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# NO DISCLOSURES

# 1940s: CORTICAL SPREADING DEPRESSION

1930s

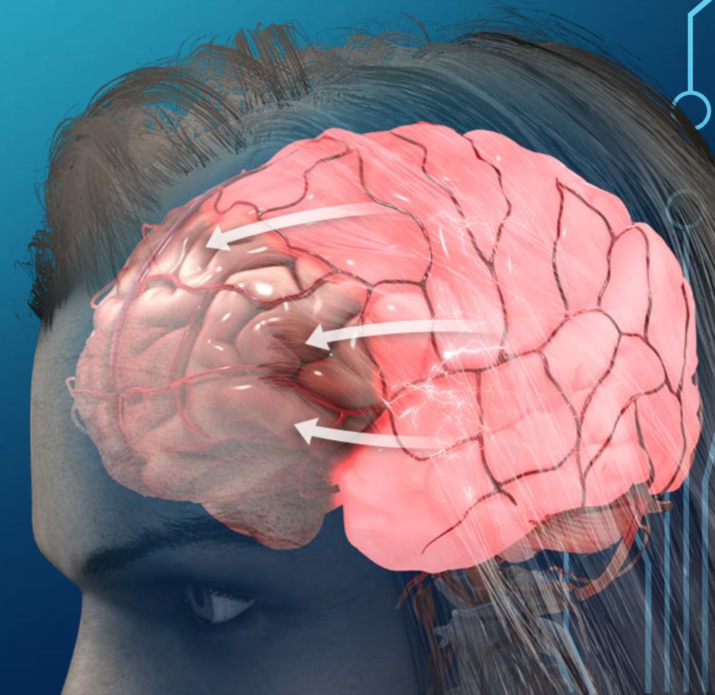
**1940s**

1950-80s

1990-2000s

CSD was discovered in the1940s and was believed to contribute to migraine aura

Presently, CSD is understood as a possible migraine generator, associated with migraine S/S



# 1950-80s: SEROTONIN AND TRIPTANS

- 1930s
- 1940s
- **1950-80s**
- 1990-2000s

- Serotonin, an endogenous neurotransmitter, was identified as active in migraine (1950s); initially it was recognized as a vasoconstrictor but now is understood to affect many physiological functions
- Research on serotonergic agonists led to the development of triptans, the first experimentally based approach to acute migraine Rx (1980s)

# 1990-2000s:
# RE- EXAMINING PATHOPHYSIOLOGY

1930s

1940s

1950-80s

**1990-2000s**

Research in the 1990s cast doubt on the vascular theory:

- Variations in blood flow occur during headache
- Triptans may help via nonvascular mechanisms

Current evidence suggests that CNS dysfunction, neurogenic inflammation, and activation of meningeal nociceptors are involved in migraine pathogenesis

# 1990-2000s: THE TRIGEMINOVASCULAR SYSTEM & CGRP

- 1930s
- 1940s
- 1950-80s
- **1990-2000s**

- The TGVS is now recognized as a key player in the development of migraine and related pain
- CGRP is one of the most abundant neuropeptides within the TGVS and likely has a central role in migraine

# INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS - ICHD3

**International Headache Society (IHS) classification system:**

- 1988 ICHD1
- 2004 ICHD2
- 2018 ICHD3 (Cephalalgia)

# ICHD3 MIGRAINE CLASSIFICATION

- 1.1 Migraine without Aura
- 1.2 Migraine with Aura
- 1.3 Chronic Migraine

# MIGRAINE

- Highly prevalent and underdiagnosed
- 38 million Americans affected
- Especially common in women of childbearing age
- $7^{th}$ leading cause of disability worldwide
- Peak age distribution 10-39 years old
- Variable frequency, duration, severity

# MIGRAINE

- Can be unilateral or bilateral
- Can be throbbing or nonthrobbing/steady
- Can be mild, moderate, or severe

**ANY headache with nausea, photophobia, and decreased function is most likely migraine**

# MIGRAINE
TRIGGERS

- Hormonal (menstruation)
- Environmental (irregular eating/sleeping, exercise)
- Dietary (aspartame, caffeine, MSG, EtOH, cheese, meats)
- Meds (BCPs, SSRIs, antihistamines, PPIs, analgesics)
- Psychosocial (stress/anxiety)

