"An Ounce of Prevention" Avoiding Migraine Before it Starts: The Preventive Role of Migraine Management

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Utica Park Clinic Headache Center

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Disclosures

- Speakers Bureau: Abbvie/Allergan, Biohaven, Eli Lilly, Impel, Teva, Lundbeck
- Consultant: Abbvie/Allergan, Biohaven, Teva
- I will be discussing off-label medications
  - Migraine prophylaxis is an FDA-labeled indication for: divalproex sodium, propranolol, timolol, topiramate, erenumab, fremanezumab, galcanezumab, and eptinezumab
  - Chronic migraine prophylaxis is an FDA-labeled indication for: onabotulinumtoxinA, erenumab, fremanezumab, galcanezumab, and eptinezumab
  - Neurostimulator devices marketing allowed by FDA for migraine prevention
  - All other prophylactic pharmaceuticals are used without FDA label for the indications discussed

Learning Objectives

- Identify patients who should be offered preventive migraine medications.
- Compare treatment options for prevention of migraine.
- Recognize new treatment options for prevention of migraine.
- Demonstrate preventive migraine treatment optimization in utilization.

Migraine

- #1 Reason for referral to a Neurologist

Lipton RB, et al. *Headache*. 2001.

Migraine

- #1 Reason for referral to a Neurologist
- 12% of the U.S. adult population (36-40 million migraine sufferers in the US)

Pietrobon D, et al. *Annu Rev Physiol*. 2013. Burch R, et al. *Headache.* 2018.; American Diabetes Associatoin. Statistics about diabetes. https://www.diabetes.org/resources/statistics/statistics-about-diabetes. 3. Centeres for Disease Control and Prevention (CDC). Epilepsy data and statistics. https://www.cdc.gov/epilepsy/data/index.html. 4. CDC. Asthma Data https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

Migraine

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- 12% of the U.S. adult population (36-40 million migraine sufferers in the US)
- **67%** of patients consult their primary care provider for migraine and **10%** of primary care visits in the U.S. are for migraine

Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache.* 2018;58(4):496-505.

Write This Down

https://primarycare.americanheadachesociety.org

Migraine

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- 12-14% of the U.S. adult population (36-40 million migraine sufferers in the US)
- **67%** of patients consult their primary care provider for migraine and **10%** of primary care visits in the U.S. are for migraine
- Effective preventive treatment can reduce migraine frequency, restore functioning, and reduce risk of progression to more severe disease

Dodick et al. *Headache.* 2016; Lipton et al. *Cephalalgia.* 2016.

Migraine

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- **67%** of patients consult their primary care provider for migraine and **10%** of primary care visits in the U.S. are for migraine
- Effective preventive treatment is essential
- Diagnosis is a critical step to optimal migraine management; however, ~50% go misdiagnosed or undiagnosed

Dodick et al. *Headache.* 2016; Lipton et al. *Cephalalgia.* 2016.

Diagnosis of Migraine

- Part 1: Primary Headaches (symptom-based)
- Part 2: Secondary (etiology-based)
- Part 3: Cranial neuralgias, facial pain, and other headaches
- Appendix

Find it at
www.ichd-3.org

ICHD-3. Cephalalgia. 2018.

BET on Migraine

MIGRAINE	
At least 5 attacks	
Headache attacks lasting 4-72 hr (untreated to unsuccessfully treated)	
• Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity	• Nausea and/or vomiting • Photophobia and phonophobia

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Just need 2 of these!

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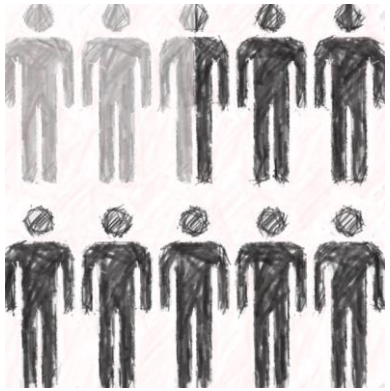
Just need 2 of these!

Just need 1 of these!

Episodic vs. Chronic Migraine (CM)

- ≥15 headache days, 8 migraine
- Many people who meet chronic migraine diagnosis are misdiagnosed.



Only **25%** of patients who see ***any physician*** received a Chronic Migraine diagnosis

Dodick et al. *Headache.* 2016; Lipton et al. *Cephalalgia.* 2016; Data on file, Allergan, 2014; Barriers to Chronic Migraine Care.

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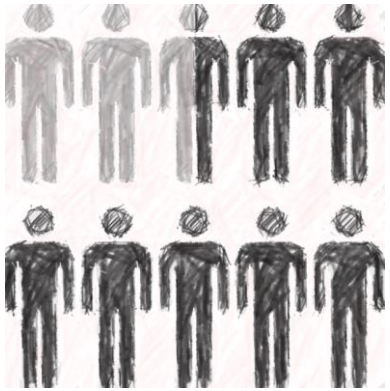

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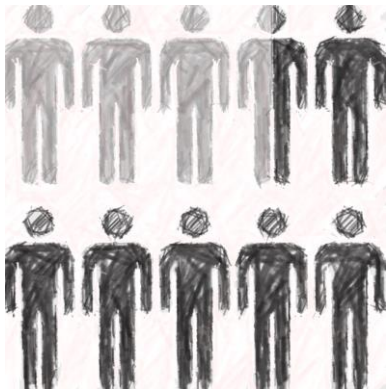


Only **36%** of patients who see a ***specialist*** received a Chronic Migraine diagnosis[2,3]

Dodick et al. *Headache.* 2016; Lipton et al. *Cephalalgia.* 2016; Data on file, Allergan, 2014; Barriers to Chronic Migraine Care.

Migraine Prevention

- Of the 38% of individuals that should be considered for preventive treatment of migraine, only 13% actually receive it.

We are under-utilizing preventives

Dodick et al. *Headache.* 2016; Lipton et al. *Cephalalgia.* 2016; Data on file, Allergan, 2014; Barriers to Chronic Migraine Care.

Migraine Prevention

- Reduce attack frequency, severity, and duration
- Improve responsiveness to and avoid escalation in use of acute treatment
- Improve function and reduce disability, including headache-related distress, improved quality of life, and/or psychological symptoms
- Enable patients to manage their own disease to enhance a sense of personal control
- Reduce overall cost associated with migraine treatment

Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States [published online February 15, 2018]. Headache. doi: 10.1111/head.13275.
American Headache Society. Headache. 2019;59:1-18.

When to Consider Prevention…

- Attacks that significantly interfere with a patient's quality of life and daily routine despite trigger management, appropriate use of acute medications, and lifestyle modification strategies.
- Frequent headaches (**four** or more attacks per month or eight or more headache days per month).
- Failure of, contraindication to, overuse of, or troublesome side effects from acute medications.
- Patient preference, that is, the desire to have as few attacks as possible.
- Presence of certain migraine conditions: hemiplegic migraine, migraine with brainstem aura, frequent, prolonged, or uncomfortable aura symptoms, or migrainous infarction.

American Headache Society. Headache. 2019;59:1-18

When to Consider Prevention…

Episodic Migraine

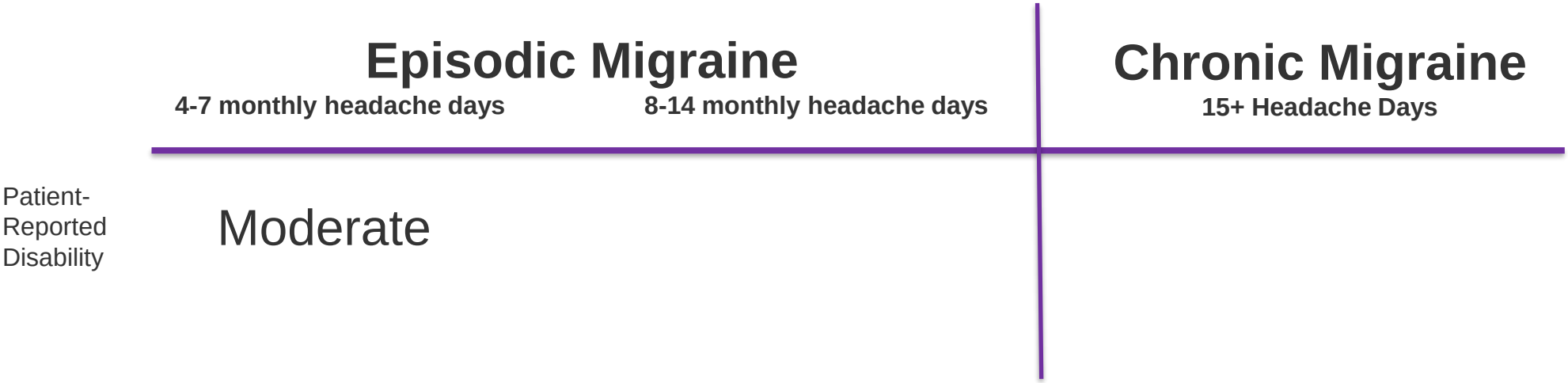
4-7 monthly headache days **8-14 monthly headache days**

