Challenges and Advances In the Diagnosis and Treatment of Migraine

50th Annual OAPA CME Conference
Tulsa, OK
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HEADACHE SPECIALISTS
OF OKLAHOMA

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Disclosures

THE OK HeadacheDoctor

Speakers Bureau: Abbvie/Allergan, Biohaven/Pfizer, Biodelivery Sciences, Eli Lilly, Impel, Lundbeck, Teva

Consultant: Abbvie/Allergan, Biohaven/Pfizer, Lundbeck, Teva

Learning Objectives

- Explain diagnostic criteria for episodic and chronic migraine
- Identify patients who require preventive treatment
- Summarize efficacy, safety and mechanisms of new treatments

Outline

- Diagnosis
- Pathophysiology
- Preventive Treatments
- Acute Treatments
- Non-pharmacologic treatments

Migraine

- #1 reason for referral to Neurologist

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

Migraine

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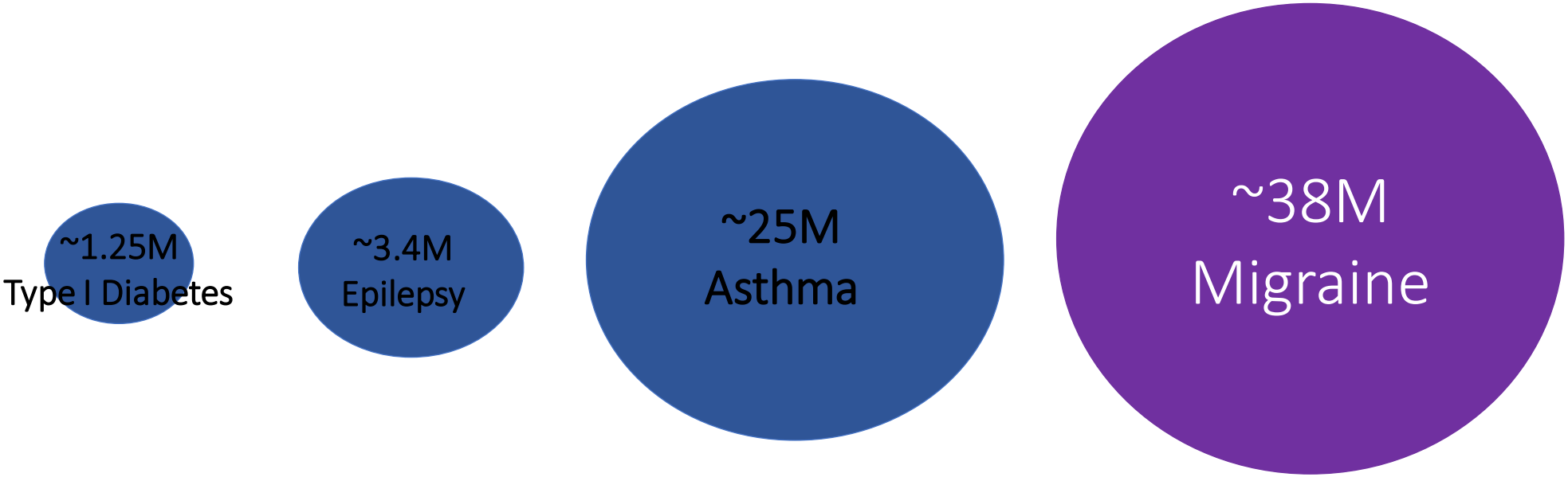
- 12% of the US adult population (36-40 million migraine suffers in the US)



