Migraine Update

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Migraine Update

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Migraine Update

Disclosures

Speakers Bureau :	AbbVie, BioHaven, ElectroCore, Eli Lilly, Impel, Teva
Advisory Board:	BioHaven, ElectroCore, Ely Lilly, Impel

Migraine Update

- Foundation
  - Think secondary causes first
- Migraine
  - Definitions & Diagnosis
  - Pathophysiology: History lessons and Current Concepts
- Migraine Treatment Options
  - Old & New
- Choosing Treatments
  - For the Patient In Front of You

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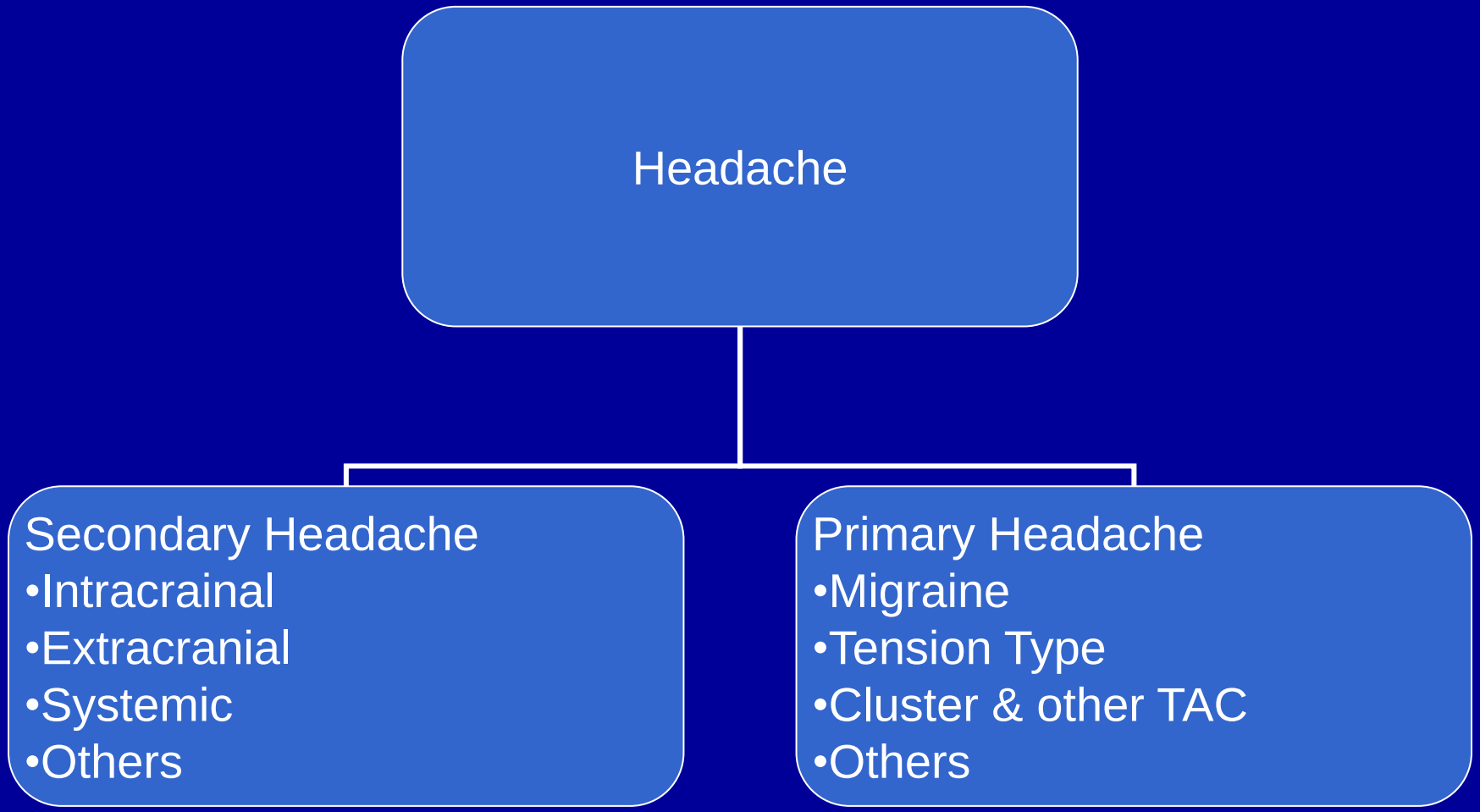
Foundation

Secondary Causes First

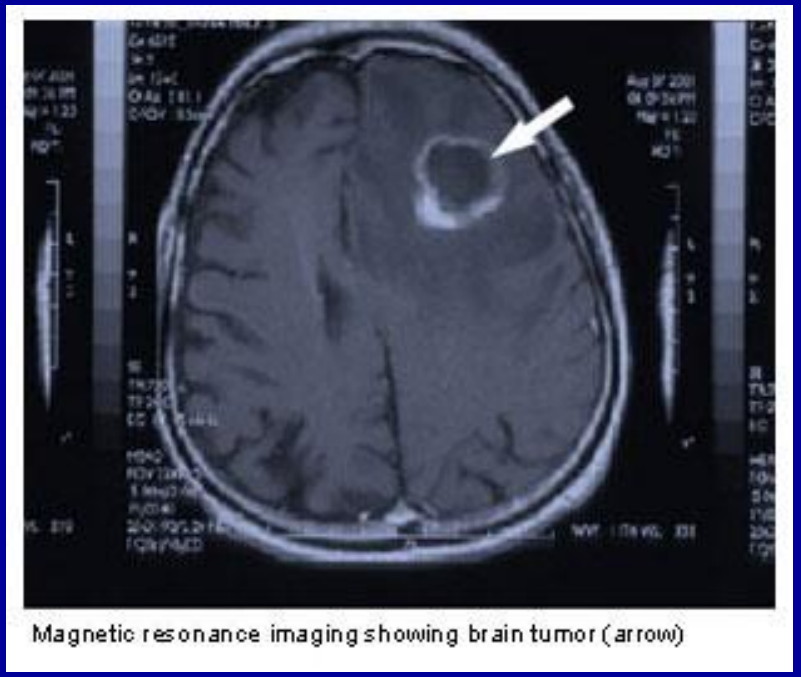


Foundation
Secondary Causes First

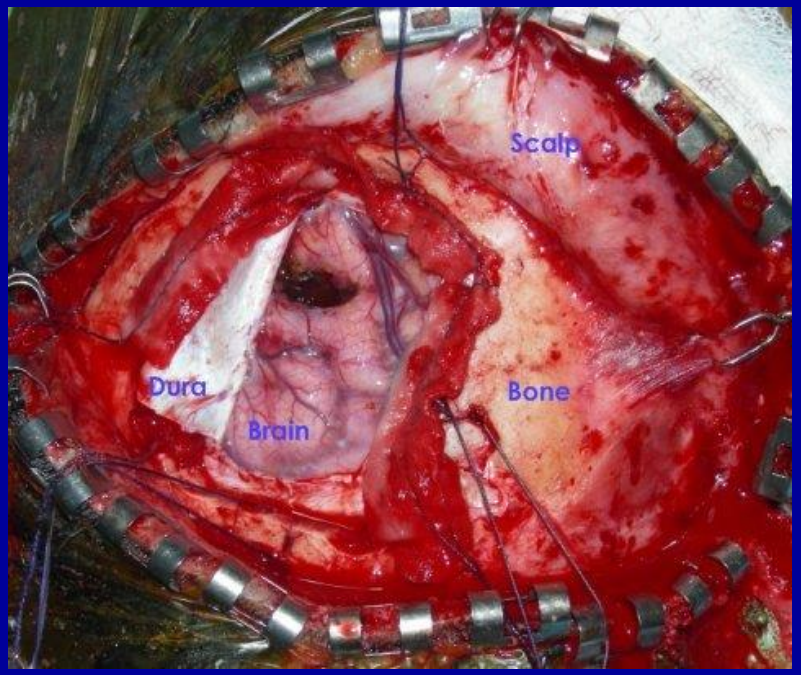
Examples – Secondary, Intracranial:

- Tumor
- Bleed/aneurysm
- Infection
- TIA/Stroke
- Obstructive Hydrocephalus
- Cerebral venous thrombosis
- CSF pressure dysregulation

Brain Tumor

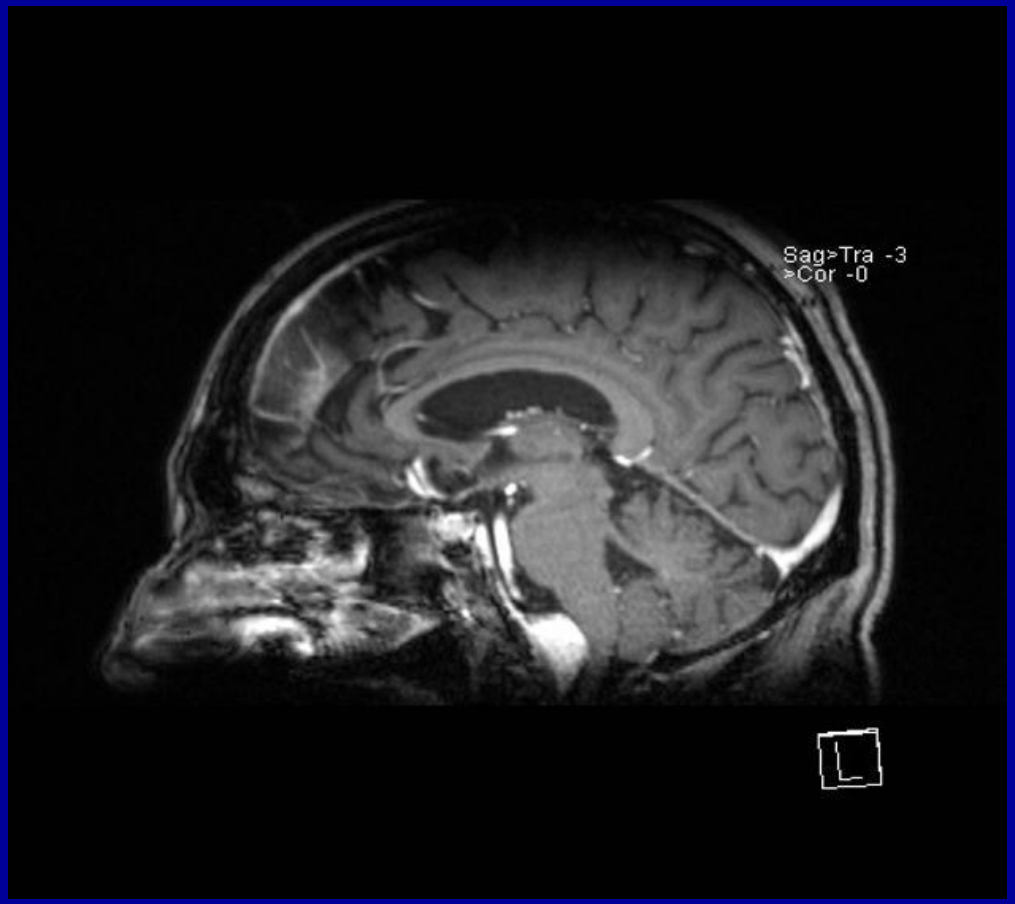


Magnetic resonance imaging showing brain tumor (arrow)