Chronic Migraine

15+ Headache Days

American Headache Society. Headache. 2019;59:1-18

When to Consider Prevention…



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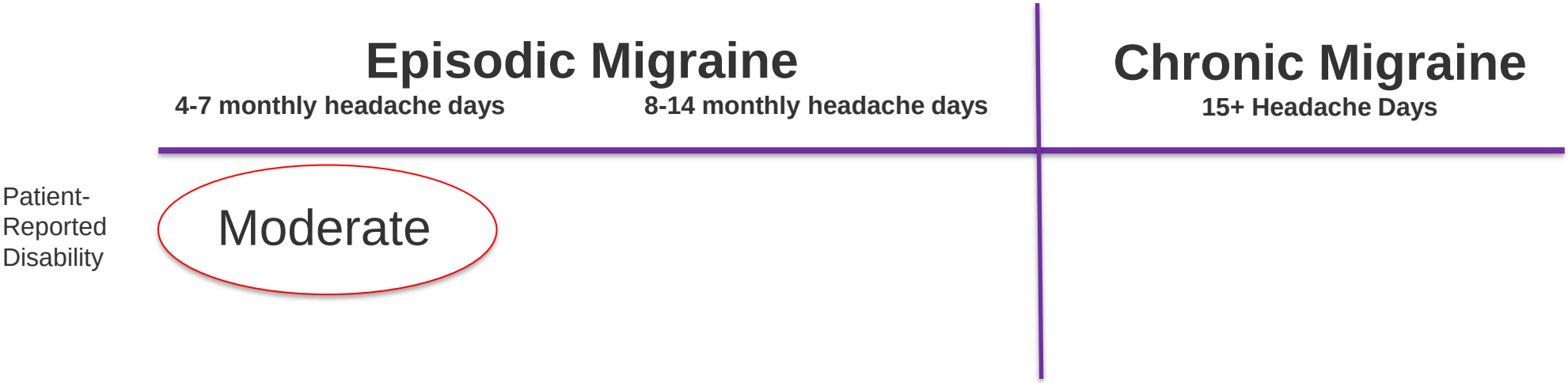


American Headache Society. Headache. 2019;59:1-18

27-Year-Old Woman

Migraine Preventives

Established Efficacy+

Antiepileptic Drugs
- Divalproex sodium[a]
- Valproate sodium[a]
- Topiramate[a]

Beta-Blockers
- Metoprolol
- Propranolol
- Timolol

Triptans: Froivatriptan[b]

OnabotulinumToxin A*

CGRP Antagonists
- mAbs, Gepants

Probably Effective++

Antidepressants
- Amitriptyline
- Venlafaxine

Beta-Blockers
- Atenolol
- Nadolol

Possibly Effective+++

ACE inhibitors: Lisinopril

Alpha-agonists
- Clonidine
- Guanfacine

Antiepileptic drugs: Carbamazepine

Beta-Blockers
- Nebivolol
- Pindolol

Antihistamines: Cyproheptadine

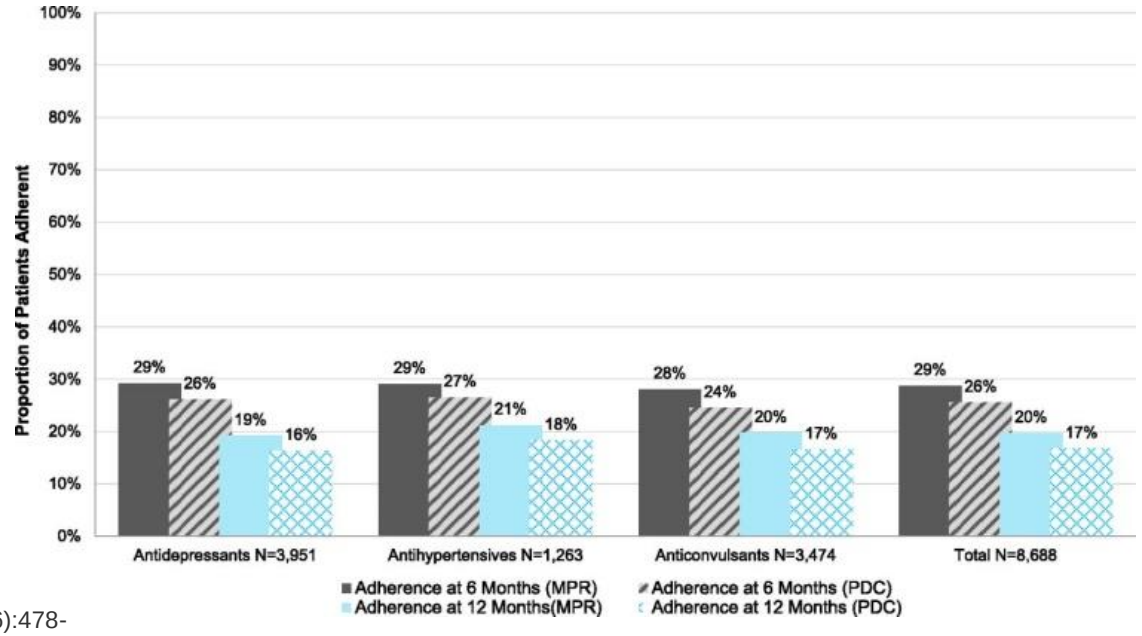
Angiotensin receptor blockers: Candesartan

+More than 2 Class I trials based on AAN Scheme for Classification of Evidence
++One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence
+++One Class II study based on AAN Scheme for Classification of Evidence
a Not for use in women of childbearing potential who are not using an appropriate method of birth control. b For short-term prophylaxis of menstrually-related migraine
*Chronic migraine only

American Headache Society. Headache. 2019;59:1-18

Poor Prevention Adherence

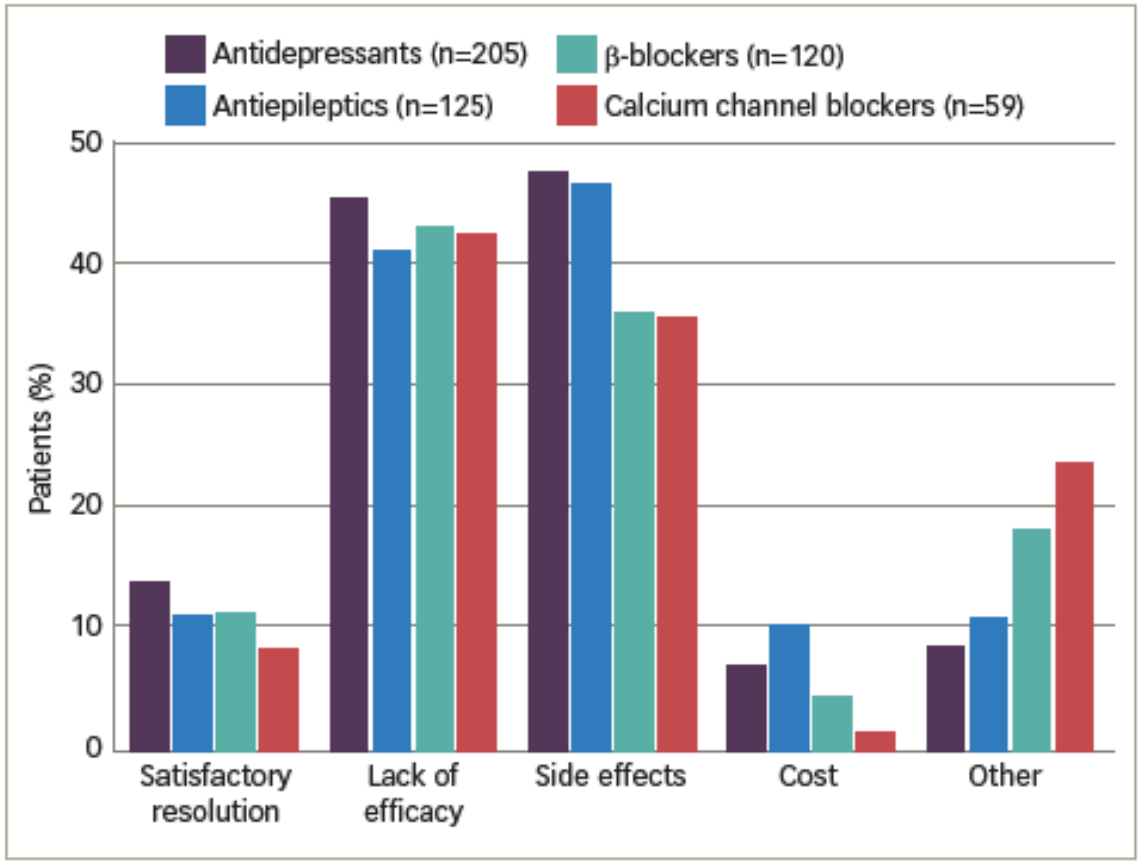
- One in five patients will discontinue a preventive medication due to tolerability or safety issues.
- 25% of those with chronic migraine continue to use oral preventives for more than one year after it was started.



Gracia-Naya et al. Rev Neurol. 2011;53(4):201-8.
Hepp Z, et al. Cephalalgia. 2015;35(6):478-88.

Why is Prevention Adherence So Low?

Figure 4. Patient-reported reasons for discontinuation of preventive treatments for migraine (IBMS-II study; n=1,165)[3]



IBMS-II = the second International Burden of Migraine study.
Data source: Blumenfeld AM et al., 2013.[3]

General Principles for Instituting Preventive Therapy

- Start low and titrate (reach a therapeutic dose) Give an adequate trial
  - *A full trial may take 2 to 6 months before the maximal response to a treatment is evident.

Hien Ha, Gonzalez A. Am Fam Physician 2019.
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- Establish realistic expectations
  - 50% reduction in frequency, duration, or severity of migraine attacks

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- Optimize drug selection
- Involve patients in their care to maximize compliance.
- Re-evaluate therapy; migraine may improve or remit independent of treatment. *If headaches are well controlled for 6-12 months, *slowly* taper and, if possible, discontinue the drug.

