5], Fanning KM[6], Reed ML[6].

# Migraine Prophylaxis

## What the evidence shows…

### Table 1. Classification of Pharmacologic Agents for Migraine Prophylaxis

| Level A[a] | Level B[b] | Level C[c] | Level U[d] | Other[e] |
|---|---|---|---|---|
| Divalproex sodium, sodium valproate, topiramate (AEDs); metoprolol, timolol, propranolol, (BBs); frovatriptan (triptan) (for prevention of MAM) | Amitriptyline, venlafaxine (antidepressants); atenolol, nadolol (BBs); naratriptan, zolmitriptan (triptans) | Lisinopril (ACE inhibitor); candesartan (ARB); clonidine, guanfacine (alpha agonists); carbamazepine (AED); nebivolol, pindolol (BBs) | Gabapentin (AED); fluoxetine, fluvoxamine, protriptyline (antidepressants); picotamide, warfarin, acenocoumarol, (antithrombotics); bisoprolol (BB); nicardipine, nifedipine, nimodipine, verapamil (CCBs); acetazolamide (CAI); cyclandelate (vasodilator) | Lamotrigine (AED); clomipramine (antidepressant); acebutolol; clonazepam; nabumetone; oxcarbazepine; telmisartan |

*[a] Established efficacy (>2 class I trials).*
*[b] Probably effective (1 class I/2 class II trials).*
*[c] Possibly effective (1 class II trial).*
*[d] Inadequate/conflicting data supporting/refuting use.*
*[e] Possibly/probably ineffective.*
*AED: antiepileptic drug; ARB: angiotensin receptor blocker; BB: beta-blocker; CAI: carbonic anhydrase inhibitor; CCB: calcium channel blocker; MAM: menstrually associated migraine.*
*Source: References 2, 3.*

Silberstein S, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345

# Who progresses from episodic to chronic migraine?

<u>Non-Modifiable</u>

- Genetics
- Age
- Race

<u>Modifiable Factors</u>

- Medication overuse
- Stress
- Sleep disturbance
- Obesity
- Caffeine

*<u>Headache.</u> 2011 Jul-Aug;51 Suppl 2:77-83. doi: 10.1111/j.1526-4610.2011.01954*