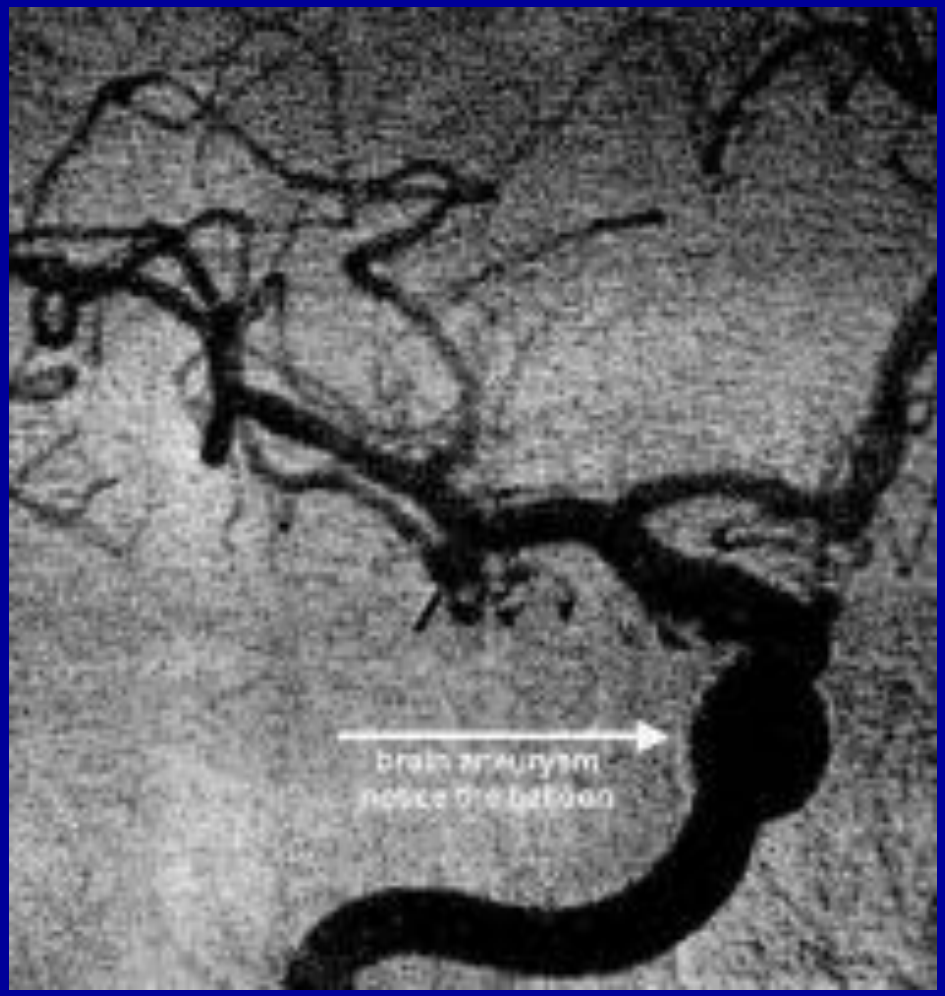


Meningioma - Clivus

- Symptoms: Headache, imbalance, snoring, slight dysphagia.



Brain Aneurysm

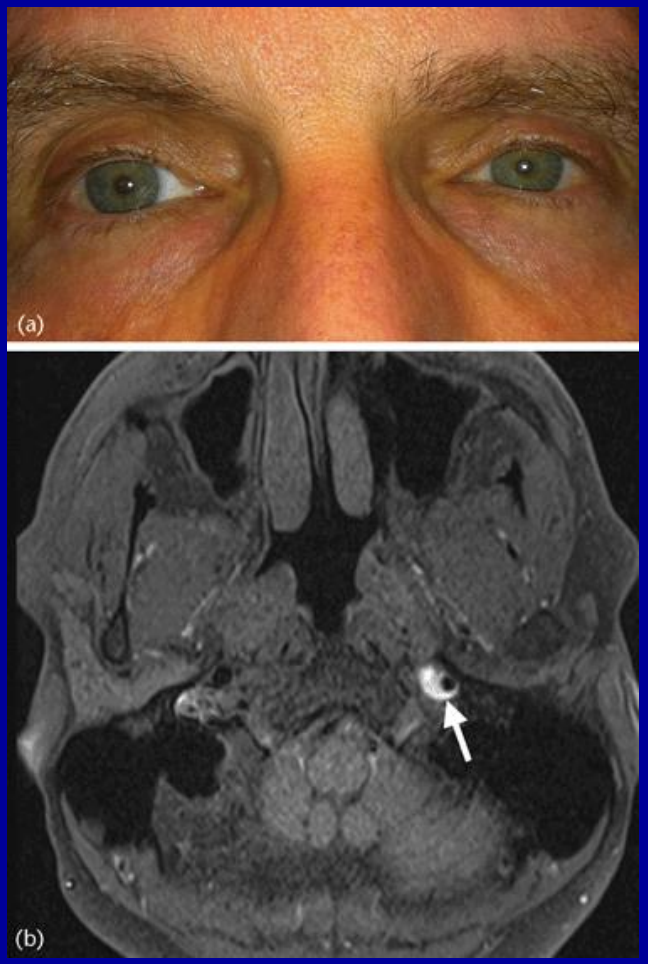


Foundation
Secondary Causes First

Examples – Secondary, Extracranial:

- Carotid/Vertebral artery dissection
- Cervical spine disorders
- Jaw & Dental disorders
- Acute Angle Glaucoma
- “True” Sinusitis

Carotid Artery Dissection



True Sinusitis

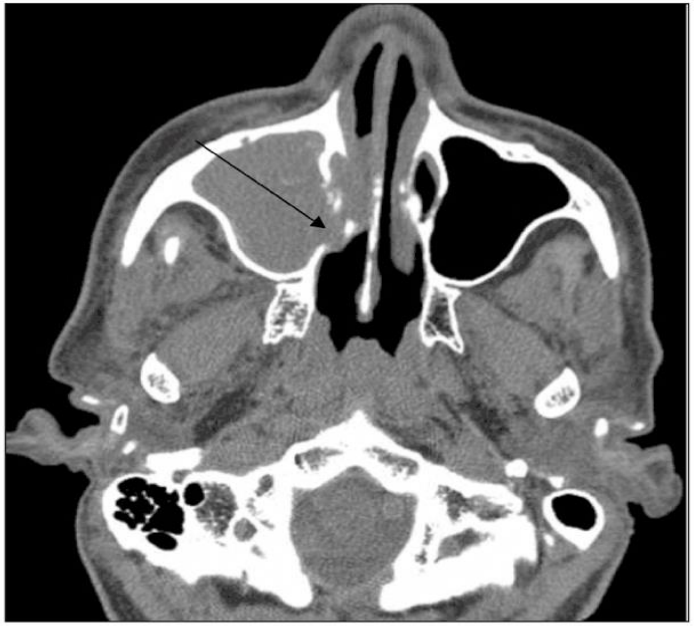


Figure 2 – *Noncontrast CT scan demonstrates complete opacification of the lumen of the right maxillary sinus with bony erosion/destruction medially (arrow) extending through the lamina papyracea. Not pictured here was the involvement of the ipsilateral orbital fossa.*

Foundation
Secondary Causes First

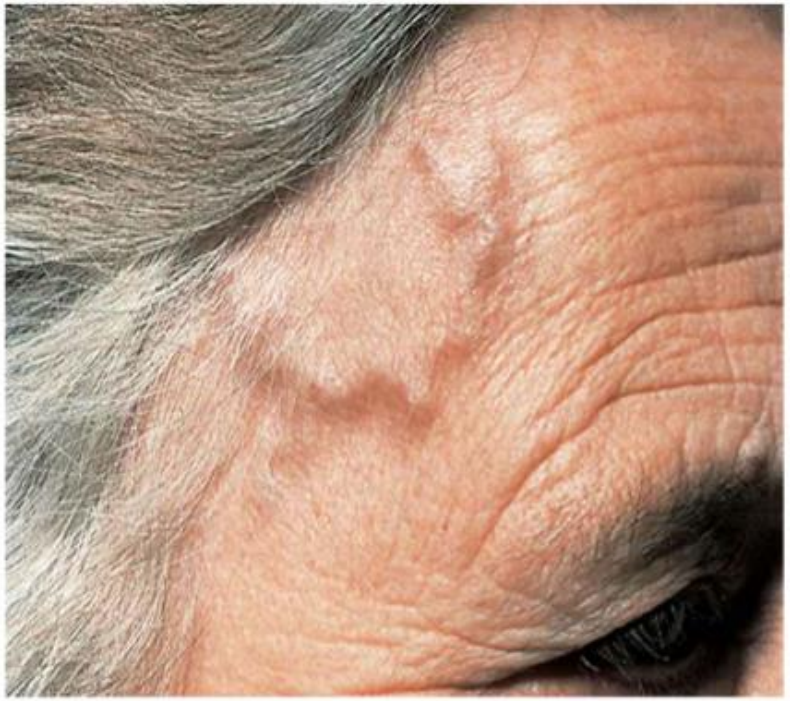
Examples – Secondary, Systemic:

- Hypertensive urgency/emergency
- Altitude sickness
- OSA/Hypoxia/Hypercapnia
- Polycythemia vera
- SLE
- Temporal arteritis and other vasculidities
- Many, many others