Hien Ha, Gonzalez A. Am Fam Physician 2019.
American Headache Society. Headache. 2019;59:1-18

Examples of Medication Trials

Topiramate (Topamax)
Week 1: 25 mg HS
Week 2: 25 mg BID
Week 3: 25 mg in the morning, 50 mg HS
Week 4: 50 mg BID

Consider: overweight, mood stabilization, severe migraine

Educate: paresthesias, kidney stones (calcium phosphate), weight loss, depression

Avoid: pregnancy, anorexia, history of kidney stones, glaucoma

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Amitriptyline (Elavil)

Week 1: 10 mg HS
Week 2: 20 mg HS
Week 3: 30 mg HS
Week 4: 40 mg HS
Week 5: 50 mg HS

Consider: insomnia, cervicalgia, generalized body pain, diarrhea, tension type headache, primary stabbing headache

Educate: dry mouth, constipation, sedation

Avoid: obesity, cardiac arrhythmias, advanced age

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Propranolol (Inderal)

Week 1: 10 mg HS
Week 2: 10 mg BID
Week 3: 10 mg in the morning, 20 mg at bedtime
Week 4: 20 mg BID
Week 5: 60 mg LA daily vs. 40 mg BID

Consider: tachycardia/HTN, anxiety

Educate: lethargy, dizziness, exercise intolerance, depression

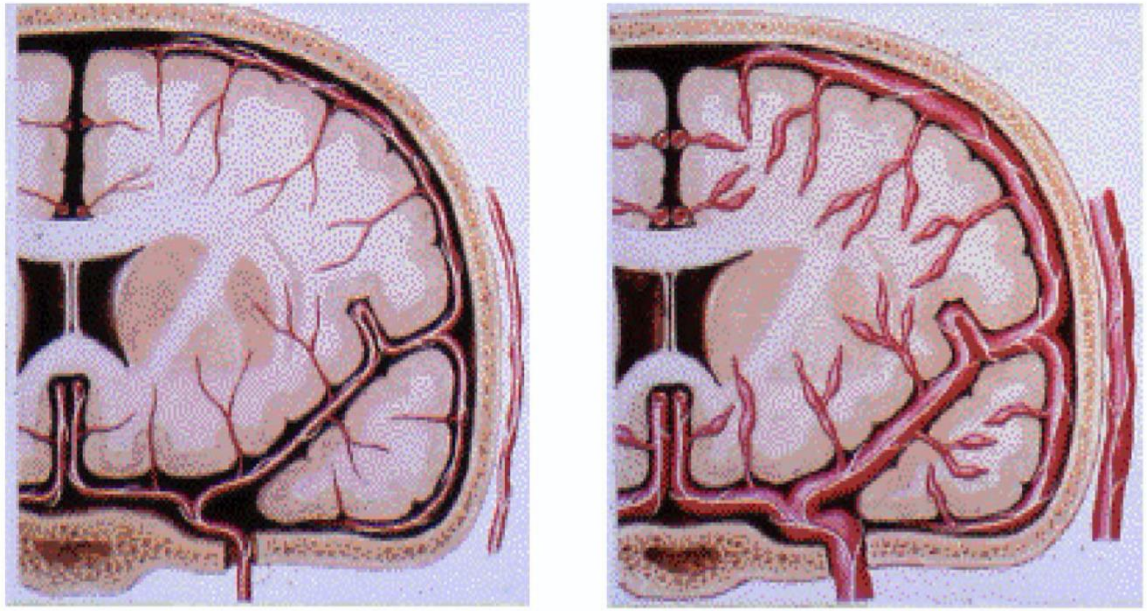
Avoid: asthma, diabetes, bradycardia, congestive heart failure

American Headache Society. Headache. 2019;59:1-18

So, what's NEW in Migraine Treatment…

Vascular Theory of Migraine

- Wolf (1940s-1960s)
- Aura caused by vasocontriction, pain caused by reactive vaso



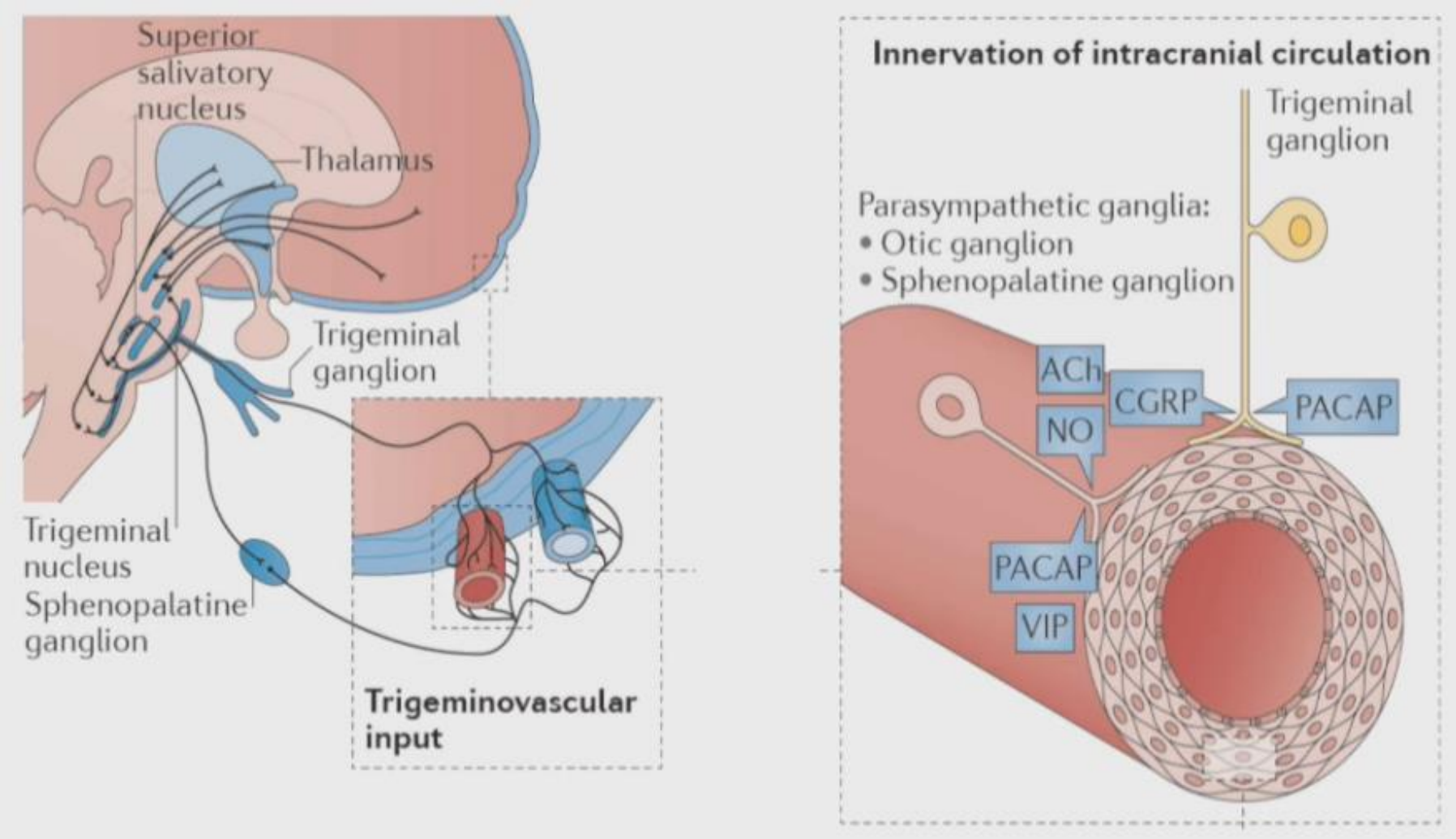
Vascular Theory of Migraine

- Errors:
  - Most patients don't have aura
  - Does not explain premonitory systems
  - Some migraine medications don't affect blood vessels
  - Blood flow studies suggest that vasodilation is an epiphenomenon, NOT the cause of pain.
- **Dilation of blood vessels is neither necessary nor sufficient for causing migraine pain.