# What does the evidence report as the best options for management of chronic headaches?

# Migraine Prophylaxis

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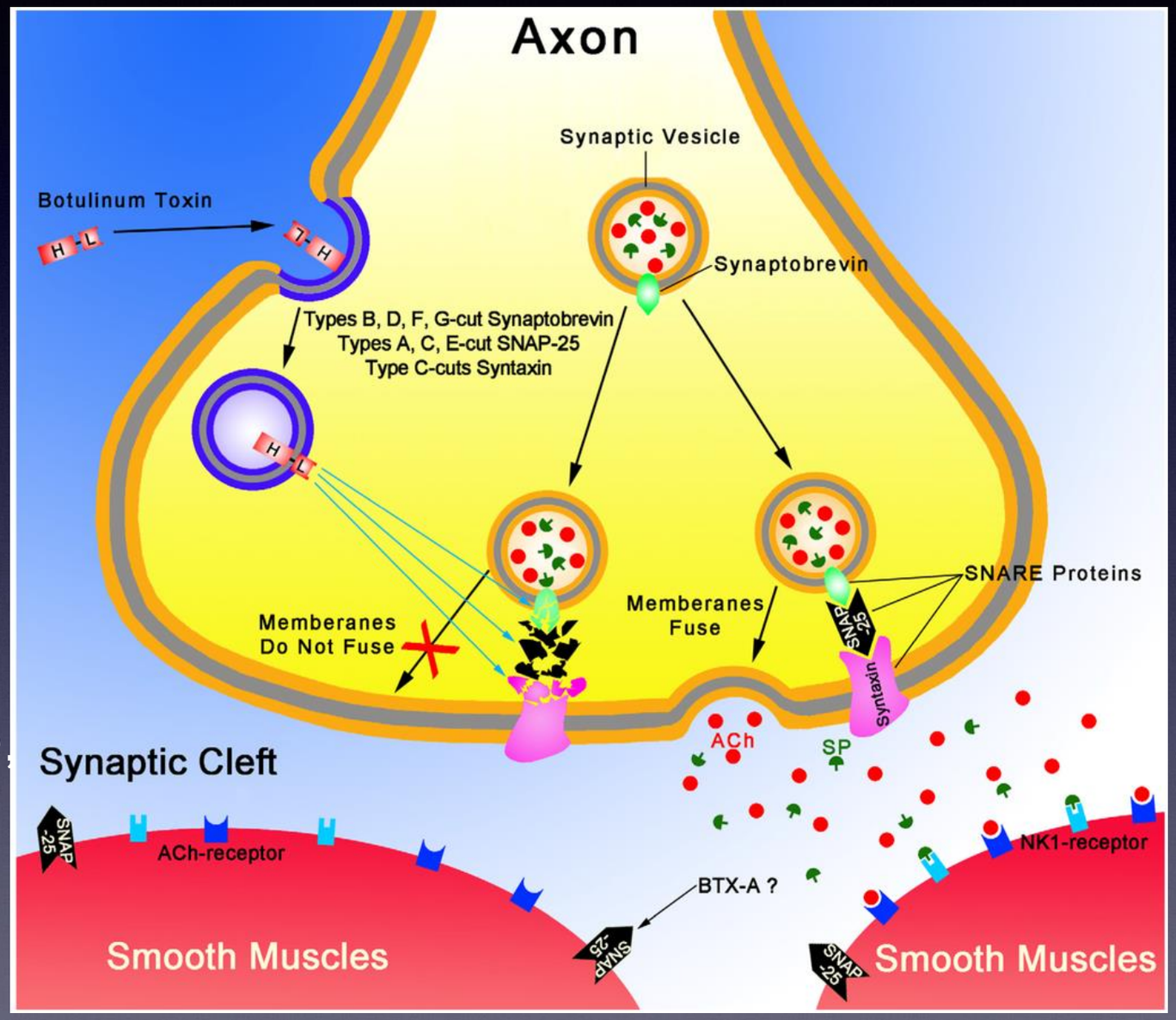
# Onabotulinum Toxin: Chemodenervation