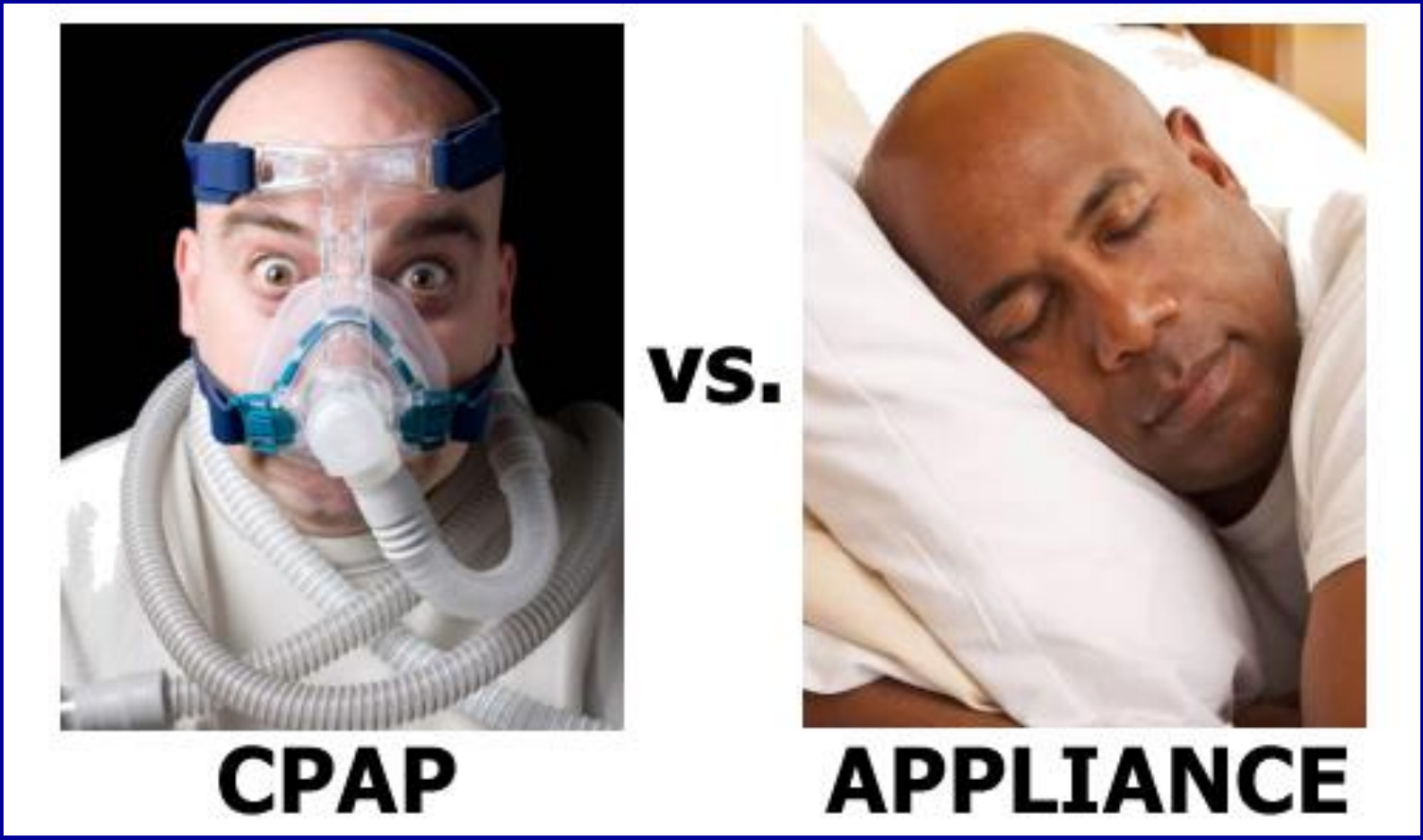
Temporal Arteritis

Diagnose it...

- Pain over temporal arteries
- Thickened, tortous artery
- Jaw claudication
- Visual loss



Obstructive Sleep Apnea



Foundation
Secondary Causes First

Take home message:

1. Secondary Causes First
   a) Intracranial
   b) Extracranial
   c) Systemic

2. Then think primary headache disorder
   a) Migraine
   b) Cluster
   c) Etc.

*Headache Management, Saper 42-60; Wolff's Headache, Goadsby 57-72; The Headaches, Olesen 9-16 55-217.The International Classification of Headache Disorders, 3beta, 2013. 629-808.

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Migraine
Definitions & Diagnosis

Diagnostic Criteria for Migraine (ICHD-3-beta)

History of ≥5 headache attacks that last 4-72 hours, with at least 2 of the following features:

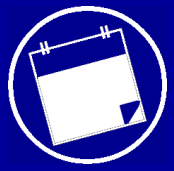
- ❑ Unilateral location
- ❑ Pulsating quality
- ❑ Moderate or severe pain intensity
- ❑ Aggravated by, or causing avoidance of, routine physical activity

Headache is accompanied by at least 1 of:

- ❑ Nausea and/or vomiting
- ❑ Phonophobia and/or photophobia

May be accompanied by aura:

Spreads gradually, affecting visual, sensory, speech/language, or motor function



Chronic migraine:

- ❑ Headache on ≥15 days/months for at least 3 months
- ❑ Features of migraine on at least 8 days/month

Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2013;33(9):629-808.

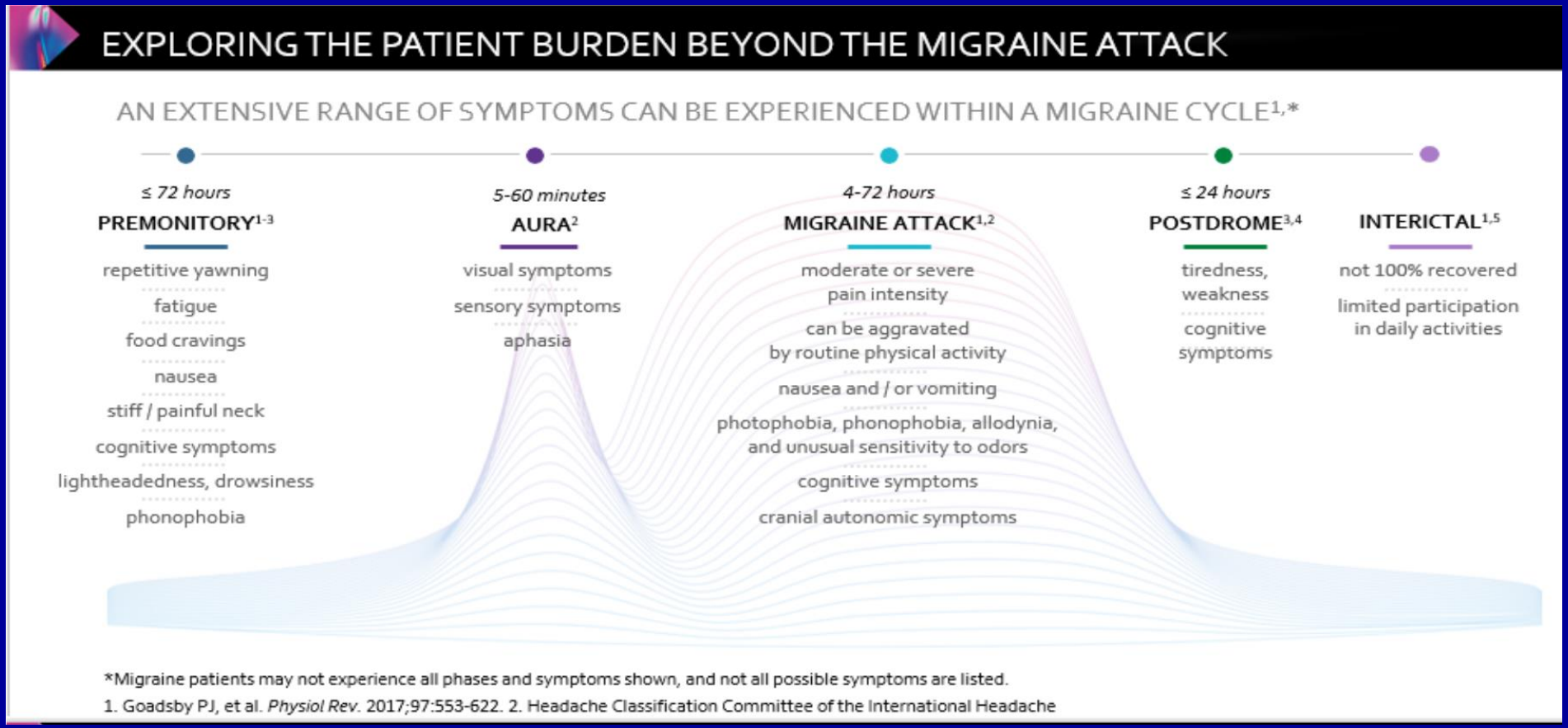
Migraine
Definitions & Diagnosis

Simplified Migraine Criteria (2 out of 3):

1. Light sensitivity with headache
2. Nausea with headache
3. Decreased function with headache
   - *Not attributable to other causes*

Lipton R.B., et. al

Migraine
Definitions & Diagnosis



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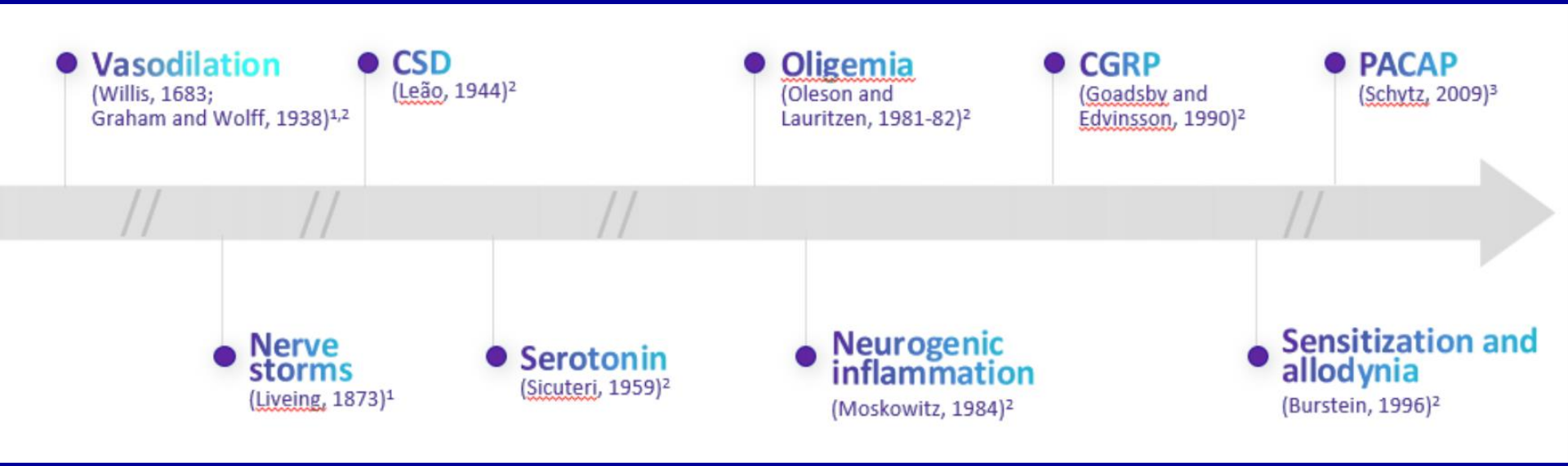
Pathophysiology: History lessons and Current Concepts

The Understanding of Migraine Pathophysiology has Evolved



CSD, cortical spreading depression; CGRP, calcitonin gene-related protein; PACAP, pituitary adenylate cyclase–activating polypeptide.