Trigeminovascular Theory of Migraine

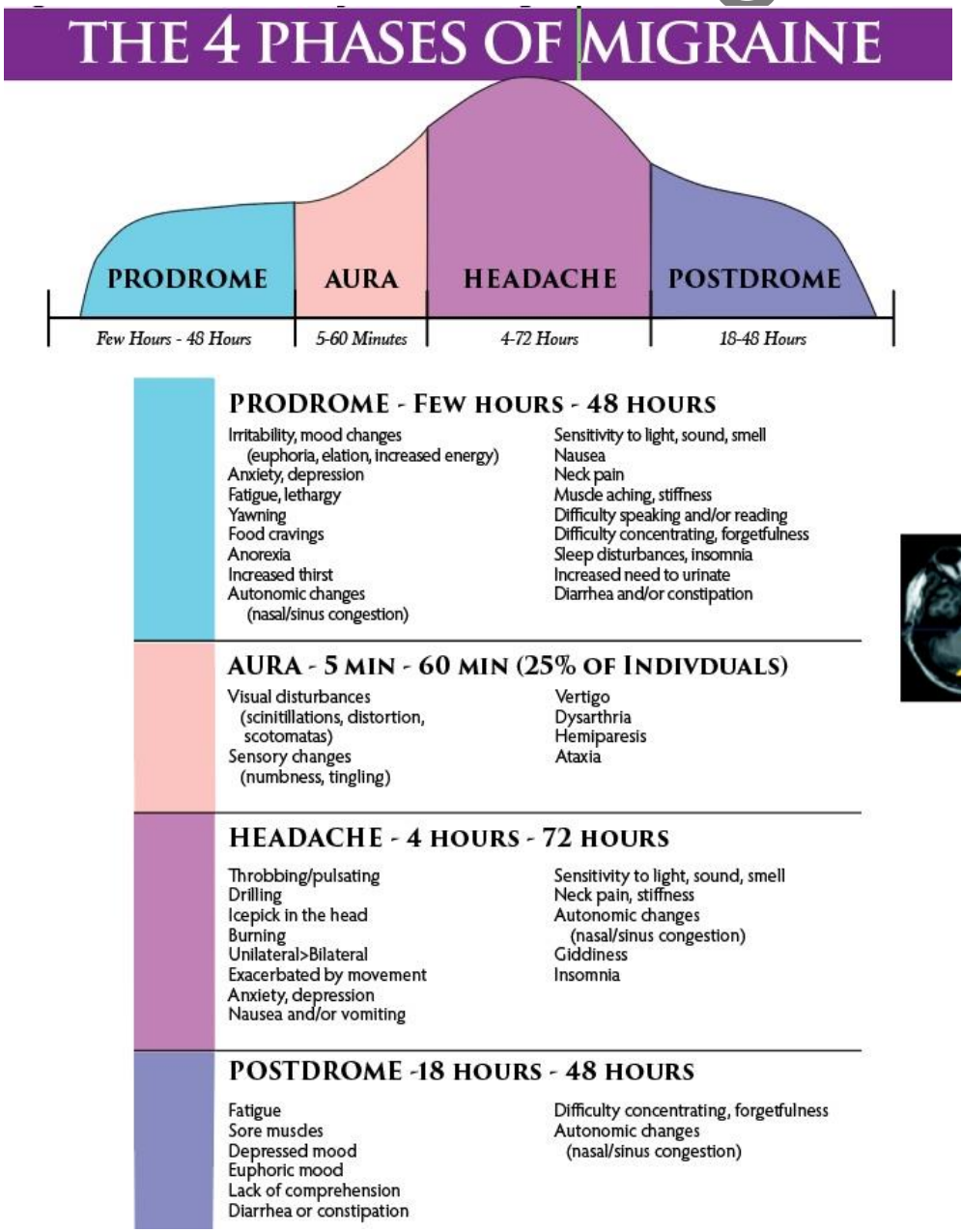
- Migraine is primarily a disease of brain hyperexcitability
- Vasodilation may occur as part of the disorder, but is not required for migraine pain
- Migraine therapies do not work by constricting blood vessels
- Conclusion: Migraine is an inherited complex brain disorder, not a vascular headache

Trigeminovascular Theory of Migraine

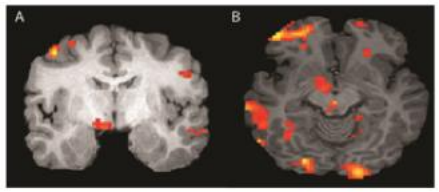


Ashina et al. *Nat Rev Neurol*. 2017.

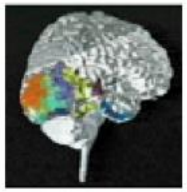
Phases of Migraine



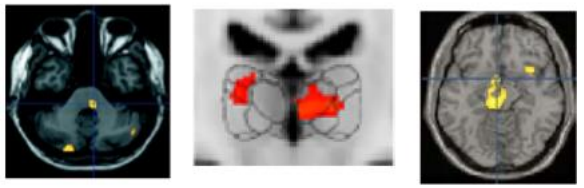
Postdrome:
-hypothalamus
-brainstem
-cortex



Aura:
-cortex



Headache:
-brainstem
-thalamus
-hypothalamus



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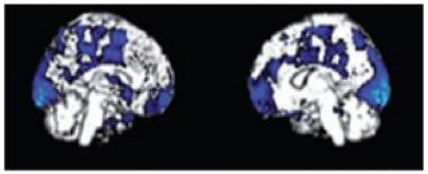
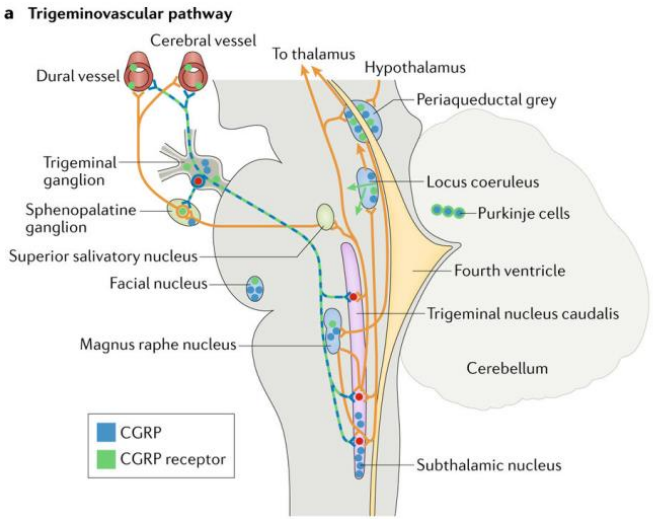


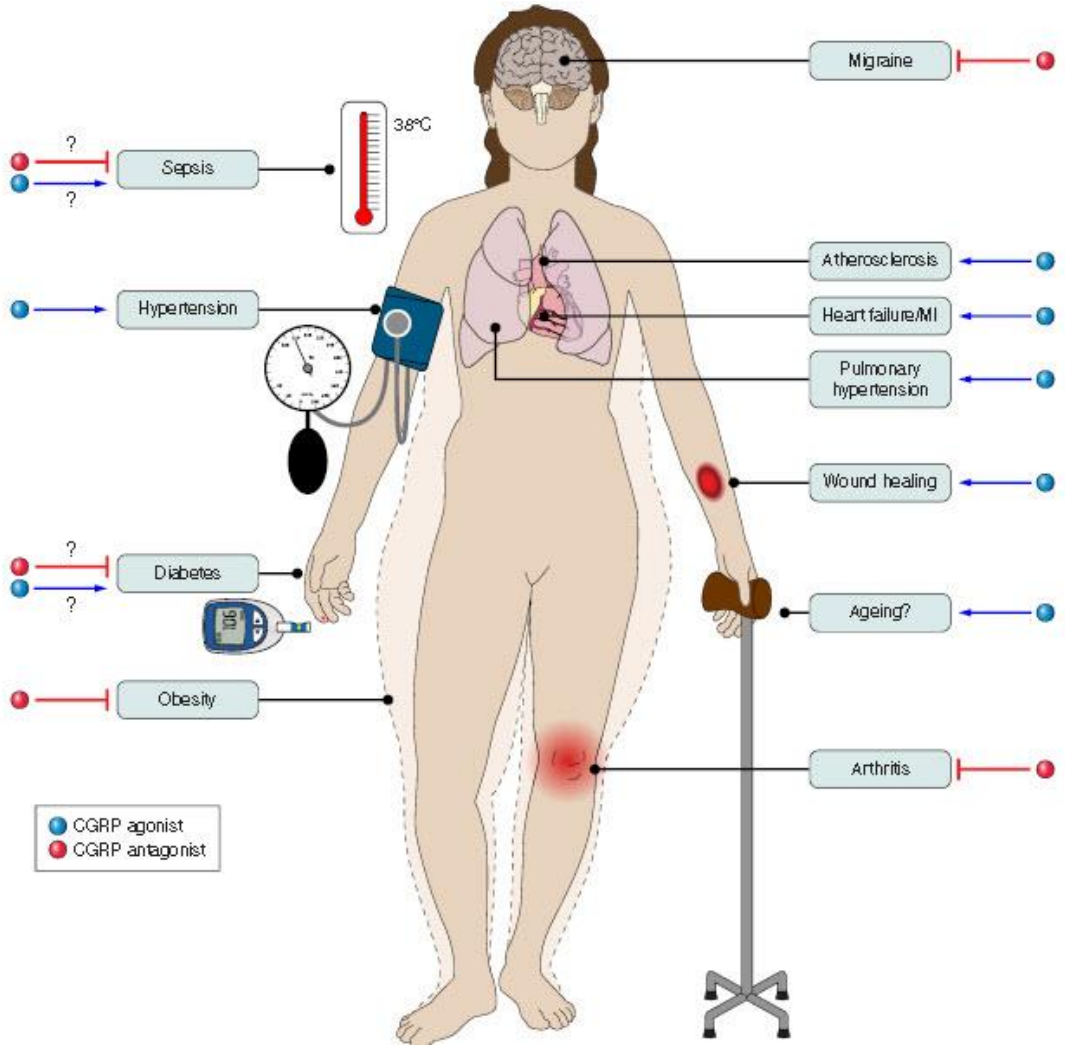
Calcitonin Gene-Related Peptide (CGRP)

- Neuropeptide widely distributed throughout the nervous system; and throughout many portions of the trigeminovascular pathway
- Elevated in plasma from the external jugular vein in acute attacks of migraine, cluster headache, and paroxysmal hemicrania.
- Levels of CGRP is highest in young adults (age 20-40) and declines with age similar to the pattern seen with migraine.
- Infusions provoke migraine
- Blockade prevents migraine
- Potent vasodilator
- 4 current FDA approved monoclonal antibodies to CGRP ligand or its receptor