**NO confirmatory randomized trials re: lifestyle changes**

# MIGRAINE
# PRODROME AND POSTDROME

- May precede and follow headache by several hours
- Some “triggers” may actually be part of the prodrome:
  - **Yawning**
  - **Nausea**
  - **Mood Swings**
  - **Photophobia/Phonophobia/Osmophobia**
  - **Neck Pain**
  - **Fatigue**

# **MIGRAINE**
# AURA

- Visual – spots, flashing lights, zigzag lines, colors, "fortification spectra" lasting 10 – 30", rarely 60+"
- Somatosensory
- Vertigo
- Nausea/Vomiting
- Speech/Language dysfunction
- Allodynia – normal touch is unpleasant

# **MIGRAINE WITHOUT AURA**
# DIAGNOSTIC CRITERIA

- At least 5 attacks lasting 4-72 hours
- At least 2: unilateral, pulsating, moderate to severe, aggravated by/causing avoidance of physical activity
- At least 1: N/V, photo/phonophobia
- No better ICHD3 Dx

# ICHD-3 DIAGNOSTIC CRITERIA FOR 1.1 MIGRAINE WITHOUT AURA

A. At least 5 attacks[a] fulfilling Criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[b,c]
C. Headache has ≥2 of the following 4 characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache ≥1 of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

# MIGRAINE WITH AURA

- 30% of migraineurs
- Old names : complicated, complex, retinal, hemiplegic
- Aura may occur before, during, or after the headache
- Associated with increased risk of stroke (embolic, hypercoagulability, hyperviscosity, PFO, genetics)

# MIGRAINE WITH AURA
## DIAGNOSTIC CRITERIA

- At least 1 reversible aura type: visual, sensory, speech/language, motor, brainstem, retinal
- At least 3 aura symptom characteristics: spreads over 5+”, 2 or more in succession, 5-60” duration, unilateral, “positive”, headache with or after w/in 60”
- No better ICHD3 Dx

# ICHD-3 DIAGNOSTIC CRITERIA FOR 1.2 MIGRAINE WITH AURA

A. At least 2 attacks fulfilling Criteria B and C

B. 1 or more of the following fully reversible aura symptoms:

- Visual
- Sensory
- Speech and/or language
- Motor
- Brainstem
- Retinal

C. At least 2 of the following 4 characteristics:

1. At least 1 aura symptom spreads gradually over ≥5 minutes, and/or 2 or more symptoms occur in succession
2. Each individual aura symptom lasts 5-60 minutesa
3. At least 1 aura symptom is unilateralb
4. The aura is accompanied or followed within 60 minutes by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack excluded

# RED FLAGS

- New onset
- Duration > 72 hours
- "Aura" symptoms lasting > 1 hour
- Abnormal neurologic examination
- Associated signs (fever, stiff neck, rash, weight loss)

# MIGRAINE
## EVALUATION

- Complete History
- Physical/Neurologic Examinations
- NO need for routine brain imaging
- Consider: CBC, ESR, CT/MRI, LP in specific circumstances

# MIGRAINE
## ABORTIVE RX

- Whatever is used, “the sooner the better”
- Avoid excessive Rx…
- 8.2 Medication Overuse Headache (MOH) Diagnostic
- Criteria:
  - At least 15 headache days/month
  - At least 10 pain Rx days/month x 3+ months

# MIGRAINE
## ABORTIVE RX

- Analgesics (NSAIDs, acetaminophen, tramadol, narcotics)
- Ergots (DHE)
- Triptans
- Steroids, IV $Mg^{2+}$, $O_2$
- Phenothiazines (chlorpromazine, prochlorperazine)
- External neuromodulation devices
- Gepants

# **CHRONIC MIGRAINE**
# DIAGNOSTIC CRITERIA

- Headache 15+ days/month x 3+ months
- Headache 8+ days/month x 3+ months with response to triptan/ergot Rx
- No better ICHD3 Dx

# ICHD-3 DIAGNOSTIC CRITERIA FOR 1.3 CHRONIC MIGRAINE

A. Headache (tension-type-like and/or migraine-like) on ≥15 days/month for >3 monthsa and fulfilling Criteria B and C

B. Occurring in a patient who has had ≥5 attacks fulfilling criteria for migraine without aura and/or criteria for migraine with aura