1. Eadie MJ. *J Clin Neurosci*. 2005;12(4):383-388. 2. Tfelt-Hansen PC et al. *Headache*. 2011;51(5):752-778. 3. Schytz HW et al. *Neurotherapeutics*. 2010;7(2):191-196.

Pathophysiology:
History lessons and Current Concepts

MECHANISM OF MIGRAINE HEADACHE AND ACTION OF ERGOTAMINE TARTRATE

J. R. GRAHAM, M.D.
AND
H. G. WOLFF, M.D.
NEW YORK

The observation that administration of ergotamine tartrate regularly and promptly ends the migraine headache introduced a new approach to the experimental study of this syndrome (Tzanck,[1] Lennox and von Storch,[2] O'Sullivan [3]). With this effective tool the attack can be sufficiently shortened to permit convenient analysis of certain changes that take place in the transition from the peak to the termination of the headache. Because ergotamine tartrate predominantly affects smooth muscle, inquiry concerning its action during migraine headache was centered on the cranial blood vessels. The experiments described here were performed when the phenomena which characterize the onset of an attack, namely, scotomas, blurring of vision, paresthesias and aphasia, had already passed and had been supplanted by headache. Hence these results have no bearing on preheadache phenomena. They concern only the origin of migraine pain.

MATERIAL

Experimental analyses were made during thirty-two attacks of migraine occurring in sixteen subjects. Additional, less complete, observations were made during twenty attacks in six other subjects. The diagnosis of migraine was based on a history of periodic headache, unilateral in onset, often preceded by visual phenomena and accompanied by nausea and sometimes by vomiting. Such periodic headache often occurred in other members of the family. Fifty series of observations and records were made on forty-six subjects used as controls who were either healthy laboratory workers or patients in the general medical wards of the New York Hospital and who, after having been told the nature of the procedure, volunteered their cooperation.

From the New York Hospital, Department of Medicine, and Cornell University Medical College.

1. Tzanck, A.: Le traitement des migraines par le tartrate d'ergotamine, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1057, 1928.

2. Lennox, W. G., and von Storch, T. J. C.: Experience with Ergotamine Tartrate in One Hundred and Twenty Patients with Migraine, J. A. M. A. **105**: 169 (July 20) 1935.

3. O'Sullivan, M. E.: Termination of One Thousand Attacks of Migraine with Ergotamine Tartrate, J. A. M. A. **107**:1208 (Oct. 10) 1936.

MATERIAL

Experimental analyses were made during thirty-two attacks of migraine occurring in sixteen subjects. Additional, less complete, observations were made during twenty attacks in six other subjects. The diagnosis of migraine was

Pathophysiology:
History lessons and Current Concepts

Prophylactic and Therapeutic Properties of 1-Methyl-Lysergic Acid Butanolamide in Migraine

Preliminary Report

By Federigo Sicuteri

University of Florence, General Medical Clinic, Headache Clinic
(Director: Prof. Enrico Greppi)

The painful manifestations of the migraine attack are due to stimulation of the adventitial and periadventitial pain-sensitive receptors in the branches of the carotid artery situated on the side of the pain. The fact that pressure exerted on the extracranial arteries during the attack is particularly painful shows that the pain is of vascular origin. During the migraine attack the superficial temporal artery is always turgid and tortuous. The sensitivity to pain and tortuosity is probably due – as we have frequently pointed out (1, 4, 5, 10, 11) – to vasodilatation and oedema not of the largest arterial branches, but of the minute vessels whose purpose it is to irrigate the larger blood vessels. In its turn, the dilatation and oedema of the vasa vasorum – which is easy to reproduce experimentally – decreases the tonus of the arteries from which they arise.

It is well known that the circulatory system is regulated by nervous and humoral mechanisms. The latter comprise not only the hormones, secreted by certain glands and distributed throughout the organism by the blood, but also certain substances which are deposited in a biochemically inactive form and can become active in particular circumstances and thus modify the circulatory equilibrium. These tissue substances accumulate in the mast cells which are found in great numbers in the tunica adventitia of the larger vessels. It is possible that during the migraine attack these substances, for instance histamine, serotonin, bradykinin, etc. modify the

Material and Methods

We have treated 18 patients with migraine, and two patients, both physicians, suffering from daily violent and recurrent attacks which may be classified as cases of Horton's histaminic cephalalgia (11 females and 9 males). Ten of the migraine cases were particularly severe and resistant to therapy; some of these were refractory to all forms of treatment, including ergotamine.

Pathophysiology:
History lessons and Current Concepts

Vasoactive Peptide Release in the Extracerebral Circulation of Humans During Migraine Headache

P. J. Goadsby, MD, PhD,* L. Edvinsson, MD, PhD,† and R. Ekman, MD‡

The innervation of the cranial vessels by the trigeminal nerve, the trigeminovascular system, has recently been the subject of study in view of its possible role in the mediation of some aspects of migraine. Since stimulation of the trigeminal ganglion in humans leads to facial pain and flushing and associated release of powerful neuropeptide vasodilator substances, their local release into the extracerebral circulation of humans was determined in patients who had either common or classic migraine. Venous blood was sampled from both the external jugular and the cubital fossa ipsilateral to the side of headache. Plasma levels of neuropeptide Y, vasoactive intestinal polypeptide, substance P, and calcitonin gene-related peptide were determined using sensitive radioimmunoassays for each peptide, and values for the cubital fossa and external jugular and a control population were compared. A substantial elevation of the calcitonin gene-related peptide level in the external jugular but not the cubital fossa blood was seen in both classic and common migraine. The increase seen in classic migraine was greater than that seen with common migraine. The other peptides measured were unaltered. This finding may have importance in the pathophysiology of migraine.

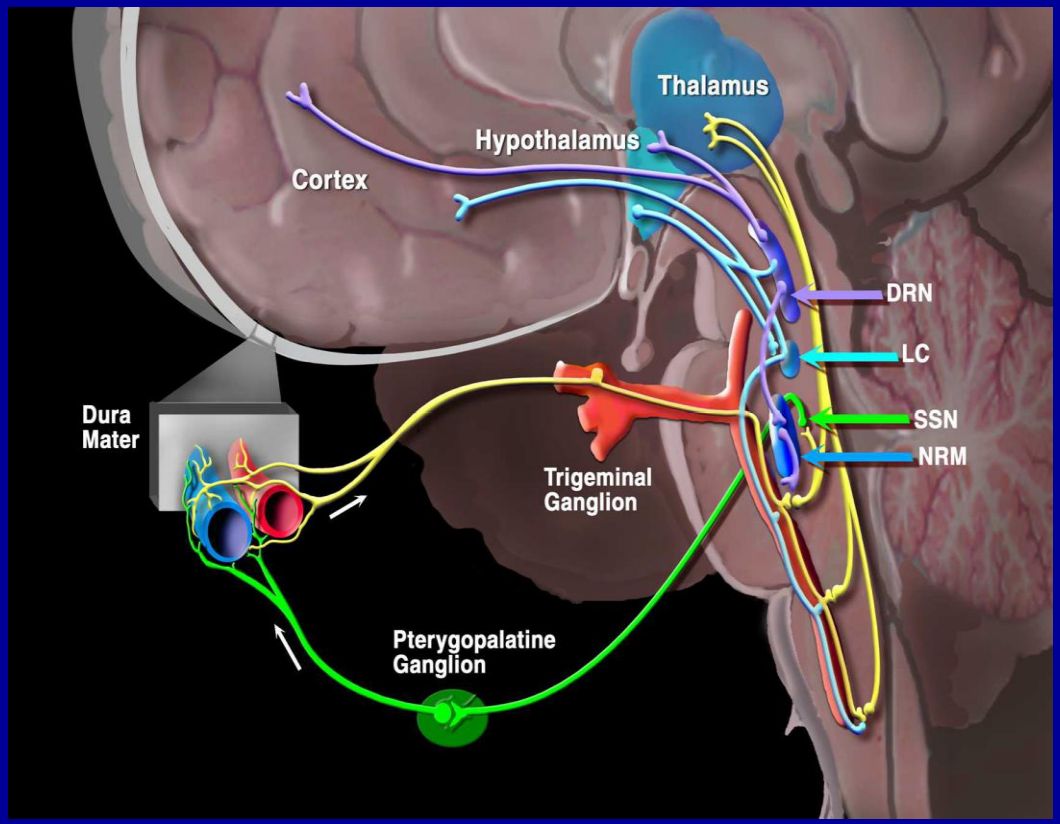
Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 1990;28:183–187

Methods

Patients

Data were collected from 22 patients who presented to the Neurology Outpatients and Casualty Department complaining of symptoms consistent with either common or classic migraine [8]. The study protocol was reviewed by an Institutional Ethics Committee (P. J. G.'s) and the patients

Pathophysiology:
History lessons and Current Concepts
Trigeminal-Vascular System



What is released?

- Serotonin
- CGRP
- Kinins
- Others

What is the result?

Sensitization

Central & Peripheral

Clinical Result

Allodynia

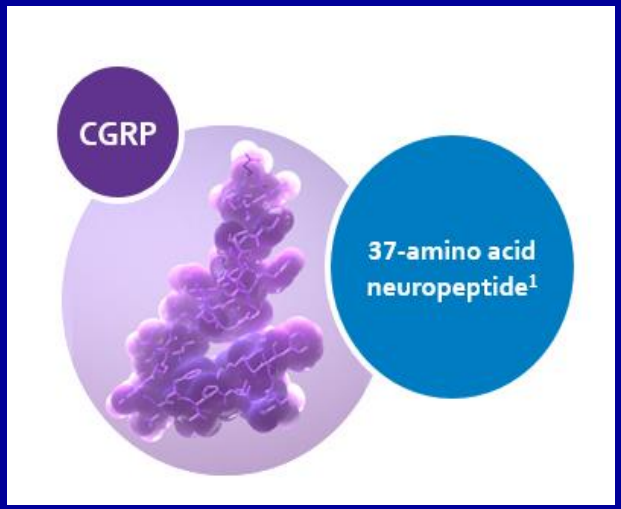
Pathophysiology:
History lessons and Current Concepts

CGRP

Role in Migraine

CGRP – What is it?