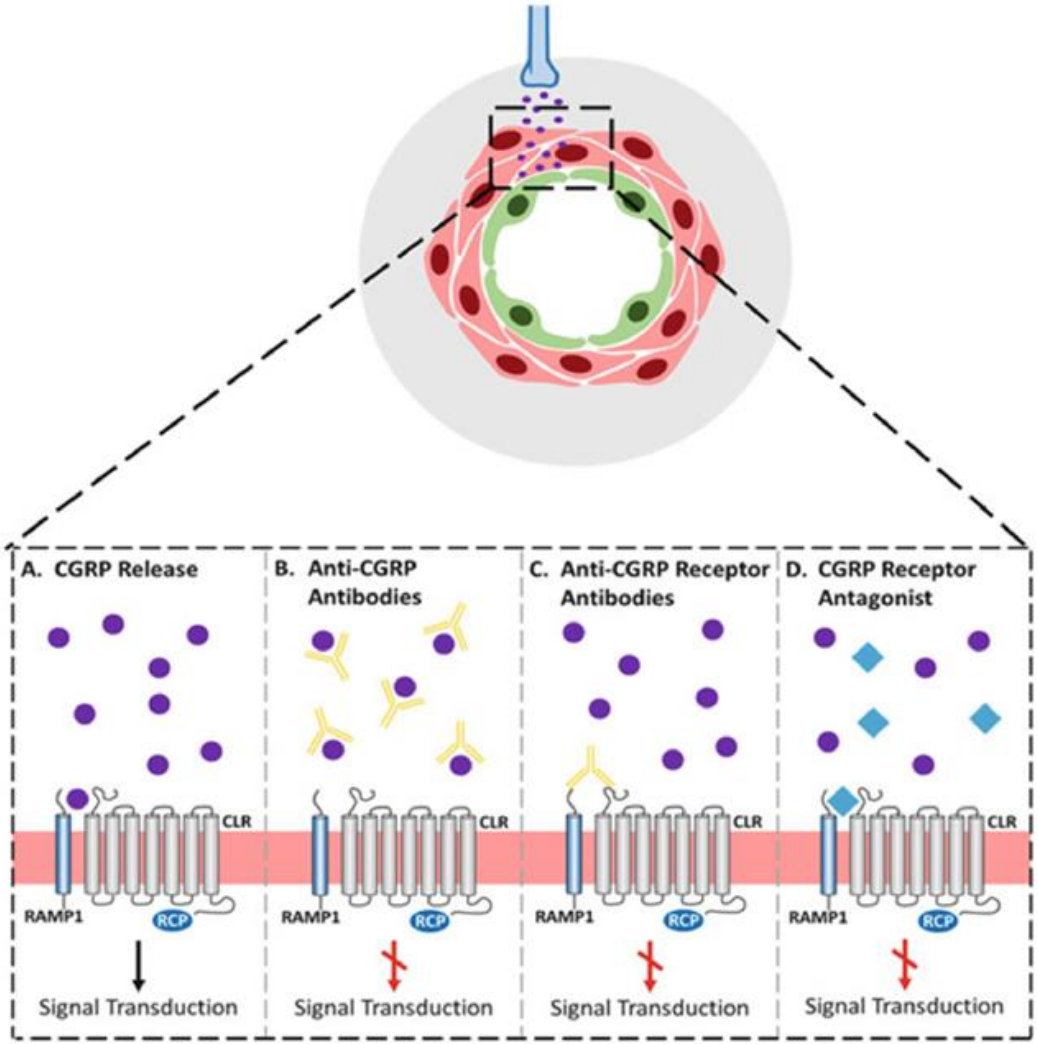
CGRP in the Body

- Found throughout the body and modulates a variety of functioning.



CGRP Antagonists

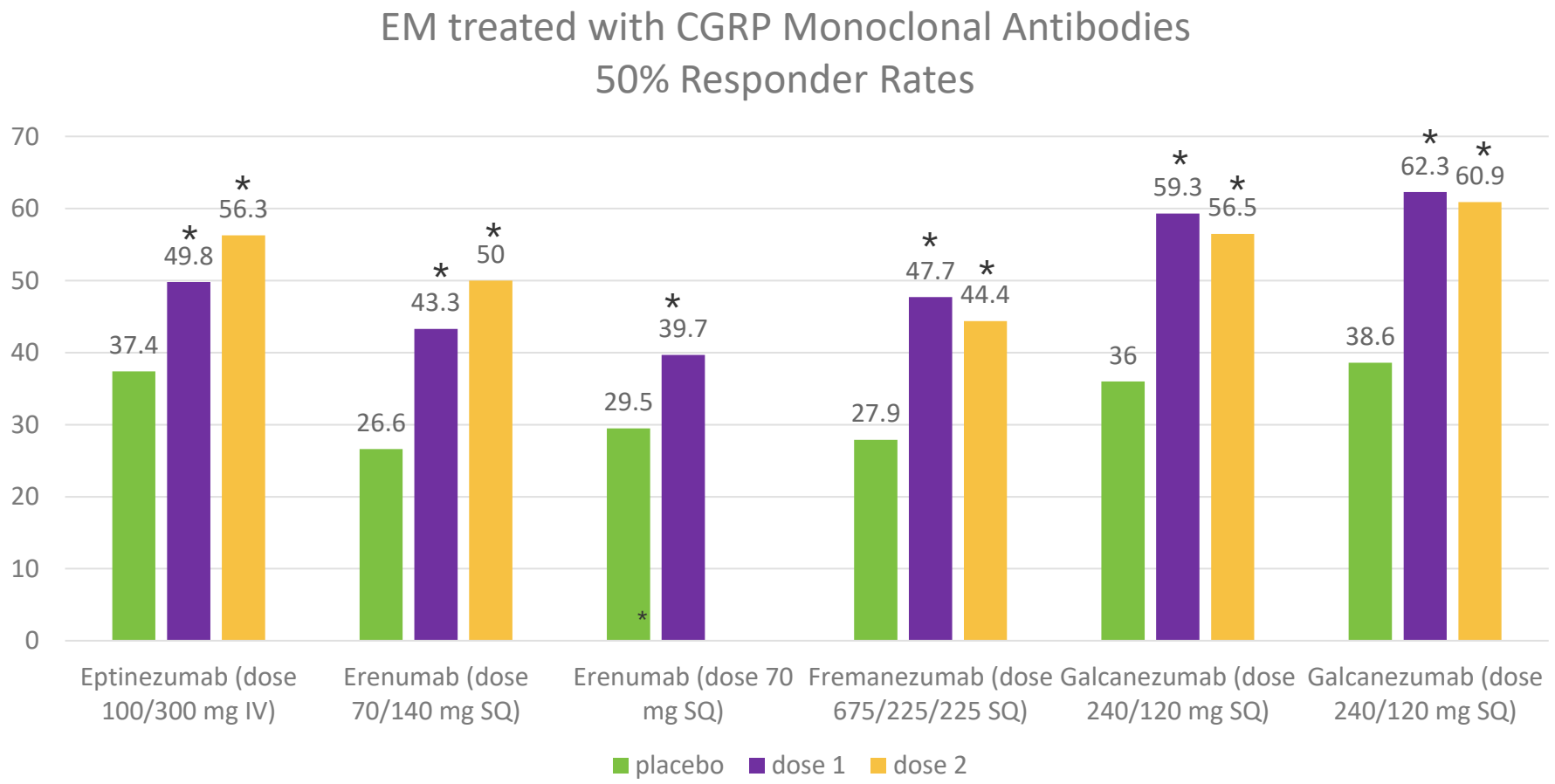
- Monoclonal Antibodies (all preventive):
  - Ligand
  - Receptor
- Gepants (acute and preventive):
  - Receptor



Aubdool A. *British Pharmacology*. 2019.

	Erenumab (Aimovig®)	Fremanezumab (Ajovy®)	Galcanezumab (Emgality®)	Eptinezumab (Vyepti®)
				
Target	Receptor	Ligand	Ligand	Ligand
Subclass	Human ("-umab")	Fully humanized (>95% human) ("-zumab")	Humanized (>90% human) ("-zumab")	Humanized (>90% human) ("-zumab")
Half-life	~ 28 days	~31 days	~27 days	~27 days
Dose and schedule	70 mg or 140 mg monthly SQ	225 mg monthly or 675 mg quarterly SQ	240 mg loading dose, then 120 mg monthly SQ	100 mg or 300 mg Quarterly IV, 30 minute infusion
Status	FDA approved, May 2018	FDA approved, September 2018	FDA approved, September 2018	FDA approved, February 2020
IgG	IgG2	IgG2Δa	IgG4	IgG4
Side Effects	Hypersensitivity reactions, Injection site reactions Constipation *New onset or worsening HTN	Hypersensitivity reactions, Injection site reactions	Hypersensitivity reactions, Injection site reactions	Hypersensitivity reactions, nasopharyngitis

