Migraine and Other Headaches

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Disclosures

- Consultant / Advisor
  - Amgen
  - Biohaven
  - Dolor Technologies
  - Eli Lilly
  - Lundbeck
  - Promius
  - Teva
  - Theranica

Learning Objectives

- 1. Become familiar with the newer treatment options for migraine and other headache syndromes.
- 2. Enhance knowledge of currently available devices for treatment of refractory headache
- 3. Become aware of interventional treatments for chronic headache including peripheral nerve blocks and appropriate use of botulinum toxin therapy

What is More Common?

Chronic Pain

Diabetes

Heart Disease

Cancer

People are very understanding
But not always….

"Can I sign your cast?"
"Let me help you with that"

"What is wrong with you?"
"We need you to get back to work"

How you help will make a lasting impression

Migraine Anatomy

Meningeal Nerves

- Innervate the lining of the brain (meninges)
- First branches of the trigeminal nerves
- V2 branch is middle meningeal nerve

Trigeminal Nerves

- Innervate the face and scalp
- Transmit pain from the meninges to the brain

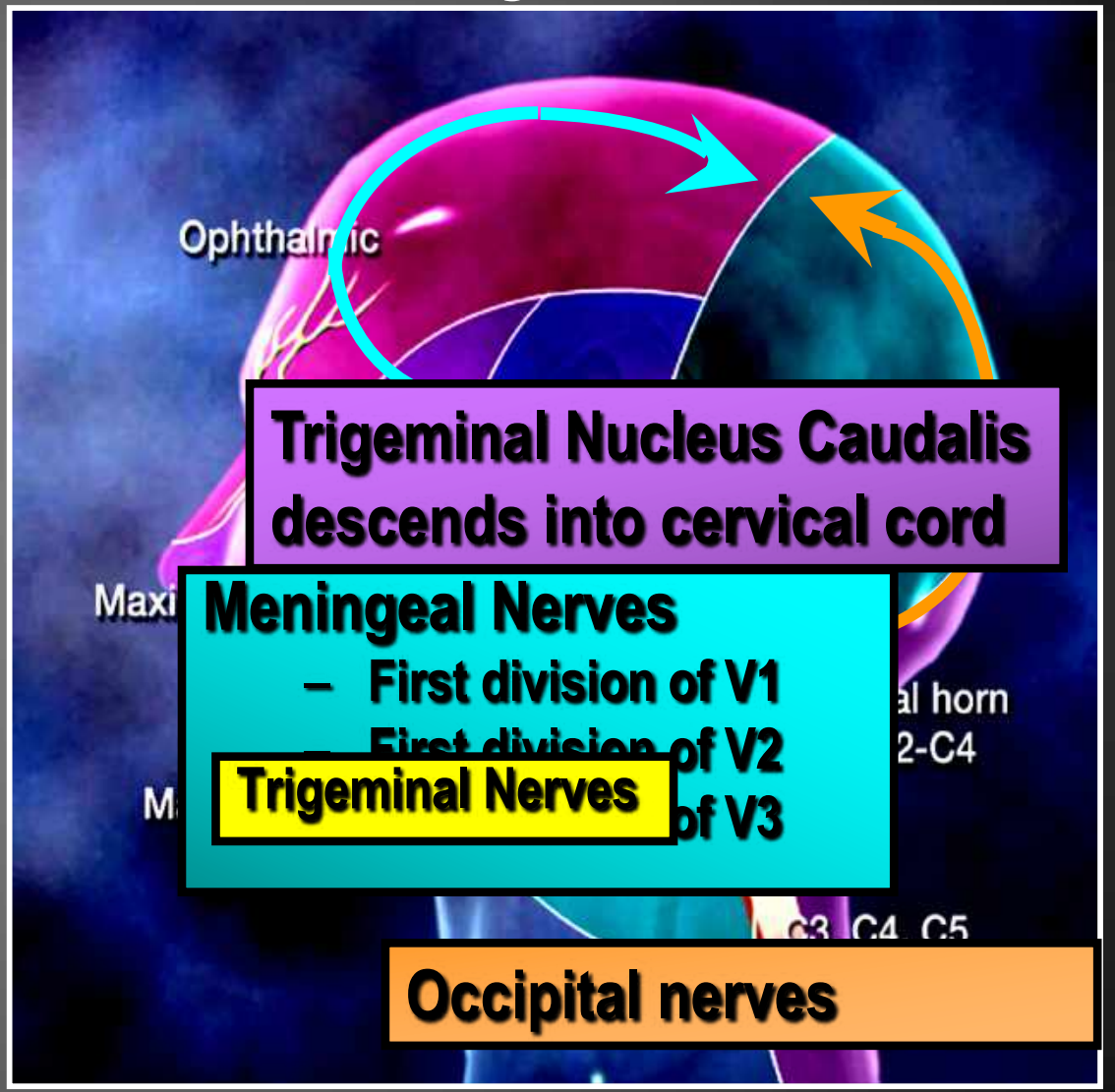
Trigeminal Nucleus Caudalis

Trigeminal signals enter brain stem

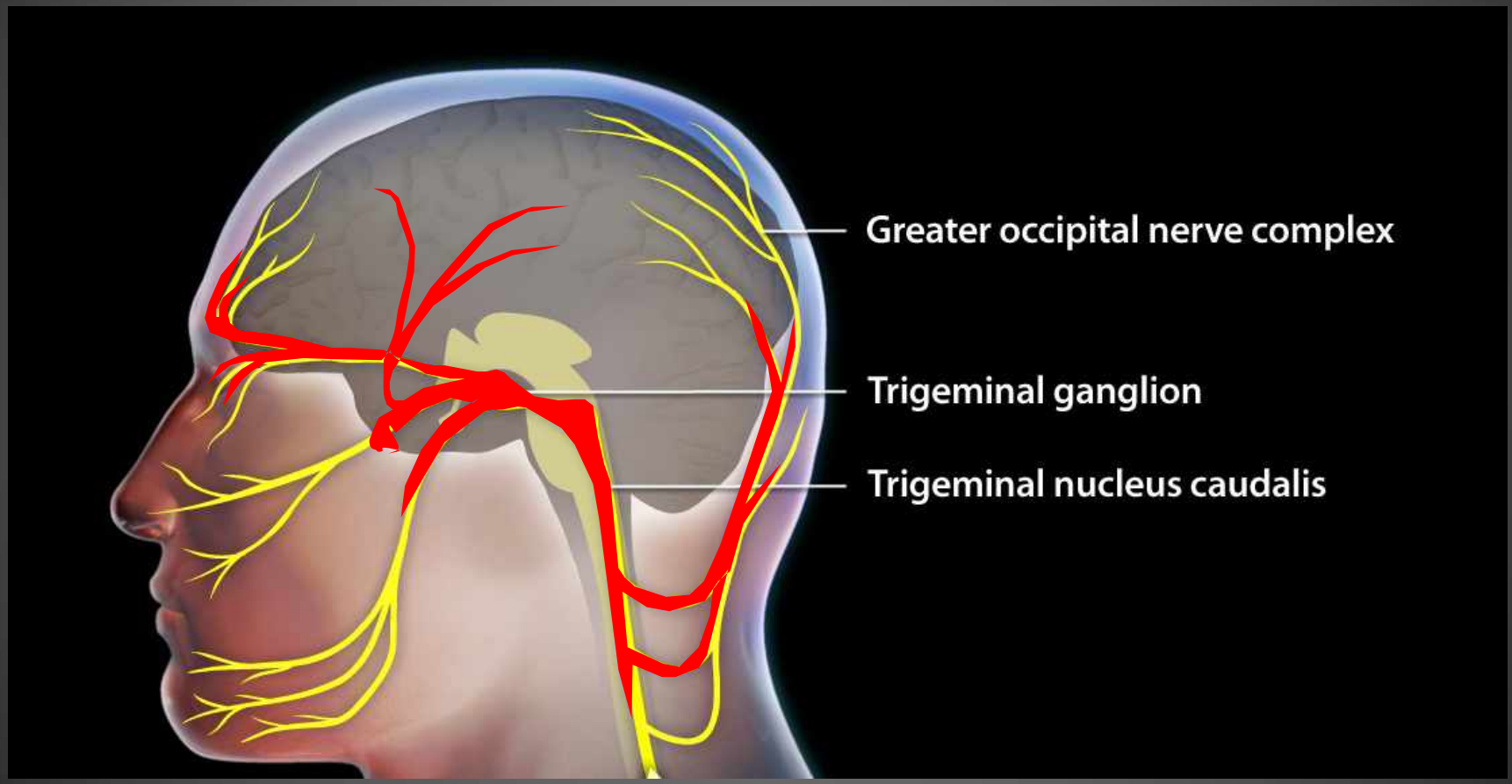
- Descend to the high cervical regions
- Ascend to pain processing regions of the brain

Occipital Nerves

- Innervate occipital scalp
- Contribute to trigeminal nucleus caudalis

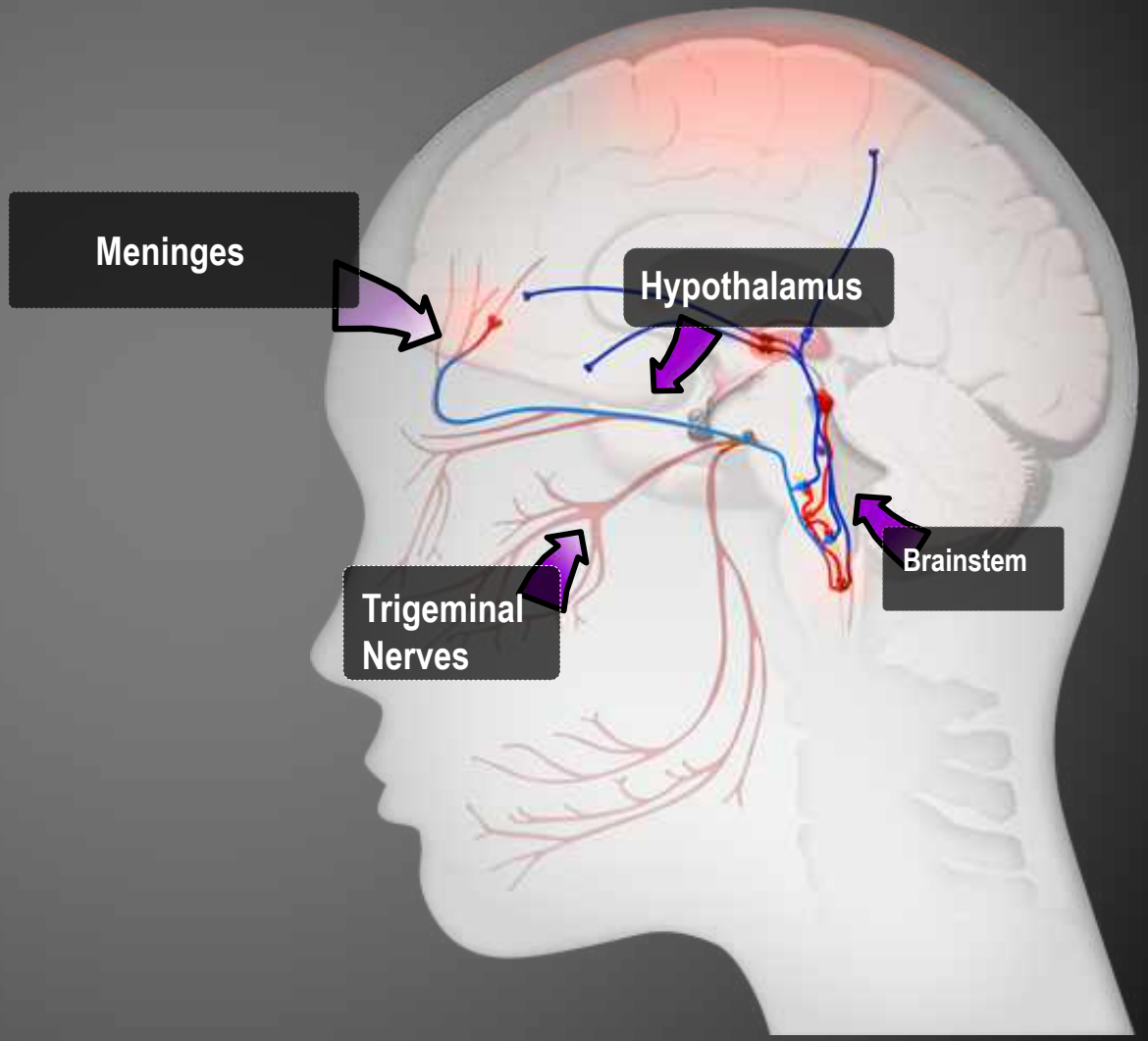


Trigeminal Nucleas Caudalis



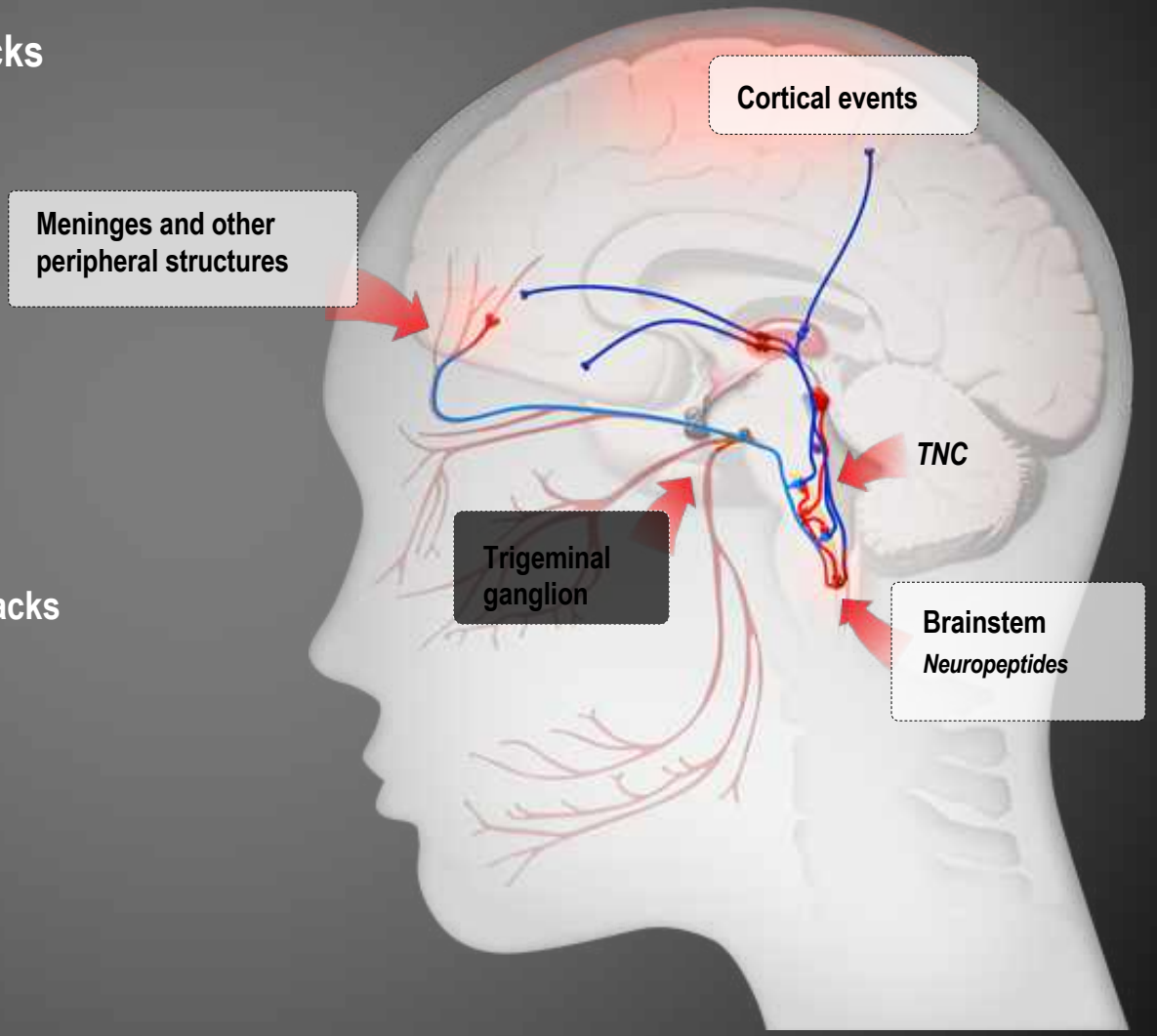
Head Pain Anatomy

- Meninges - Pain sensitive lining of the brain
- Trigeminal Nerves – Pain nerves that go to the meninges, face, and head
- Brainstem – Receives the trigeminal nerves and sends them to the deep brain
- Hypothalamus – Area of the brain that regulates response to stress, hunger, mood, and sleep



What Is Migraine?

- A chronic disorder with episodic attacks
- Integrated mechanisms and complex pathophysiology
- During attacks
  - Headache
  - Several associated symptoms
  - Functional disability
- In-between attacks
  - Enduring predisposition to future attacks
  - Anticipatory anxiety
  - Changes in brain function, eg,
    - Lack of habituation
    - Reduced nociceptive threshold

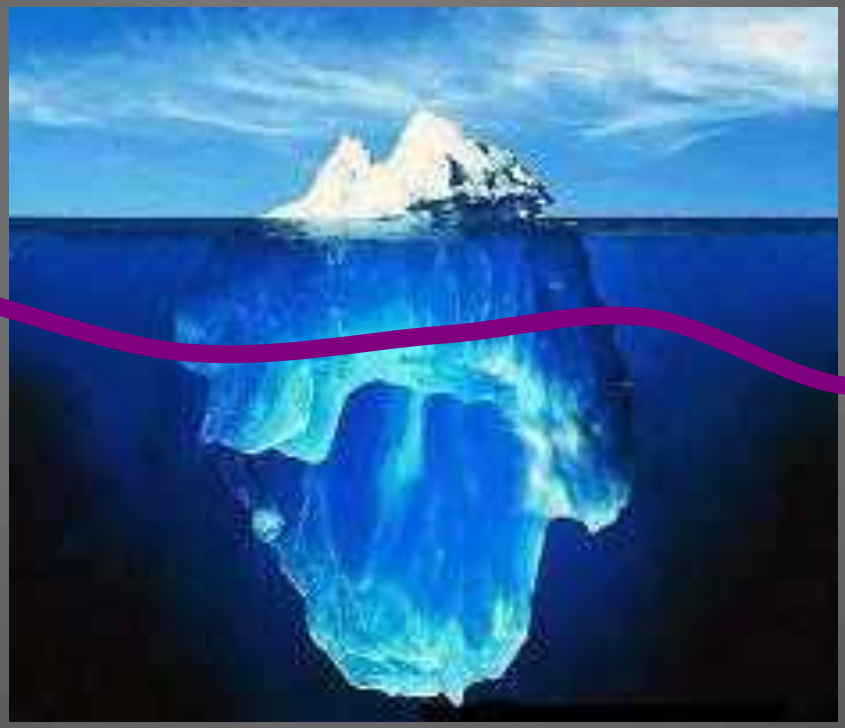


TGS = trigeminal system; TNC = trigeminal nucleus candalis; Bigal ME et al. *Neurology.* 2008;71:848–855;
Brandes JL. *Headache.* 2008;48:430–441; Coppola G et al. *Cephalalgia.* 2007;27:1429–1439; Goadsby PJ et al. *N Engl J Med.* 2002;346:257–270;
Haut SR et al. *Lancet Neurol.* 2006;5:148–157; Lovati C et al. *Headache.* 2008;48:272–277; Pietrobon D. *Neuroscientist.* 2005;11:373–386.