- 37-Amino Acid Signaling Neuropeptide
- Wide distribution in both PNS & CNS
- Expressed in ~50% of neurons in the trigeminal ganglia
- PNS - Released by C fibers of Trigeminal Nerve during Migraine attacks
- CNS – Signals from Trigeminal Nerve to Trigeminal Nucleus Caudalis (TNC)



Thought to regulate

- Pain transmission, including meningeal nociception
- Neurogenic inflammation
- Vasodilation

Russo AF. Annu Rev Pharmacol Toxicol. 2015;55: 533-552
Raddant et al. Expert Rev Mol Med. 2011; 13:e36
Edvinsson et al. Eur J Neurol. 1998;5:329-341

Pathophysiology:
History lessons and Current Concepts

CGRP
Role in Migraine

Evidence:

- During a Migraine attack, CGRP increased >2x in jugular blood
- CGRP levels return to normal after effective migraine attack treatment
- CGRP infusion can induce a migraine attack in migraineurs
- Perivascular release of CGRP can induce plasma protein leakage from tissues

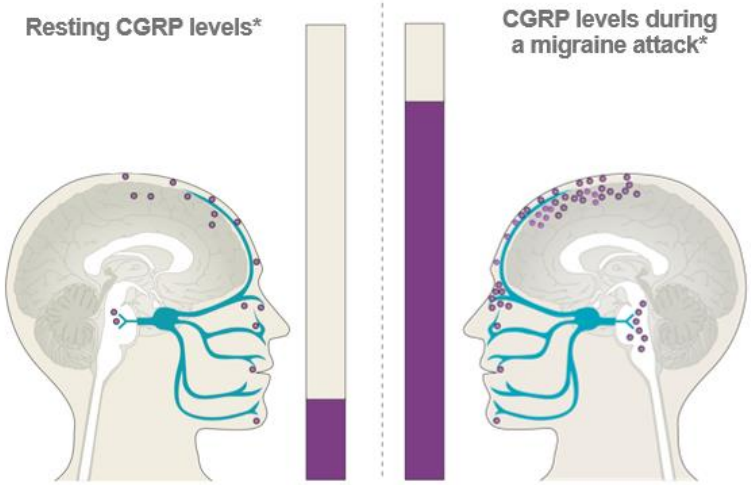
Goadsby et al, Ann Neurol. 1990;28 92 0: 183-187
Goadsby et al, Ann Neurol. 1993;33(1): 48-56
Lassen LH, et al, Cephalalgia. 2002;22: 54-61
Charles A. Lacet Neurol. 2018;17(2):174-182. Epub 2017 Dec 8.

Pathophysiology:
History lessons and Current Concepts

CGRP

CGRP Is a Chief Mediator of Migraine and Has Rapidly Become an Important Target of Migraine Treatment

Plasma CGRP levels increase during a migraine attack[1-3]



CGRP is a pain-signaling neuropeptide and potent vasodilator[1]

- Released from trigeminal sensory afferents and the spinal trigeminal nucleus

Studies have shown that CGRP[1,4]:

- Plasma levels are elevated during and outside of migraine attacks in people with migraine
- Infusion into patients with migraine can trigger a migraine attack

*CGRP levels in blood and saliva.[3]

1. Ho TW et al. *Nat Rev Neurol*. 2010;6(10):573-582. 2. Noseda R, Burstein R. *Pain*. 2013;154(Suppl 1):S44-53. 3. Schuster NM, Rapoport AM. *Nat Rev Neurol*. 2016;12(11):635-650.
4. Ashina M et al. *Pain*. 2000;86(1-2):133-138.

Pathophysiology:
History lessons and Current Concepts

CGRP Receptors
What & Where?

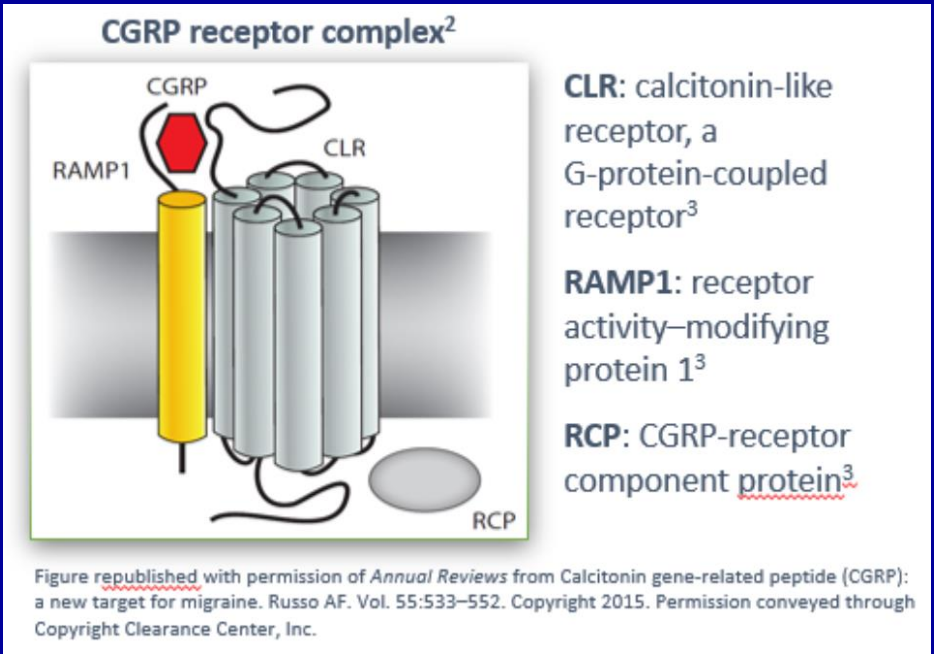


Figure republished with permission of *Annual Reviews* from Calcitonin gene-related peptide (CGRP): a new target for migraine. Russo AF. Vol. 55:533–552. Copyright 2015. Permission conveyed through Copyright Clearance Center, Inc.

CGRP Receptor Locations:

PNS

- Trigeminal **Nerve A-delta fibers**
- Meningeal Vessels, Smooth muscle cells
- Satellite glial cells
- Mast cells

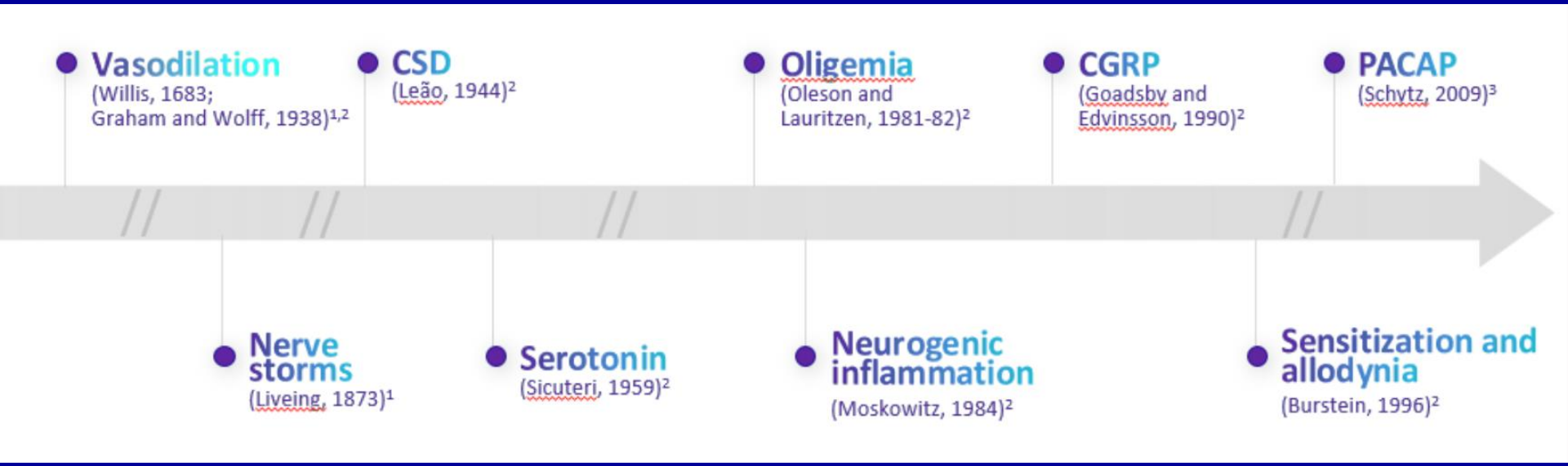
CNS

- Second order neurons
  - Trigeminal Nucleus Caudalis
  - Spinal cord dorsal horn
- Thalamus

1. Charles A. *Lancet Neurol*. 2018;17(2):174-182. Epub 2017 Dec 8. 2. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552. 3. Raddant AC et al. *Expert Rev Mol Med*. 2011;13:e36.

Pathophysiology: History lessons and Current Concepts

Migraine Pathophysiology – We've come a long way, baby



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Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - The Basics, Pre-2020
  - 2020 – GePants, Ditans, & Twists on old favorites
- Migraine Prevention
  - The Basics, Pre–2018
  - 2018 – CGRP MAb revolution
  - 2021 – GePants
- Neuromodulation/Devices
  - It's not a pill, it's not a shot, but can you get it for your patient?

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Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - The Basics, Pre-2020
  - Typical treatments are less effective until
    - Roadblocks are removed
      - Medication overuse (Fioricet, Darvocet, Acetaminophen, Midrin, Triptans)
      - Caffeine
      - *Opioids*
    - Contributing factors are addressed
      - Sleep hygiene
      - Psychological barriers
      - Trauma/Musculoskeletal dysfunction
      - Bruxism/TMJ dysfunction
      - Sinus pathology (sphenoid/ethmoid)
      - Stress, weather, food triggers, wine

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - The Basics, Pre-2020

    Top choices

    - Triptans
    - Ergotamine derivatives
    - NSAIDs: aspirin, celecoxib, diclofenac, ibuprofen, naproxen, flurbiprofen, ketoprofen, ketorolac
    - Combination analgesic: Excedrin,
    - Antiemetics: chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine
    - Isometheptine-containing compounds
    - IV Treatments: IV Fluids, Metoclopramide, DHE, Ketorolac, Valproate, Dexamethasone, Diphenhydramine, chlorpromazine, Magnesium

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020 - GePants, Ditans

Ubro*gepant*

Tablet format, 50mg & 100mg, max 200mg/24hrs
Blocks the CGRP receptor peripherally, well tolerated
20% Pain-free rate @ 2hrs

Rime*gepant*

ODT formulation, 75mg, max 75mg/24hrs
Blocks the CGRP receptor peripherally, well tolerated
20% Pain-free rate @ 2hrs

Lasmi*ditan*

Tablet format, 50mg & 100mg, max 200mg/24hrs
Blocks 5HT1-f receptors *centrally* & peripherally
23%-39% Pain-fre rate @ 2hrs
Don’t drive for 8 hours

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020
    Twists on Old favorites – (1) Triptan +

Tosymra
(approved; available)
sumatriptan + 0.2% DDM (1-0-n-Dodecyl-beta-D-Matopyroside);
one spray, one nostril; box of six (6) max 3/24 hours; may be given an hour after another sumatriptan formulation; 44% pain free at 2 hours (very good)

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020
    Twists on Old favorites – (2) DHE +

Impel's Trudhesa, (INP104)
(approved, not yet available)
DHE 0.725mg;
Delivered via Precision Olfactory Delivery (POD) technology.
38% pain-free rate @ 2hrs.
SE: nasal congestion 16.7%, nausea 7.9%, nasal discomfort 5.4%, abnormal taste 5.1%

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020
    Twists on Old favorites – (3) Celecoxib +

    Elyxyb
    (approved, not yet available);
    Celecoxib, oral solution* 120mg/4.8mL
    max 1/24 hours. Each carton contains nine (9) glass bottles.
    32.8% pain-free rate @ 2hrs; SE: Dysgeusia, 3%

    (*formulated using a self-micro emulsifying drug delivery system. improves solubility, absorption & bioavailability.)