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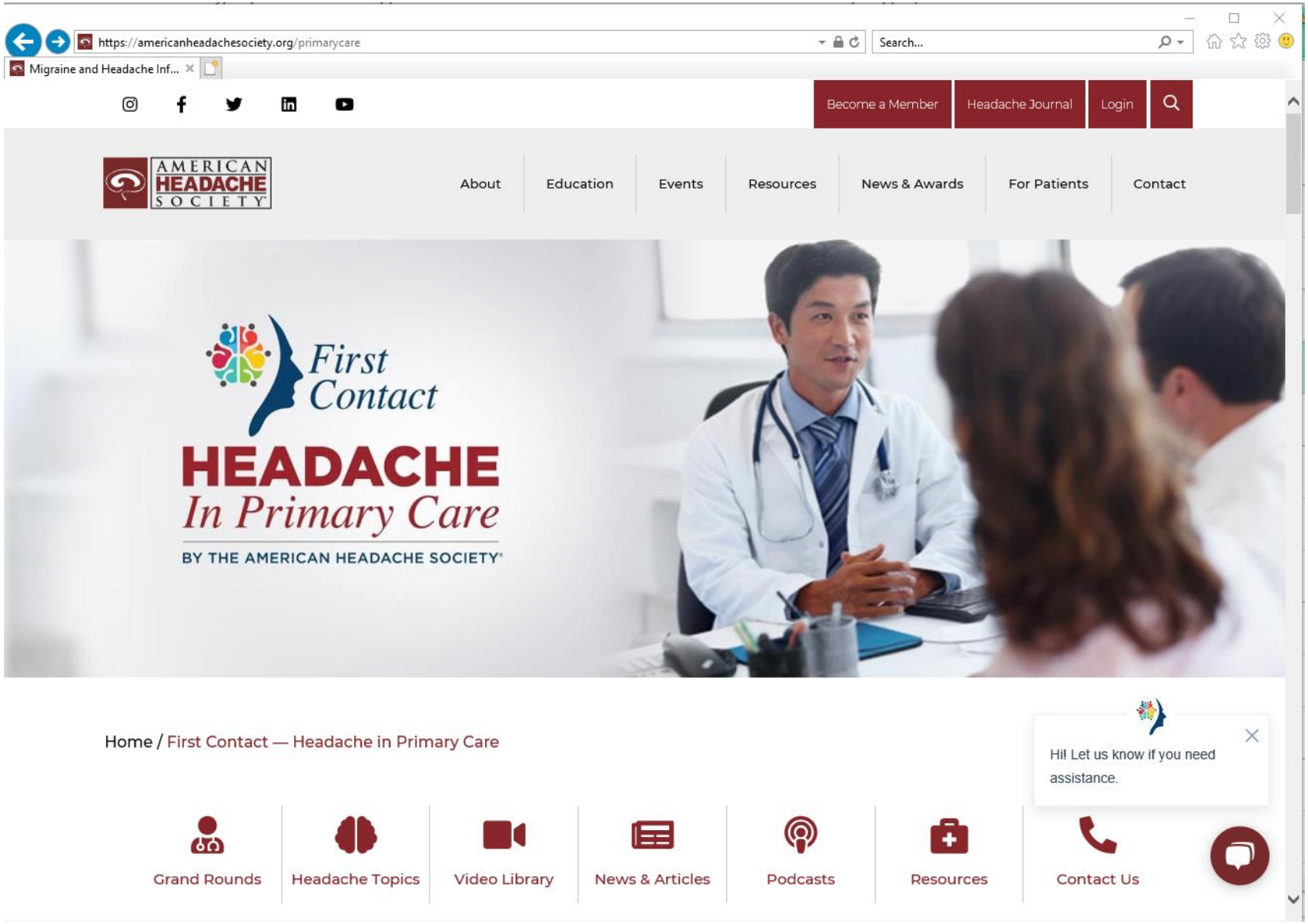
- 12% of the US adult population (36-40 million migraine suffers in the US)
- **67%** of patients consult their primary care provider for migraine and **10%** of primary care visits in the U.S. are for migraine

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



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- 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.

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- Diagnosis is a critical step to optimal migraine management; however, ~50% go misdiagnosed or undiagnosed
- Effective preventive treatment can reduce migraine frequency, restore functioning, and reduce risk of progression to more severe disease

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Approach To Diagnosis

Diagnosis of Migraine

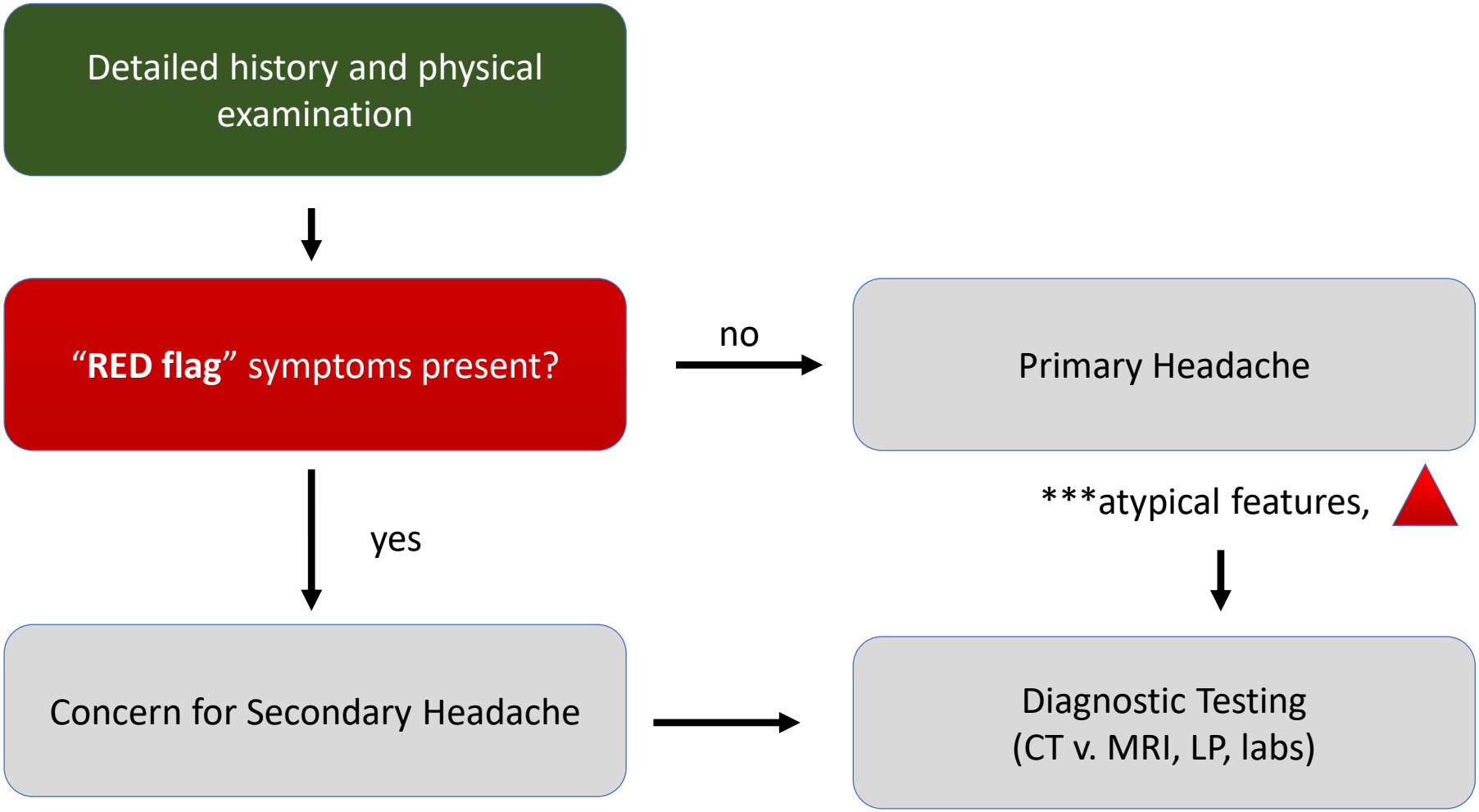
- Part 1: Primary Headaches (symptom-based: Headache itself is the disorder with no underlying causes identified)
  - Migraine, Tension type headache, Cluster/TACs
- Part 2: Secondary (etiology-based: Headache is a symptom of another disorder recognized as a potentially underlying cause)
- Part 3: Cranial neuralgias, facial pain, and other headaches
- Appendix