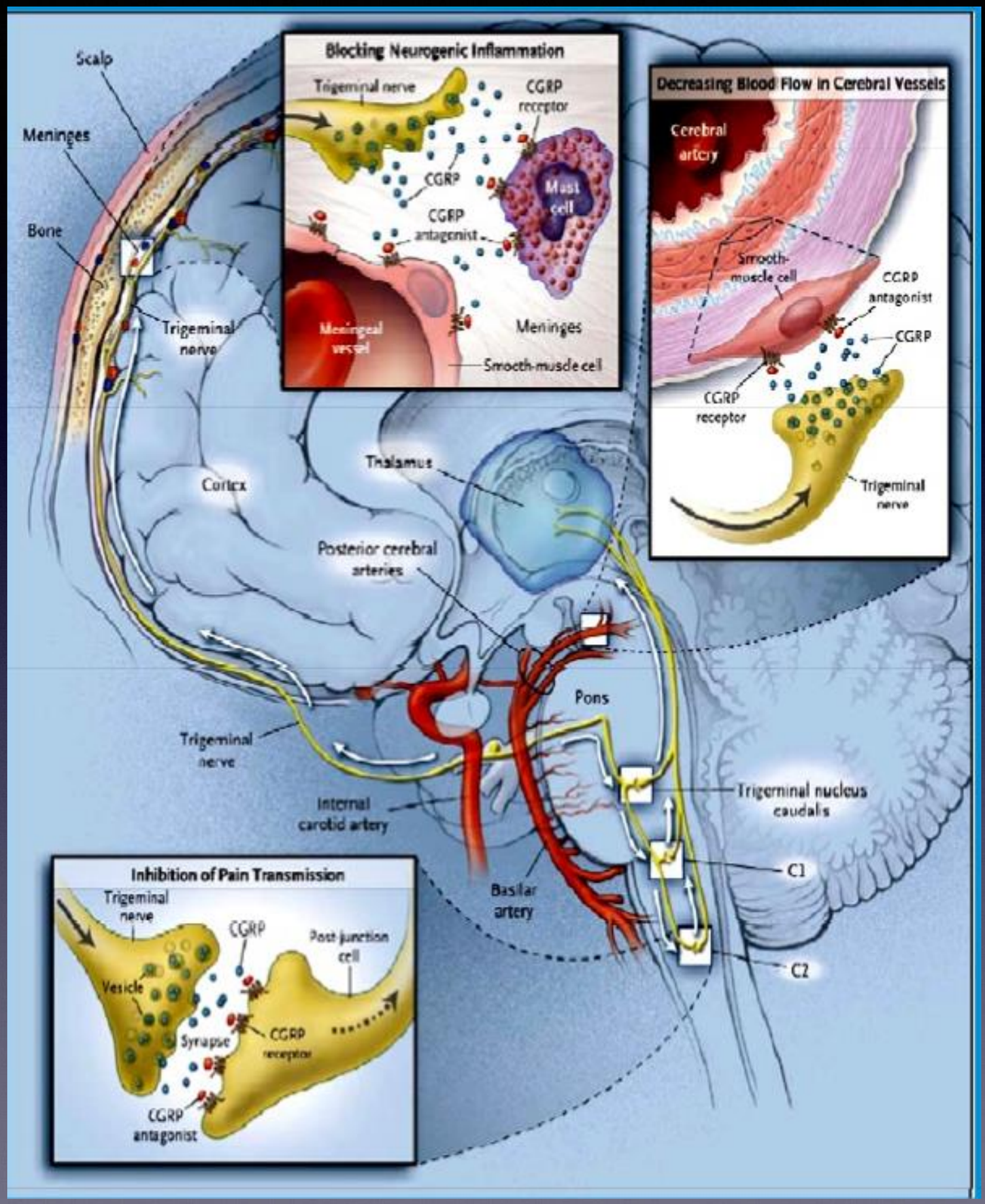
- 30 years of safety data
- 31 injections every 12 weeks
- Inhibits release of pain mediators thereby decreasing peripheral / central sensitization
- Efficacy improves over time
- FDA approved for chronic migraine, 15 or more headache days
- AE: allergy, neck pain, drooping eyelid




Ramachandran R, Yaksh TL. Therapeutic use of botulinum toxin in migraine: mechanisms of action. *Br J Pharmacol*. 2014;171(18):4177-92.

# New Target:CGRP

- Increased in CSF in migraine
- CGRP levels are normalized by triptans
- CGRP infusion triggers migraines
- It is the most abundant neuropeptide expressed in the trigeminal pathways. It is found in 35-50% of trigeminal neurons
- Implicated in vasodilation, nociception and mast cell degranulation