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020

    Twists on Old favorites – (4) rizatriptan, meloxicam +

    Axsome AXS 07

    (not approved, not available*)

    meloxicam + rizatriptan + MoSEIC (*Molecular Solubility Enhanced Inclusion Complex*)

    SE nausea, dizziness, vomiting

    38% pain free @ 2hrs

    *Prescription Drug User Fee Act (PDUFA) target action date of April 30, 2022 for the NDA.

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - NEW choices Post-2020

    Twists on Old favorites – (5) Zolmitriptan +

    Qtrypta

    (not approved, not available)

    Zolmitriptan “intracutaneous” titanium microneedles coated with drug; penetrates the epidermis and dermis; a reusable applicator and a microneedle array containing patch, the size of a quarter

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - The Basics, Pre-2020
  - 2020 – GePants, Ditans, & Twists on old favorites

- Migraine Prevention
  - The Basics, Pre–2018
  - 2018 – CGRP MAb revolution
  - 2021 – GePants

- Neuromodulation/Devices
  - It's not a pill, it's not a shot, but can you get it for your patient?

Migraine Treatment Options
Old & New

Migraine Prevention
The Basics, Pre - 2018

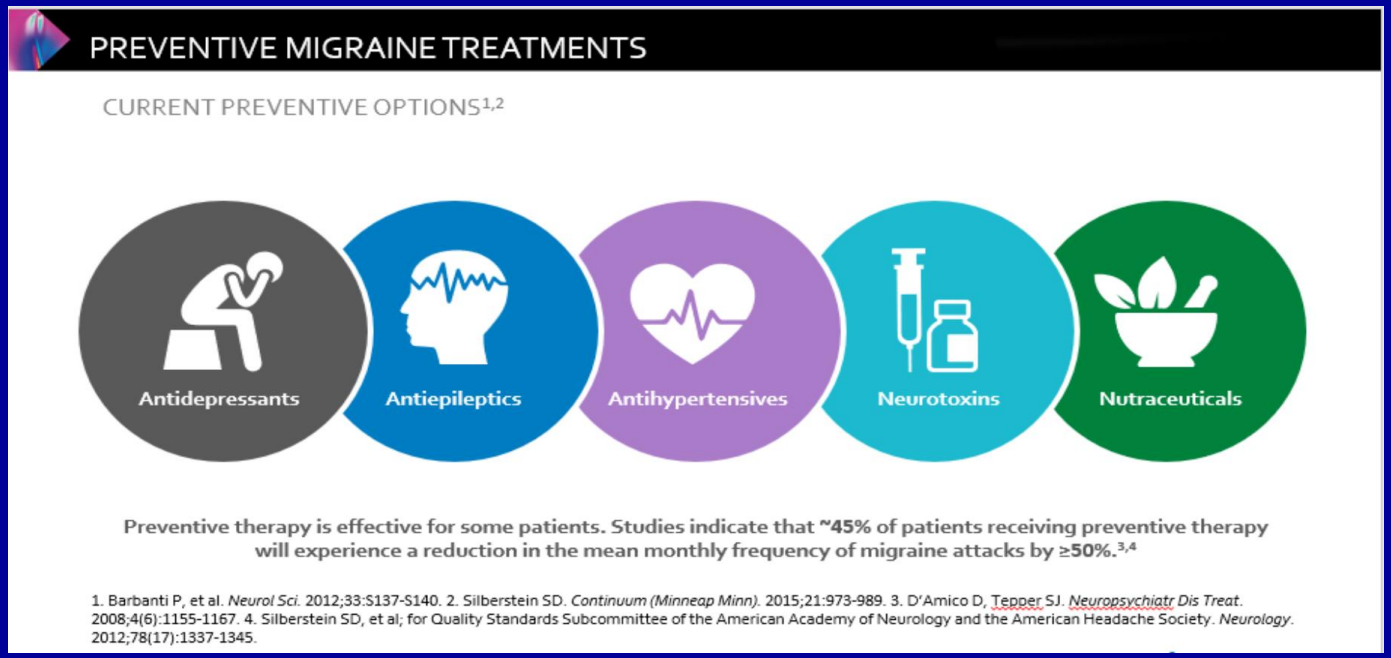
- Goals
  - Reduce frequency, severity, disability
  - Prevent disease progression

- When to use
  - If >4 severe headache days per month
  - If <15 days/month head pain free

- How to pick (pre 2018)
  - No option designed specifically for migraine
  - Pick based on comorbid symptoms
    (AKA – the “Two for One” plan)

Migraine Treatment Options
Old & New

Migraine Prevention, Pre 2018
The “Two for One” Plan Options

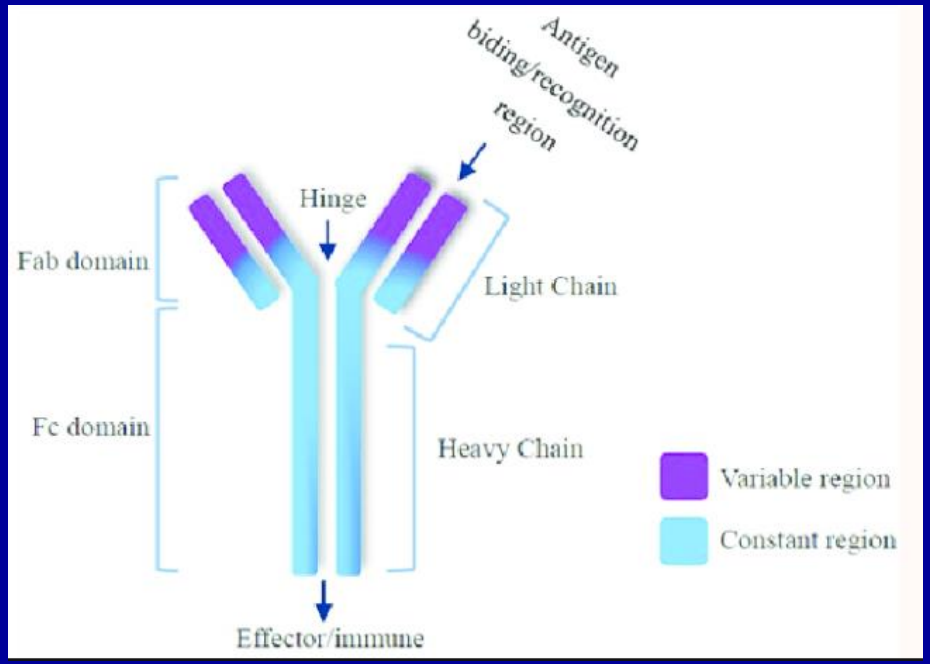


Examples

Amitryptyline Topiramate Propranolol Botulinum Toxin A Magnesium

Migraine Treatment Options
Old & New

Migraine Prevention, 2018 and beyond
CGRP MAb Revolution



- CGRP MAbs are FDA approved for Migraine Prevention in adults
- The "First ~~& Only~~" class of meds specifically designed for Migraine Prevention
- Mechanism of action
  - targets scientifically proven disease-specific pathophysiology.

Migraine Prevention, 2018 and beyond
CGRP MAb Revolution

- Rationale
  - Interrupt CGRP Signaling pathway
    - Binds to either the ligand (CGRP) or its receptor
  - High specificity
  - Long duration - half-life approximately 1 month
  - Does not activate the host immune system
  - Does not cross the Blood-Brain Barrier
  - Cleared through reticulo-endothelial system
  - Not eliminated by the hepatic and renal pathways
  - Rate of cytochrome P450 metabolism is not a consideration
  - Not subject to interaction with other medications

Migraine Prevention – 2018
CGRP MAb Revolution

	Aimovig	Ajovy	Emgality	Vyepti
Generic name	Erenumab-aooe	Fremanezumab-vfrm	Galcanezumab-gnim	Eptinezumab-jimr
Marketed by	Amgen & Novartis	Teva	Eli Lilly	Lundbeck
Approved for	Prevention of migraine in adults, chronic and episodic	Prevention of migraine in adults, chronic and episodic	Prevention of migraine in adults, chronic and episodic	Preventive treatment of migraine in adults
Target	Blocks CGRP receptor	Attaches to CGRP peptide	Attaches to CGRP peptide	Attaches to CGRP peptide
Molecular Format	IgG2	IgG2	IgG4	IgG1-IV
	Human	Humanized	Humanized	
Frequency	Monthly	Monthly or quarterly	Monthly	Quarterly
Route	Subcutaneous	Subcutaneous	Subcutaneous	IV
Device	Autoinjector	Prefilled syringe	Autoinjector	N/A

Migraine Prevention – 2018
CGRP MAb Revolution, continued

continued	Aimovig	Ajovy	Emgality	Vyepti
Dose	70mg or 140mg	225mg (m) or 675mg (q)	240mg load & 120mg thereafter	100mg or 300mg
Listed side effects	- Injection site pain/rxn – 6% - Constipation – 3% (in 140mg trial)	- Injection site pain/rxn: 43%	- Injection site pain/rxn: 18%	- Nasopharyngitis: 6-8% - Hypersensitivity reactions – 1-2%
Cost	$575/month For both 70mg & 140mg dosing	$575/month or $1,725/quarterly	$575/month	$1,495/quarter
50% responder rate, episodic	43% @ 70mg 50% @ 140mg	45%	60%	50%

Migraine Treatment Options
Old & New

Migraine Prevention, "The List" 2018
Including all 4 CGRP MAbs

TABLE 6 Medications with evidence of efficacy in migraine prevention[a,20,85]

Established efficacy[b]		Probably effective[c]	
Oral	Parenteral	Oral	Parenteral
Candesartan	Eptinezumab	Amitriptyline	OnabotulinumtoxinA + CGRP mAb[d,e]
Divalproex sodium	Erenumab	Atenolol	
Frovatriptan[f]	Fremanezumab	Lisinopril	
Metoprolol	Galcanezumab	Memantine	
Propranolol	OnabotulinumtoxinA[d]	Nadolol	
Timolol		Venlafaxine	
Topiramate			
Valproate sodium			

Abbreviations: CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody.