>35 Million Americans with Migraine

Diagnosed Migraine

48%



52%

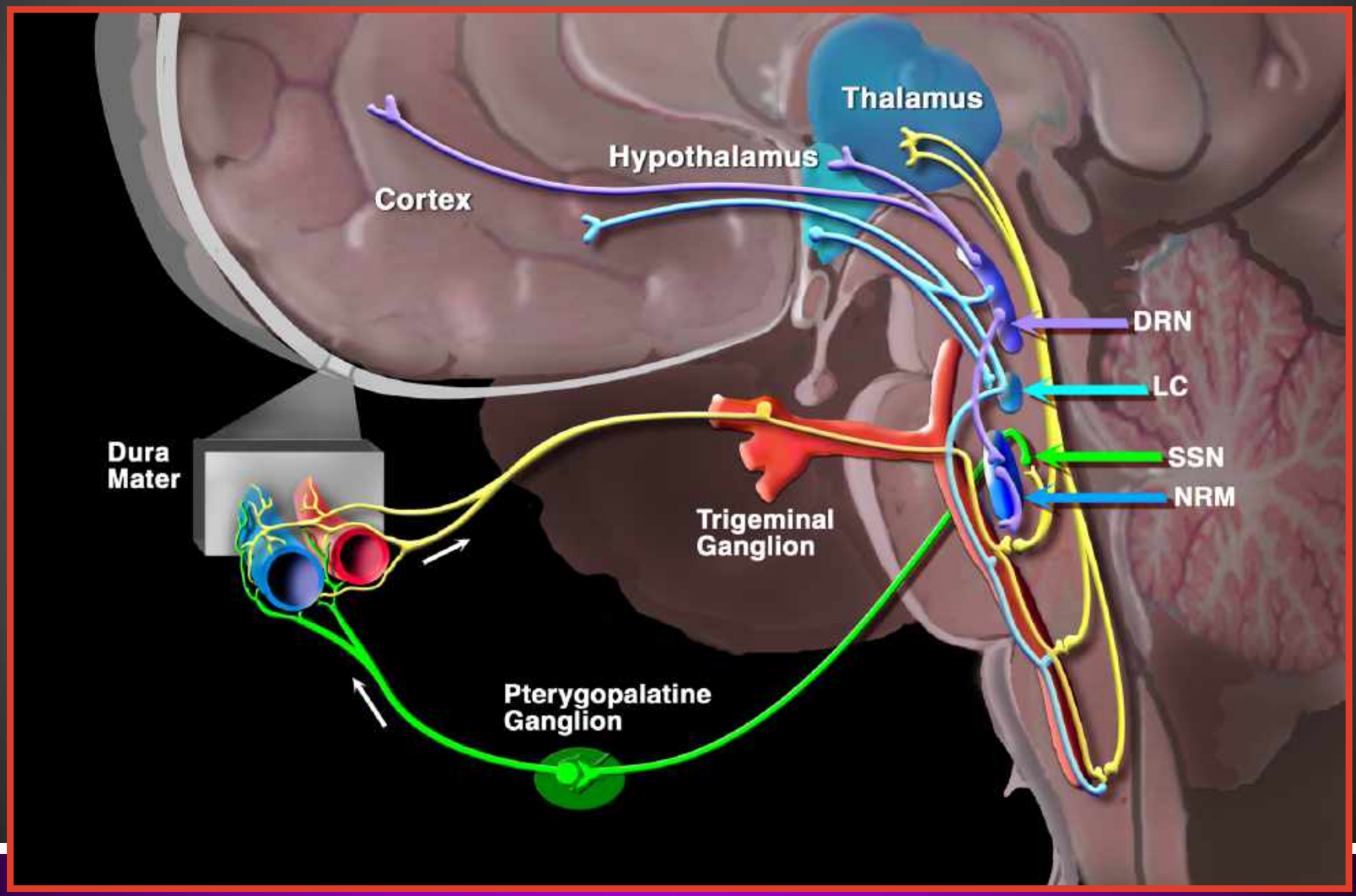
Undiagnosed Migraine

1999

Lipton et al., 2001

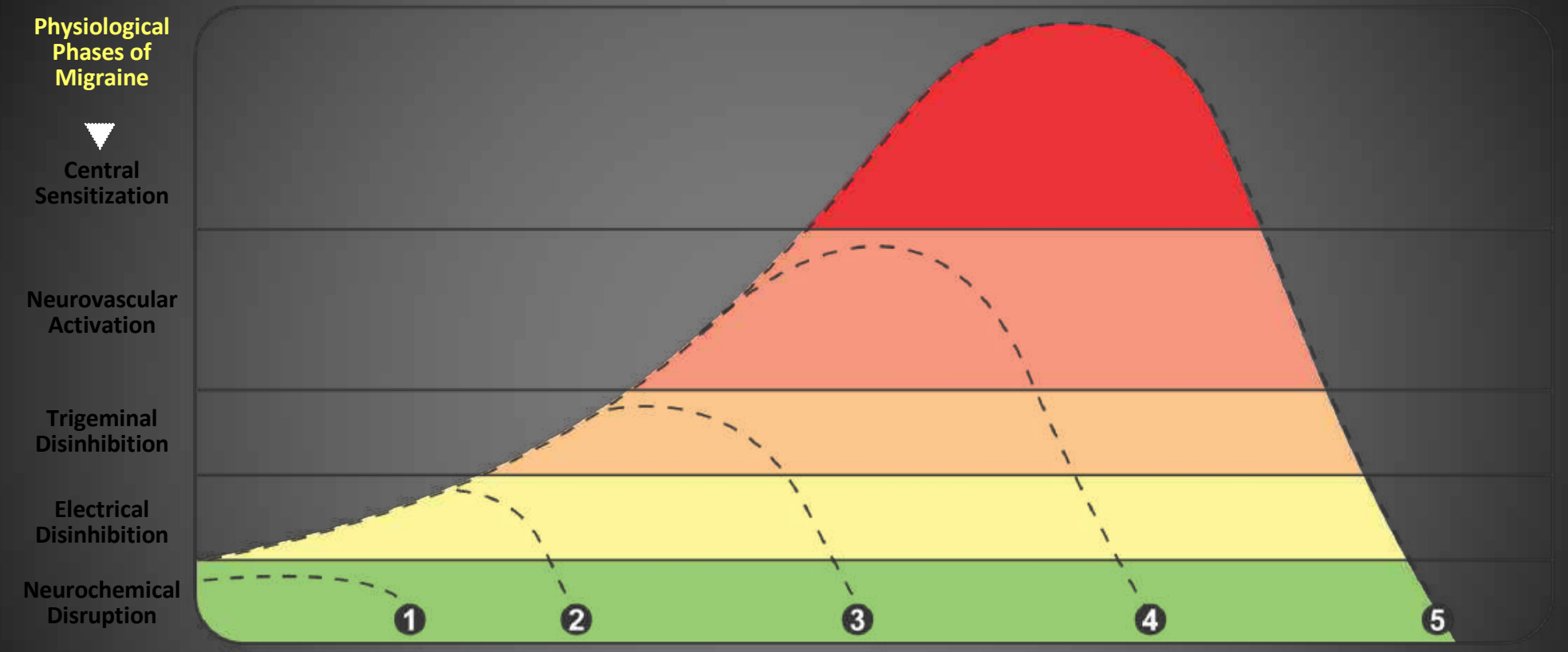
American Migraine Study I & II

CNS MODULATION OF MIGRAINE?



Goadsby, 2000.

Convergence Hypothesis



Cady RK, et al. *Headache.* 2002;42:204-216.

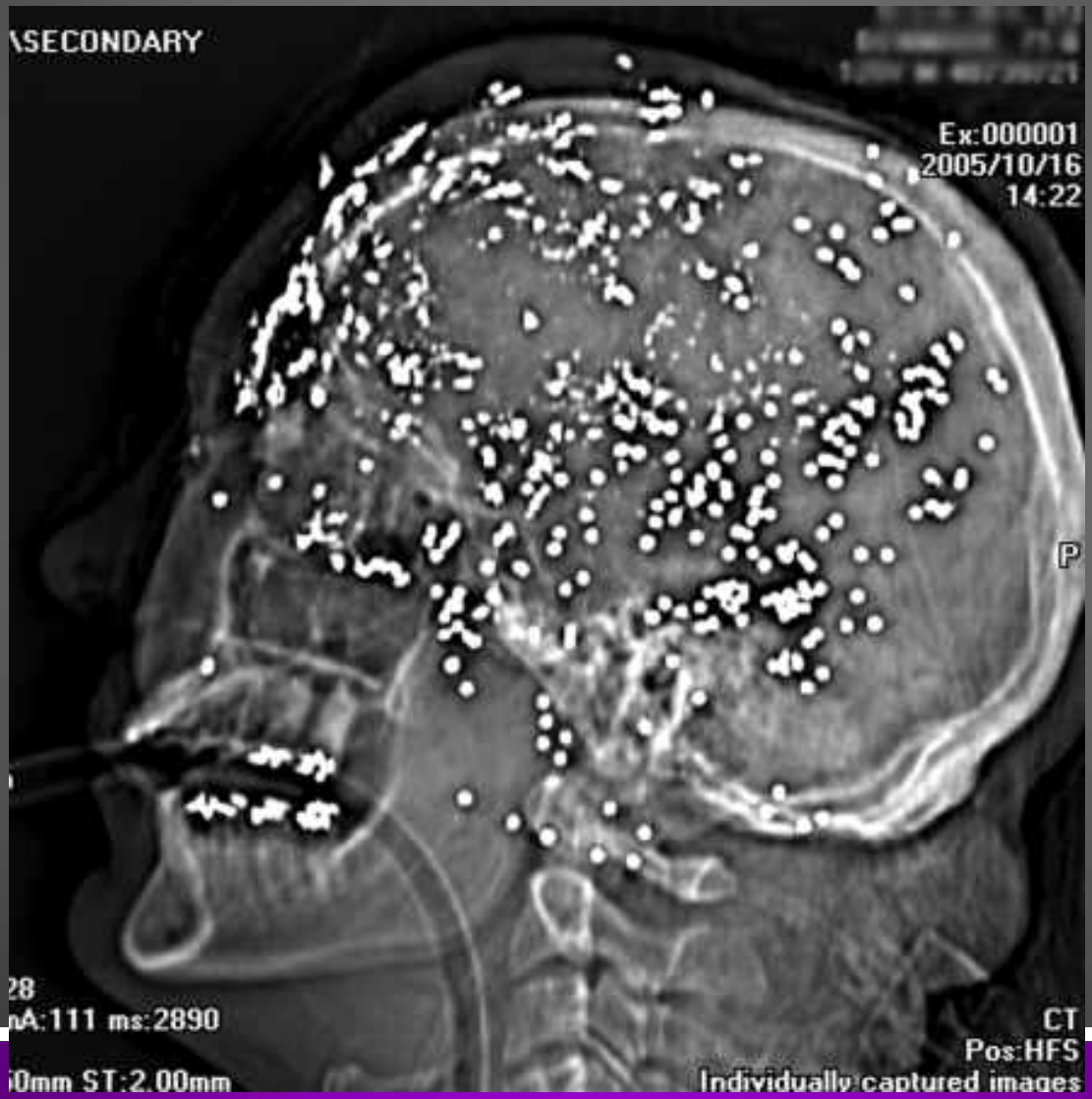

cvs/ harmacy
STOP


EXCEDRIN
BACK & BODY
EXTRA STRENGTH
NEW!
EXTRA STRENG
The pain stops. You don't.™
EXCEDRIN®

In-Law


Excedrin
MIGRAINE
100 COATED CAPLETS

Pt. with Cluster Headache



Cluster Headache

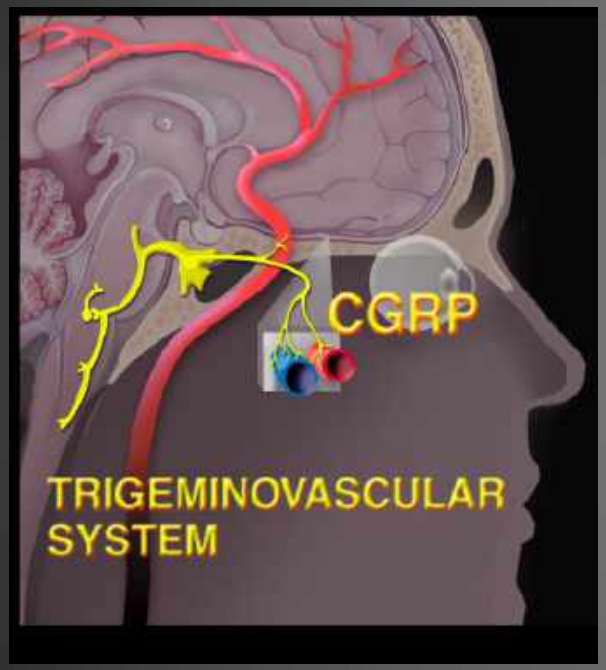
- Clinically separate from Migraine
- 4 male :1 female
- Pain episode lasts 30 min – 3º
  - May get aura
  - Usually pain free in between episodes
- Agitation prominent feature

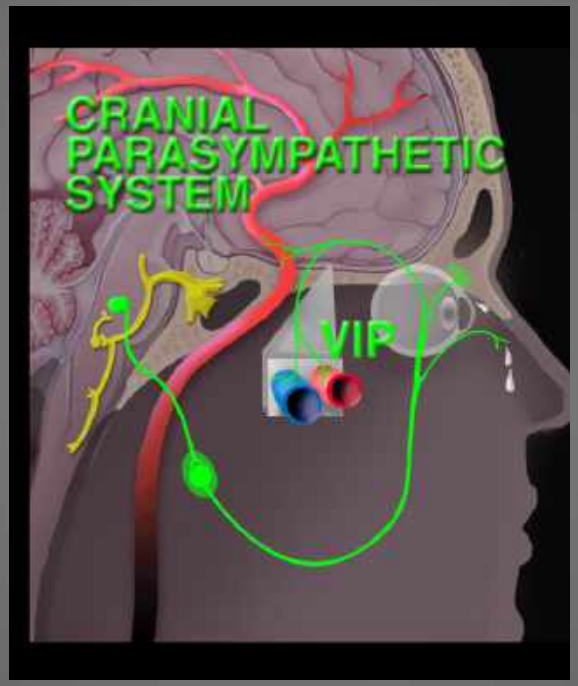
Patient description of Cluster

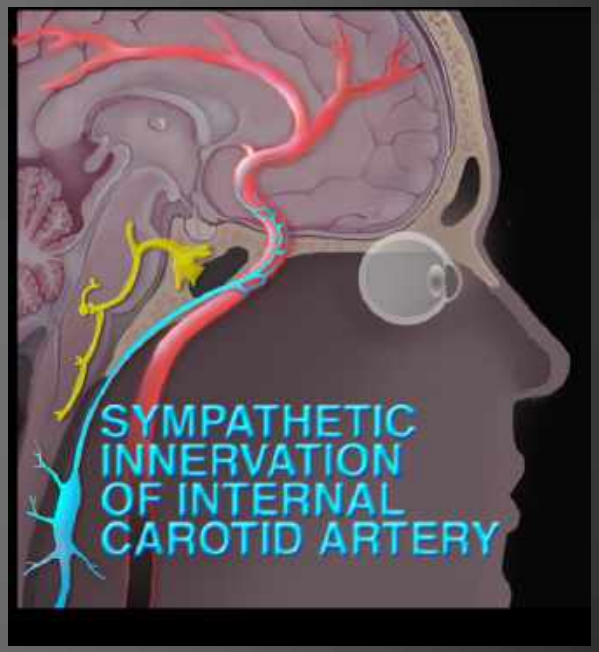
Autonomic Features

- Conjunctival injection and lacrimation
- Nasal congestion / rhinorrhea
- Partial Horner's syndrome
- Facial flushing / sweating
- Periorbital edema
- Foreign body sensation

Pain / Autonomic Signs





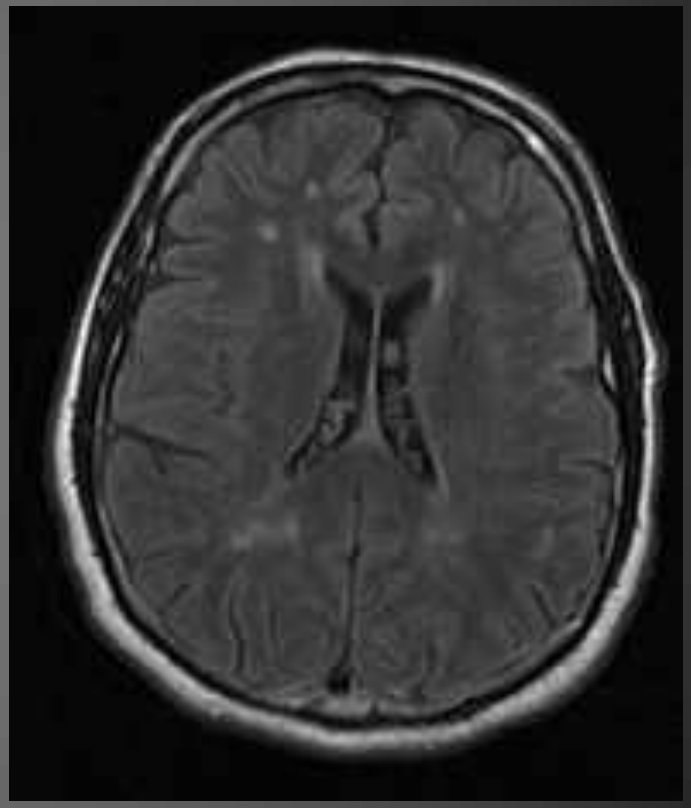


CGRP **VIP** **Mechanical**

(Edvinsson and Goadsby, 1998)

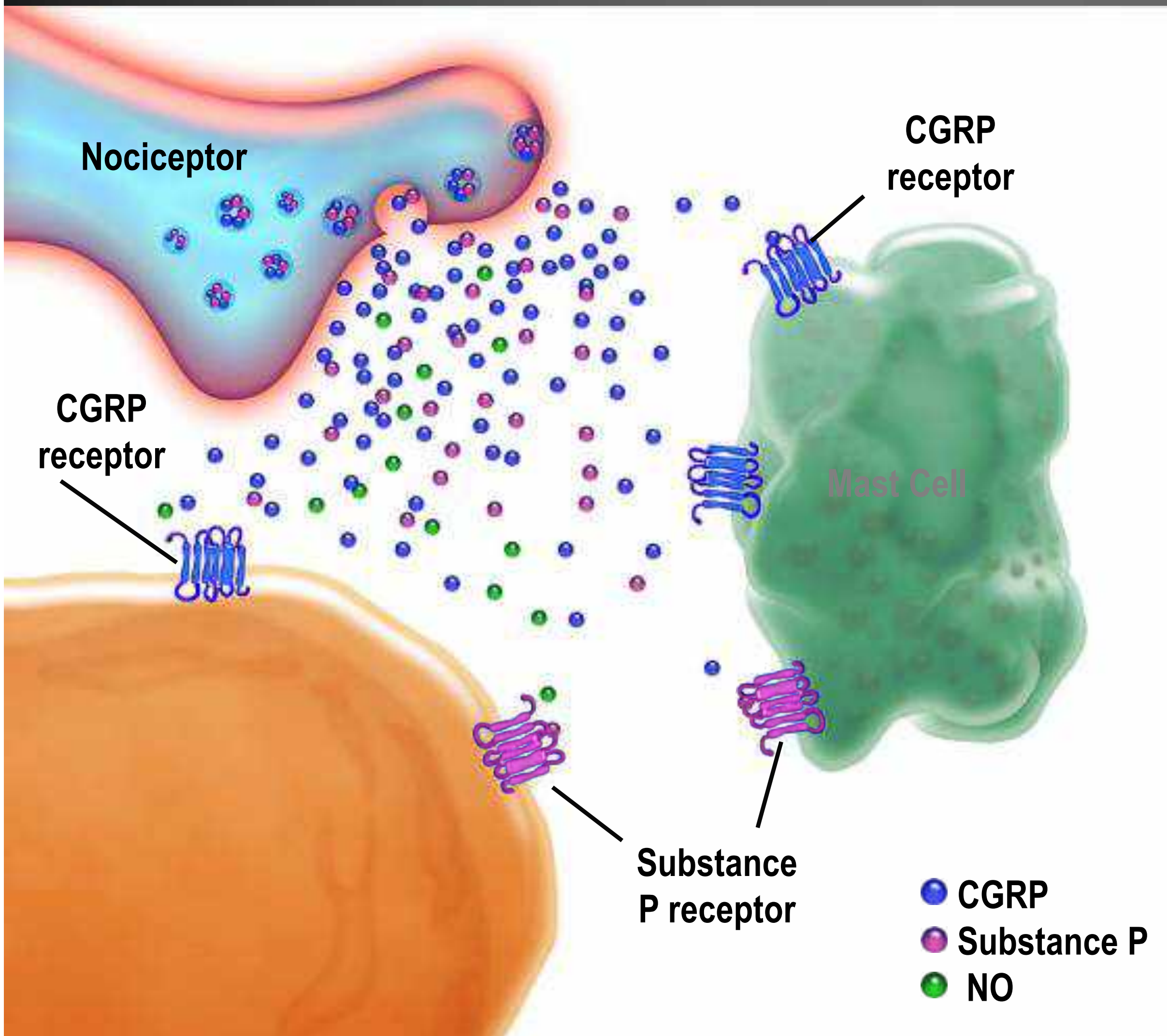
Brain MRI

- "Non specific T2 weighted white matter hyperintensities"
- "May be seen in migraine, hypertension, head trauma, other etiologies"
- "Can not rule out MS, vasculitis, stroke"
- "Also can be seen in CADASIL, Leukoencephalopathy, HIV, MELAS…



Your most anxiety provoking diagnosis here

Neuroinflammation



- Activated nociceptors release CGRP and substance P
- NO also released
- Leads to
  - Vasodilation
    CGRP, NO, substance P
  - Mast cell degranulation
    CGRP, substance P
  - Plasma extravasation
    substance P

- CGRP and substance P activate mast cells
- Mast cell degranulation
  - Histamine
  - NGF
  - Serotonin
  - Proinflammatory cytokines
    - TNF-α, IL-1, IL-6

- Cause an inflammatory response
- Mast cells sensitize nociceptors

Mast Cells and Migraine

- Reside in the dural layer of the meninges
- Close proximity to blood vessels and nociceptors
- Plasma Histamine is elevated in migraine subpopulations
- Histamine infusion may trigger migraine

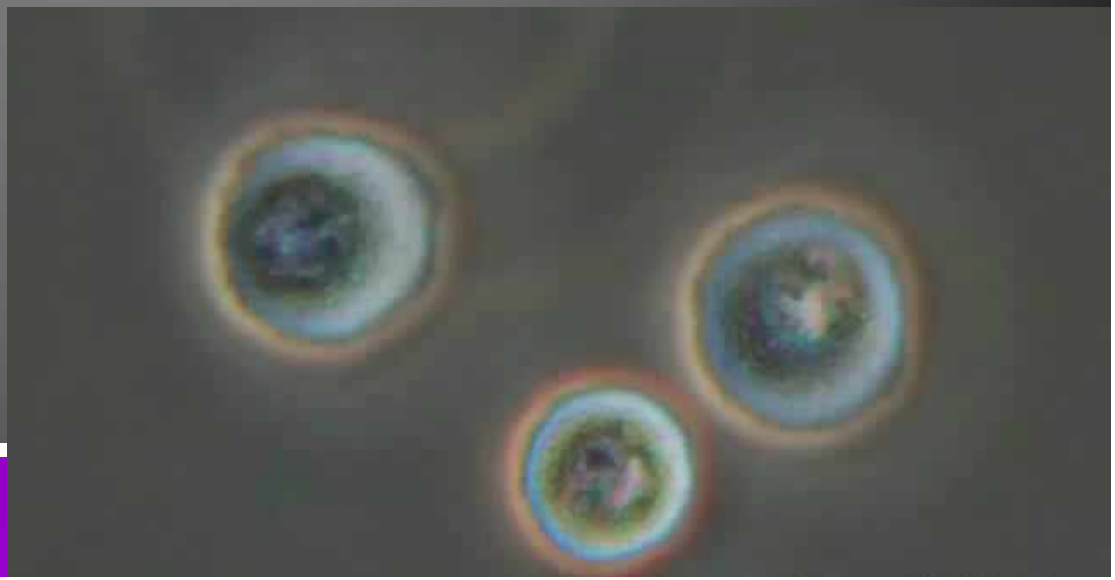
- Known triggers of migraine also trigger mast cell activity
  - Stress
  - Estrogen
  - Foods
  - Environmental stimuli
  - Alcohol

(Levy D, 2011)

Activated Mast Cells

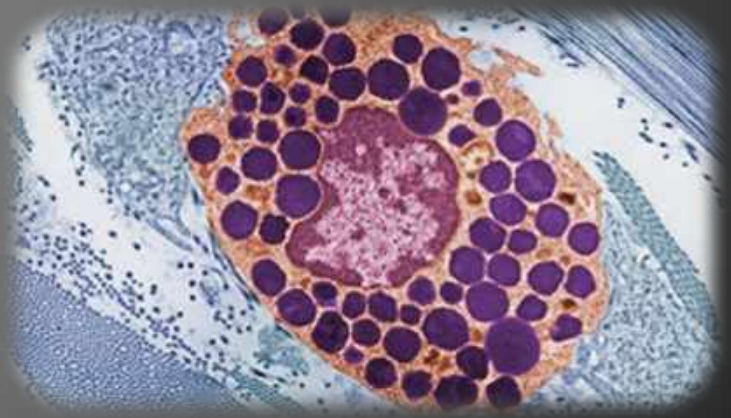
- Release proinflammatory substances
  - Histamine
  - Serotonin
  - Cytokines
  - Leukotrienes
    - IL6
    - LTC_4
  - Prostaglandins
    - PGD_2
    - PGI_2

> 200 substances are associated with mast cell activation



Mast Cell Activation Syndrome

- Exacerbations of symptoms related to overactive mast cell activity
  - Flushing
  - Abdominal pain/diarrhea
  - Skin lesions
  - Fatigue
  - Headache
  - Myalgia
  - Cognitive concerns



(Mastocytosis Society 2011 annual meeting)