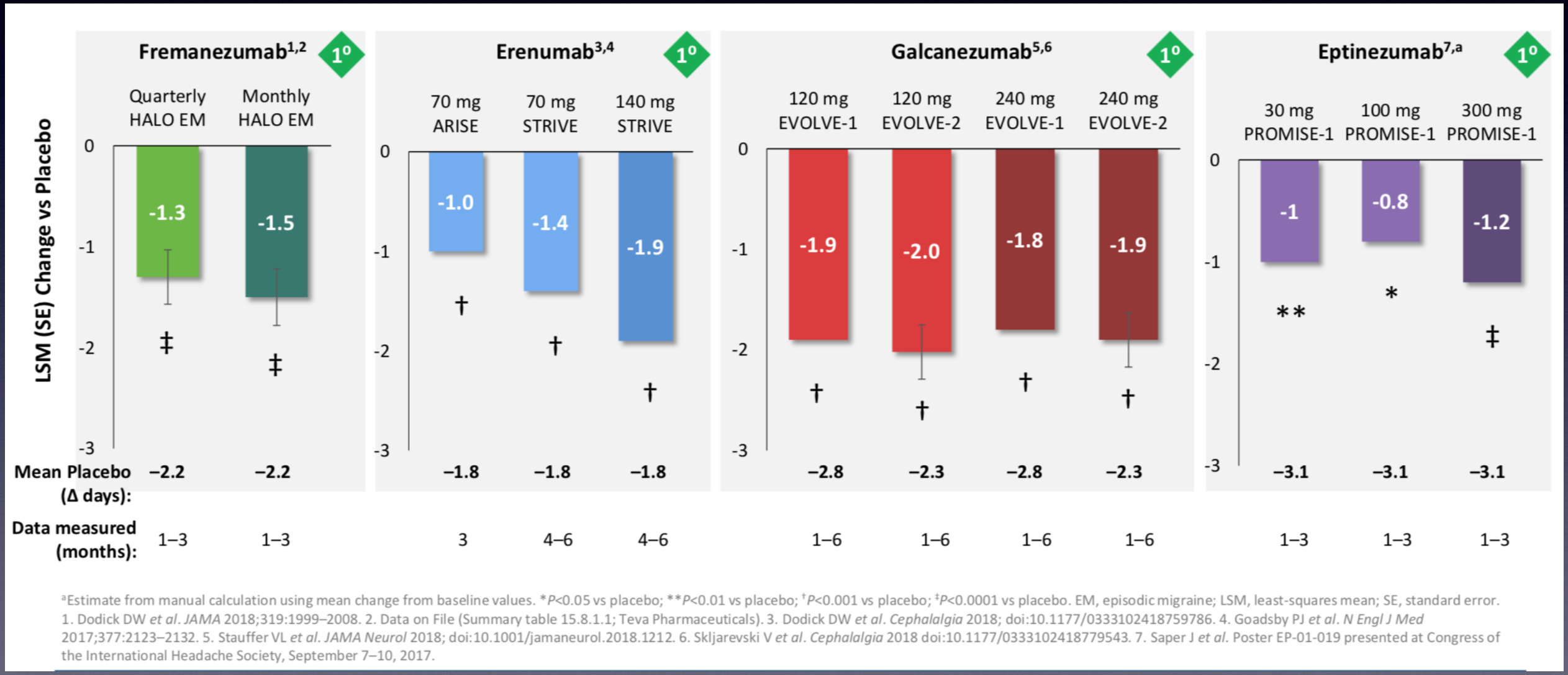


**Gadsby PJ, et al. Ann Neurol. 1988; 23 (2): 193-196**
**Lassen LH, et al. Cephalalgia 2002; 22 (1): 54-61**
**Juhasz G, metal. Cephalalgia 2005; 25 (3): 179-183**
**Cernuda et al, Neurology 2013; 81:1191-1196)**

# CGRP Monoclonal Antibodies

| | Erenumab | Fremanezumab | Galcanezumab | Eptinezumab |
|---|---|---|---|---|
| **Route of Administration** | Subcutaneous injection | Subcutaneous injection | Subcutaneous injection | Subcutaneous or intravenous |
| **Dosing** | Monthly | Monthly or quarterly | Monthly | Quarterly |
| **Half Life** | 28 days | 31 days | 27 days | ~32 days |
| **Human Sequences** | Human (100% human) | Fully Humanized (>95% human) | Humanized (>90% human) | Humanized (>90% human) |
| **Target** | CGRP receptor | CGRP ligand | CGRP ligand | CGRP ligand |
| **IgG subtype** | IgG2 | IgG2 | IgG4 | IgG1 |

# Comparison of Anti-CGRP Monoclonal Antibodies




[a]Estimate from manual calculation using mean change from baseline values. *$P$<0.05 vs placebo; **$P$<0.01 vs placebo; †$P$<0.001 vs placebo; ‡$P$<0.0001 vs placebo. EM, episodic migraine; LSM, least-squares mean; SE, standard error.