[a]The decision to prescribe preventive therapy in women who are pregnant or of childbearing potential should be based on the needs of individual patients and available safety data.

[b]Two or more Class I trials based on American Academy of Neurology evidence classification.[84]

[c]One Class I or 2 Class II trials based on American Academy of Neurology evidence classification.[84]

[d]Prevention of chronic migraine.[86]

[e]One Class IV trial based on American Academy of Neurology evidence classification.[84]

[f]Short-term prevention of menstrual-related migraine; evaluated and rejected by the FDA for this indication.

Migraine Treatment Options
Old & New

Migraine Prevention

2021 – GePants*

Rime*gepant*

- ODT formulation, 75mg, QOD dosing (16/month)
- Blocks the CGRP receptor peripherally
- 4.3 day reduction in MMDs; 30% reduction in Week-1
- SE: abdominal pain/dyspepsia 2.4%

Ato*gepant*

- Tablet formulation, 10mg, 30mg, 60mg
- Blocks the CGRP receptor peripherally
- 50% reduction rate of 55.6%-60.8%
- SE: constipation 6.9-7.7%, nausea 4.4-6.1%, URI 3.9%-5.7%

*Paradigm shift - Acute + Prevent = “TREATMENT”

Migraine Treatment Options
Old & New

- Migraine Acute Treatment
  - The Basics, Pre-2020
  - 2020 – GePants, Ditans, & Twists on old favorites
- Migraine Prevention
  - The Basics, Pre–2018
  - 2018 – CGRP MAb revolution
  - 2021 – GePants
- Neuromodulation/Devices
  - It's not a pill, it's not a shot, but can you get it for your patient?

Neuromodulation/Devices

Four available options, and one in the wings:

1. GammaCore Vagal Nerve Stimulator (nVNS)
2. Spring TMS mini - Transcranial Magnetic Stimulator (sTMS)
3. Cefaly - Transcutaneouos Supraorbital Neurostimulation (tSNS)
4. Nerivio Migra - Remote Neuromodulation – Upper Arm (REN)
5. Relivion - Combined Occipital & Trigeminal Neuromodulation (eTNS)

* Devices Section gratefully adapted from Alan M. Rapoport, M.D. Past-President, IHS; Founder, NEHC.

Neuromodulation/Devices
gammaCore VNS

Non-Invasive Vagal Nerve Stimulator (gammaCore, nVNS)

- Handheld, patient-controlled device, which preferentially activates afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction
- Multiple possible MOAs related to headache/pain
  - Inhibits CSD
  - Decrease in Glutamate
  - Suppresses Neuronal firing in TCC
  - Modulates Trigeminal Autonomic Reflex
- CE Mark for Primary Headache
- FDA Approved
  - Acute treatment of episodic cluster (ACT1 & ACT2 RCTs)
  - Prevention of Cluster (PREVA and Real World OL Study vs. SoC)
  - Acute treatment of migraine (PRESTO RCT, Class I Evidence)

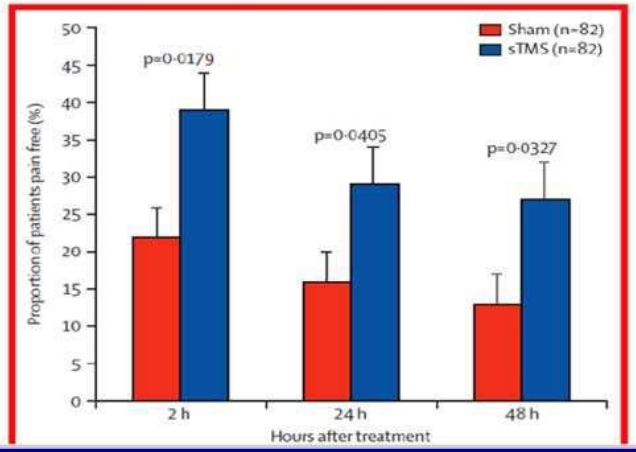
* Devices Section gratefully adapted from Alan M. Rapoport, M.D. Past-President, IHS; Founder, NEHC.

Neuromodulation/Devices

Single Pulse Transcranial Magnetic Stimulation

sTMS mini

- Magnetic pulses disrupt cortical spreading depression (CSD), the basis for aura, and down-regulate thalamocortical pain pathways
- 1 RCT for acute treatment of migraine with aura, N=167
  - 2 hours pain-free: 39% sTMS vs 22% sham (*P*=0.0179)
- 2 open label studies for prevention of migraine with prn extra pulses for acute use, N=249
  - 4-25 headache days for inclusion; 4 pulses BID with extra prn up to 17 pulses per day
- FDA-approved in 2017 as nonsignificant risk device for preventive and acute treatment of migraine
- Rental cost $225/month



Andreou et al. *Brain*. 2016;139:2002-2014.
Lipton et al. *Lancet Neurol*. 2010;9:373-380.
Bhola et al. *J Headache and Pain*. 2015;16:535.
Starling et al Cephalalgia 2018;38:1038–1048.

Neuromodulation/Devices

Transcutaneouos Supraorbital Neurostimulation (tSNS)

Cefaly

Primary Outcome Measure: Change in Pain Score on VAS at 1 hour Compared to Baseline (n=99)

Outcome measures are detailed in Table 2. The primary outcome (mean change in pain score at 1 hour compared to baseline) was significantly decreased ($p<0.0001$) in the verum and sham groups, but much more in the verum (–59%) than in the sham group (–30%); the effect size was large, with a Cohen's d value of 0.88 (Figure 4). Applying the aforementioned post hoc ANCOVA sensitivity analysis, the treatment effect defined by the primary outcome measure remained highly significant ($p<0.0001$).

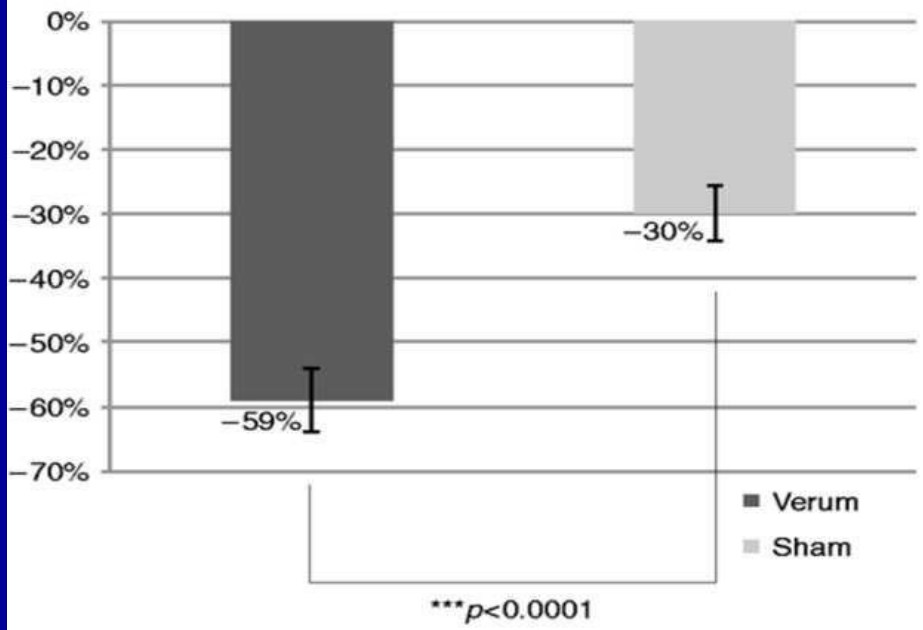
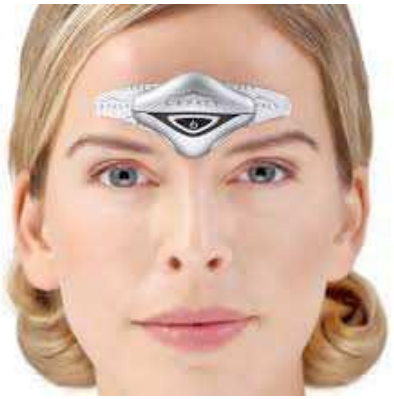


Figure 4. Relative change in pain intensity at 1 hour.

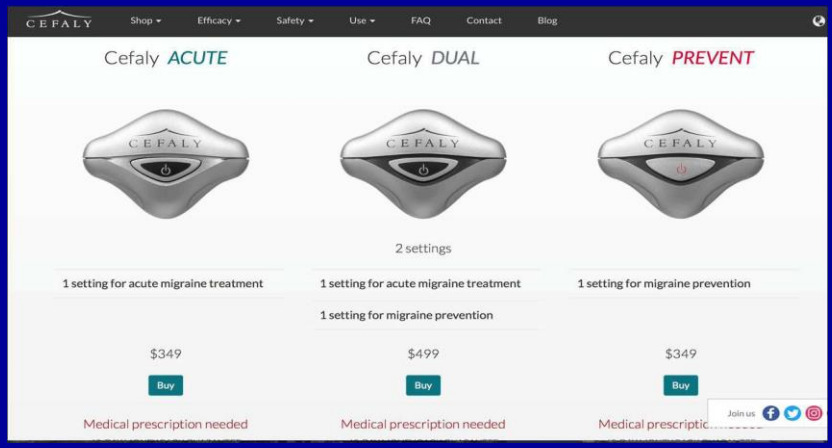


Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial
Denise E Chou, Marianna Shnayderman Yugrakh, Dana Winegarner, Vernon Rowe, Deena Kuruvilla, Jean Schoenen. Cephalalgia 2018.