CGRP Mabs: Episodic Migraine Prevention

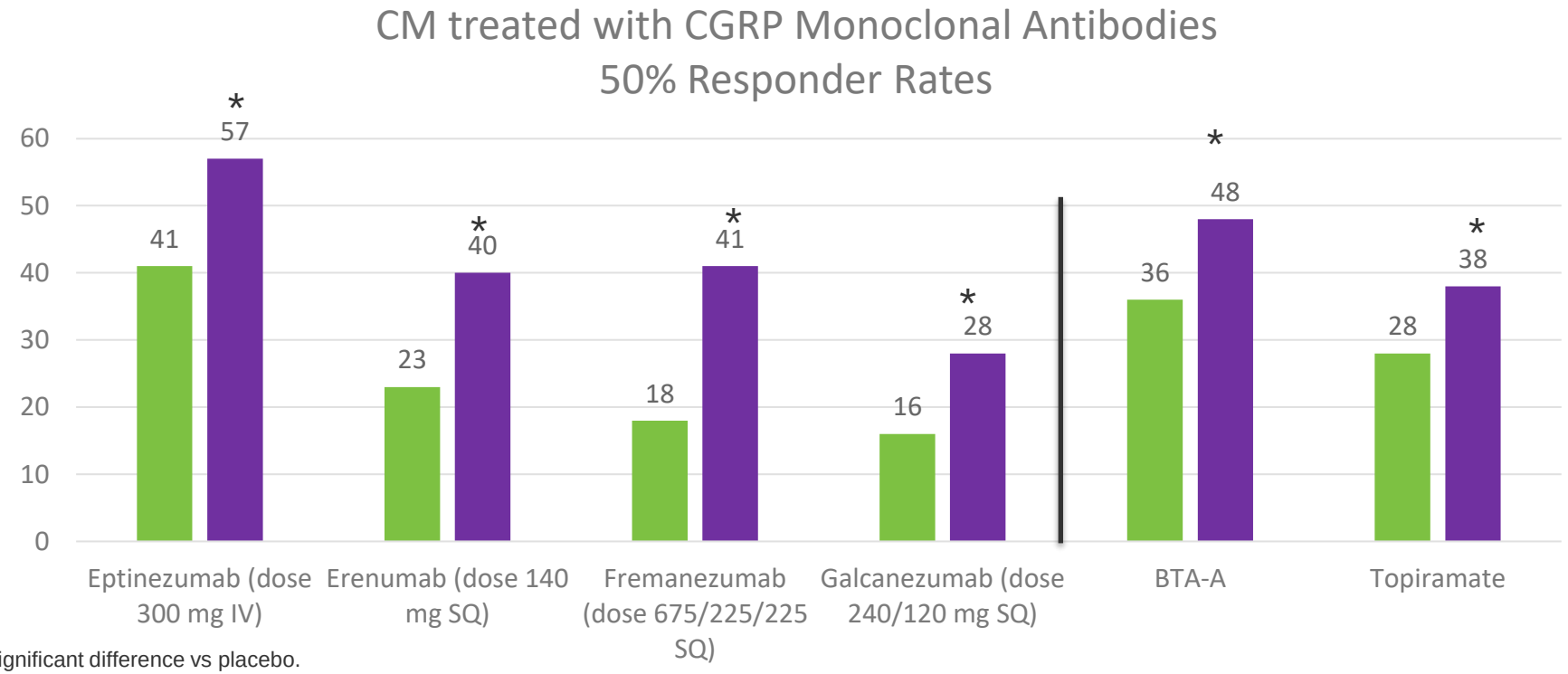


[a] Statistically significant difference vs placebo.

Goadsby PJ et al. *N Engl J Med*. 2017.; Dodick DW et al. *Cephalagia*. 2018.; Dodick DW et al. *JAMA*. 2018.; Stauffer VL et al. *JAMA Neurol*. 2018.; Skljarevski V et al. *Cephalalgia*. 2018. Saper R et al. AAN 2018. Abstract.

CGRP mAbs: Chronic Migraine Prevention

For comparison, the 50% response rate across all trials was 37%.



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Smith et al. Headache 2017; 57:130; Silberstein et al. New Engl J Med 2017; 377:2113; Aurora et al. Headache 2011; 51:1358; Tepper et al. Lancet Neurol 2017;16:425; Detke et al. Headache 2017;57:1336-1337; Silberstein et al. Headache 2006;46:838; Brandes et al. Headache 2017;57:197; Bigal et al. Lancet Neurol 2015;14:1091 (note: phase II data); Detke et al. Cephalalgia 2017;37(1S):338; Dodick et al. Cephalalgia 2011;31:87.

CGRP mAbs vs. Standard Rx

	Monthly Migraine Days (mean change from baseline)	Days Using Acute Medications (mean change from baseline)	50% Responders (odds ratio)
Placebo	Reference	Reference	Reference
Erenumab 70 mg monthly	-1.3 (-1.8, -0.8)	-0.9 (-1.4, -0.4)	1.9 (1.4, 2.5)
Erenumab 140 mg monthly	-1.9 (-2.7, -1.2)	-1.6 (-2.4, -0.9)	2.2 (1.4, 3.3)
Fremanezumab 675 mg quarterly	-1.2 (-2.2, -0.3)	-1.1 (-2.0, -0.3)	1.7 (1.1, 2.7)
Fremanzeumab 225 mg monthly	-1.6 (-2.5, -0.8)	-1.2 (-2.0, -0.4)	1.9 (1.4, 2.9)
Galcanezumab 120 mg monthly	-1.8 (-2.4, -1.2)	-1.8 (-2.4, -1.2)	2.5 (1.9, 3.3)
Galcanezumab 240 mg monthly	-1.8 (-2.5, -1.2)	-1.7 (-2.3, -1.1)	2.4 (1.7, 3.2)
Topoiramate 50 mg/day	-0.2 (-1.0, 0.6)	-0.4 (-1.3, 0.4)	1.6 (1.1, 2.3)
Topiramate 100 mg/day	-1.2 (-1.7, -0.7)	-1.0 (-1.4, -0.5)	2.7 (2.1, 3.5)
Topiramate 200 mg/day	-1.0 (-1.5, -0.4)	-0.7 (-1.3, -0.2)	2.3 (1.7, 3.1)
Amitriptyline 25-100 mg/day	-1.1 (-2.2, 0.1)	-1.2 (-2.4, 0.1)	2.0 (1.2, 3.2)
Propranolol 160 mg/day	-1.2 (-2.0, -0.4)	-1.1 (-1.9, -0.3)	2.7 (1.7, 4.1)

https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf

CGRP mAbs vs. Standard Rx

	Monthly Migraine Days (mean change from baseline)	Days Using Acute Medications (mean change from baseline)	50% Responders (odds ratio)
Placebo	Reference	Reference	Reference
Erenumab 70 mg monthly	-1.3 (-1.8, -0.8)	-0.9 (-1.4, -0.4)	1.9 (1.4, 2.5)
Erenumab 140 mg monthly	-1.9 (-2.7, -1.2)	-1.6 (-2.4, -0.9)	2.2 (1.4, 3.3)
Fremanezumab 675 mg quarterly	-1.2 (-2.2, -0.3)	-1.1 (-2.0, -0.3)	1.7 (1.1, 2.7)
Fremanzeumab 225 mg monthly	-1.6 (-2.5, -0.8)	-1.2 (-2.0, -0.4)	1.9 (1.4, 2.9)
Galcanezumab 120 mg monthly	-1.8 (-2.4, -1.2)	-1.8 (-2.4, -1.2)	2.5 (1.9, 3.3)
Galcanezumab 240 mg monthly	-1.8 (-2.5, -1.2)	-1.7 (-2.3, -1.1)	2.4 (1.7, 3.2)
Topoiramate 50 mg/day	-0.2 (-1.0, 0.6)	-0.4 (-1.3, 0.4)	1.6 (1.1, 2.3)
Topiramate 100 mg/day	-1.2 (-1.7, -0.7)	-1.0 (-1.4, -0.5)	2.7 (2.1, 3.5)
Topiramate 200 mg/day	-1.0 (-1.5, -0.4)	-0.7 (-1.3, -0.2)	2.3 (1.7, 3.1)
Amitriptyline 25-100 mg/day	-1.1 (-2.2, 0.1)	-1.2 (-2.4, 0.1)	2.0 (1.2, 3.2)
Propranolol 160 mg/day	-1.2 (-2.0, -0.4)	-1.1 (-1.9, -0.3)	2.7 (1.7, 4.1)

https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf

Caveats

- Long term safety unknown
  - CGRP may be important fail-safe mechanism in ischemic emergencies
- Studies excluded complex, refractory patients
- Anecdotal reports of hair loss, joint pain
- Effect during pregnancy unknown
  - Recommend using effective birth control methods
  - Discontinue antibody therapy 6 months prior to conception
- Cost may be an issue for some