1. Dodick DW *et al*. *JAMA* 2018;319:1999–2008. 2. Data on File (Summary table 15.8.1.1; Teva Pharmaceuticals). 3. Dodick DW *et al*. *Cephalalgia* 2018; doi:10.1177/0333102418759786. 4. Goadsby PJ *et al*. *N Engl J Med* 2017;377:2123–2132. 5. Stauffer VL *et al*. *JAMA Neurol* 2018; doi:10.1001/jamaneurol.2018.1212. 6. Skljarevski V *et al*. *Cephalalgia* 2018 doi:10.1177/0333102418779543. 7. Saper J *et al*. Poster EP-01-019 presented at Congress of the International Headache Society, September 7–10, 2017.

# Neuromodulation

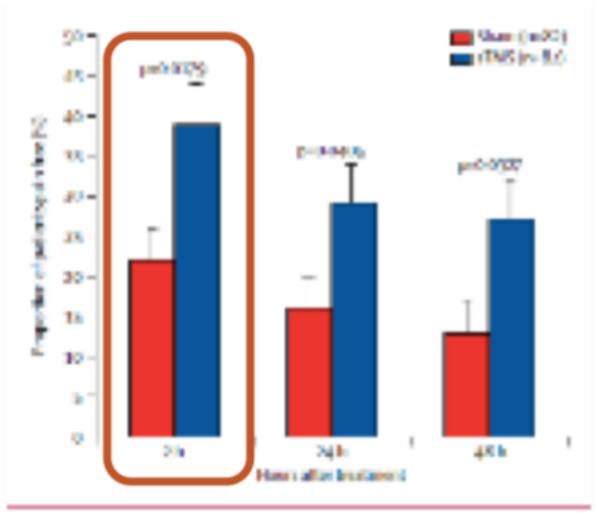
- Transcranial Magnetic Stimulation
- External Trigeminal Nerve Stimulation
- Noninvasive Vagal Nerve Stimulation
- Sphenopalantine Ganglion Stimulation
- Occipital Nerve Stimulation
- Caloric Vestibular Stimulation, DBS

# Transcranial Magnetic Stimulation

How does it work?

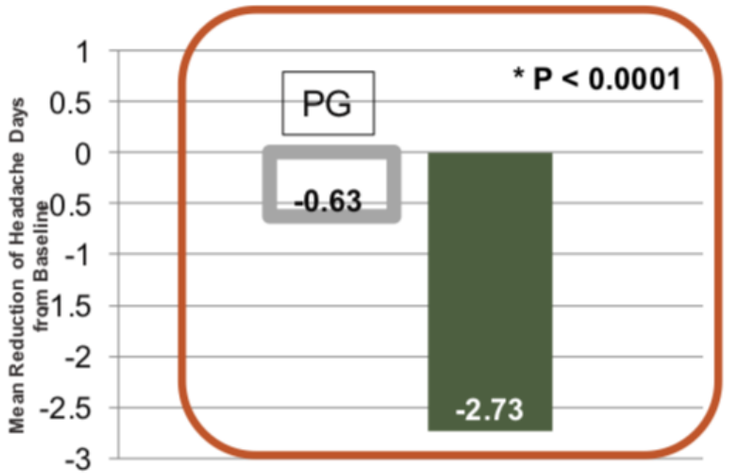
- Inhibits CSD, modulates thalamo-cortical signaling

- Acute treatment of migraine
  - **RCT**, N=164 (82 in each group)
  - Migraine with aura
  - Pain freedom at 2h
    - 39% vs 22%



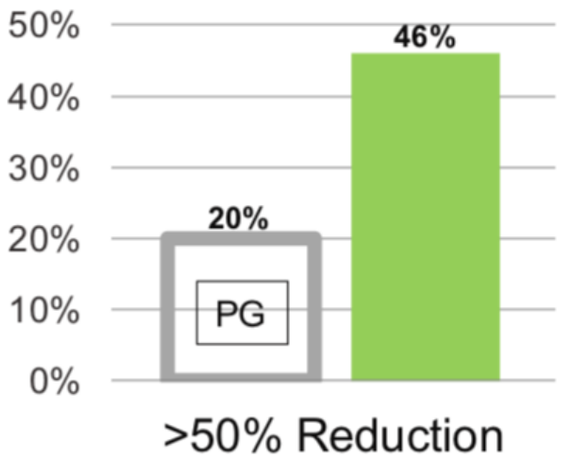
Lipton *et al., Lancet Neurol* 2010;9:373-80