Neuromodulation/Devices

Transcutaneouos Supraorbital Neurostimulation (tSNS)

Cefaly



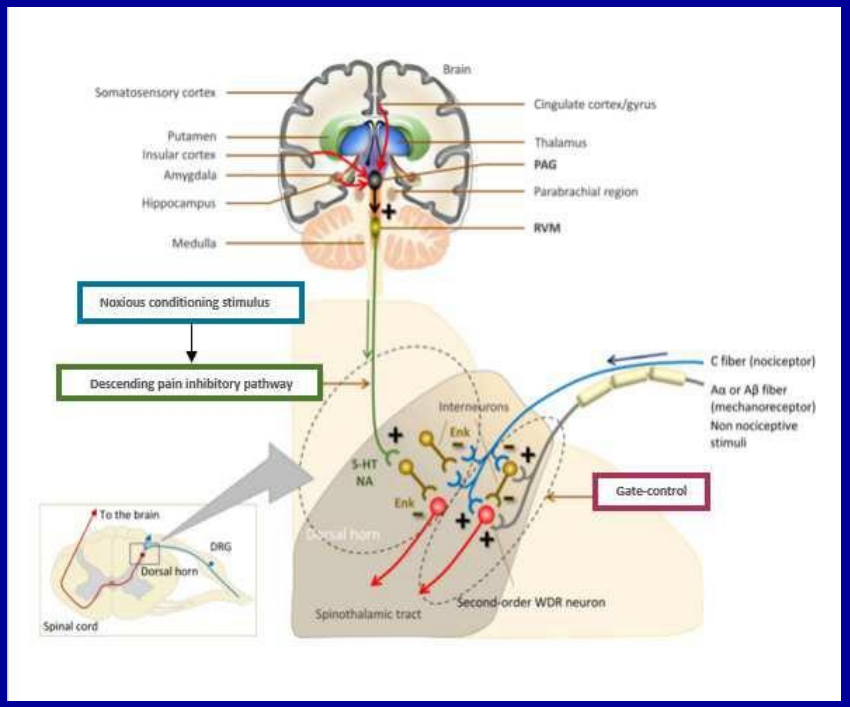
Neuromodulation/Devices
Remote Neuromodulation – Upper Arm
Nerivio Migra

- **Peripheral nerves of the upper arm are stimulated to induce conditioned pain modulation (CPM) – a descending endogenous analgesic "pain inhibits pain" mechanism**
- **Peripheral nociceptive information just below the perceived pain threshold can activate the descending pain inhibitory pathway and inhibit the headache**

Neuromodulation/Devices

Remote Neuromodulation – Upper Arm

Nerivio Migra



Nerivio Migra

	Clinical manifestation	Signaling	Spatial effect	Duration
CPM	Pain inhibits pain	Noradrenalin serotonin	Global	A few minutes after stimulus exposure
Gate control	Touch inhibits pain	GABA	Local	Only during stimulus exposure

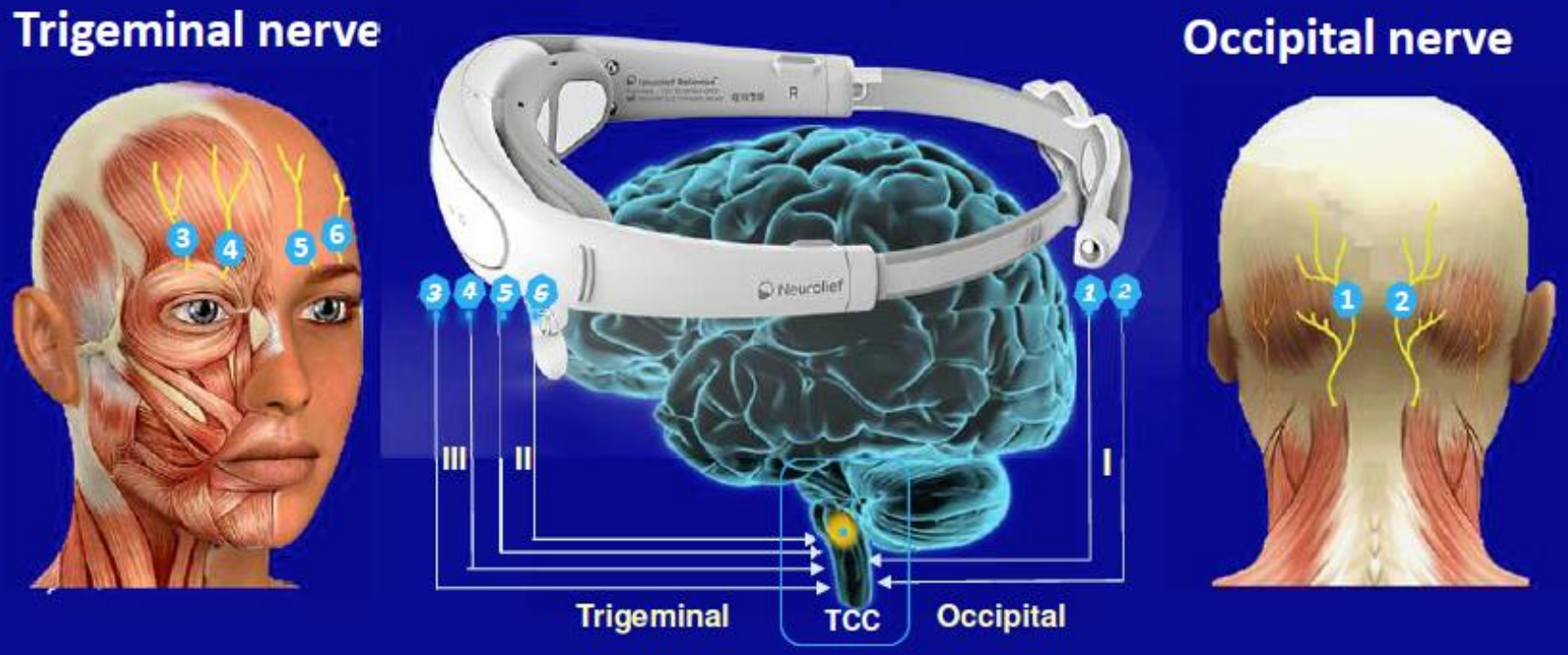
Neuromodulation/Devices

Combined Occipital & Trigeminal Neuromodulation

Relivion*

- **Neuromodulation technology delivers precise modulated pulses simultaneously to six branches of the occipital & trigeminal nerves, via 3 adaptive output channels.**
- **The occipital & trigeminal nerves conduct the signals directly to the brainstem for maximal synergistic effect.**

*** Under FDA Review**



Migraine Update

- Foundation
  - Think secondary causes first
- Migraine
  - Definitions & Diagnosis
  - Pathophysiology: History lessons and Current Concepts
- Migraine Treatment Options
  - Old & New
- Choosing Treatments
  - For the Patient In Front of You

Choosing Treatments
For the Patient In Front of You

- Foundation
  - Think secondary causes first
- Evidence-based treatments
  - Use them first, second, third
- CGRP
  - Join the revolution: MAbs & GePants
- New Choices & Twists on old favorites
  - Pick one or two, get good at the PA process
- Devices
  - Pick one, figure out how to get it into patient's hands

Choosing Treatments
For the Patient In Front of You

"Plan"

- **Imaging**: MRV
- **Labs**: CBC, ESR, CRP, ANA
- **Testing/Procedures**: LP, Home Sleep Study
- **Therapy**: Physical Therapy, Trauma Therapy
- **Referrals/Evals**: Rheumatology, Sleep Medicine
- **Meds/Rx**: CGRP MAb/Botox, Triptan, H2 blocker, NSAID
- **Device w/ Rx**: VNS
- **DME**: Cervical Traction
- **Patient Activities**: HA diary, Tai Chi
- **Records/MD Calls**: Call to Primary, Records from ER
- **Follow up**: Virtual, 6-8 weeks

"Reality"

Extrinsic Factors

- **Insurance/Money**
- **Location/Access**

Intrinsic Belief System

- **Dr. Google Consult**
- **Pharma Conspiracy Theorist**
- **Holistic**
- **Medication Sensitive**
- **Poly-Allergy**
- **Mister or Miss "*Personality*"**
  - **Basic – Grumpy, Weepy, Anxious**
  - **Complex – Narcisistic, Dependent, Borderline**

Choosing Treatments
For the Patient In Front of You

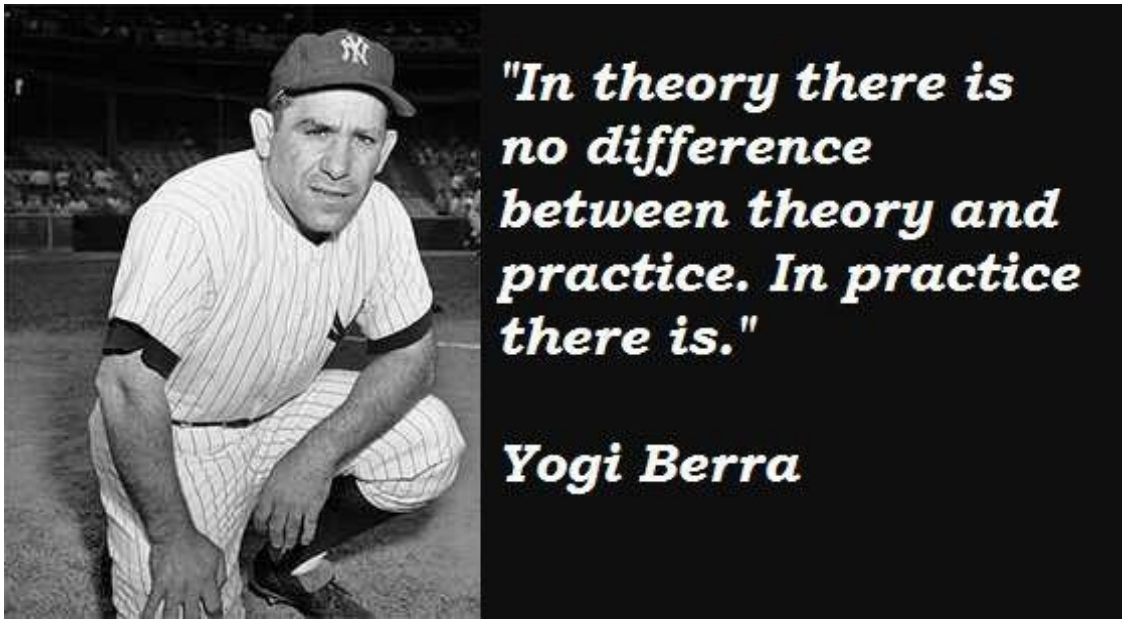
Doctor

- Establish a therapeutic relationship.
- Obtain a thorough & accurate history.
- Perform the appropriate examination.
- Arrive at the accurate diagnoses.
- Communicate clearly, educate, advise.
- Create and offer a plan
  - based on the science of medicine,
  - to investigate, diagnose and treat,
  - with the patient's best interest at heart.

Patient

- The Doctor was personal, respectful, caring, empathetic.
- The Doctor spent time with me and was thorough.
- I was listened to, heard, and understood.
- I was appreciated for who I am.
- I know more than I did before the visit.
- The Doctor offered suggestions, involved me in the decision making, and was confident in the final plan.

Choosing Treatments
For the Patient In Front of You



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  - For the Patient In Front of You
- Questions?

THANK YOU!

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