Mast Cell Activation Syndrome

- Triggers
  - Heat
  - Exercise
  - Food
  - Sun
  - Stress
  - Sex
- Clues to consider:
  - Multiple atypical allergies
  - Multiple food intolerances
  - Exercise intolerant
  - Diarrhea with migraine
  - Multiple skin syndromes
    - Eczema
    - Chronic foliculitis
  - Rhinitis
  - Asthma

(Mastocytosis Society 2011 annual meeting)

Mast Cell Activation Syndrome

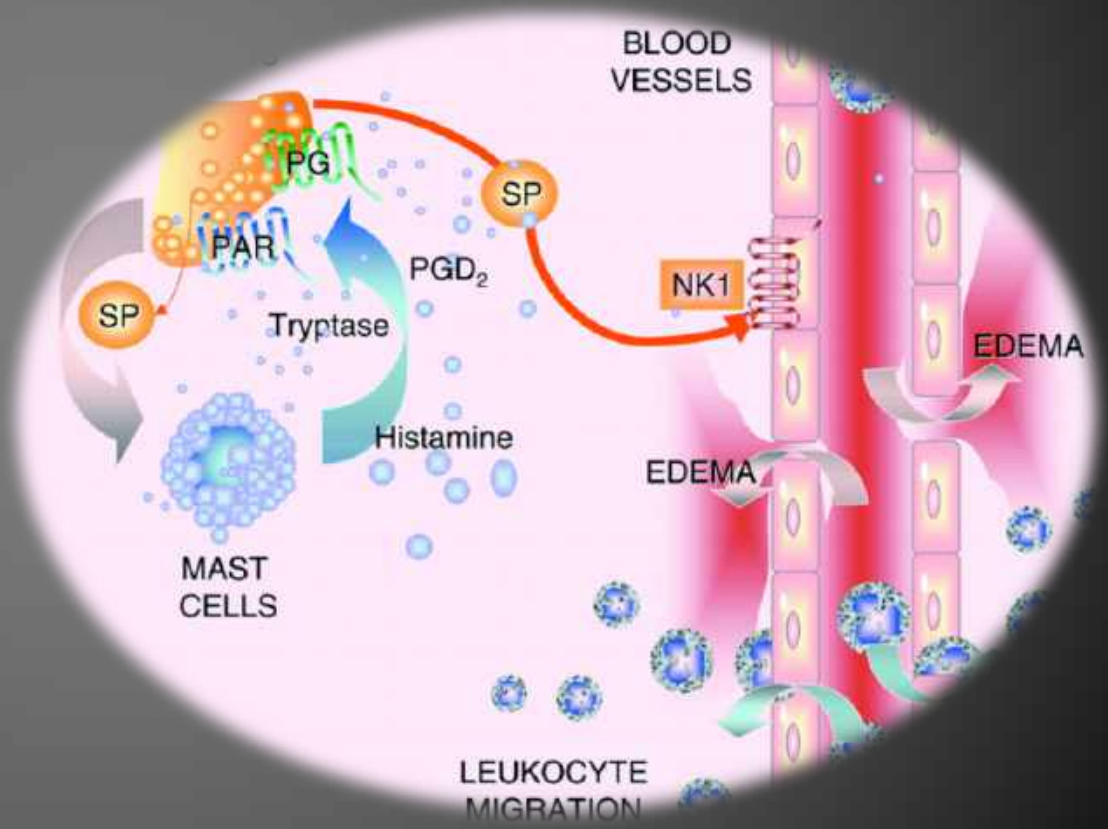
- Diagnosis is based on clinical history
- Serologies include:
  - Tryptase
    - Baseline and during symptom exacerbation
  - Prostaglandin D2 levels
  - Urine studies
    - N-methyl histamine
    - Leukotriene E4
      - 24 hour collection following symptom exacerbation
  - Bone marrow biopsy

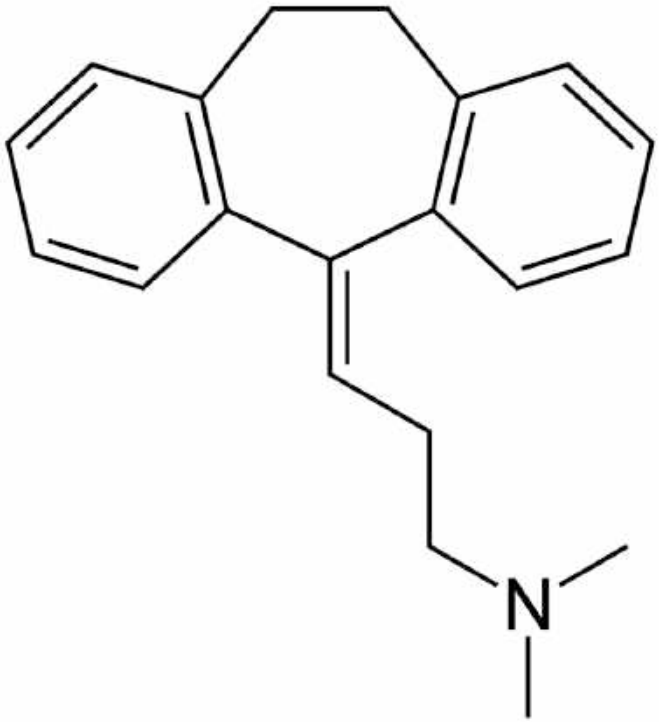
Mast Cell Activation Syndrome

- Treatment options
  - Ranintidine (H2 receptor blocker)
  - Certirizine (H1 receptor blocker)
  - Aspirin
  - Cromolyn
  - Monoleukast
  - Ketotifen
  - Others

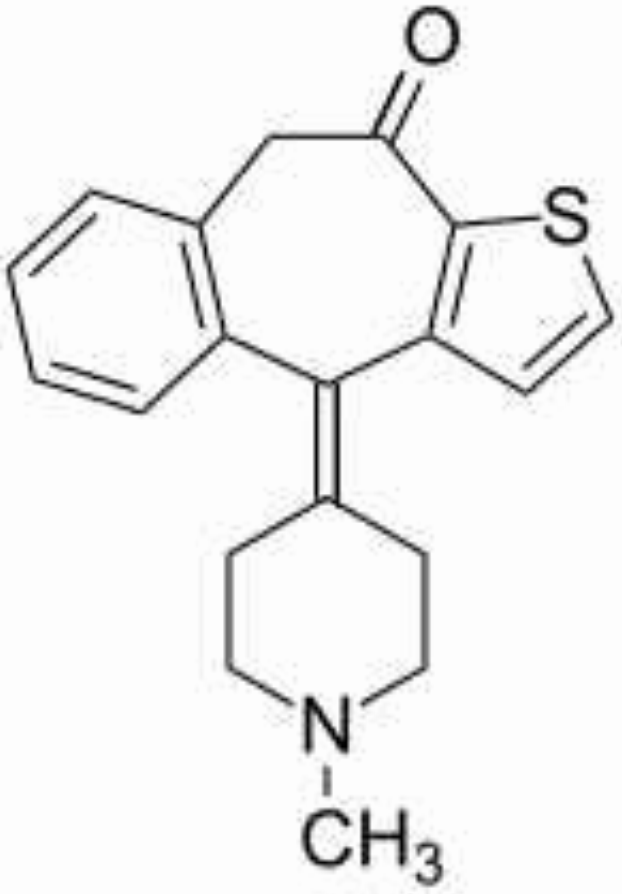
Notable Medications with Mast Cell Stabilizing properties

- Diphenhydramine
- Amitriptyline
- Doxycycline
- Promethazine
- Droperidol
- Diazepam





Amitriptyline



Loratadine

Mast Cell Activation Syndrome

- Empiric therapy based on history
  - Ranitidine 150mg twice a day
  - Certirizine 10mg twice a day
  - Singulair 10-20mg daily

Chronic Pain and Hypermobility

Childhood Joint hypermobility identified as predisposing factor for Chronic Pain

(Murray & Woo, 2001)

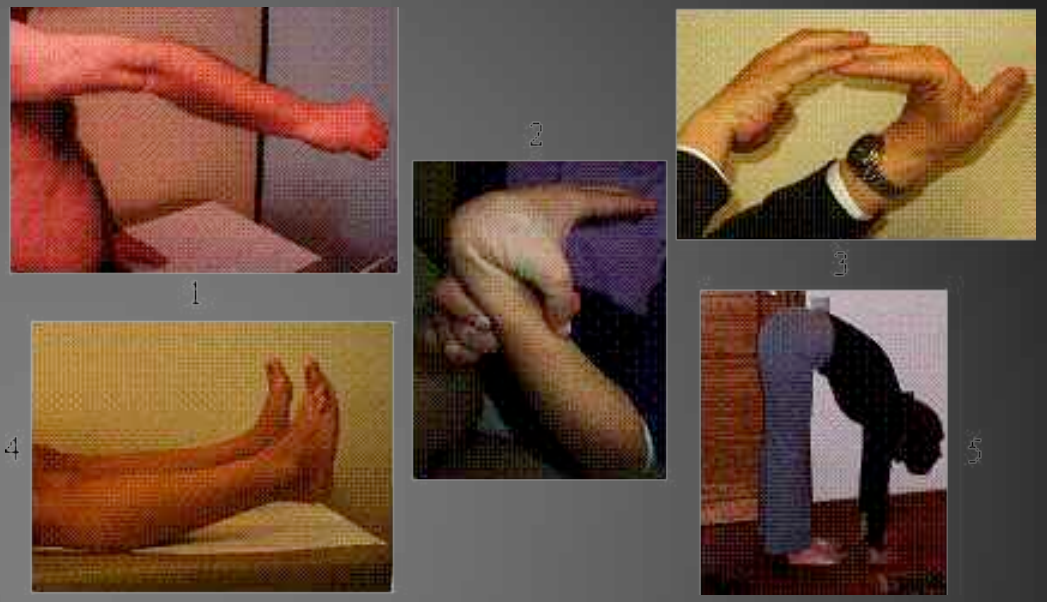


Table 2 Beighton score (9). One point given for each positive manoeuvre. Each limb tested separately

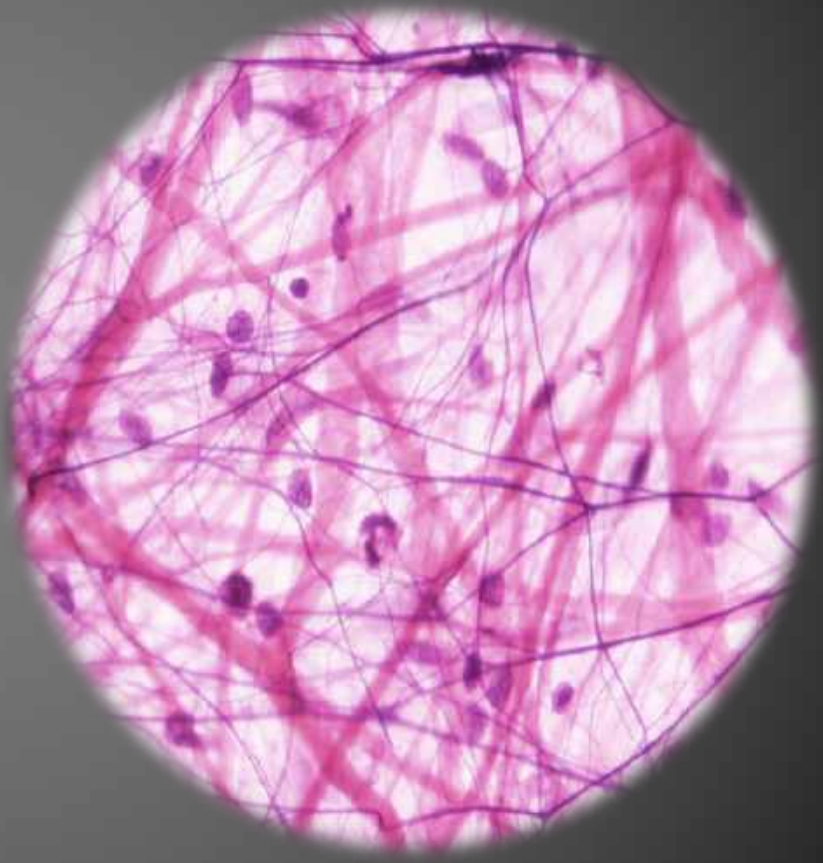
1. More than 10° hyperextension of the elbows
2. Passively touching the forearm with the thumb, while flexing the wrist
3. Passive extension of the fingers or a 90° or more extension of the fifth finger
4. Knee hyperextension greater than or equal to 10°
5. Touching the floor with the palms of the hands when reaching down without bending the knees

Hypermobility associated with fibromyalgia and New Daily Persistent Headache Syndrome

(Rozen, 2007)

Increased Mast Cell Count and Activity Undifferentiated Connective Tissue Dysplasia

- ↑ Mast Cell Density
  - 1.7 fold increase in UCTD compared to controls
- ↑ Intracellular Chymase Activity
- Increased mast cell count in benign joint hypermobility
- Increased in skin samples of patients with fibromyalgia



(Luzgina et al., 2010)
(Enestrom S. et al., 1997)

Migraine Comorbidity

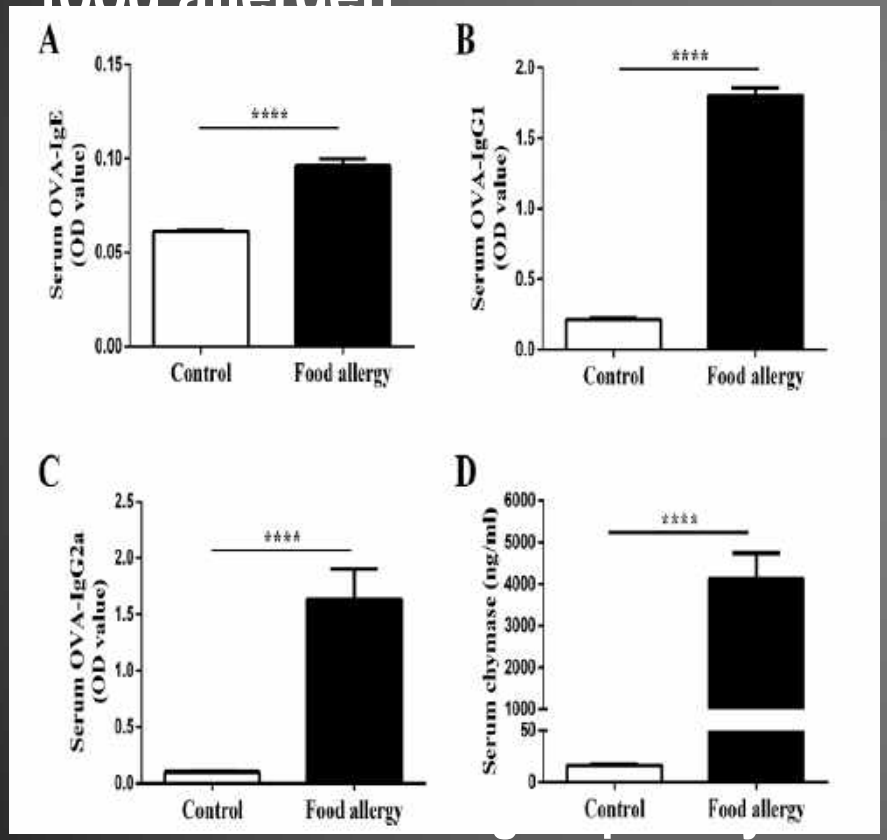
Disorders highly associated with migraine that occur at a rate significantly greater than chance

Gut Cluster

- Irritable bowel syndrome
- Gastritis
- Peptic ulcer disease
- H. pylori
- GERD
- Colitis

Food Allergy and Brain Inflammation

- Mice were sensitized to a food allergen
-
-
  - Increased microglia activity



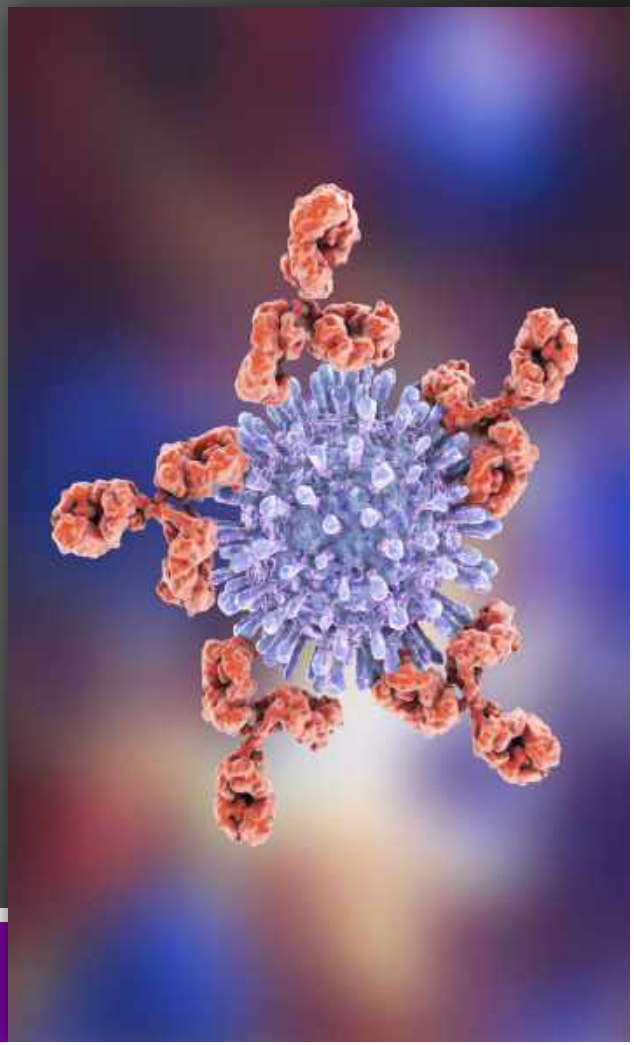
- Staining of tissue revealed:
  - ↑ IgG in cortex
  - ↑ Chymase in cortex
    (marker of mast cell activation)
  - ↑ TNFα in the cortex
    (inflammatory cytokine)
  - ↑ IgG1 & IgG2a
    (Consequence of mast cell activation)

Zhou L, Chen L, Li X, Li T, Dong Z, Wang YT. Food allergy induces alteration in brain inflammatory status and cognitive impairments. *Behav Brain Res*. 2018. pii: S0166-4328(17)31460-2.

CGRP, a neurotransmitter of enteric sensory neurons, contributes to the development of food allergy due to the augmentation of microtubule reorganization in mucosal mast cells

Ji-Hyun Kim, Takeshi Yamamoto, Jaemin Lee, Tomoe Yashiro, Takayuki Hamada, Shusaku Hayashi, and Makoto Kadowaki
Division of Gastrointestinal Pathophysiology, Institute of Natural Medicine, University of Toyama, Toyama 930-0194, Japan
(Received 31 May 2014; and accepted 6 June 2014)

- **CGRP augments Ig-E independent/non-antigenic stimuli induced mucosal mast cell degranulation**
- **CGRP dysregulation in the gut contributes to the development of food allergy**



Kim JH, Yamamoto T, Lee J, Yashiro T, et al. CGRP, a neurotransmitter of enteric sensory neurons, contributes to the development of food allergy due to the augmentation of microtubule reorganization in mucosal mast cells. Biomed Res. 2014;35(4):285-93.

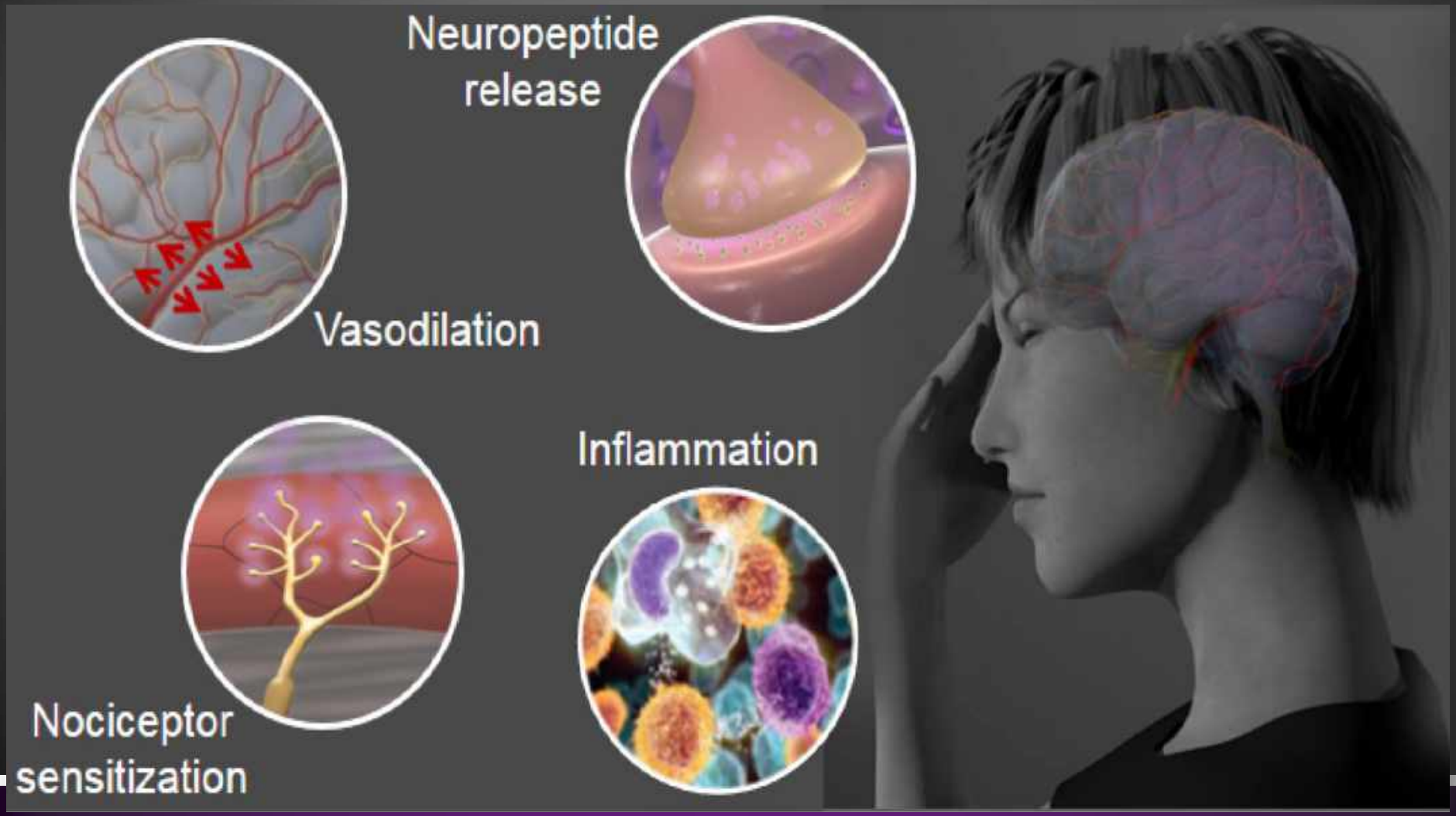
CGRP

(Calcitonin Gene-Related Peptide)