- Preventive treatment of migraine




- **Open label,** N=132
- Mostly EM, BL = 9 days
- Performance goal (PG) = statistically-derived estimate of placebo effect

- Reduction in headache days
- Reduction in disability
- Reduction in acute medication use



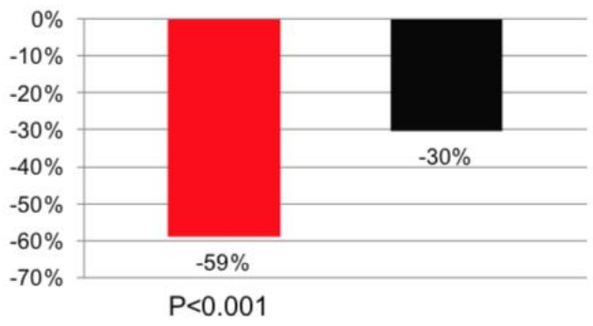

Starling et al., Cephalalgia 2018

# External Trigeminal Nerve Stimulation


- Transcutaneous targets supraorbital and supratrochlear nerves > trigeminal nerve
- Goal of normalization of trigeminal pain modulation
- Central effects: FDG-PET normalization of fronto-temporal hypometabolism

- Acute treatment of migraine
  - **RCT, N=106**
  - EM and CM
  - Intervention: **1h eTNS session**
  - Primary endpoint

Mean change in pain score at 1h




  - **Survey study**

15% *I cannot bear the feeling during an attack*

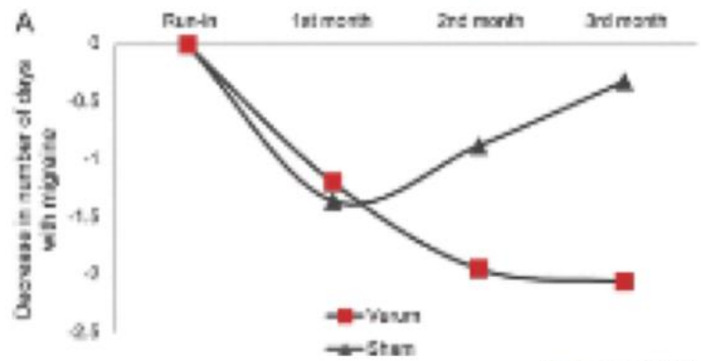
49% *It does not provide sufficient relief*

Chou et al., Proceedings of the IHC of the HIS, Vancouver, BC, Canada. HIS;2017

Penning et al., ActaNeurol Belg 2017 117(2):547-549

- Preventive treatment of migraine
  - **RCT**, N=67, episodic migraine
  - Intervention: 20min daily x 3 months
  - Primary outcome measure

1) Change in monthly migraine days
   -2.1 v 0.3, p=0.054 ← did NOT meet endpoint
2) 50% responder rate
   38.2% v 12.1%, p=0.02