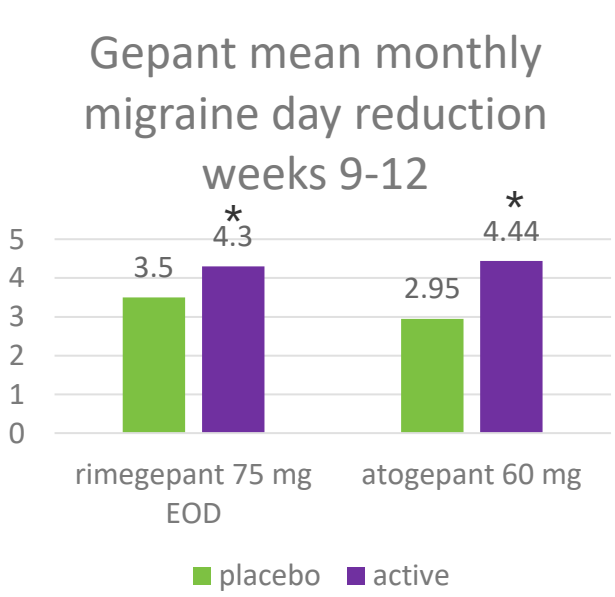
CGRP mAbs in Clinical Practice

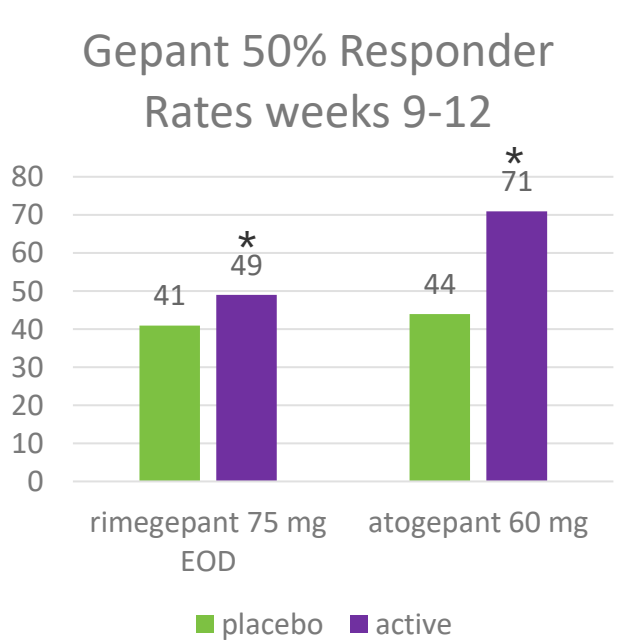
- Consider prescribing in:
  - Patients with lack of response, inadequate response, or intolerance to 2-3 conventional preventive therapies
  - Conventional preventives contraindicated because of co-existing medical conditions
- Only listed contraindications to their use is hypersensitivity reactions
- No drug interactions*
- Insurance coverage varies widely
  - Assistance programs available, but some are limited to people who already have private insurance
- Discuss unknowns and document

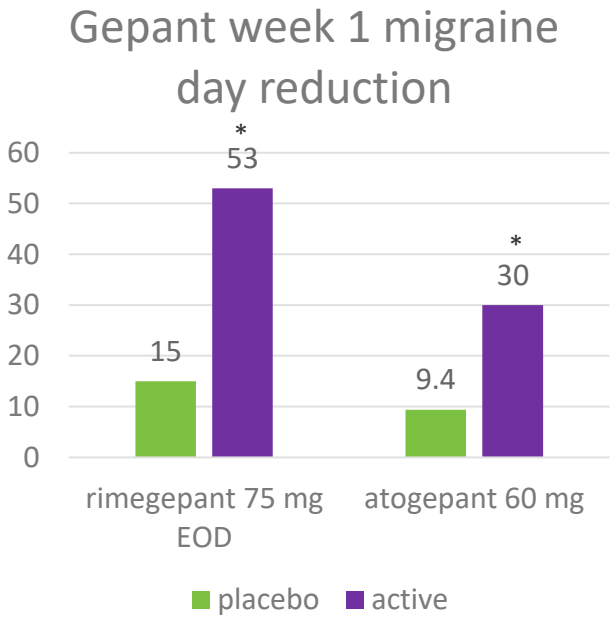
CGRP Antagonists: Gepants

- Small molecule CGRP receptor antagonists
- Initial studies (olcegepant, telcagepant, MK3207) with difficulty with poor oral bioavailability and hepatotoxicity.
- New FDA approved Gepants:
  Ubrogepant 50/100 mg (acute),
  Rimegepant 75 mg ODT (dual),
  Atogepant 10/30/60 mg (preventive)

CGRP Antagonists: Gepant EM Preventive Treatment







[a] Statistically significant difference vs placebo.

- Side effects: Rimegepant 75 mg EOD (nausea, abdominal pain/dyspepsia), Atogepant 10/30/60 mg (nausea, constipation, fatigue/somnolence, decreased appetite)

Croop R et al. *Lancet* 2019.; Croop R et al. Poster AAN. 2021.; Ailani J et al. *N Engl J Med*. 2021.

CGRP Antagonists: Gepant Clinical Pearls

- Side effects: fatigue/somnolence, nausea, constipation, decreased appetite
- 52 week open label studies without any additional safety/tolerability findings; majority of side effects mild-moderate
- May see response as early as the first week
- No MOH warnings
- No cardiovascular contraindications; still CGRP may be important fail-safe mechanism in ischemic emergencies
- Cost may be an issue, but not currently

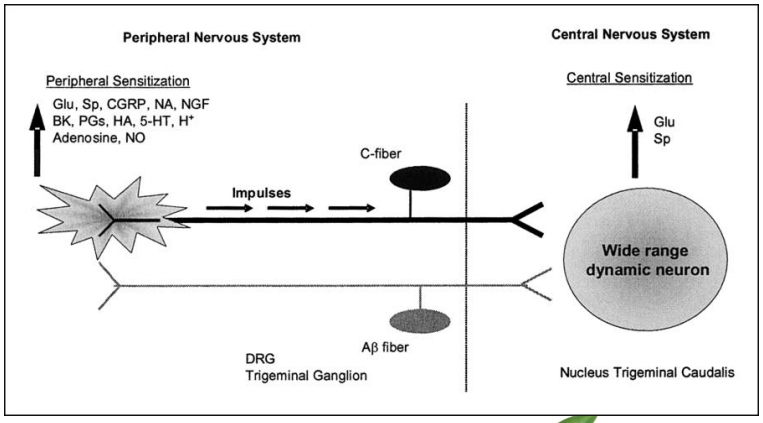
OnabotulinumtoxinA (Botox®) for Chronic Migraine

- 1989 – BTX FDA approved for strabismus
- 2010 PREEMPT Trials (Phase III REsearch Evaluating Migraine Prophylaxis Therapy)
  - Two large, parallel, randomized, double-blind, placebo-controlled trials for BOTOX in chronic migraine
  - Age 18-65 with chronic migraine (MOH, as long as not opiates)
  - 155 UN, 31 injection sites. Optional extra 40 units in painful areas at discretion of investigator.

Aurora SK, et al. Cephalalgia 2010; 30(7): 793-803.
Diener HC, et al. Cephalalgia 2010; 30(7): 804-814.

How does Botox® work?

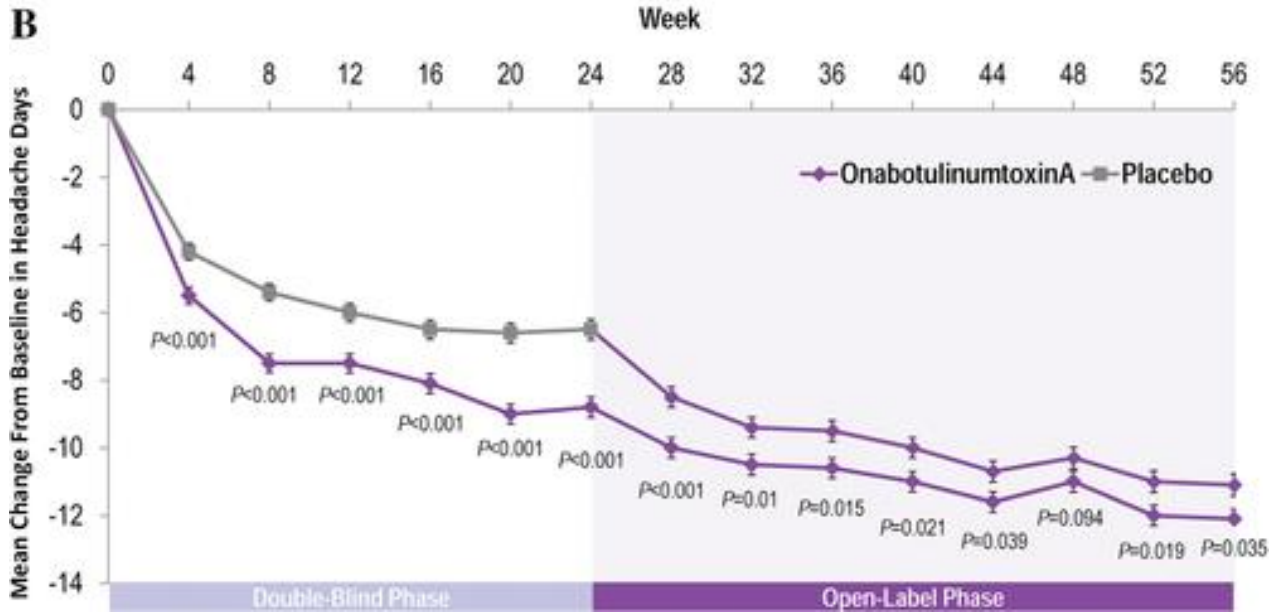
- Precise mechanism is **unknown**
- Effect on muscle contraction does not fully explain pain response
  - Early studies on dystonia/hemifacial spasm noted some patients with minimal motor benefit but dramatic improvements in pain, sometimes outside the region of neuromusclar effect.
  - Patients can have dramatic improvement in migraines, with minimal muscle weakness.
- May prevent release of inflammatory mediators
  - Animal and in vitro studies show BTX blocks stimulated release of a variety of neuropeptides/neurotransmitters
    - Substance P from cultured dorsal root ganglion neurons
    - CGRP form trigeminal ganglia neurons
    - Glutamate from peripheral nerve terminals
  - May block peripheral sensitization directly and central sensitization indirectly



Brin MF, et al. Neurotoxicology 2005; 26(%):785-793.