- Inflammatory protein thought to play a role in headache
  - Initiating headache
  - Propagate headache
- CGRP is found in almost every organ system in the body

CGRP

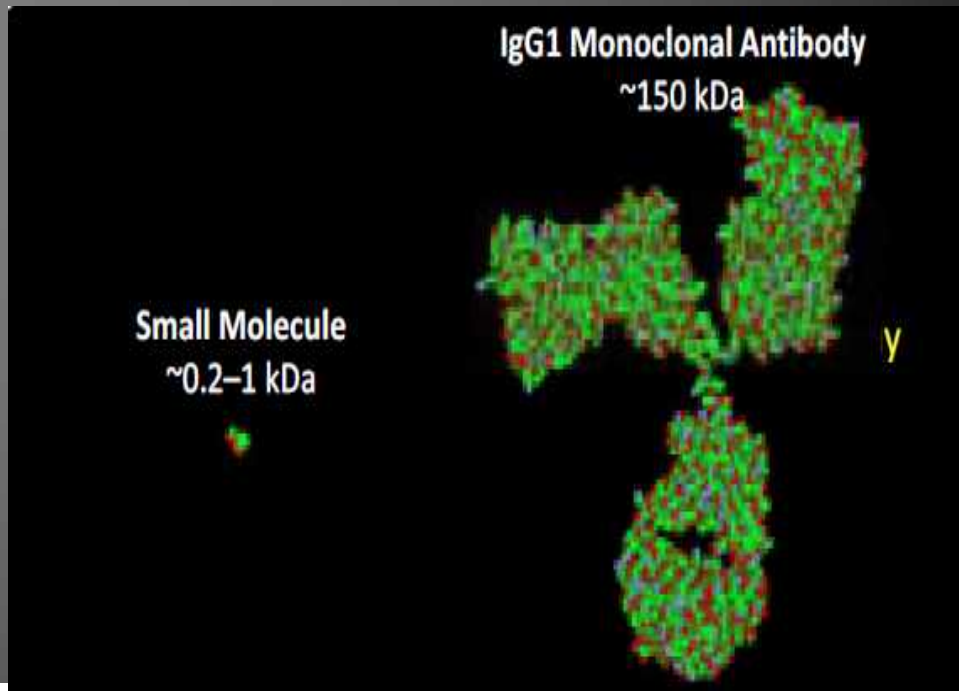
(Calcitonin Gene-Related Peptide)



Monoclonal Antibodies to CGRP or the CGRP receptor

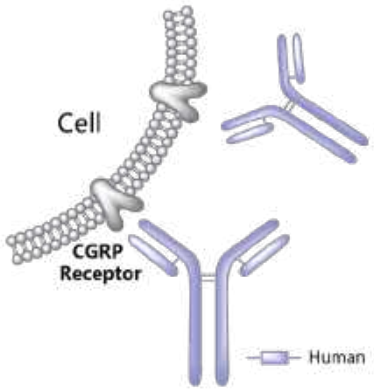
- The monoclonal antibodies (MABs) are big molecules
- Minimal pass through of the blood brain barrier
- MABs are eliminated by the reticuloendothelial system
  - Minimal / no? risk for liver toxicity

- Because MABs work, it means that peripheral, not central CGRP action is sufficient to trigger migraine



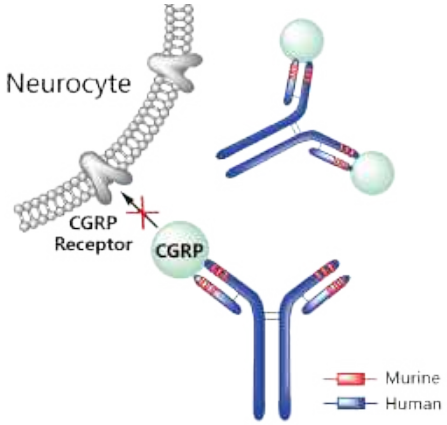
Four Key Monoclonal Antibodies in Migraine

Erenumab



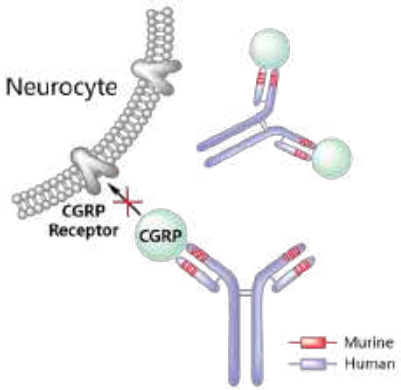
- Monoclonal antibody (MAB) against the CGRP receptor
- Erenumab is the only MAB in the group that is fully human

Fremanezumab



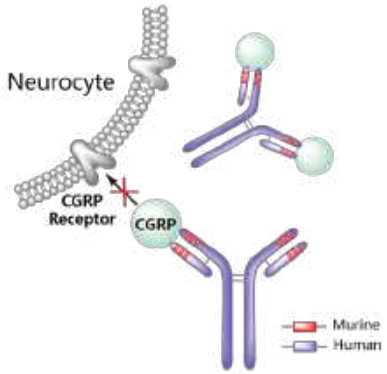
- Antibody against the CGRP ligand or peptide
- Fully humanized (95%)

Galcanezumab



- Antibody against the CGRP ligand or peptide
- Humanized (90% human)

Eptinezumab



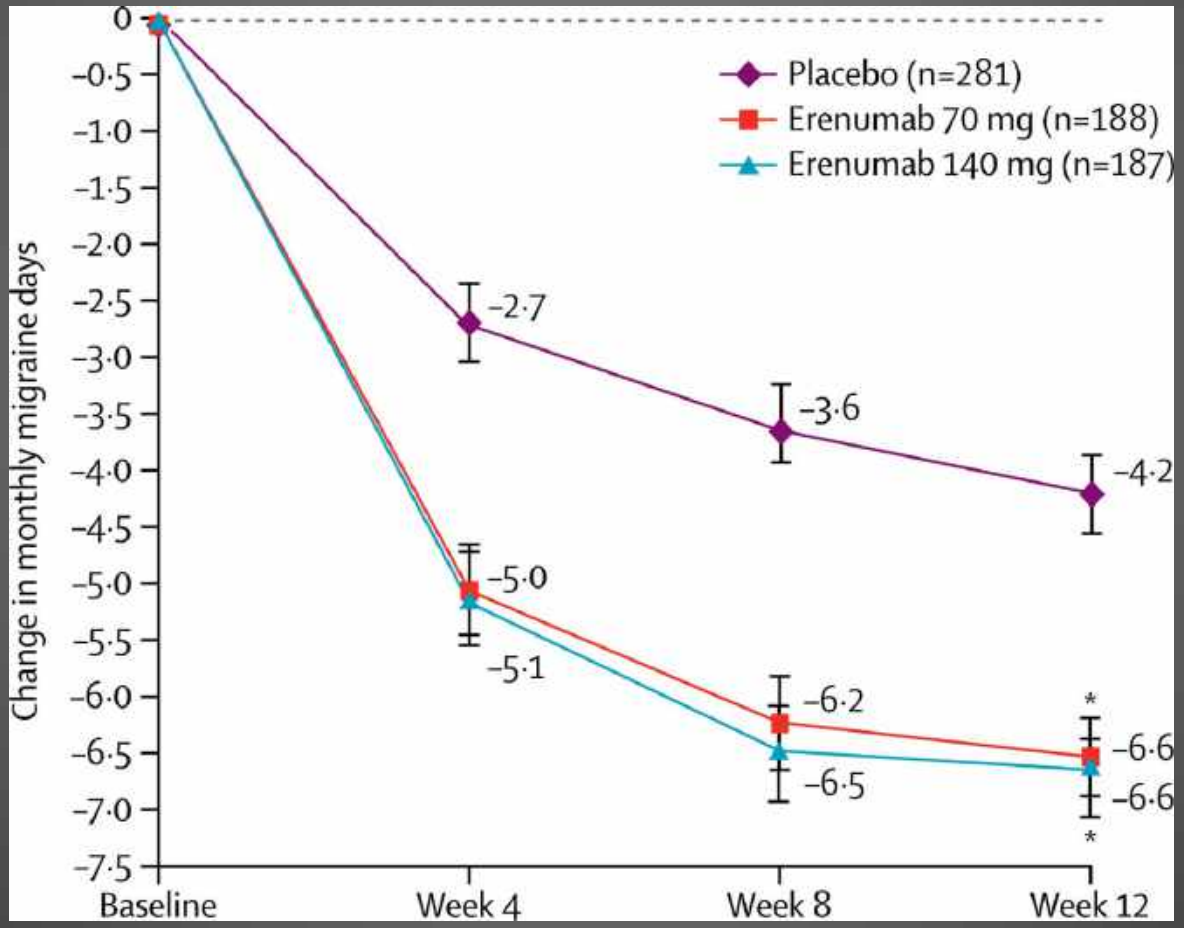
- The only anti-CGRP MAB administered intravenously initially for migraine
- Antibody against the CGRP ligand or peptide
- Humanized (90%)

Pellesi L, Guerzoni S, Pini LA. Spotlight on Anti-CGRP Monoclonal Antibodies in Migraine: The Clinical Evidence to Date. Clin Pharmacol Drug Dev. 2017 Apr 14. doi: 10.1002/cpdd.345. [Epub ahead of print}

The Four MABs

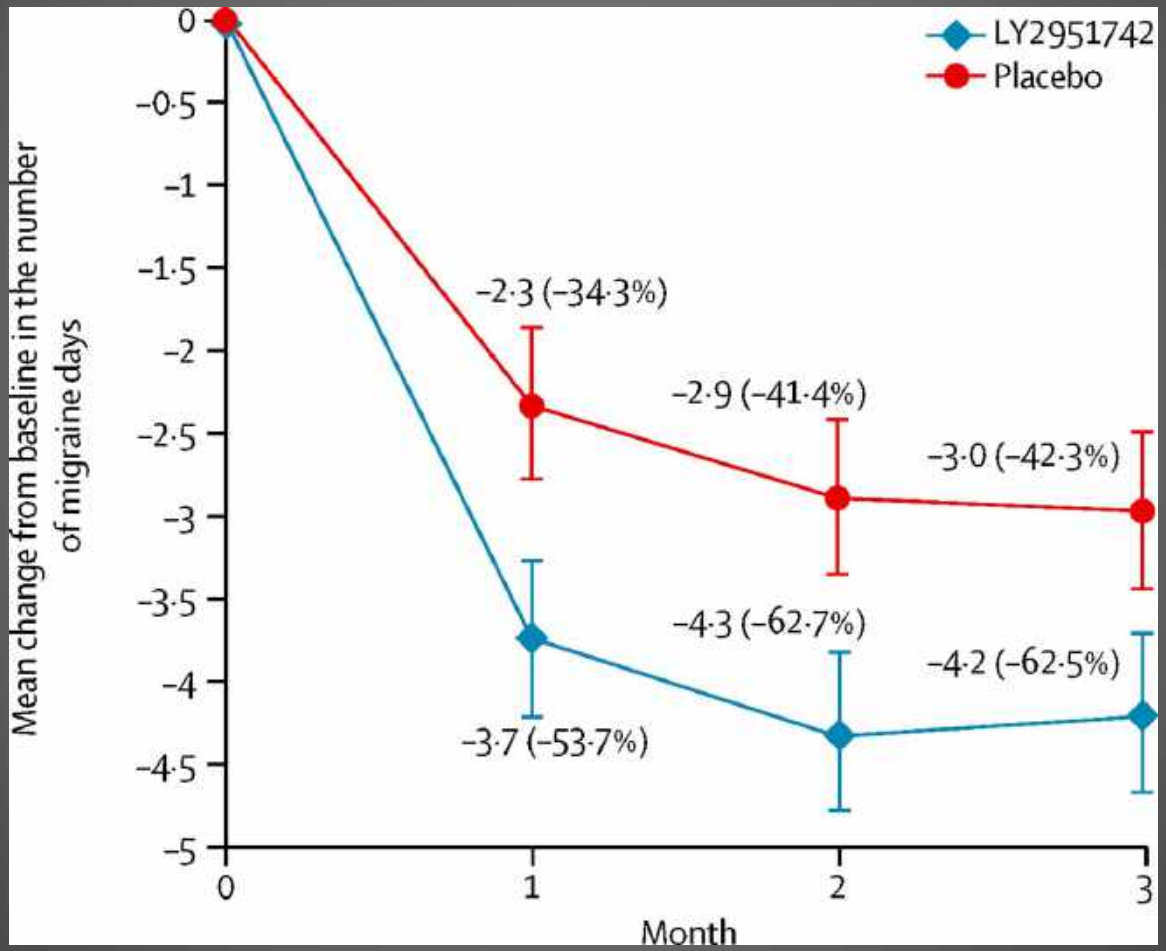
- US FDA suggested a consistent primary endpoint:
  Reduction of monthly migraine days
- All four are positive in regulatory EM and CM trials
- **40-60% of the CM registration study subjects had medication overuse**
- All four:
  - have quick onset, separating from placebo within 1 week
  - show clinically meaningful response by one month
  - have favorable responder rates for ≥50% and higher
  - have safety and tolerability similar to placebo
- Almost all secondary endpoints are also positive, with decreased acute medication days, improved impact, disability, and/or quality of life

Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial



Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017 Jun;16(6):425-434

Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study



Dodick DW, Goadsby PJ, Spierings EL, et al. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2014 Sep;13(9):885-92.

Acute Therapies for Migraine

- Previous non specific acute therapies
  - NsAIDs
  - Dopamine receptor agonists
  - Sedatives
  - Opioids

  - Numerous adverse events
  - Non specific therapy lead to complications related to the medication

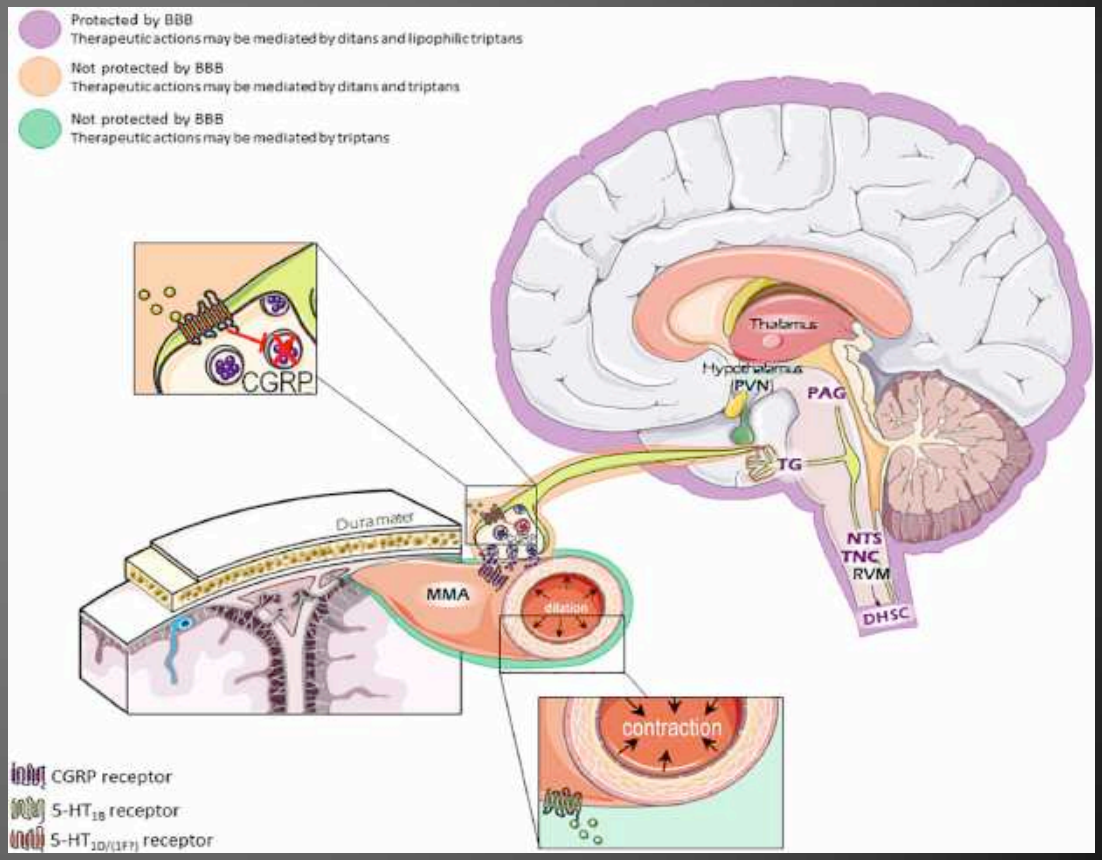
Acute Therapies for Migraine

Standard of care

specific therapies

- Triptans
  - 5-HT1B agonist
  - 5-HT1D agonist

- Clinically effective
- Peripheral acting
- Vasoconstricting
- Adverse events
  - Chest pain / tightness / pressure
  - Neck / throat / Jaw tightness / pressure



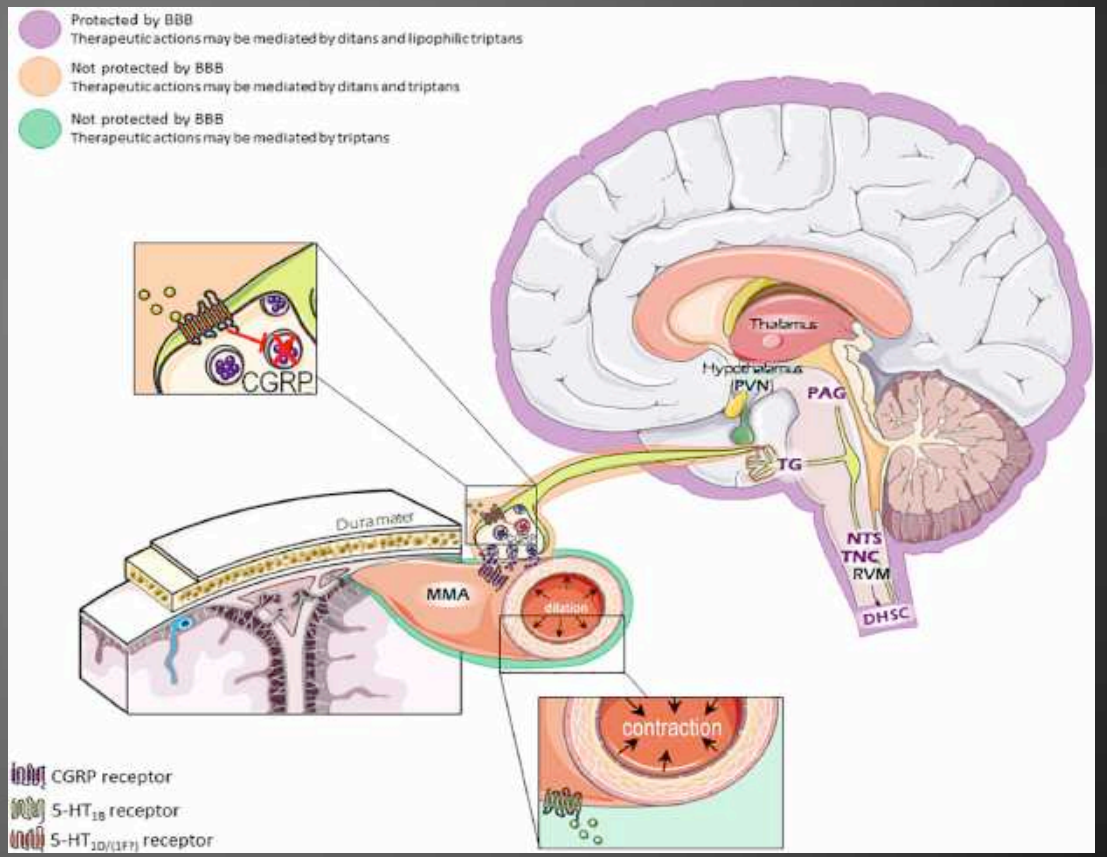
Designer Specific Agents for Acute Migraine

CGRP targeted therapies

"Gepants"

- Ubrogepant
- Rimegepant

- Clinical trials encouraging
- Minimal adverse events
- No vasoconstriction
- Mechanism of action
  - Peripheral CGRP blockade

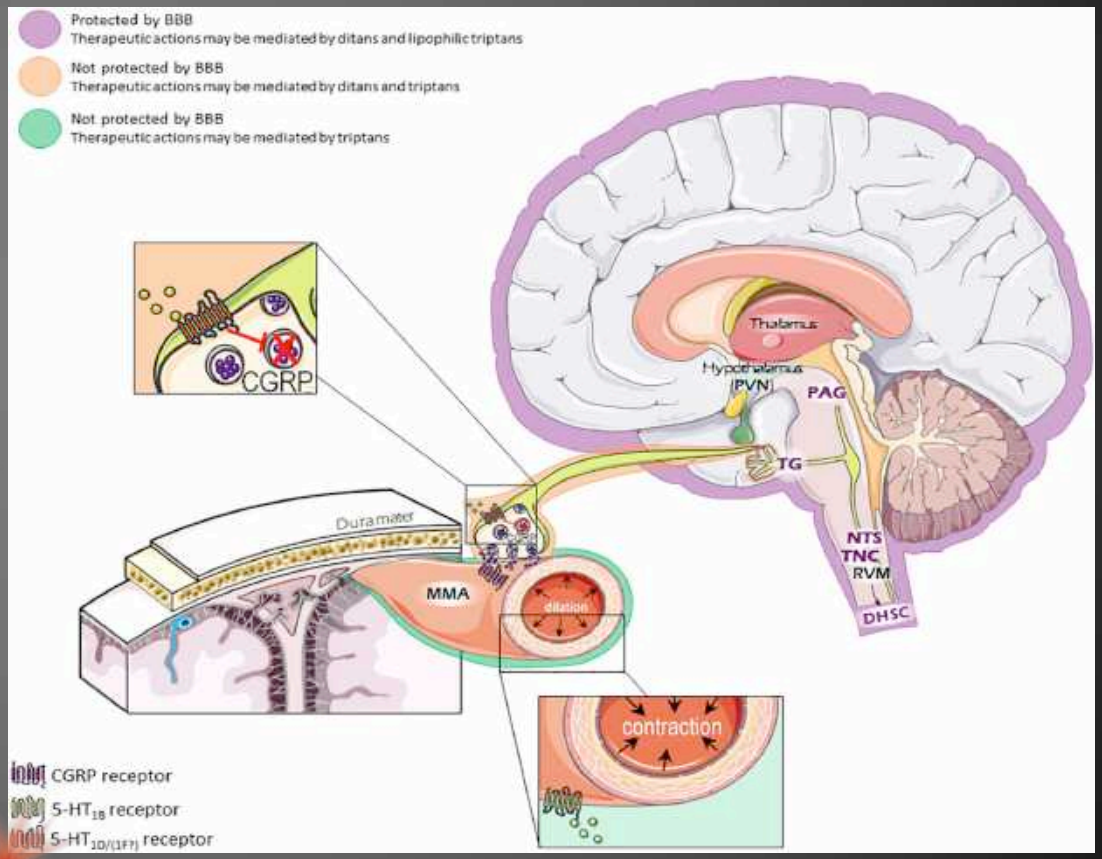


Ceriani CEJ, Wilhour DA, Silberstein SD. Novel Medications for the Treatment of Migraine. Headache. 2019 Oct;59(9):1597-1608.