C. On ≥8 days per month for >3 months, fulfilling any of the followinga:

   1. Criteria C and D for 1.1 Migraine Without Aura
   2. Criteria B and C for 1.2 Migraine With Aura
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis

# **MIGRAINE**
# PROPHYLACTIC RX

- Typically reserved for patients with chronic migraine
- Reasonably used for others, especially if attacks are severe, incapacitating, threatening to life/livelihood
- Ex: driver/pilot, prior migrainous stroke or TIA

# MIGRAINE
## PROPHYLACTIC RX - MODALITIES

- Biofeedback
- CBT (cognitive behavioral therapy)
- PT (physical therapy)
- Massage
- Occipital nerve block(s)
- Acupuncture

# MIGRAINE
# PROPHYLACTIC RX – NONSPECIFIC ORAL AGENTS

**Choose side effect profile to benefit the patient:**

- Plant extracts (feverfew, butterbur)
- CoQ10, B-vitamins, oral Mg2+
- Antihypertensives (beta-blockers, verapamil, candesartan)
- Anticonvulsants (valproic acid, topiramate)
- Tricyclic antidepressants (amitriptyline, nortriptyline)

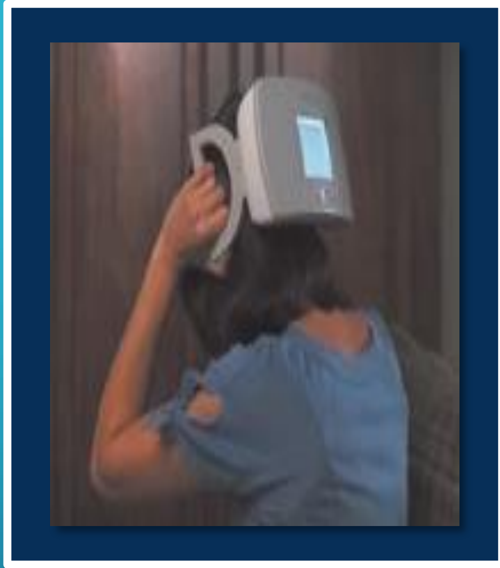
# MIGRAINE
## PROPHYLACTIC RX – BOTULINUM

- FDA-approved for chronic migraine only
- Multiple hurdles, variable insurance coverage, expensive
- Rx is an art – best performed an experienced neurologist
- May fall out of favor due to newer options

# MIGRAINE
## PROPHYLACTIC RX - DEVICES

Three FDA-approved noninvasive neuromodulation devices for acute and preventive migraine Rx:

- GammaCore > (cervical) vagus nerve stimulator (acute Rx only)
- Cerene/Spring > (occipital) transcranial magnetic stimulator
- Cefaly > (frontal) supraorbital nerve stimulator
- Nerivio Migra > armband neurostimulator



# CALCITONIN GENE-RELATED PEPTIDE

- 37-amino acid neuropeptide marker of primary afferent neurons
- Member of calcitonin family of peptides (calcitonin, adrenomedullin, amylin, intermedin)
- Potent vasodilator
- Distributed in both CNS + PNS, in the dorsal root (DRG) + trigeminal ganglia, spinal cord, GI tract