OnabotulinumtoxinA (Botox®) for Chronic Migraine

- BTX: 8.4 fewer days/mo (p<0.001)
- Placebo: 6.6 fewer days/mo
- Baseline average: approx 20 days/mo



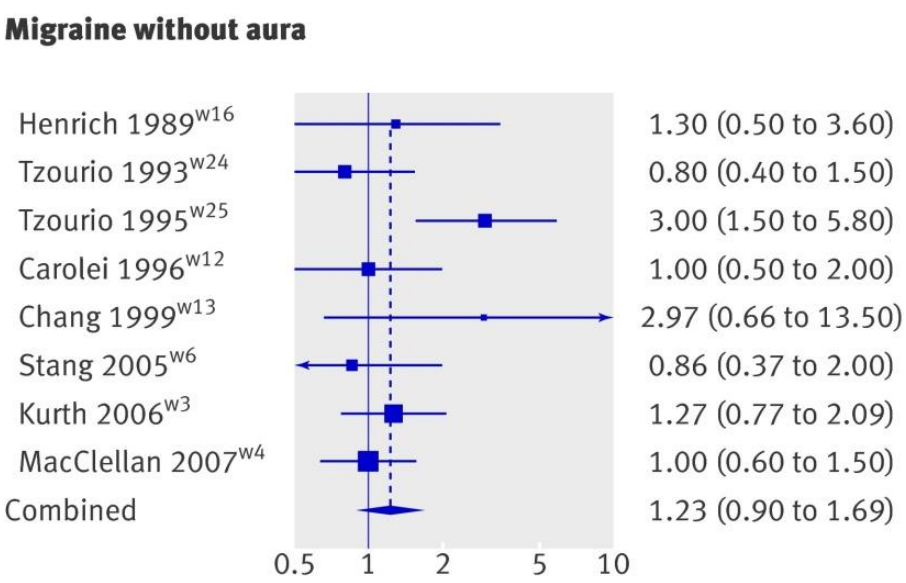
Annals of the New York Academy of Sciences
Volume 1329, Issue 1, pages 67-80, 18 AUG 2014 DOI: 10.1111/nyas.12488

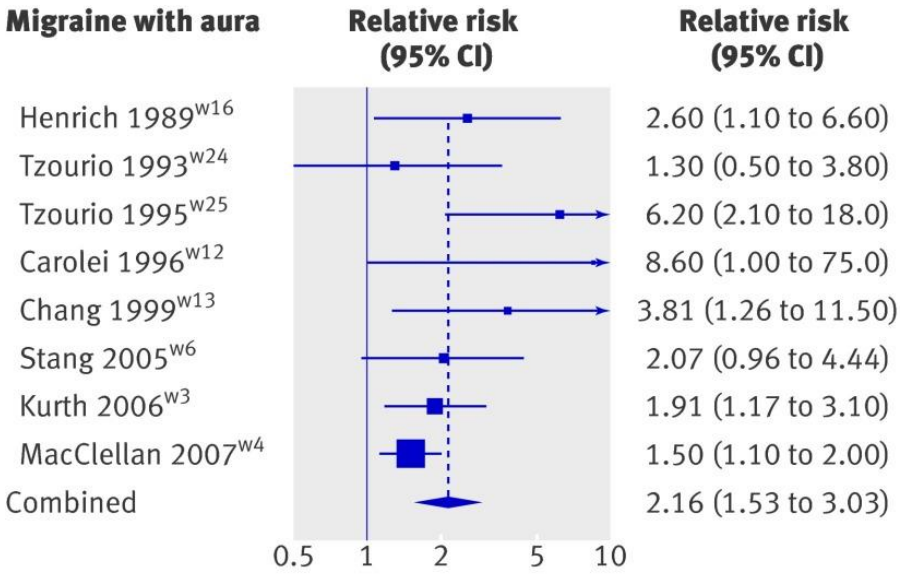
Summary

- Migraine is an inherited complex brain disorder that is primarily a disease of brain hyperexcitability; while vasodilation may occur as part of the disorder, it is not required nor sufficient to explain all migraine pain.
- Preventive migraine treatment is under-utilized and may have a significant positive impact on a patient's quality of life.
- Consider migraine prevention for patients with frequent migraine attacks (1-2 per week or more), significant disability associated with individual attacks, or poor response to acute treatment.
- There are many ways to optimize preventive treatment of migraine and new medications available with different mechanism of action that may be better tolerated.

Thank You

Migraine and risk of Ischemic Stroke





Migraine and cardiovascular disease: systematic review and meta-analysis .Markus Schürks, Pamela M Rist, Marcelo E Bigal, Julie E Buring, Richard B Lipton, Tobias Kurth. *BMJ 2009;339:doi:10.1136/bmj.b3914 (Published 27 October 2009).*

Estrogen Containing Contraceptives and Migraine With Aura

- No contraindication to exogenous estrogen in women who have migraine without aura
- Exogenous estrogens contraindicated in women who have migraine with aura
- Paucity of data about risk with low estrogen formulations
- *Individualized approach* with shared decision making often appropriate and increasingly emphasized

Migraine and cardiovascular disease: systematic review and meta-analysis .Markus Schürks, Pamela M Rist, Marcelo E Bigal, Julie E Buring, Richard B Lipton, Tobias Kurth. *BMJ 2009;339:doi:10.1136/bmj.b3914 (Published 27 October 2009).*

Serotonin Toxicity (ST)

- An acute toxic reaction to substances that enhance serotoninergic activity within the central nervous system.
- Most common with combined exposures to monoamine oxidase inhibitors (MAOIs) with selective or nonselective serotonin reuptake inhibitors (SRIs).
- Triad:
  - Altered mental status (confusion, agitation)
  - Neuromuscular hyperactivity (clonus, myoclonus, hyperreflexia, tremor, shivering, rigidity)
  - Autonomic hyperactivity (tachypnea, tachycardia, fever, diaphoresis, mydriasis)

SSRI/SNRI and Triptan Co-Prescription

Table. Incidence of Serotonin Syndrome in Patients Receiving Triptans and Selective Serotonin Reuptake Inhibitors or Selective Norepinephrine Reuptake Inhibitors[a]

Year	No. of Patients Receiving a Triptan Prescription[b]	No. (%) Exposed to Coprescription [95% CI]	No. of Definite Cases/Total No. of Cases[b]
2001	1444	717 (49.6) [47.1-52.2]	0/0
2002	2347	503 (21.4) [19.8-23.1]	0/0
2003	2827	647 (22.9) [21.3-24.4]	0/0
2004	3615	889 (24.6) [23.2-26.0]	0/0
2005	4767	1230 (25.8) [24.6-27.1]	0/0
2006 (FDA advisory)	6941	1827 (26.3) [25.3-27.4]	0/0
2007	8284	2163 (26.1) [25.2-27.1]	0/0
2008	9132	2244 (24.6) [23.7-25.5]	0/1
2009	9737	2326 (23.9) [23.1-24.7]	0/0
2010	10 288	2433 (23.6) [22.8-24.5]	0/1
2011	11 566	2729 (23.6) [22.8-24.4]	0/2
2012	14 397	3665 (25.5) [24.8-26.2]	1/1
2013	16 833	4645 (27.6) [26.9-28.3]	1/1
2014	17 353	4910 (28.3) [27.6-28.9]	0/1
Total	119 531	30 928 (25.9)[25.6-26.1]	2/7

Abbreviation: FDA, US Food and Drug Administration.

[a] The incidence rate per 10 000 person-years was 0.6 (95% CI, 0-1.5) for definite cases and 2.3 (95% CI, 0.6-3.9) for total cases.

[b] The total number of cases included definite and possible cases. Definite cases were those that met diagnostic criteria for serotonin syndrome with documented coprescriptions during the year of the event. Possible cases were those in which serotonin syndrome was suspected but did not meet diagnostic criteria, had insufficient information to apply diagnostic criteria, or in which triptan ingestion did not occur in temporal relation to the event but had documented coprescriptions during the year of the event.

ST: $5HT_{2A}$ Triptans: antagonize $5HT_{1D/1B/1F}$

- Annual prevalence of presumptive “triptan-associated ST” appears to be no greater than 0.7%. A published estimate of ST prevalence due to SRI treatment alone is 0.5 to 0.9 cases per 1,000 patient-months of SRI treatment.

Orlova Y et al, JAMA Neurology Published online February 26, 2018. doi:10.1001/jamaneurol.2017.5144.
SKLAR DA et al. Headache. (2012) 52:198-203.

What About Marijuana?

- Paucity of good quality evidence, some positive case reports
- Many positive anecdotal patients reports
- Marijuana use is a risk factor for Reversible Cerebral Vasoconstriction Syndrome
- Lack of good information about safety in psychiatrically vulnerable populations.
- Emerging concerns for central sensitization
- General consensus in the headache world: “Not for, not against”

BTX, Does everyone respond?

- No
- Active studies trying to figure out predictors of response
- Patients with cutaneous allodynia may respond better
- Stopping after 2 rounds may be insufficient for some*
- After 5 cycles:
  - Headache days per month: 23.3 ± 5.7 → 9.2 ± 3.6
  - Migraine days per month: 18.5 → 8.7 ($p<0.0001$)
  - Acute medication days : 17.4 → 8.1 ($p<0.0001$)
  - HIT-6 score: 72.4 ± 5.7 → 50.2 ± 4.3