Designer Specific Agents for Acute Migraine

5ht1F receptor agonist

- Lasmiditan
- Highly efficacious in clinical trials
- Adverse events reflect CNS activity
  - Dizziness / driving restriction?
- No vasoconstriction
- Mechanism of action
  - Peripheral reduction of CGRP
  - Central 5ht1F receptors at key areas of migraine
    - » Hypothalamus
    - » Thalamus
    - » Trigeminal nucleus caudalis
    - » Periaqueductal Gray



Rubio-Beltrán E, Labastida-Ramírez A, Villalón CM, MaassenVanDenBrink A. Is selective 5-HT(1F) receptor agonism an entity apart from that of the triptans in antimigraine therapy? Pharmacol Ther. 2018 Jun;186:88-97

IGG Food Sensitivity Testing

- Foods may trigger migraine
- Challenge to identify which food may trigger migraine
- Accepted diagnostic tool
  - Celiac Disease
  - Asthma
  - Eosinophilic Esophagitis

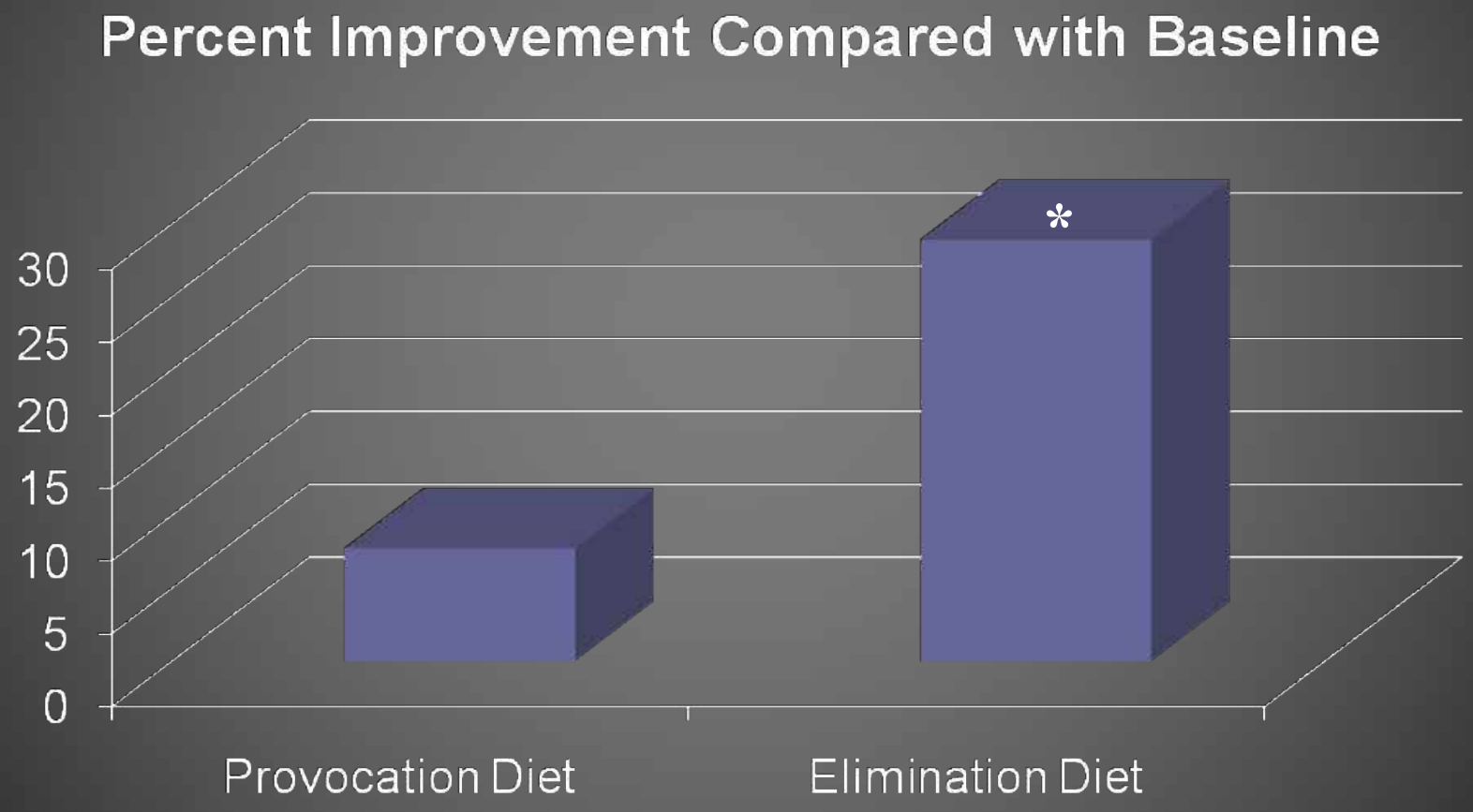
Pasquel J & Orterino A. Cephalalgia 2010;30:777-81

Foods Associated with CNS Inflammation

- What are the top foods to consider eliminating for chronic migraine?

1. Gluten
2. Egg
3. Dairy
4. Corn
5. Caffeine

IgG Antibody Based Elimination Diet



*P<0.05 vs baseline

Alpay K. Cephalalgia 2010; 30: 829-835,

IgG Elimination Diet

- 65 patients
- Not placebo controlled
- Used IgG testing to identify possible food triggers

- 43/65 patients substantial improvement / complete remission

Arroyave Hernández CM, Echavarría Pinto M, Hernández Montiel HL. Food allergy mediated by IgG antibodies associated with migraine in adults. Rev Alerg Mex. 2007;54:162-168.

IgG- based Elimination Diet in migraine plus IBS

- 21 subjects with both IBS and migraine
- Double blind, randomized, controlled, cross over trial
- Diets
  - Usual diet
  - Elimination diet
  - Provocation diet

- Elimination diet effect on headache
  - ↓ Attack count
    (4.8 [2.1] vs 2.7 [2.0]; *P* < .001)
  - ↓ Mean attack duration
    (1.8 [0.5] vs 1.1 [0.8] days; *P* < .01)
  - ↓ Attack severity
    (vas 8.5 [1.4] vs vas 6.6 [3.3]; *P* < .001)
  - ↓ Acute medication use
    (4.0 [1.5] vs 1.9 [1.8]; *P* < .001)

- ↓ pain-bloating severity
- ↑ quality of life

Avdinlar EI, DIkmen PY, Tiftikci A, et al. IgG-based elimination diet in migraine plus irritable bowel syndrome. Headache. 2013;53:514-525.

Cost of testing

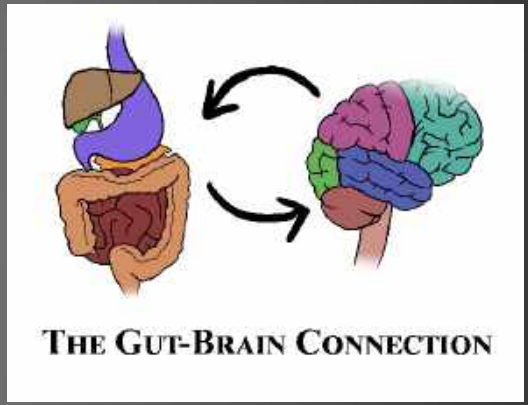
- IgG food sensitivity testing
  - $1,200 (pt. pays $100)

- MRI Brain
  - $3,500

- Onabotulinum toxin A
  - $17,000 annual
  - 1970s = $40 /vial

Migraine comorbid with Celiac Disease and Gluten Sensitivity

- Chronic headache reported by
  - 30 % of Celiac disease
  - 56 % of Gluten sensitivity
  - 23 % of Irritable bowel syndrome
  - 14 % of controls



- Migraine reported by
  - 21% Celiac Disease
  - 40% of Gluten sensitivity

*all significantly higher than controls

Dimitrova AK, Ungaro RC, Lebwohl B, et al. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. Headache. 2013;53:344–55.

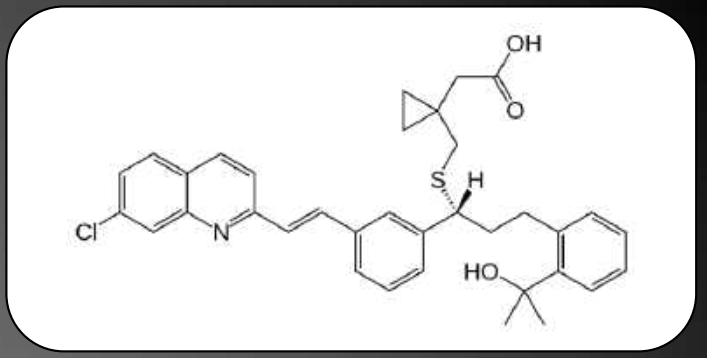
Nutritional intervention for migraine

- 36 week cross over study
- 16 week treatment periods
  - Placebo
  - Diet modification
    - Low fat vegan x 4 weeks
    - Trigger elimination then reintroduction

- Significant decrease in headache
  - ↓ severity of worst pain (P=.030)
  - ↓ number of headaches (P=.04)
  - ↓ acute medication use (19% less)
- Significant health improvements

Bunner AE, Agarwal U, Gonzales JF, Valente F, Barnard ND. Nutrition intervention for migraine: A randomized crossover trial. *J Headache Pain*. 2014;Oct 23;15:69.

Monoleukast



- Leukotriene Receptor Antagonist

- Trialed for migraine prophylaxis
  - No subpopulations identified
  - **Not effective** for migraine prophylaxis
  - Effective for chronic migraine?
  - Best outcomes dosed **30-40mg** daily
  - Some patients did very well

(Rapoport - discussion)

Low Dose Naltrexone

- Possible microglial antagonism
  - Toll-like receptor 4
- Possible hypthalamic pituitary adrenal homonal regulator
  - Growth Hormone
- Inexpensive
- Well tolerated
- Easy accessability

Low Dose Naltrexone - 4.5mg / night

- Double Blind, Placebo controlled, crossover trial

- Primary outcome –Reduced Pain
  - 28% reduction LDN
  - 18% reduction Placebo

YES

- Secondary endpoints
  - Improved Mood
  - Improved satisfaction with life
  - Improved sleep

YES

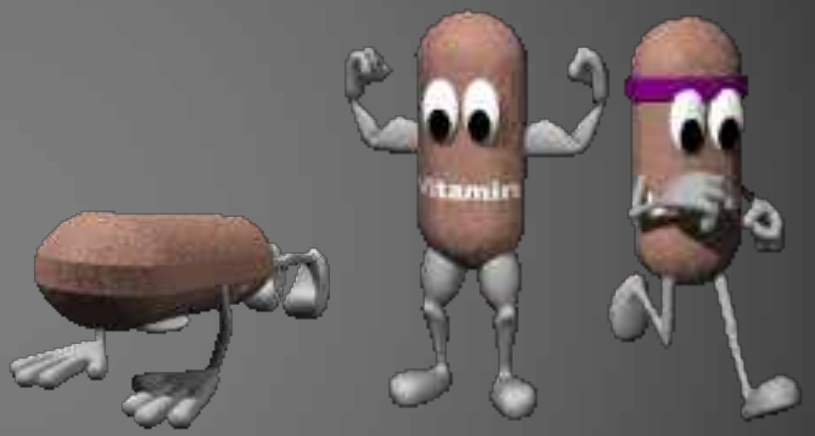
YES

No

(Younger, J et al., 2013)

Vitamin Therapy

- Magnesium glycinate (400 mg/d)
- Co enzyme Q10 (150 mg/d)
- Feverfew
- Butterbur
- Vitamin B2



- Petasites (Butterbur)
  - Caution due to hepatic toxicity
  - All forms of butterbur are banned in the United Kingdom

Magnesium and migraine

Magnesium oxide 9 mg/kg

86 of 118 completed;

"statistically significant downward trend in HA frequency over time in magnesium oxide group but not placebo group"

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 and migraine

- Start with 500 mg of magnesium oxide
  or chelated magnesium combination
- If not tolerated - magnesium citrate, Slow-Mag
- If tolerated but ineffective consider increasing the dose to 500 mg BID
- Take with food

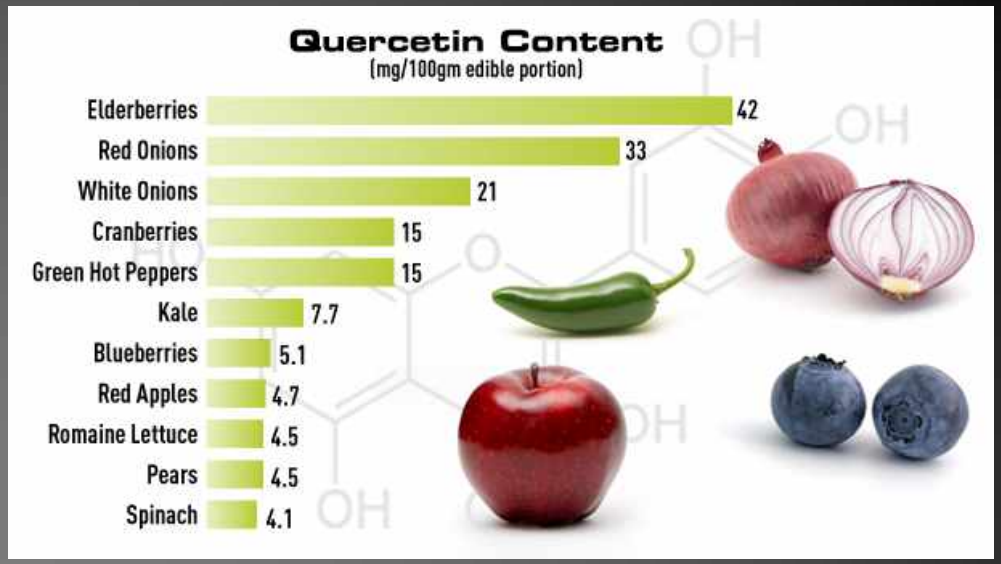
Boswellia Serrata

- Ayervedic treatment
- ↓Prostaglandin synthesis
  - Lipoxygenase (LOX) inhibitor
- Similar to indomethacin

- 375mg bid – 750mg bid
- Gliacin formulated specially for headache populations

Gliacin for the Prophylactic Treatment of Migraine: Review of an initial case series.
Eross EJ. Headache 2014. 54(8)1418-34.

Quercetin



- Bioflavanoid compound
- Mast cell stabilizer
- Reduces inflammatory markers
  - Interleukin 6
  - Histidine decarboxylase
  - tryptase

- Dose - Quercetin 500mg twice a day

- Beneficial for migraine patients with inflammatory / hypersensitivity symptoms?

Kempuraj D, Castellani ML, Petrarca C, Frydas S, Conti P, Theoharides TC, Vecchiet J. Inhibitory effect of quercetin on tryptase and interleukin-6 release, and histidine decarboxylase mRNA transcription by human mast cell-1 cell line. Clin Exp Med. 2006 Dec;6(4):150-6.

Acupuncture

- N=480 patients
- 20 treatments over 4 weeks
  - 3 treatment groups
    - (different acupuncture techniques)
  - 1 sham acupuncture group

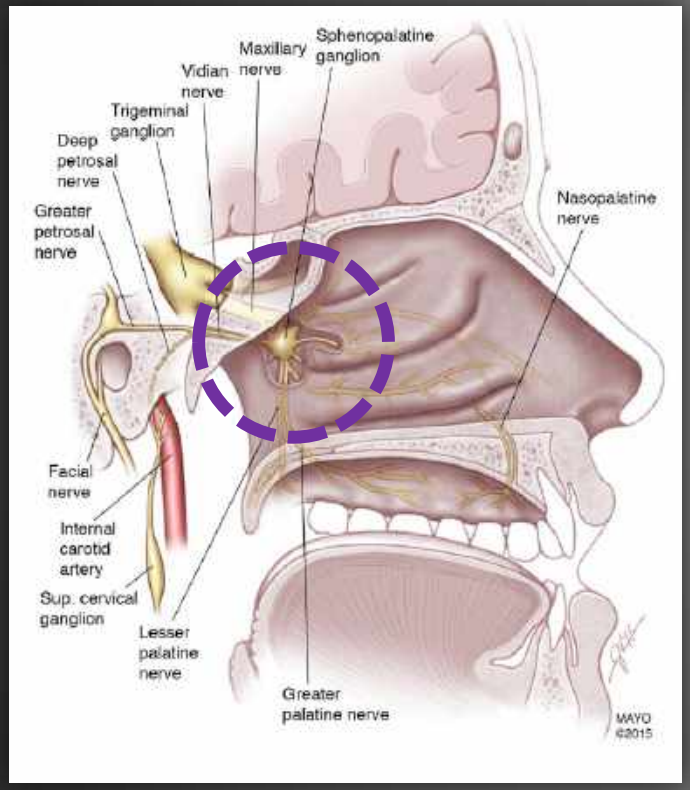
- In all 3 true treatment groups there was significant reduction of days with migraine compared to sham acupuncture at 12 weeks

Li Y, Zheng H, Witt CM, et al. Acupuncture for migraine prophylaxis: a randomized controlled trial. *CMAJ* 2011.

Autonomic Nervous System

- Autonomic nervous system
  - Regulates normal body function
    - blood pressure, temperature, sweating, heart rate
    - Eye watering, facial swelling, nasal stuffiness, blood vessel dilation, facial temperature
- Dysautonomia
  - Impaired autonomic nervous system
  - Seen in various headache types

Sphenopalatine Ganglion



- Autonomic control center of head
  - Contains autonomic nerves
    - Go to the brain and face
  - Contains pain nerves that go to the meninges
    - Includes pain locations such as behind eye and temples
- Sphenopalatine ganglion block
  - Applying anesthetic to this region to inhibit activation
  - May help headache and facial pain

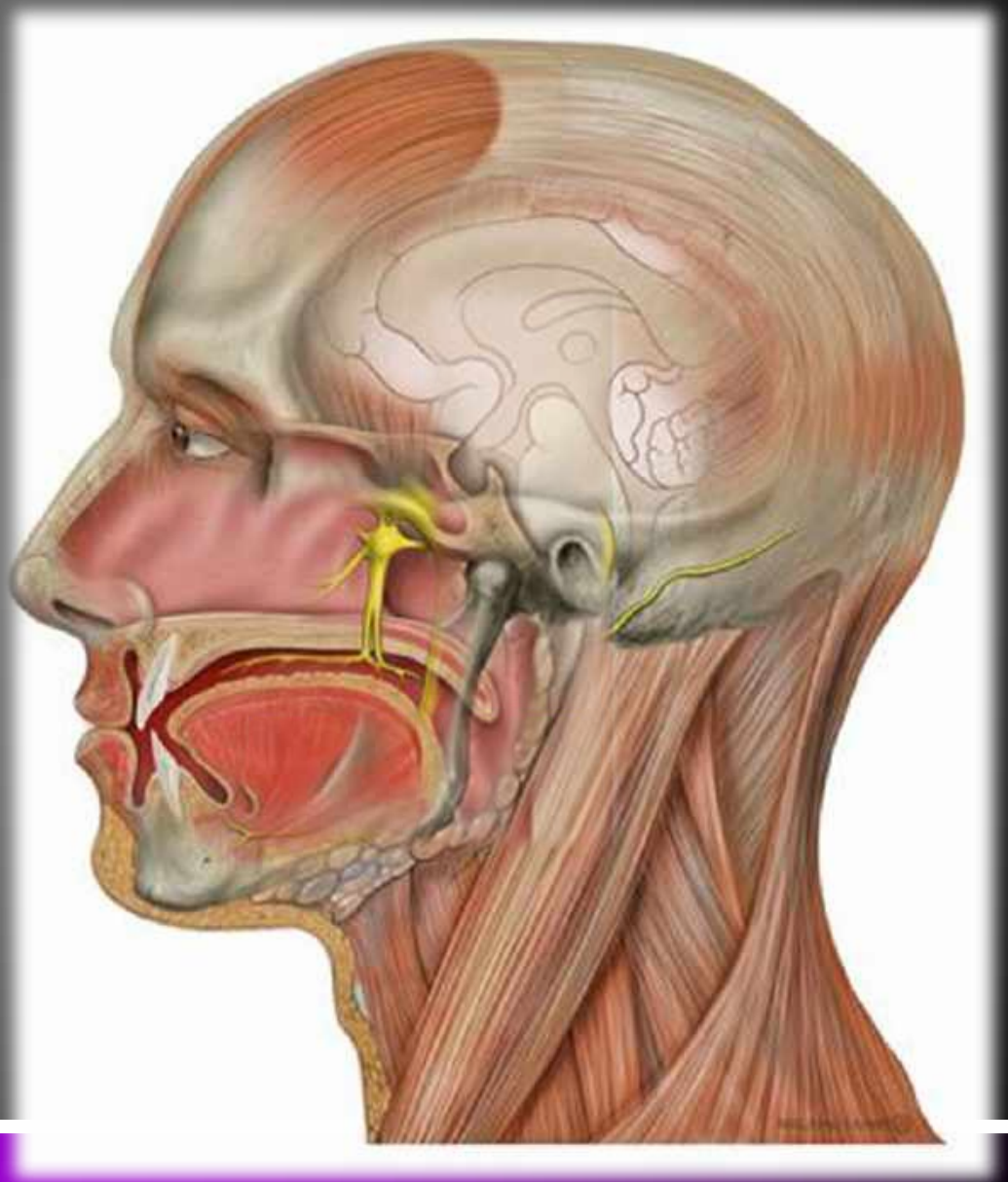
Sphenopalatine Ganglion Role in Pain

- Trigeminal nociception
  - Part of Maxillary nerve (V2)
  - Branches to the Ophthalmic nerve (V1)
    - Innervates optic nerve dura and periorbital regions
  - Middle Meningeal nerve
    - Innervates temple and parietal dura

SPG has famous receptors

5ht1D receptors

CGRP receptors

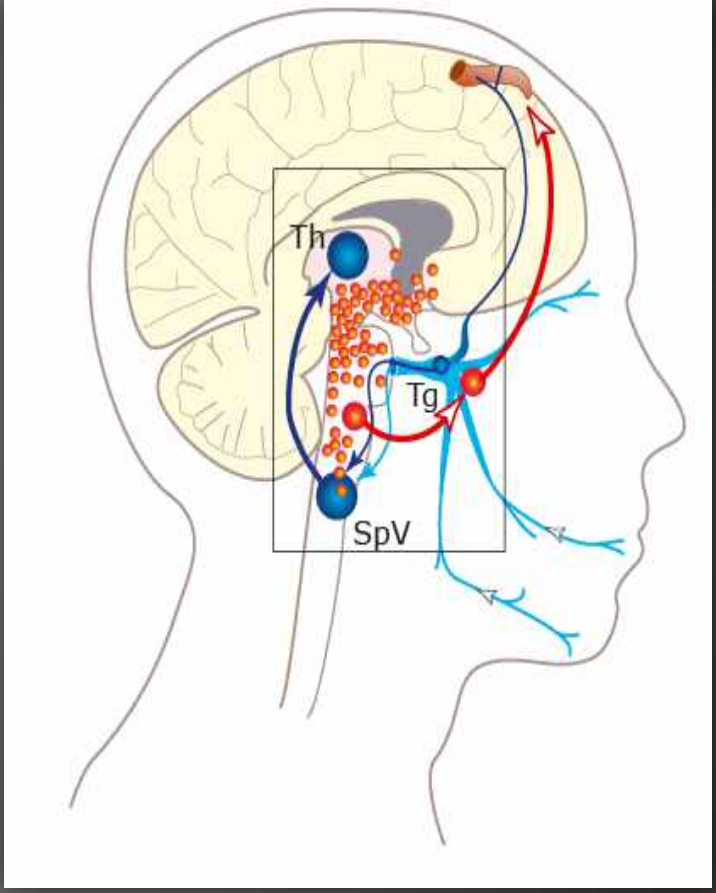


Oomen KP, Ebbeling M, de Ru JA, Hordijk GJ, Bleys RL. A previously undescribed branch of the pterygopalatine ganglion. *Am J Rhinol Allergy*. 2011;25(1):50-53.