Find it at
www.ichd-3.org

ICHD-3. Cephalalgia. 2018.

Evaluation

Although the majority of headaches in clinical practice are primary headaches, clinicians need to be mindful of secondary headaches because the underlying conditions can be **life-threatening or disabling** and may require a completely different therapeutic approach.

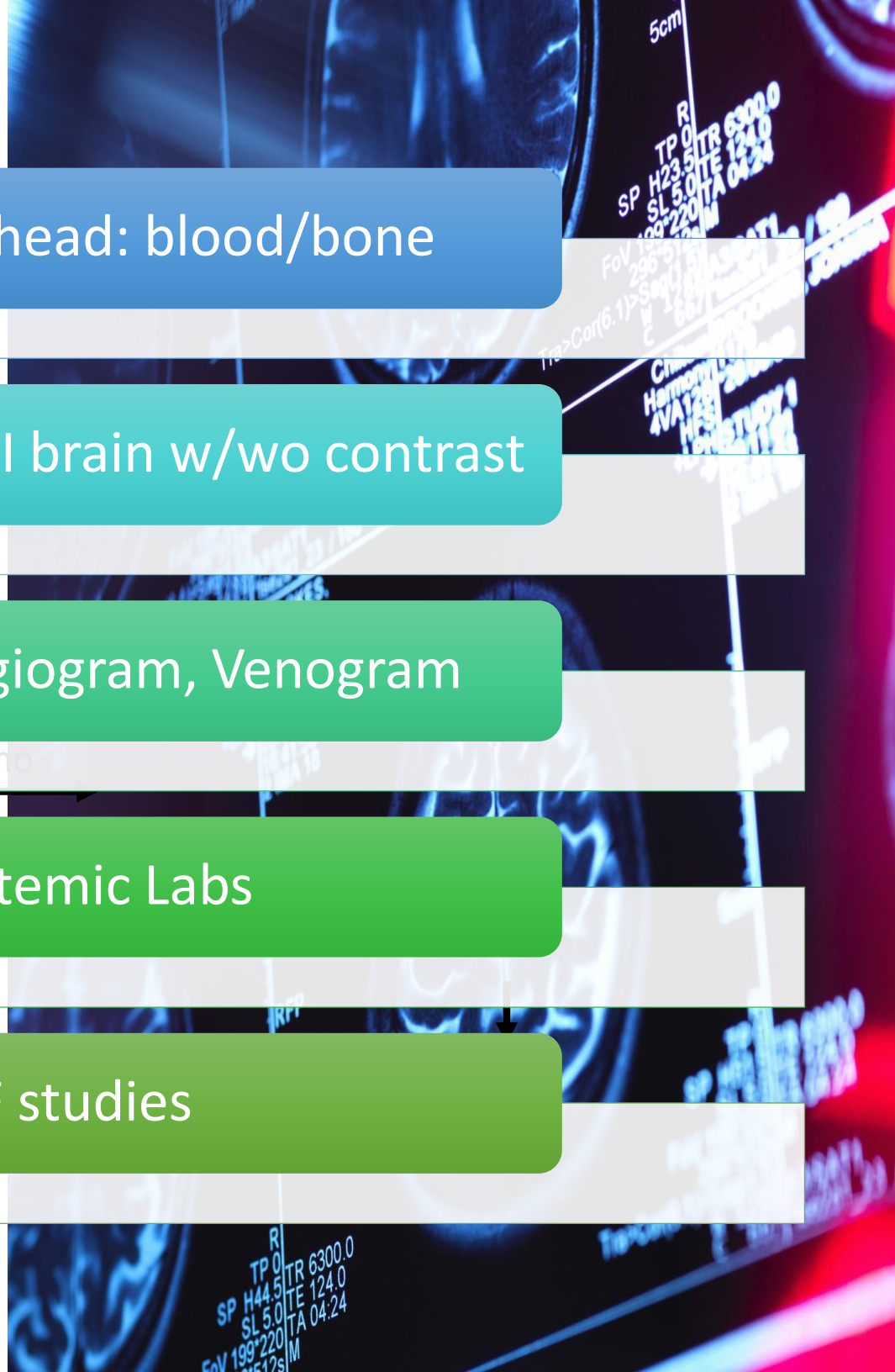


SNOOP4: “Snoop for” Red Flags

S	Systemic symptoms Secondary diseases	Fever Malignancy Weight loss Jaw claudication Night sweats	Metastases, giant cell arteritis, infection (CNS, systemic)
N	Neurologic symptoms/signs	Confusion Focal neurologic symptoms/signs Diplopia TVOs Pulsatile tinnitus	Mass lesion, structural lesion, stroke, hydrocephalus
O	Onset	Thunderclap	RCVS, stroke, subarachnoid hemorrhage, CVT, pituitary apoplexy, carotid dissection, IIH
O	Older age (>50 years)	New onset Persistent/progressive headache	Mass lesion, giant cell arteritis
P	Pattern Change (P1-P4)		
P1	Positional	Orthostatic, recumbent, worsens with change in position	Low intracranial pressure (CSF leak), mass lesion, CVT, sinus pathology