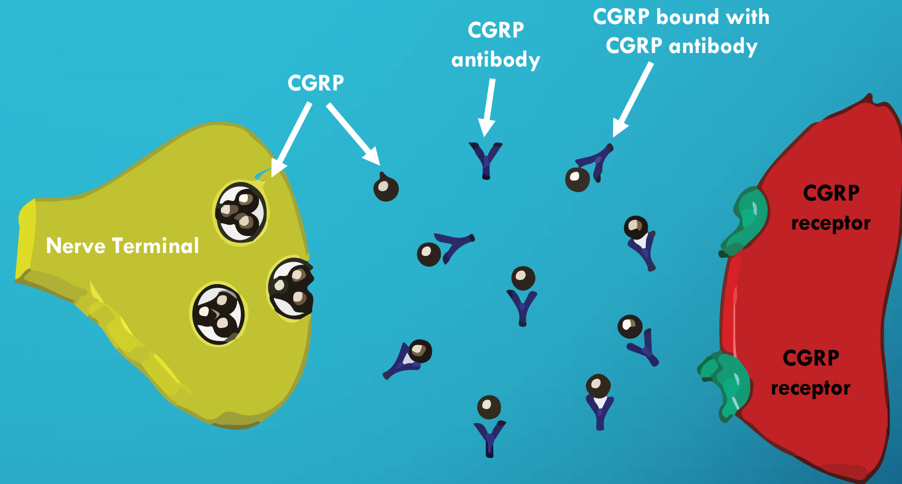
# CGRP AND MIGRAINE

- Plasma CGRP levels increased during a migraine attack and normalized with relief of the attack
- CGRP infusion induces migraine-like attacks in individuals with a history of migraine
- 6 small molecule CGRP receptor antagonists demonstrated efficacy in clinical trials for acute treatment of migraine (olcegepant, telcagepant, rimegepant, ubrogepant, MK-3207, and BI 44370 TA)
- small molecule CGRP receptor antagonists (ubrogepant, telcagepant) demonstrated efficacy in migraine abortive + prevention trials
- 3 CGRP neutralizing antibodies (galcanezumab, eptinezumab, and fremanezumab) and a CGRP receptor antibody (erenumab) demonstrated efficacy in migraine prevention trials

# ANTI-CGRP RX
# DIFFERENT MECHANISMS OF ACTION

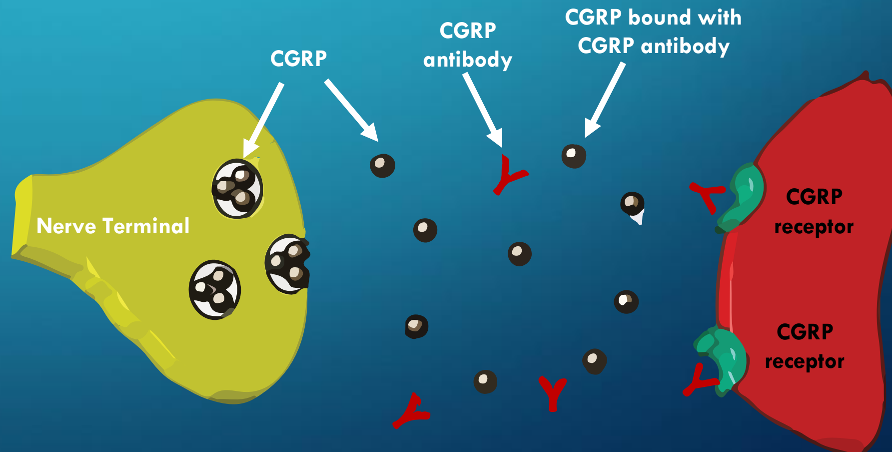
**CGRP antibodies**[1]

- Galcanezumab (LY2951742)
- Fremanezumab (TEV-48125)
- Eptinezumab (ALD403)




**CGRP receptor blockers**[1]

- Erenumab (AMG 334)
- Small molecule receptor antagonists



# MIGRAINE
## PROPHYLACTIC RX – CGRP INHIBITION

- Newest approach to Rx
- May help w/in a week in many cases
- Fewer MHDs, increased activity level
- Does not cross BBB (so no dizziness or sedation)

# MIGRAINE
PROPHYLACTIC RX – CGRP INHIBITION

**Risks:**

- Injection site reactions (most common)
- Constipation
- Hypersensitivty reactions
- Immunogenicity > neutralizing Abs
- Not studied in pregnancy

# MIGRAINE
## PROPHYLACTIC RX – CGRP INHIBITION

**SQ**

- Aimovig (erenumab - Amgen/Novartis)
- Ajovy (fremanezumab - Teva)
- Emgality (galcanezumab – Eli Lilly)

**Oral**

- Zydis (rimegepan - Biohaven)

# MIGRAINE ABORTIVE RX - GEPANTS

- Small-molecule CGRP receptor antagonists
- Ubrogepant (NEJM 2019; 381: 2230-2241)
- One 50-100 mg dose +/- second dose
- Increased freedom from pain and absence of most bothersome migraine S/S @ 2 hrs
- SE: nausea, somnolence, dry mouth

# Q&A