Autonomic Nervous System and Headache

Common headache triggers activate pain through the autonomic nervous system

- Certain odors
- Hunger
- Sleep deprivation
- Stress response



Red dots are areas of brain that coordinate headache triggers

Burstein R, Jakubowski M. Unitary Hypothesis for Multiple Triggers of the Pain and Strain of Migraine.J Comp Neurol. 2005;493(1):9-14.

What role does the Sphenopalatine Ganglion have in the head?

- Sympathetic activity
  - Sympathetic fibers course through the SPG on way to cranial structures
- Parasympathetic synapse
  - Fibers from the brainstem (superior salivatory nucleus) synapse in the SPG, then travel to cranial structures
- Trigeminal nociception

All of the above

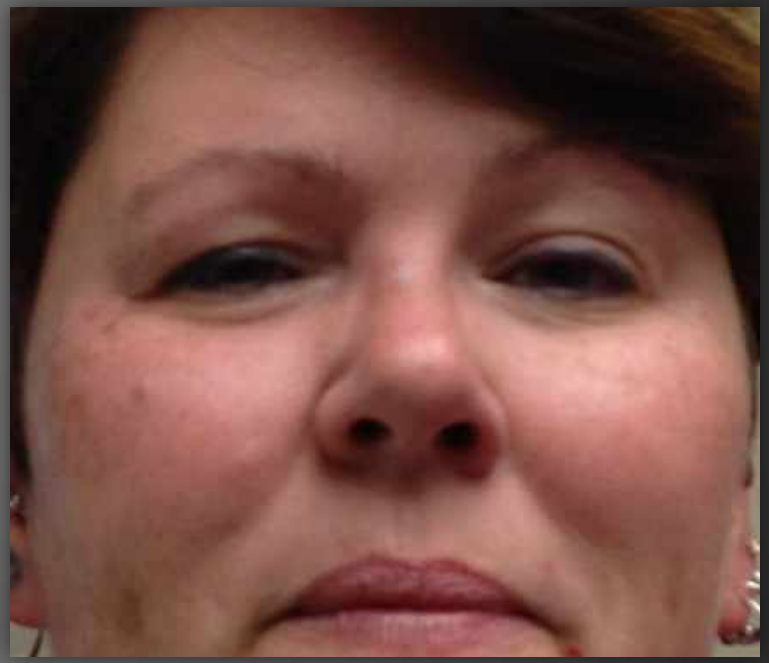
Cranial Autonomic Dysfunction

Dysautonomia during headache

82% of people with chronic migraine reported "autonomic symptoms"

- Eye watering 49%
- Eye redness 44%
- Orbit swelling 39%
- Ear fullness 30%
- Nasal congestion 20%

- Eyelid droop 42%

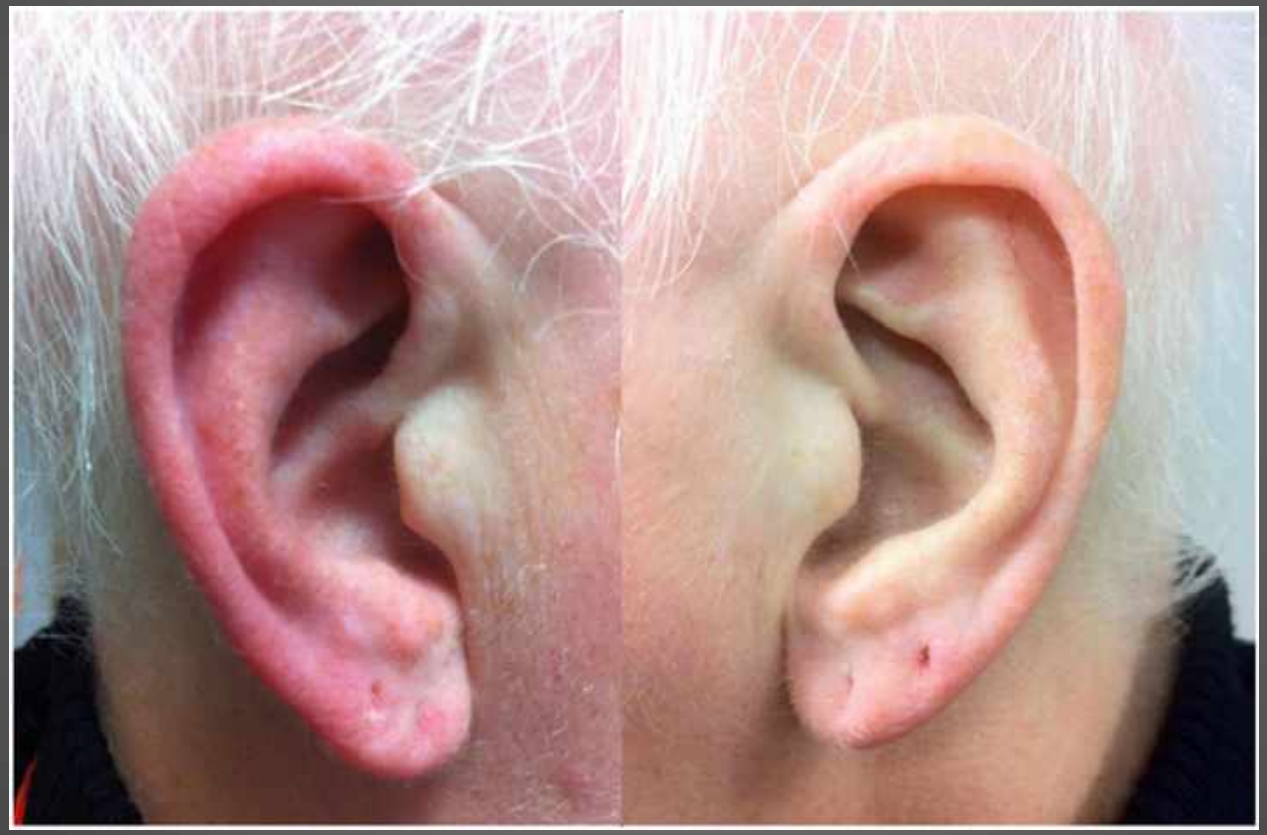


Riesco N, Perez-Alvarez AI, Verano L, Garcia-Cabo C, Martinez-Ramos J, Sanchez-Lozano P, Cernuda-Morollon E, Pascual J. Prevalence of cranial autonomic parasympathetic symptoms in chronic migraine: Usefulness of a new scale. Cephalalgia. 2016;36:346-350.

Migraine and Autonomic Instability

- Raynauds Phenomenon
  - Well established comorbidity
  - Typically not treated
  - Marker of neural hypersensitivity?
- Environmental intolerance
  - Meal skipping
  - Heat
  - Sleep pattern

Red Ear Syndrome



Lambru et al. The red ear syndrome. The Journal of Headache and Pain 2013, 14:83

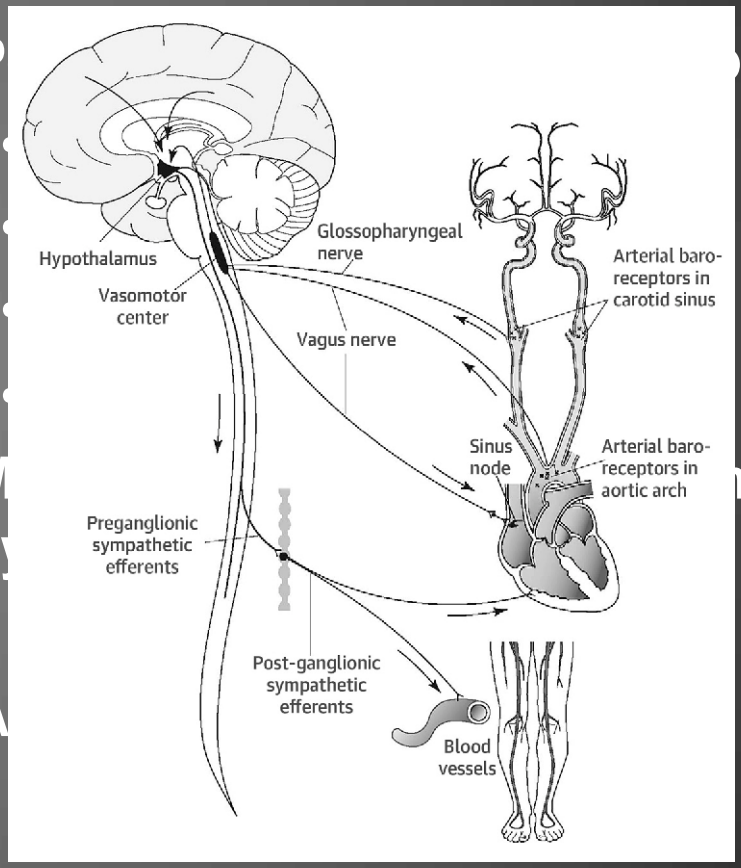
Positional Orthostatic Tachycardia Syndrome (POTS)

- Neuropathic (partial dysautonomic) POTS
  - Orthostatic Intolerance
  - 120 bpm or ↑>30bpm within 10 min of upright posture
  - Most common subtype of POTS
- Hyperadrenergic POTS
  - ↑SBP>10mm Hg during upright posture and tachycardia
  - Serum norepinephrine >600pg/ml
  - Associated with Mast Cell dysfunction?

Kanjwal K, Saeed B, Karabin B, Kanjwal Y, Grubb BP. Clinical presentation and management of patients with hyperadrenergic postural orthostatic tachycardia syndrome. A single center experience. *Cardiol J.* 2011;18(5):527-531.

Hyperadrenergic POTS

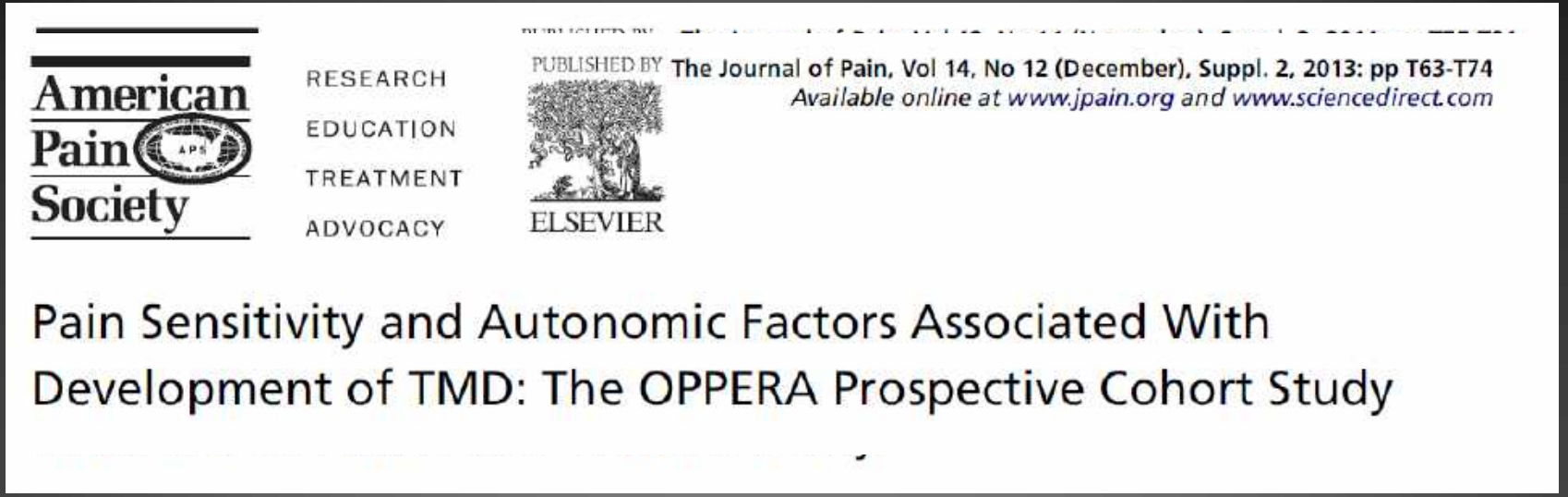
- C
- P rs:
- M a and s
- A



Shibao C, Arzubiaga C, Roberts LJ 2nd, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension*. 2005;45(3):385-390.

Hyperadrenergic Symptoms in Concussion

- 24 athletes with concussion
- How many had abnormal heart rate variability?
- How many had increased blood pressure with head up tilt table testing?



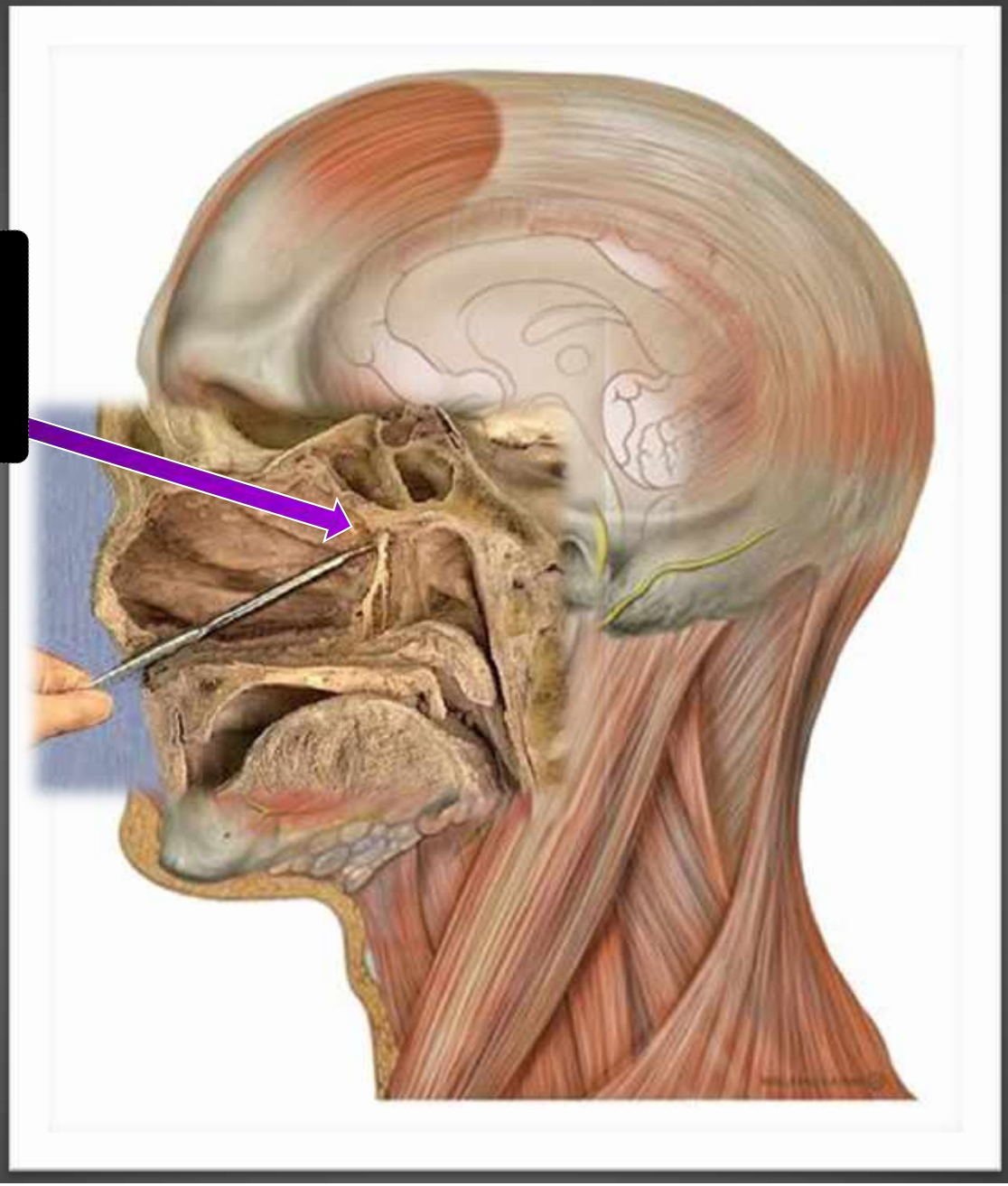
- 185 Chronic TMD vs. **2737 controls**
- followed for 5.2 years
- 260 developed TMD

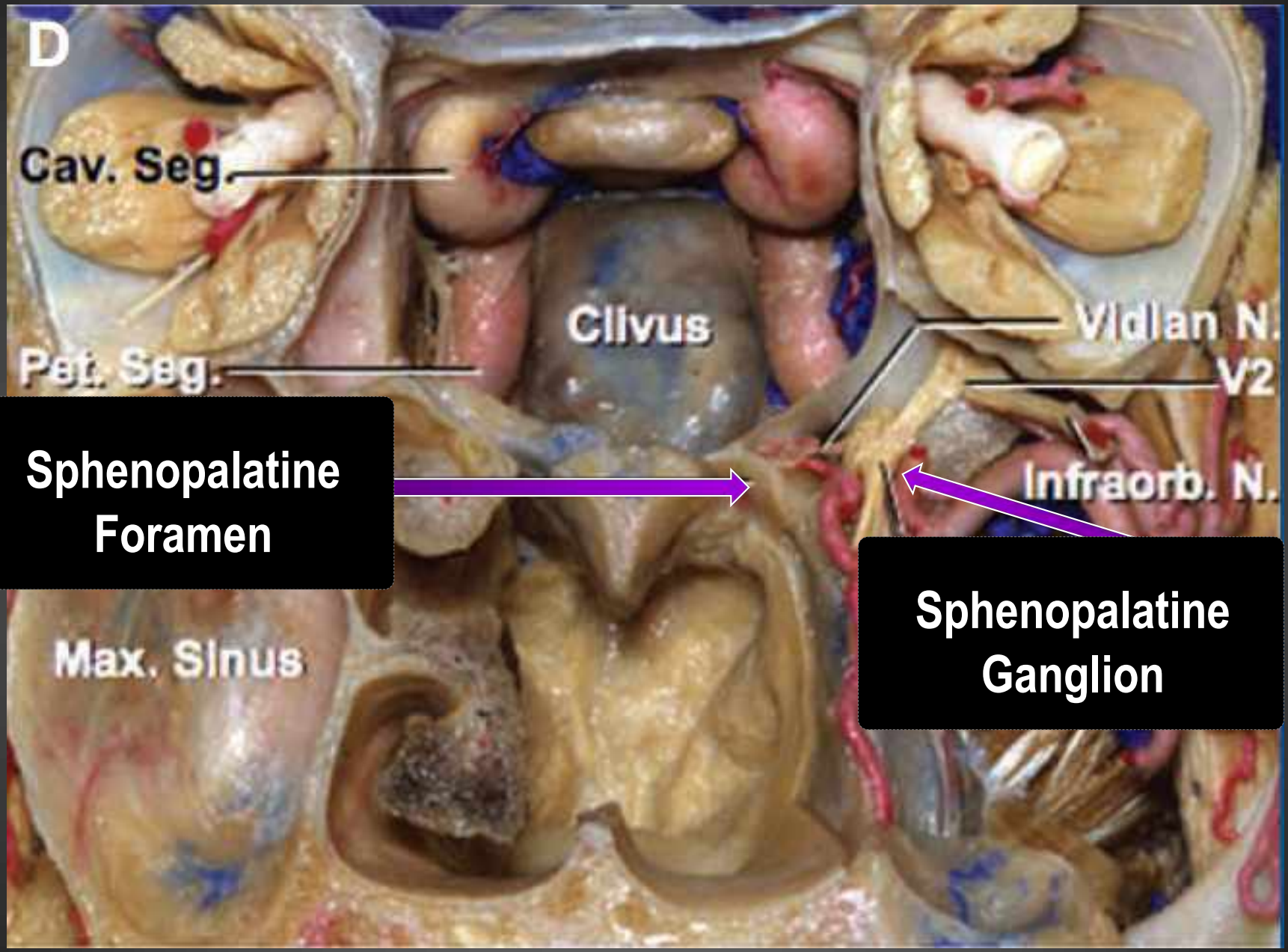
- Greater odds of TMD
  - ↑ Heart rate
  - ↓ Heart rate variability
  - ↓ Baroreflex sensitivity