P2	Prior history/Progressive	New onset or change to persistent/daily	Mass lesion, infection (CNS, systemic)
P3	Pregnancy/post-partum	New onset during pregnancy	CVT, preeclampsia, RCVS, pituitary lesion, stroke
P4	Precipitated by Valsalva	Cough, sneeze, bending, straining	Intracranial/posterior fossa mass, Chiari malformation

Dodick, DW. *Semin Neurol*. 2010.

Evaluation


CT head: blood/bone
MRI brain w/wo contrast
Angiogram, Venogram
Systemic Labs
CSF studies

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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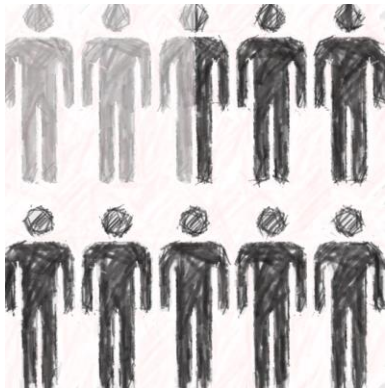
Just need 2 of these!

Just need 1 of these!

Episodic vs. Chronic Migraine

- ***Frequency of headache days****
- ≥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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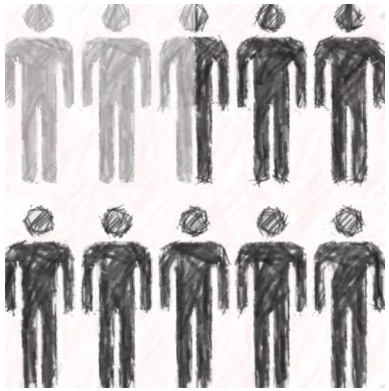

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Only **36%** of patients who see a ***specialist*** received a Chronic Migraine diagnosis[2,3]

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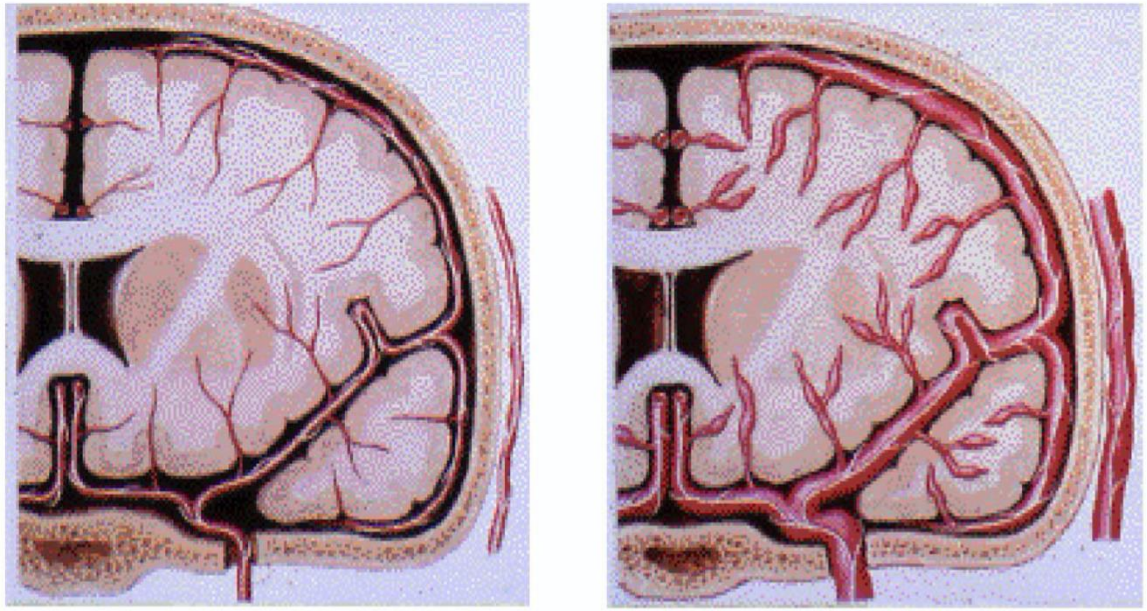
Pathophysiology