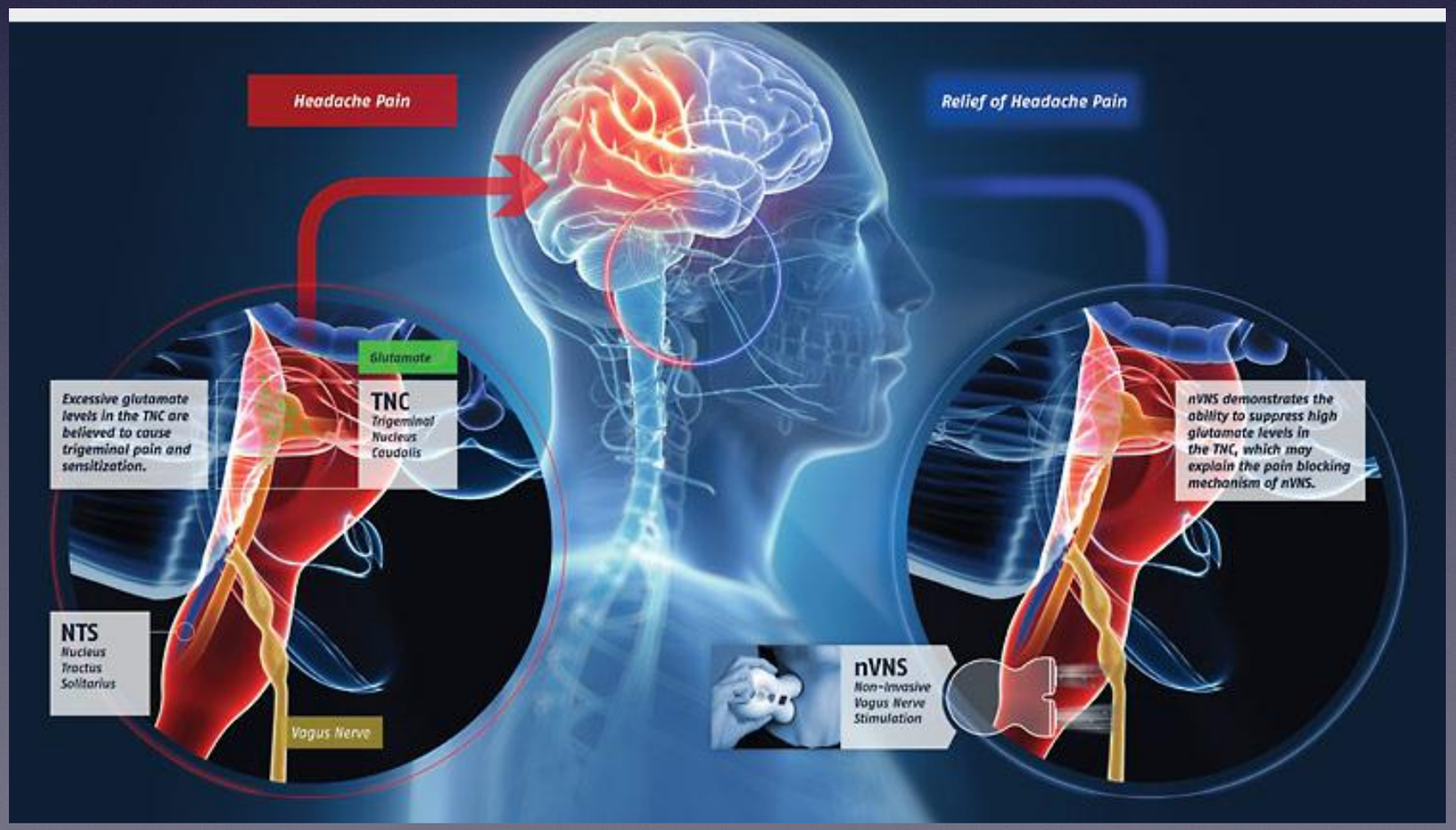

Schoenen et al., Neurology 2013;80:697-704

**Schoenen et al. Neurology 2013;80;697-704**
**Tepper D. Headache 2014;54:1415-6**

# Vagus Nerve Stimulator

- Only FDA approved device for cluster headaches
- Reduction in cortical spreading depression
- Reduce glutamate in the trigeminal nucleus
- Bilateral inhibitory effect, used abortively / preventatively
- Up to 40% receive 50% reduction in attacks
- AE: burning / tingling soreness / stinging at application site, lip or facial pulling
- Not studied with pacemaker, hearing aid, cardiovascular disease, pregnancy

de Coo IF, Marin J, Silberstein SD, et al. Non-invasive vagus nerve stimulation (nVNS): acute treatment of episodic and chronic cluster headache: pooled analysis of ACT1 and ACT2 studies



# Thank you for your attention!

## Any Questions?