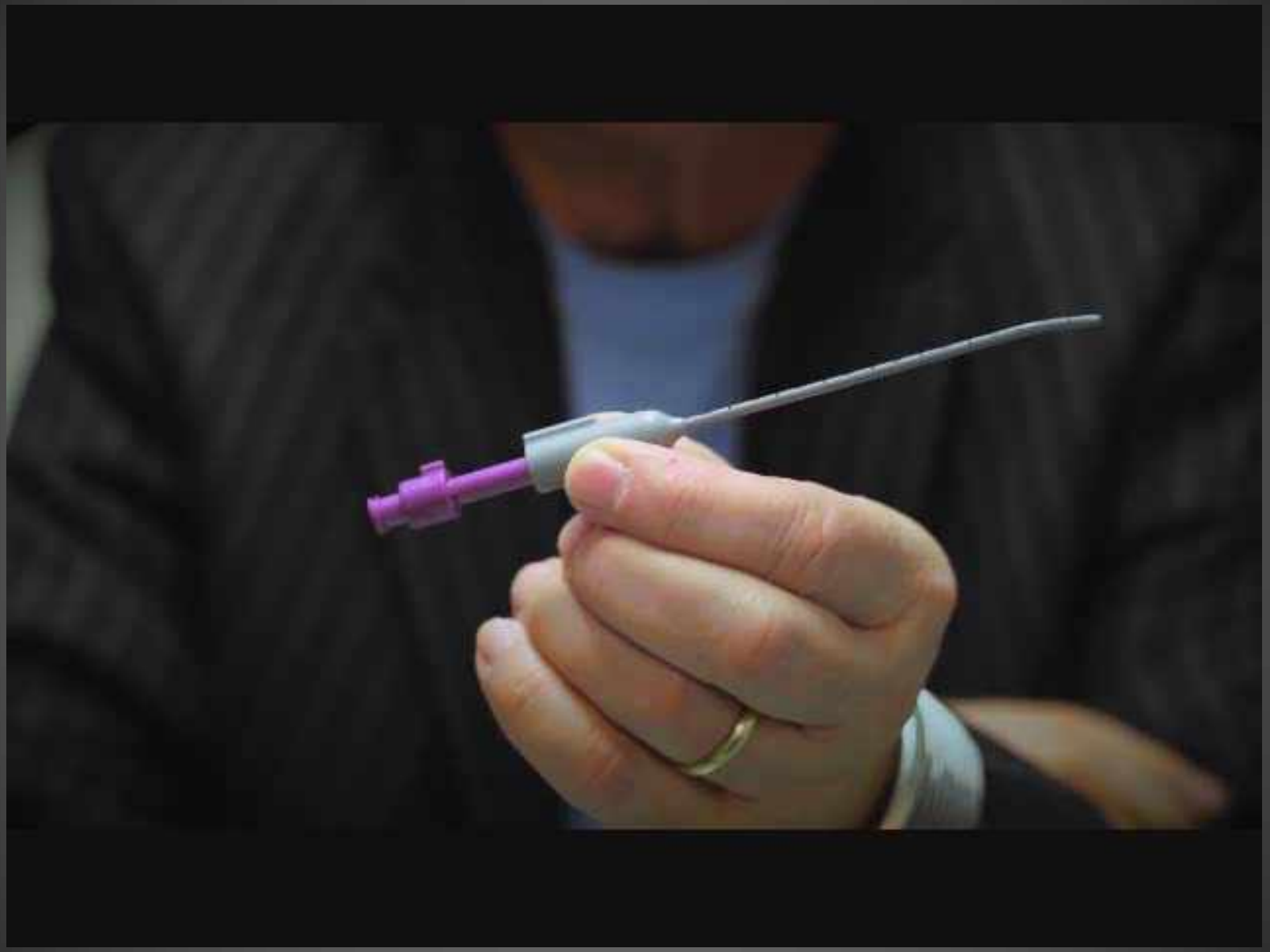
- Greater TMD incidence
  - Greater pain sensitivity
  - ↑ Heart rate
- No relation
  - ↓ Heart rate variability
  - ↓ Baroreflex sensitivity

Maixner W, Greenspan JD, Dubner R, et al. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain*. 2011;12(11 Suppl):T75-T91.
Greenspan JD, Slade GD, Bair E, et al. Pain sensitivity and autonomic factors associated with development of TMD:

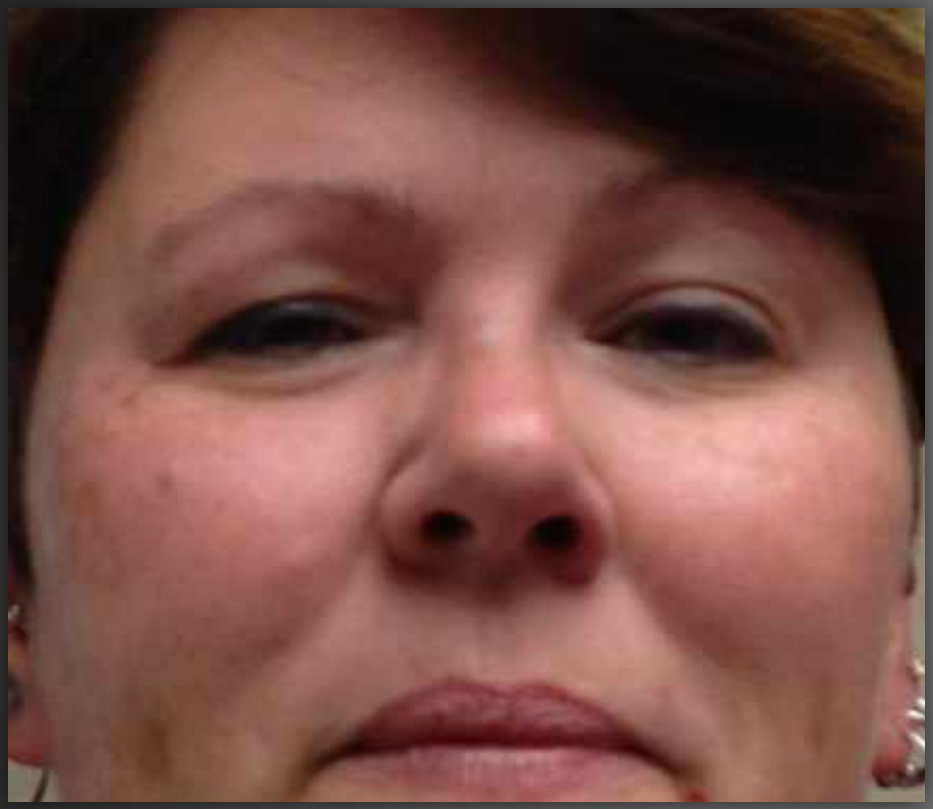
Sphenopalatine Ganglion




D
Cav. Seg.
Clivus
Vidian N.
Pet. Seg.
V2
Infraorb. N.
Sphenopalatine Foramen
Sphenopalatine Ganglion
Max. Sinus



The SPG Block Procedure



Research Submissions

2003 Wolff Award: Possible Parasympathetic Contributions to Peripheral and Central Sensitization During Migraine

David Yarnitsky, MD; Itay Goor-Aryeh, MD; Zahid H. Bajwa, MD; Bernard I. Ransil, PhD, MD; F. Michael Cutrer, MD; Anna Sottile, MD; Rami Burstein, PhD

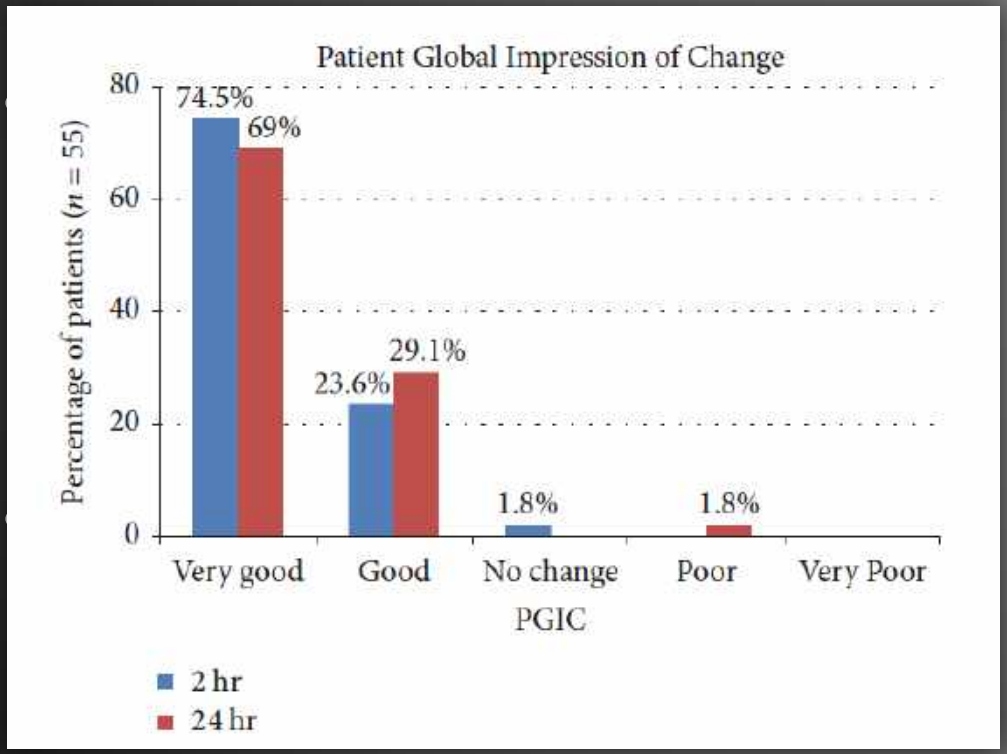
pressure. Their mean pain score was 7.5 of 10 (standard deviation, 1.4) during untreated migraine and 3.5 of 10 (standard deviation, 2.4) after the nasal lidocaine-induced sphenopalatine ganglion block ($P < .0001$). Most patients

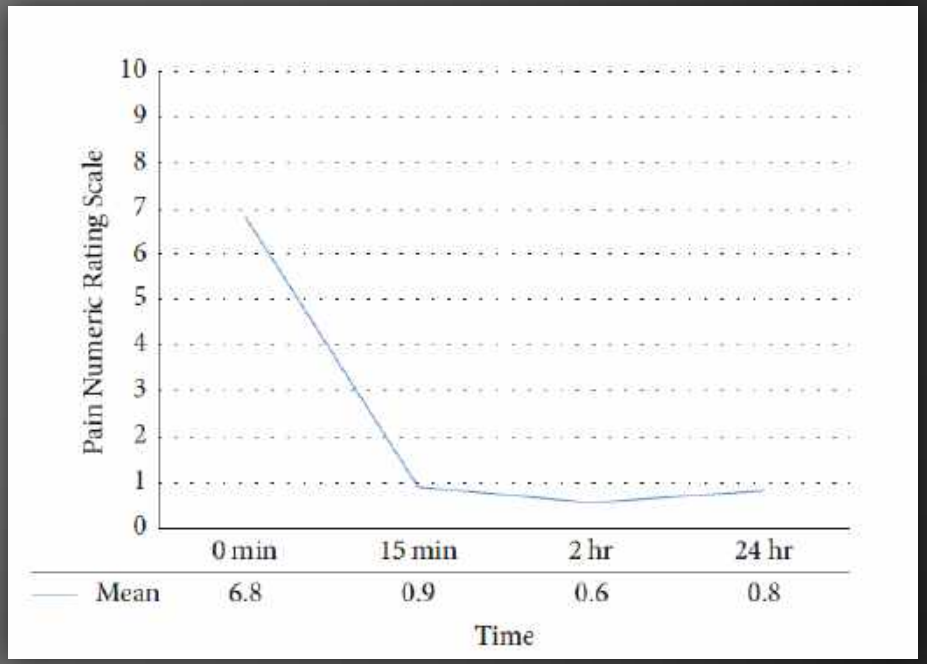
Conclusion.—These findings suggest that cranial parasympathetic outflow contributes to migraine pain by activating or sensitizing (or both) intracranial nociceptors, and that these events induce parasympathetically independent allodynia by sensitizing the central nociceptive neurons in the spinal trigeminal nucleus.

Yarnitsky D, Goor-Aryeh I, Bajwa ZH, Ransil BI, Cutrer FM, Sottile A, Burstein R. 2003 Wolff Award: Possible parasympathetic contributions to peripheral and central sensitization during migraine. *Headache* 2003;43:704-714

Sphenopalatine Ganglion Block for the Treatment of Acute Migraine

- 55 Patients with acute migraine received bilateral SPG block





Binfalah M, Alghawi E, Shosha E, Alhilly A, Bakhiet M. Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache. *Pain Res Treat.* 2018;2018:2516953.

SPG Block in Acute Facial Pain

89 patients studied in the Emergency Department with acute facial pain

- Mostly toothache (77)
- SPG block versus medication
- Statistically significant pain relief at 30 and 60 minutes
- Statistically significant improvement on McGill pain questionnaire

Transnasal
easy to perfrom, effective
of pain, and not age related
and low-cost treatment in t

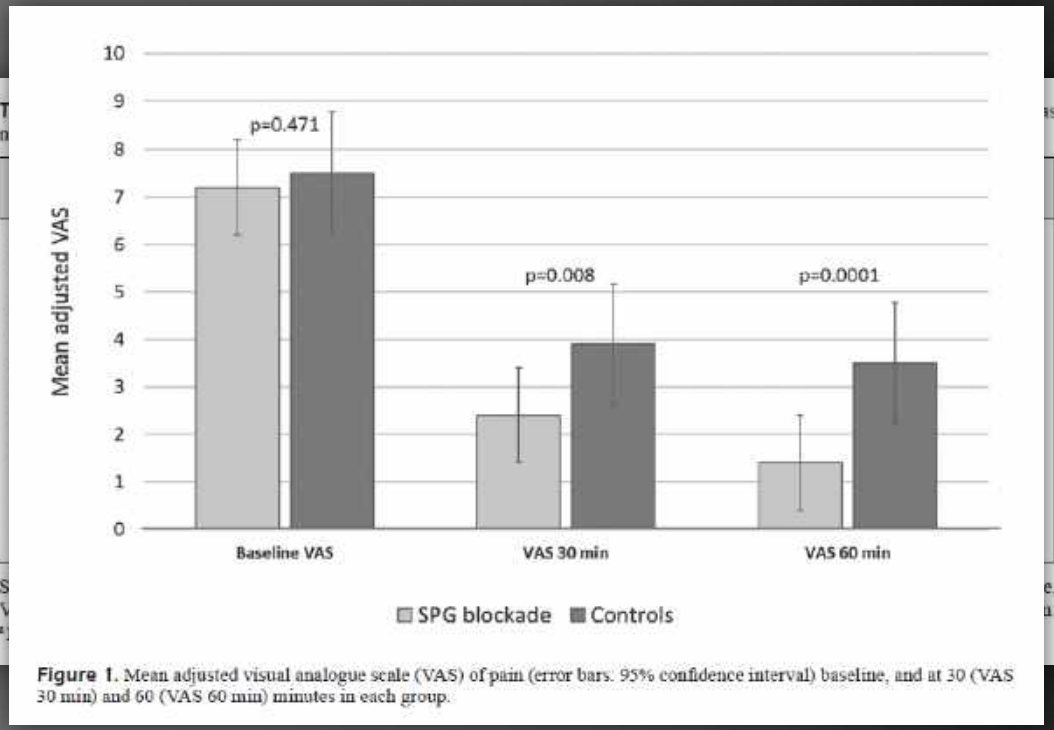


Figure 1. Mean adjusted visual analogue scale (VAS) of pain (error bars: 95% confidence interval) baseline, and at 30 (VAS 30 min) and 60 (VAS 60 min) minutes in each group.

Zanella S, Buccelletti F, Franceschi F, et al. Transnasal sphenopalatine ganglion blockade for acute facial pain: a prospective randomized case-control study. *Eur Rev Med Pharmacol Sci.* 2018;22(1):210-216.

Sphenopalatine ganglion block: an external gate to modulate cardiac autonomic tone and suppress premature ventricular beats?

Dimitrios N. Katsaras, Chrysa K. Arvaniti, [...], and Dionyssios I. Leftheriotis

- **SPG block showed increased heart rate variability at 4 hours**
- **SPG block showed reduced ventricular arrhythmic burden at 5 hours**

Conclusions

SPG block is associated with a transient increase in those HRV parameters that mainly express parasympathetic activity. It is also followed by a significant decrease in ventricular arrhythmic burden. These findings imply an effect on cardiac autonomic tone with a potential favorable clinical impact on arrhythmogenesis.

Katsaras DN, Arvaniti CK, Flevari PG, et al. Sphenopalatine ganglion block: an external gate to modulate cardiac autonomic tone and suppress premature ventricular beats?. *Ann Transl Med.* 2018;6(23):457.

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International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Bilateral sphenopalatine ganglion block reduces blood pressure in never treated patients with essential hypertension. A randomized controlled single-blinded study☆

Helen Triantafyllidi [a,*], Chrysa Arvaniti [b], Antonios Schoinas [a], Dimitris Benas [a], Stefanos Vlachos [a], Leonidas Palaiodimos [a], George Pavlidis [a], Ignatios Ikonomidis [a], Chrysanthi Batistaki [b], Costas Voumvourakis [c], John Lekakis [a]

Conclusions: SPG block is a promising, minimally invasive option of BP decrease in hypertensives, probably through SNS modulation. Additionally, due to its anesthetic effect, SPG block might act as a method of selection for those hypertensive patients with an activated SNS before any other invasive antihypertensive procedure.

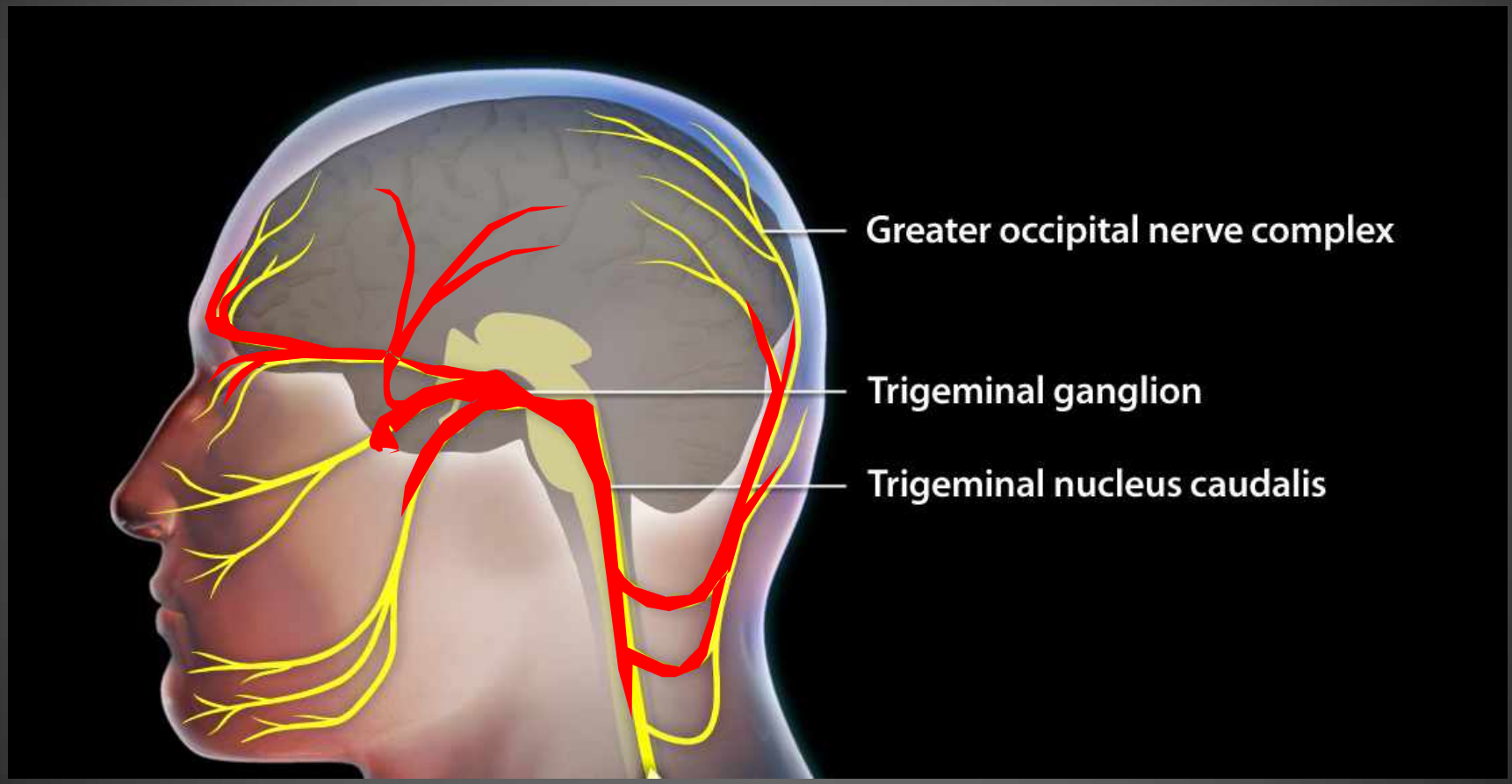
Triantafyllidi H, Arvaniti C, Schoinas A, et al. Bilateral sphenopalatine ganglion block reduces blood pressure in never treated patients with essential hypertension. A randomized controlled single-blinded study. *Int J Cardiol*. 2018;250:233-239.