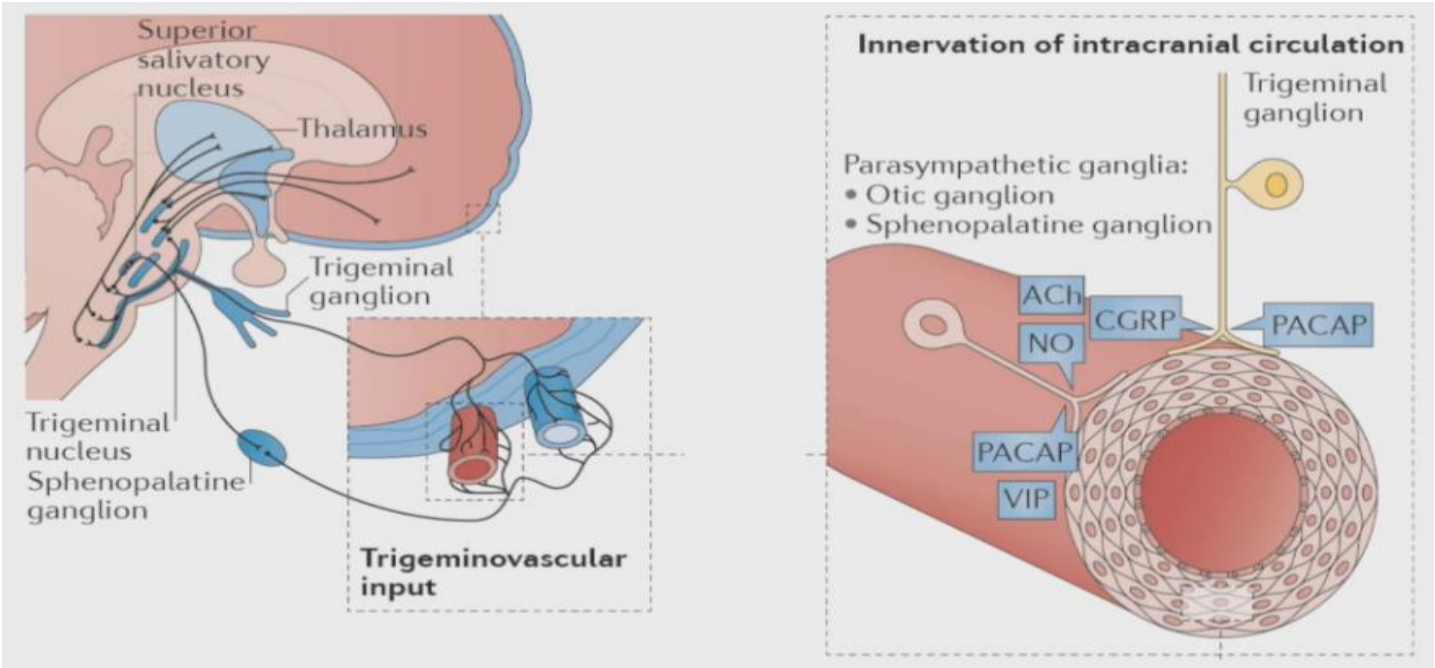
Vascular Theory of Migraine

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



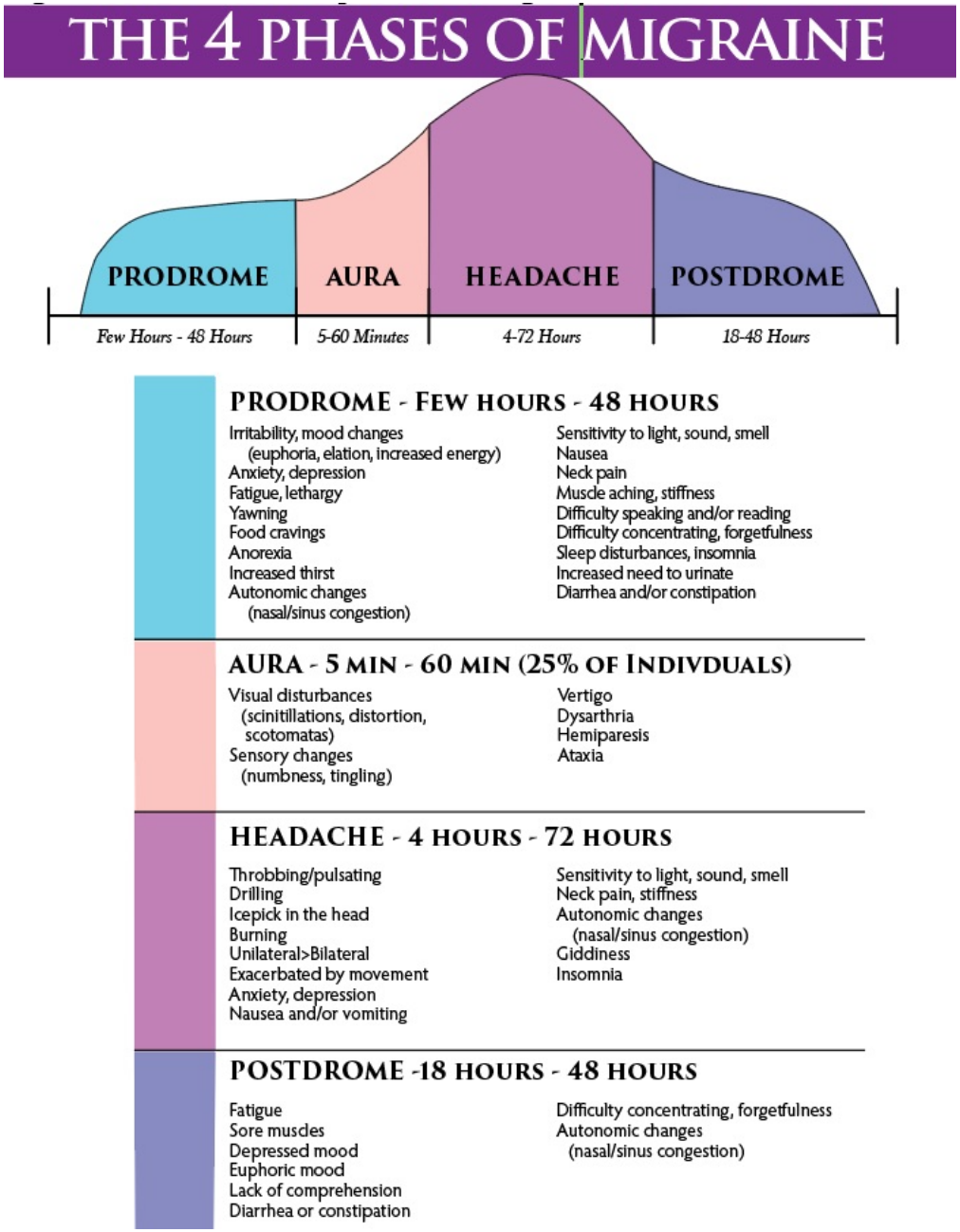
Trigeminovascular Theory of Migraine

- 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



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

Phases of Migraine



Duvall, J. *The Basics of Migraine*. 2019.

Preventive Treatment

Preventive Treatment

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

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…

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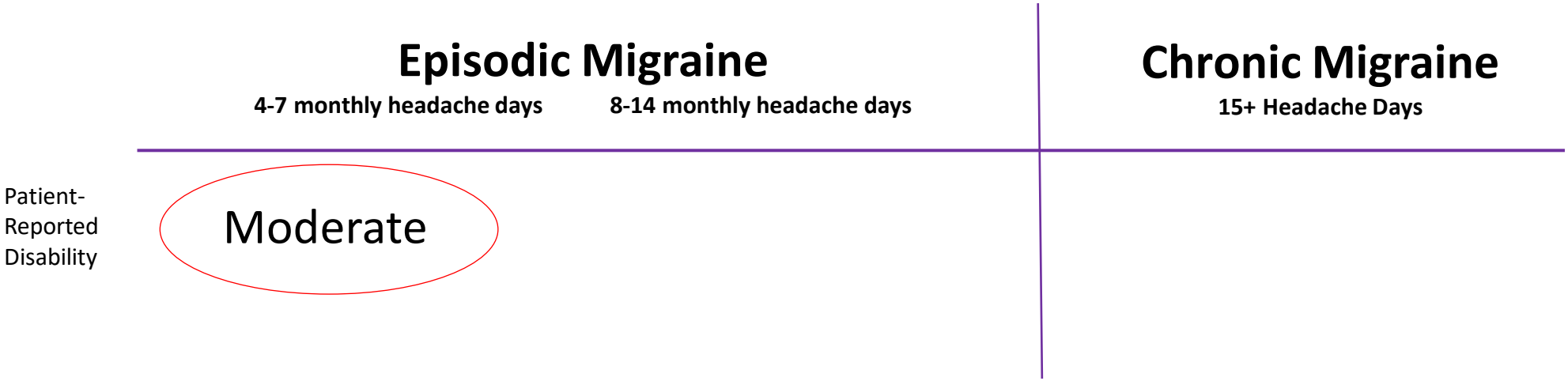

American Headache Society. Headache. 2019;59:1-18

Preventive Treatment

Nonspecific oral

OnabotulinumtoxinA

CGRP Monoclonal Antibodies

Gepants

Nerve blocks

Devices

Preventive Treatment

Established Efficacy[+]

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

Anti-Hypertensives
- Metoprolol
- Propranolol
- Timolol
- Candesartan

Triptans: Froivatriptan[b]

OnabotulinumToxin A*

CGRP Antagonists
- mAbs, Gepants

Probably Effective[++]

Antidepressants
- Amitriptyline
- Venlafaxine

Beta-Blockers
- Atenolol
- Nadolol

NMDA antagonists
- Memantine

Possibly Effective[+++]

ACE inhibitors: Lisinopril

Alpha-agonists
- Clonidine
- Guanfacine

Antiepileptic drugs:
Carbamazepine

Beta-Blockers
- Nebivolol
- Pindolol

Antihistamines: Cyproheptadine

Angiotensin receptor blockers

+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

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.
- Establish realistic expectations
  - 50% reduction in frequency, duration, or severity of migraine attacks
- 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 Preventive 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

Onabotulinumtoxin A

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

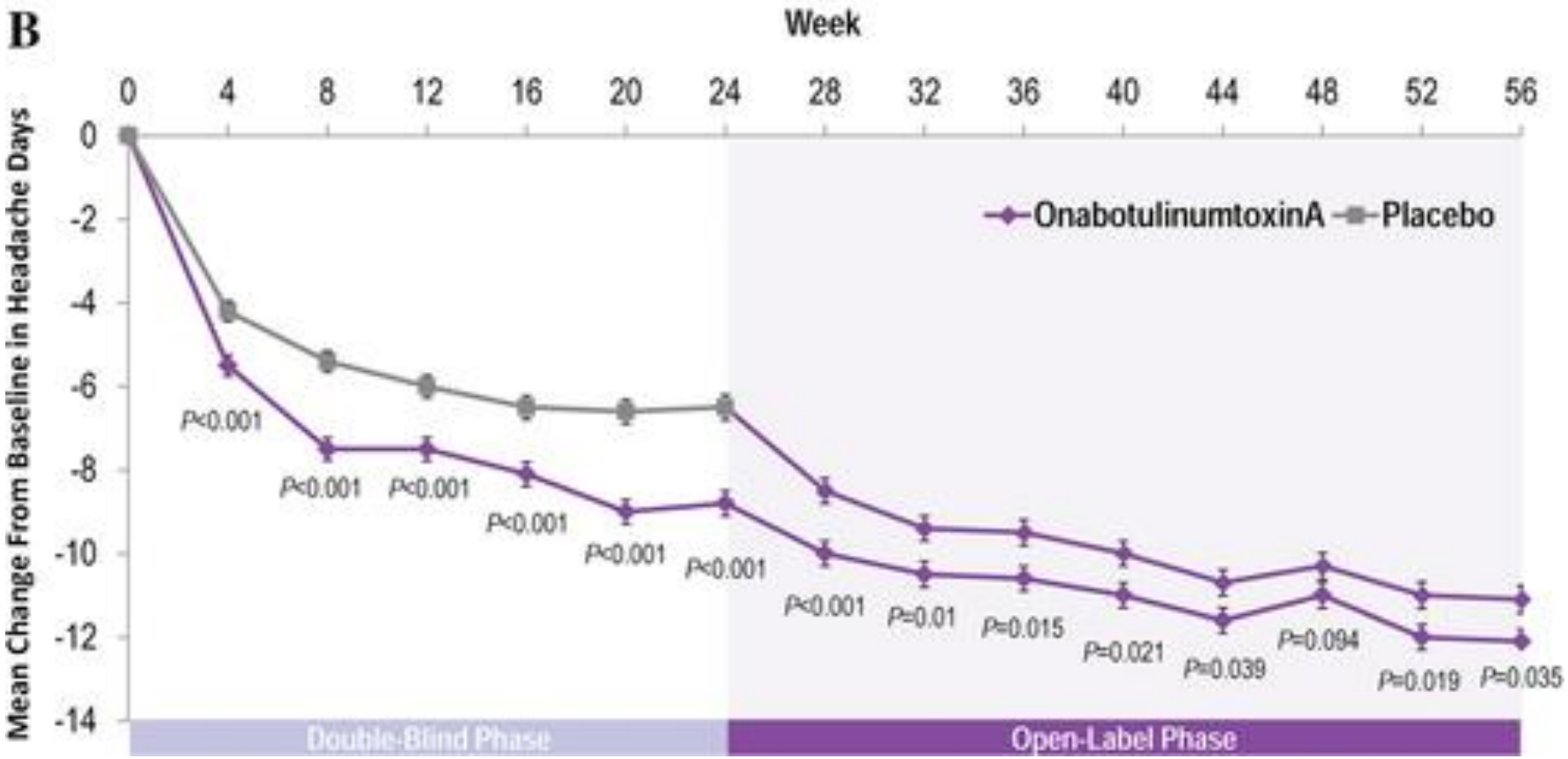
Age 18-65 with chronic migraine (MOH, as long as not opiates)

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.

Onabotulinumtoxin A

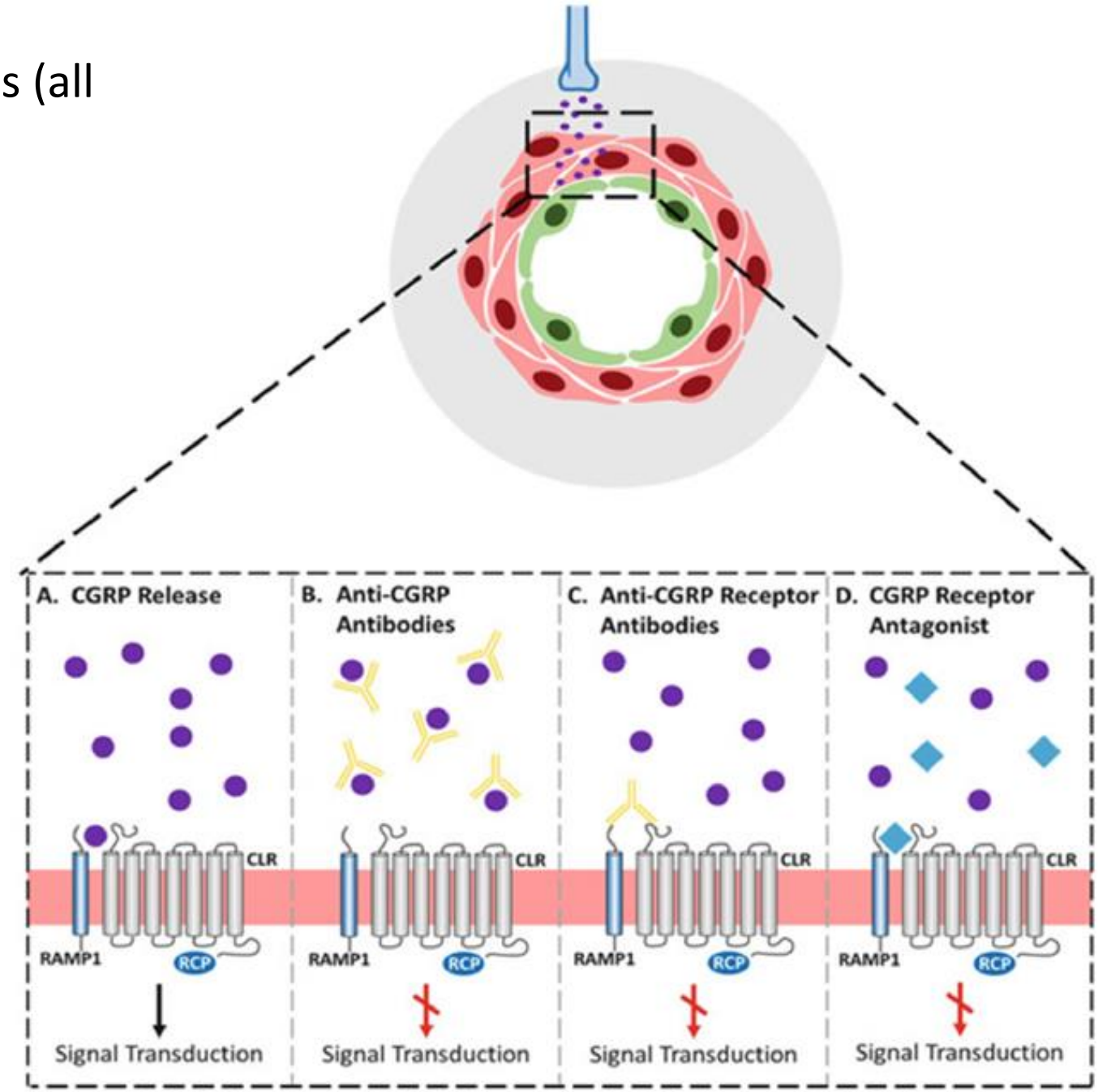
Baseline ~20d/mo; BTX 8.4 fewer days/mo (p<0.001) vs. placebo
6.6 fewer days/mo (after 2 rounds of injections)
Recommendation 3 treatment cycles