SPG block and POTS

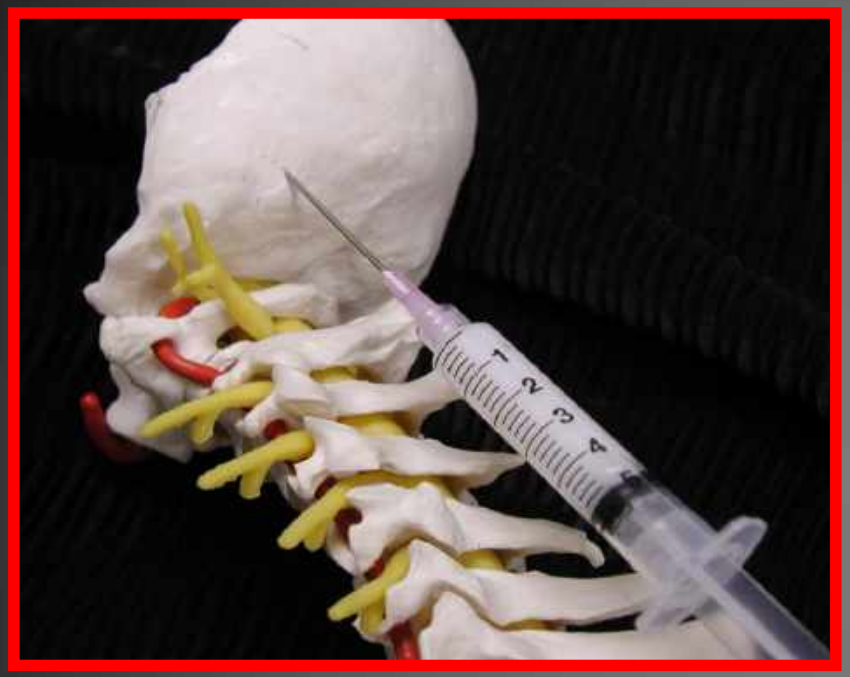
- 14 y/o female
- 3 year history of POTS
- Refractory to treatment
- Limited daily functioning
  - Absenteeism from school
  - Stopped athletics

- SPG block performed
  - ↑ Functionality
  - Return to sport

Trigeminal Nucleus Caudalis



Occipital Nerve Block

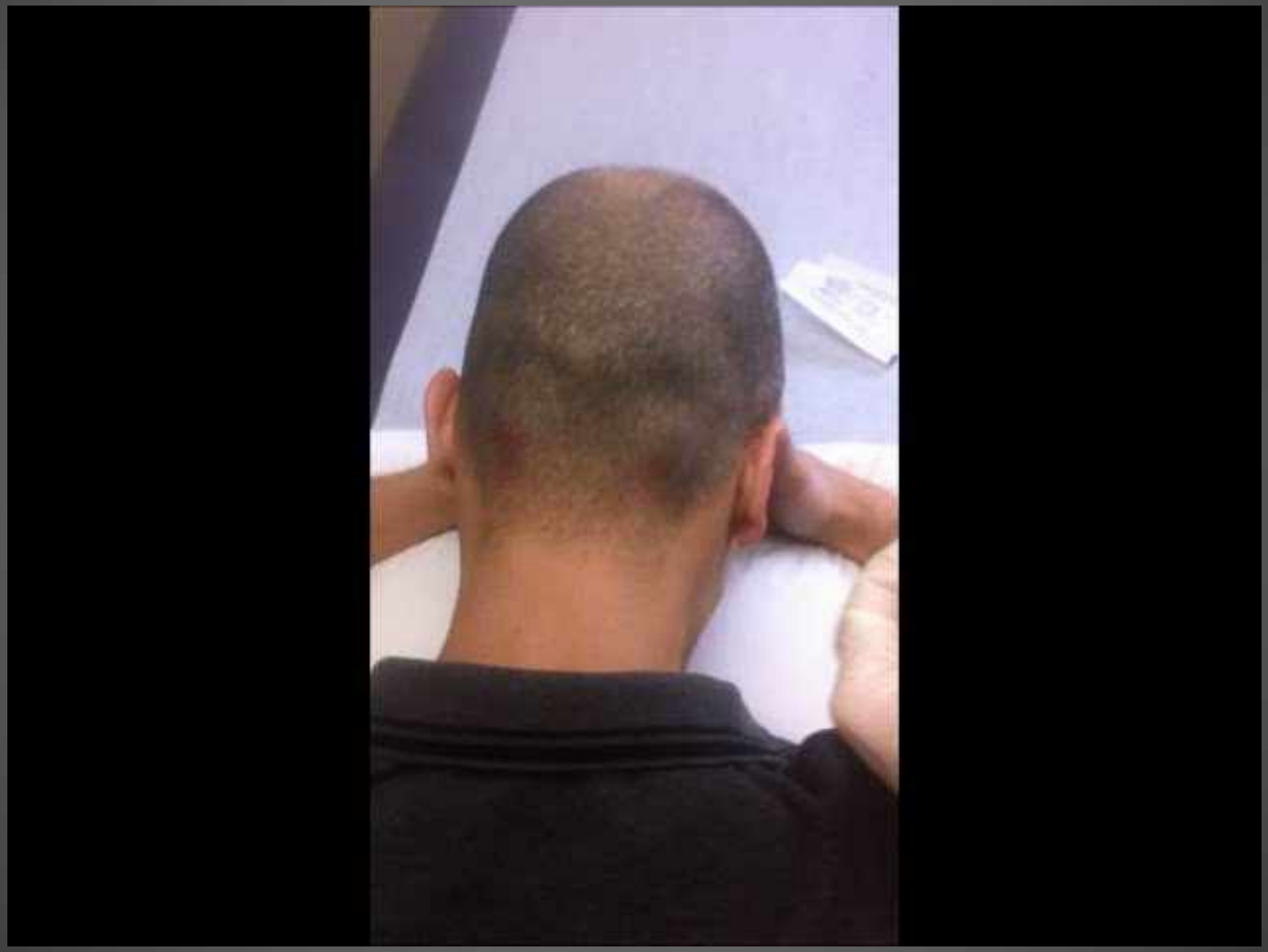


- Peripheral anesthetic blockade of the greater occipital nerve
- May end Cluster Cycle
- Effective for intractable migraine
  - Especially unilateral location
- erve
  it

Very safe procedure

- Not near brain
- Not near cervical cord
- Not near important vasculature

Occipital Nerve Block



Supraorbital and Supratrochlear Nerve Block

OnabotulinumtoxinA

- Thought to reduce release of CGRP from the trigeminal Nociceptors
- Not thought to be related to "relaxing muscles"
- May be effective in chronic migraine
- Well tolerated with minimal adverse events

Recommended injection sites for chronic migraine:

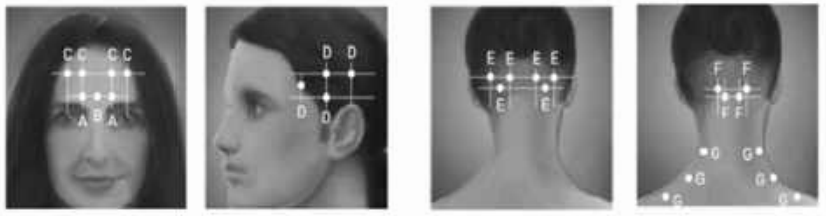


Table 1: BOTOX Dosing by Muscle for Chronic Migraine

Head/Neck Area	Recommended Dose (Number of Sites[a])
Frontalis[b]	20 Units divided in 4 sites
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis[b]	30 Units divided in 6 sites
Temporalis[b]	40 Units divided in 8 sites
Trapezius[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
Total Dose:	**155 Units** divided **in 31 sites**

[a] **Each IM injection site = 0.1 mL = 5 Units BOTOX**
[b] **Dose distributed bilaterally**

Pooled Efficacy of OnabotulinumtoxinA at Week 24

Endpoint, Mean Change From Baseline	BOTOX® (n=688)	Placebo (n=696)	p Value*
Frequency of HA days	-8.4	-6.6	<0.001
Frequency of migraine days	-8.2	-6.2	<0.001
Frequency of moderate/severe HA days	-7.7	-5.8	<0.001
Total cumulative HA hours on HA days	-119.7	-80.5	<0.001
% Patients with severe (≥ 60) HIT-6 score	67.6	78.2	<0.001
Total HIT-6 score	-4.8	-2.4	<0.001
Frequency of HA episodes	-5.2	-4.9	0.009
Frequency of migraine episodes	-4.9	-4.5	0.004
Frequency of acute HA pain medication intake (all categories)	-10.1	-9.4	0.247
Frequency of triptan use	-3.2	-2.1	<0.001

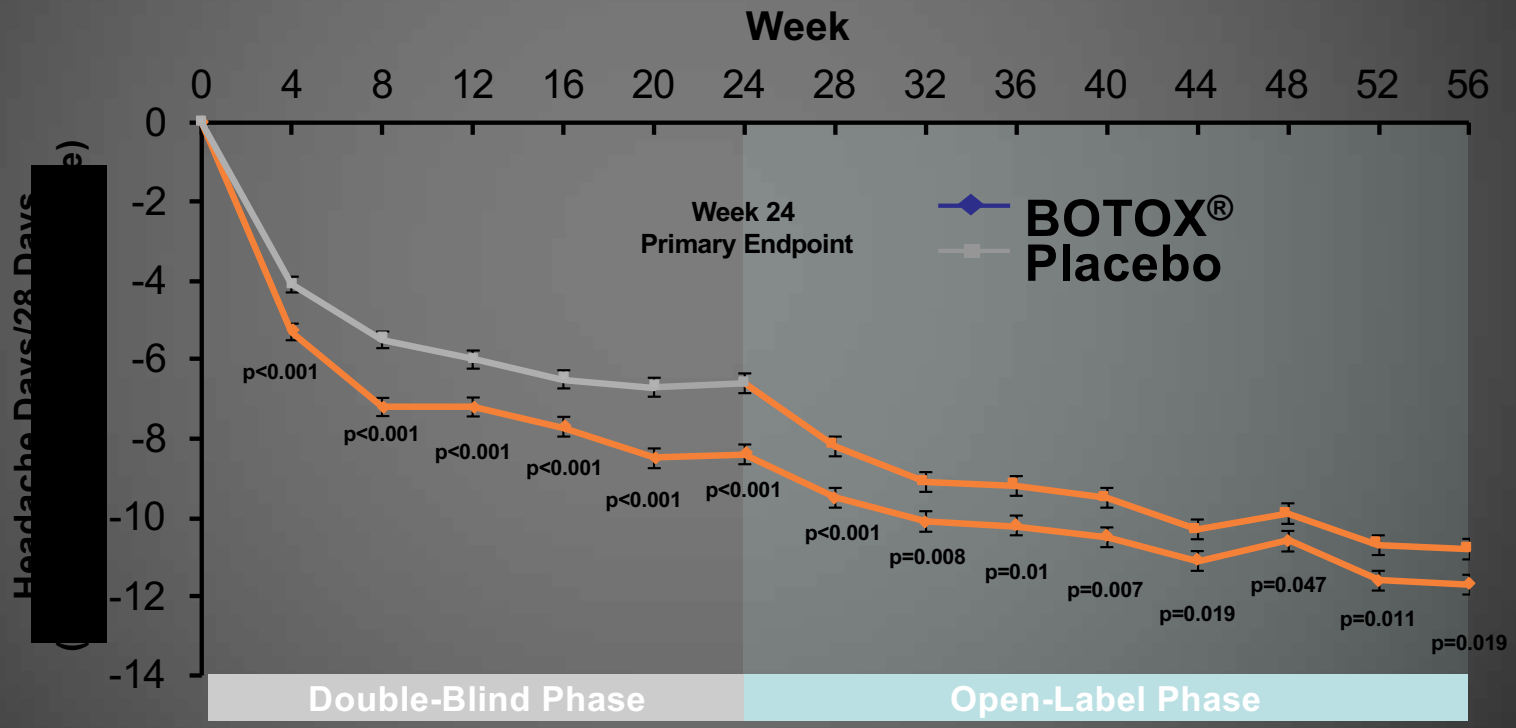
OnabotulinumtoxinA was statistically significantly more effective than placebo in reducing mean frequency of headache days at every visit in the double-blind phase starting at the first post-treatment study visit (Week 4)

HA = headache; HIT = Headache Impact Test.

Dodick DW et al. *Headache*. 2010;50:921-936.

PREEMPT Pooled Analysis: ~70% of Patients Achieved ≥50% Reduction in Headache Days at 56 Weeks

– Change in Headache Days: Primary Endpoint



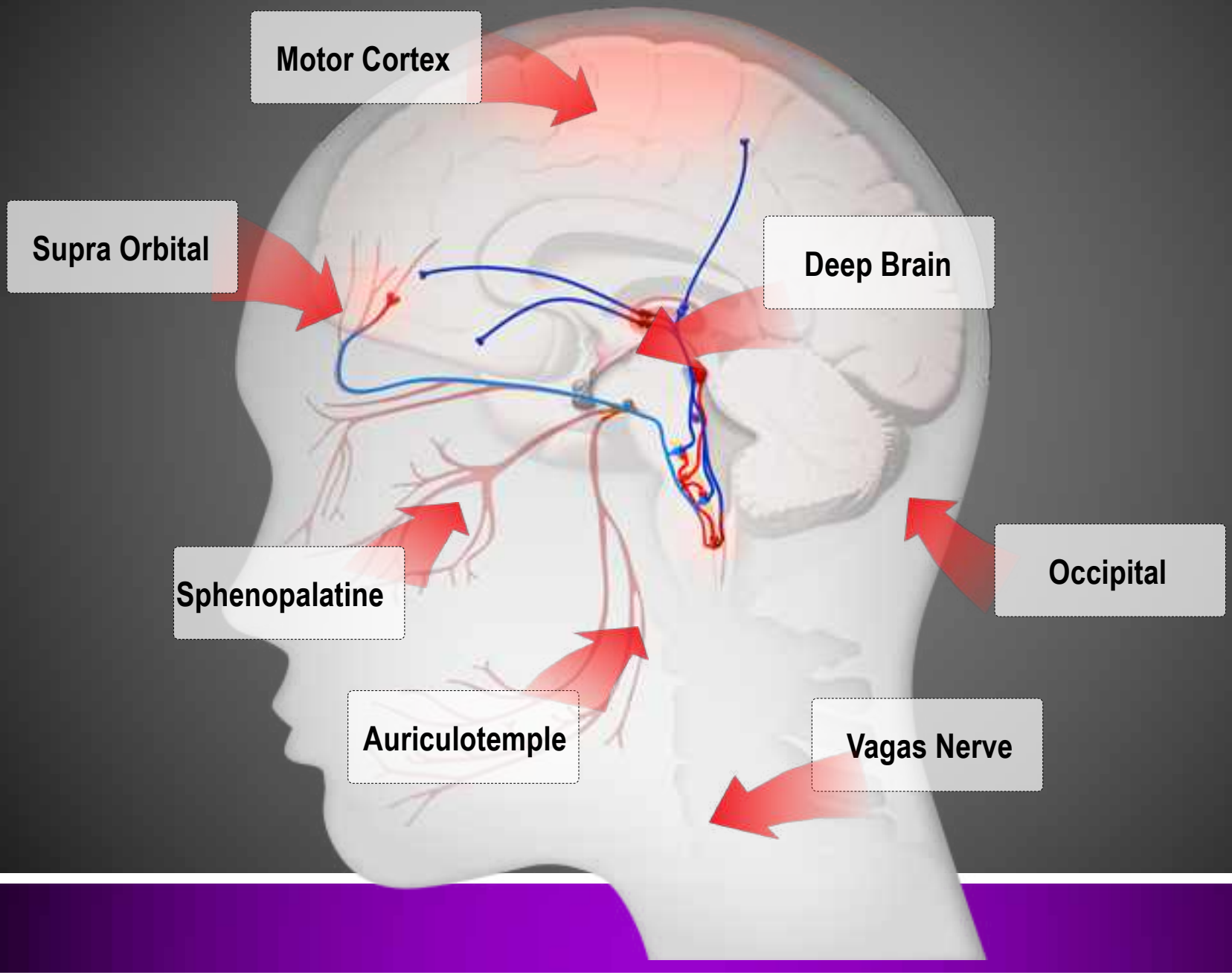
Mean ± standard error.

The double-blind phase included 688 subjects in the BOTOX® group and 696 in the placebo group.

Headache days at baseline: 19.9 onabotulinumtoxinA group vs 19.8 placebo group, p=0.498.

Aurora SK et al. Presented at IHC 2009.

Various Stimulator Locations



Noninvasive Vagus Nerve Stimulation

- Hand held device
  - (not implanted)
- Applies pulsed stimulation to the Vagus Nerve in the neck
- Well tolerated
  - Minimal discomfort
  - Platysmus muscle activation implies correct placement
- FDA approval for acute migraine, acute cluster ha, adjunctive prevention of migraine

Noninvasive Vagus Nerve Stimulator (nVNS)

Treatment of migraine pain (FDA approved)

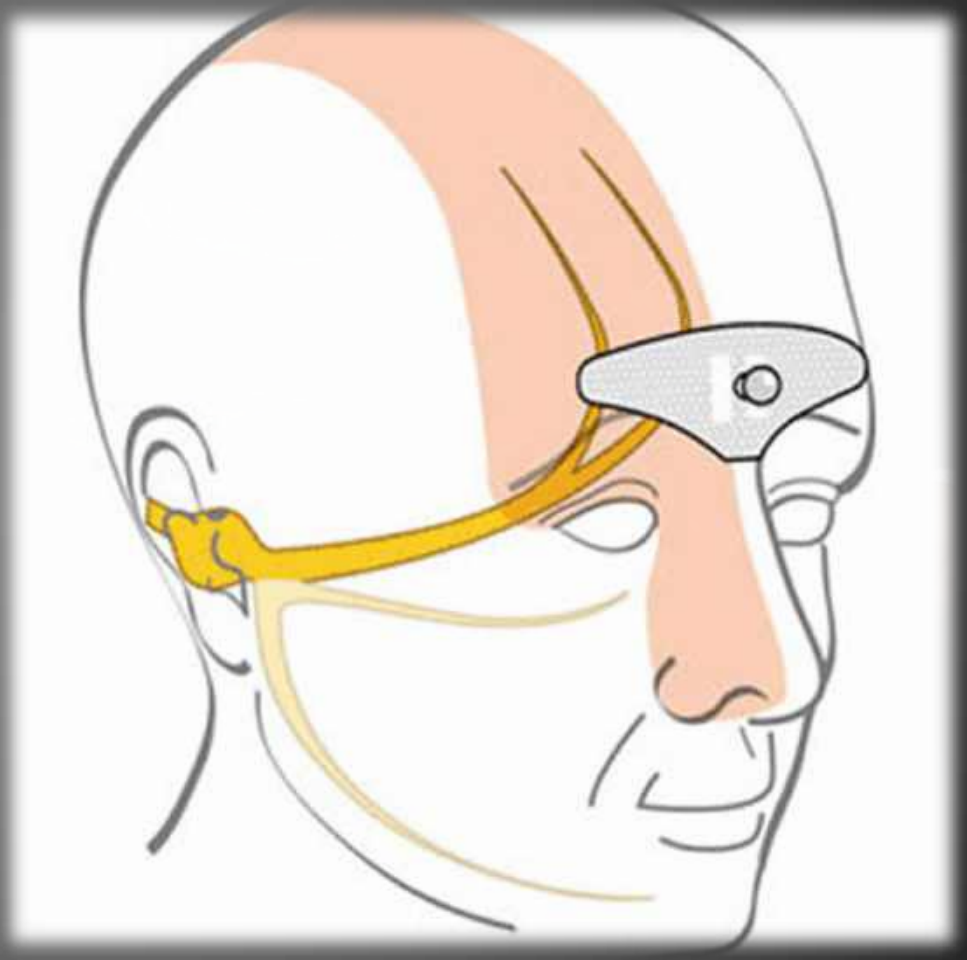
- PRESTO trial
  - N=243 subjects
  - Active nVNS vs. Sham device
  - Pain free
    - 30 mins (12.7% vs. 4.2%)
    - 60 mins (21.0% vs. 10.0%
  - Similar efficacy at 2 hours compared to triptans ?
  - Pain relief (mild to no pain)
    - 120 mins (40.8% vs 27.6%)

Tassorelli C, Grazzi L, de Tommaso M, Pierangeli G, et al. PRESTO Study Group. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. Neurology. 2018 [Epub ahead of print]

Trigeminal Nerve Stimulation (eTNS)

Peripheral TENs unit

FDA cleared for migraine, both acute and prevention



Acute Migraine

Prospective, open label

- N=30
- Migraine relief (VAS)
  - 1 hour - 57.1%
  - 2 hour - 52.8%

Chou DE, Gross GJ, Casadei CH, Yugrakh MS. External Trigeminal Nerve Stimulation for the Acute Treatment of Migraine: Open-Label Trial on Safety and Efficacy. Neuromodulation. 2017;20(7):678-683.

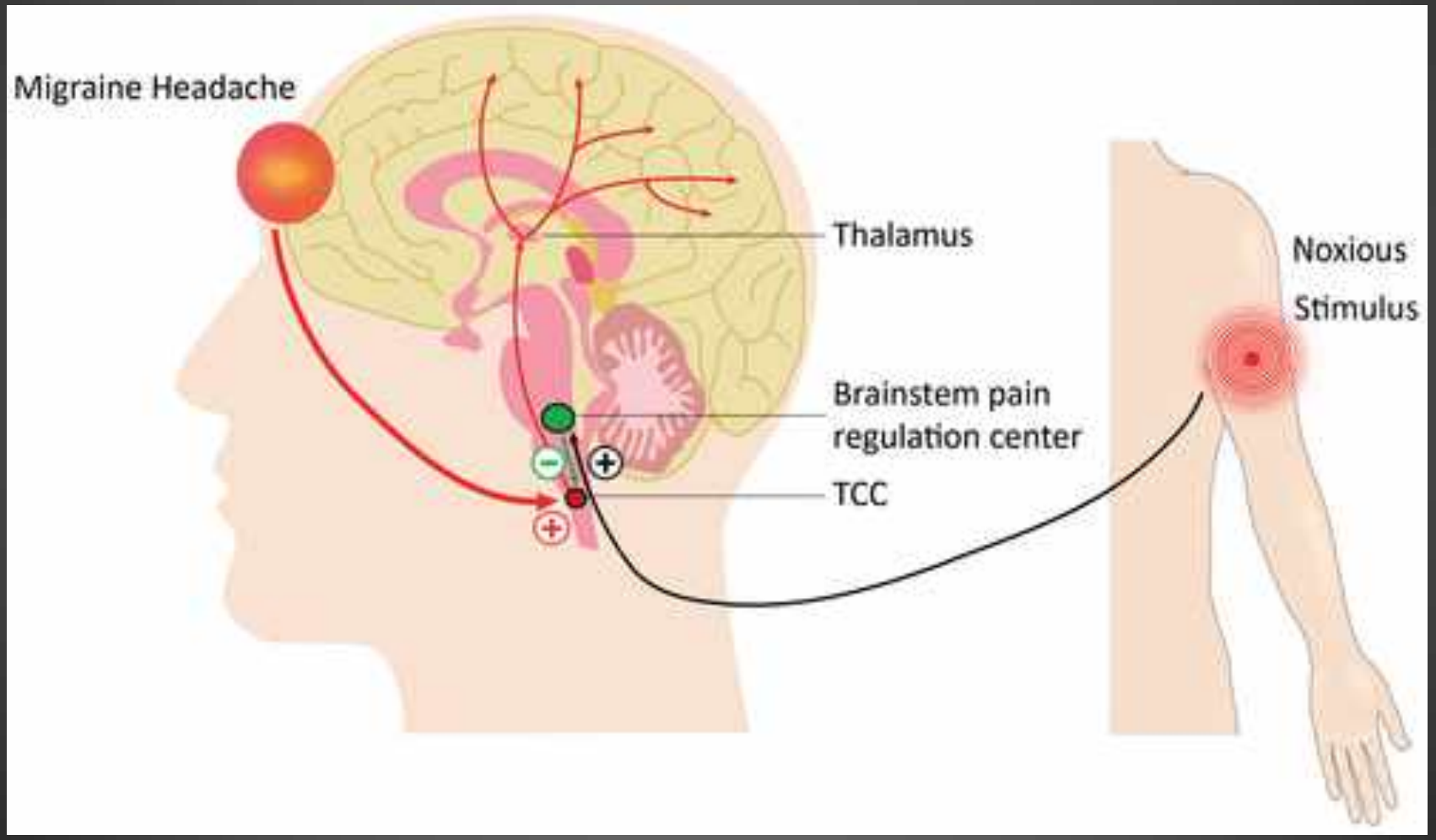
Trigeminal Nerve Stimulation (eTNS)

Migraine prevention

- Double-blind, randomized, sham controlled trial
- N=67 patients
- Treatment of 20mins daily
- Mean migraine days
  - T-SNS – 6.9 days to 4.8 days
    - 50% responder rate – 38.1%
  - Sham – 6.54 days – no difference
    - 50% responder rate – 12.1%

Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 2013;80(8):697-704.

Remote Electrical Neuromodulation (REN)



REN – Acute Migraine

- Double-blind, randomized, sham controlled trial
  - N= 202 patients
- Treatment
  - 30-45 mins device application
  - Within 1 hour of attack onset
- Primary endpoint was pain relief
  - Severe/moderate to mild / None or mild to none

  - REN – 66.7%
  - Placebo – 38.8%

Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, Lin T, Silberstein SD. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache. 2019 May 9. doi: 10.1111/head.13551. [Epub ahead of print]

Optimism for the Future

Therapies targeting the underlying "cause" of migraine

- Not just cover up symptoms!

Therapies designed specifically for headache

- About time!

Improved understanding of inflammation and pain

- See the big picture!