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

Calcitonin Gene Related Peptide (CGRP) Antagonists

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

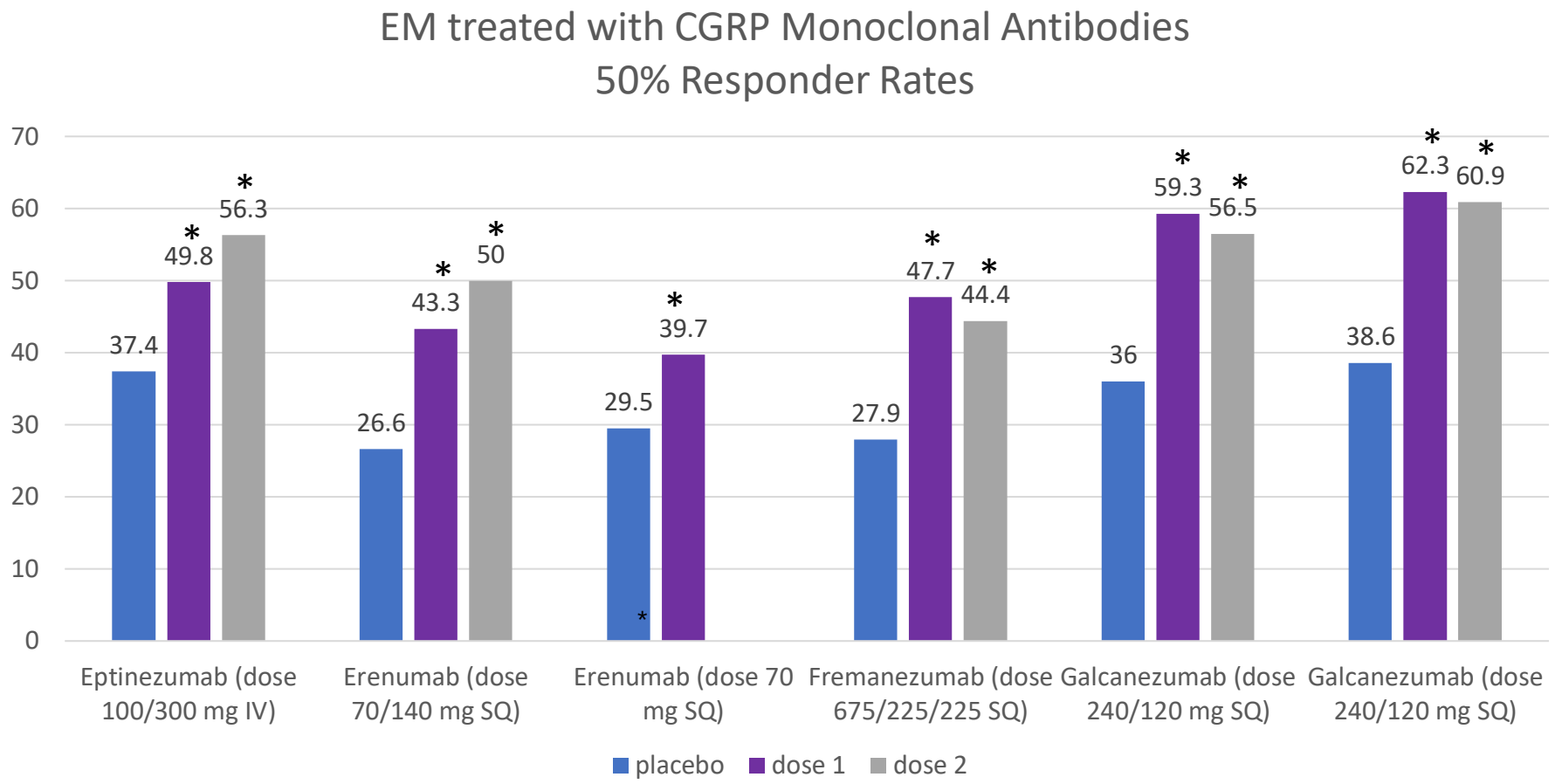


Aubdool A. *British Pharmacology*. 2019.

CGRP MAbs

	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

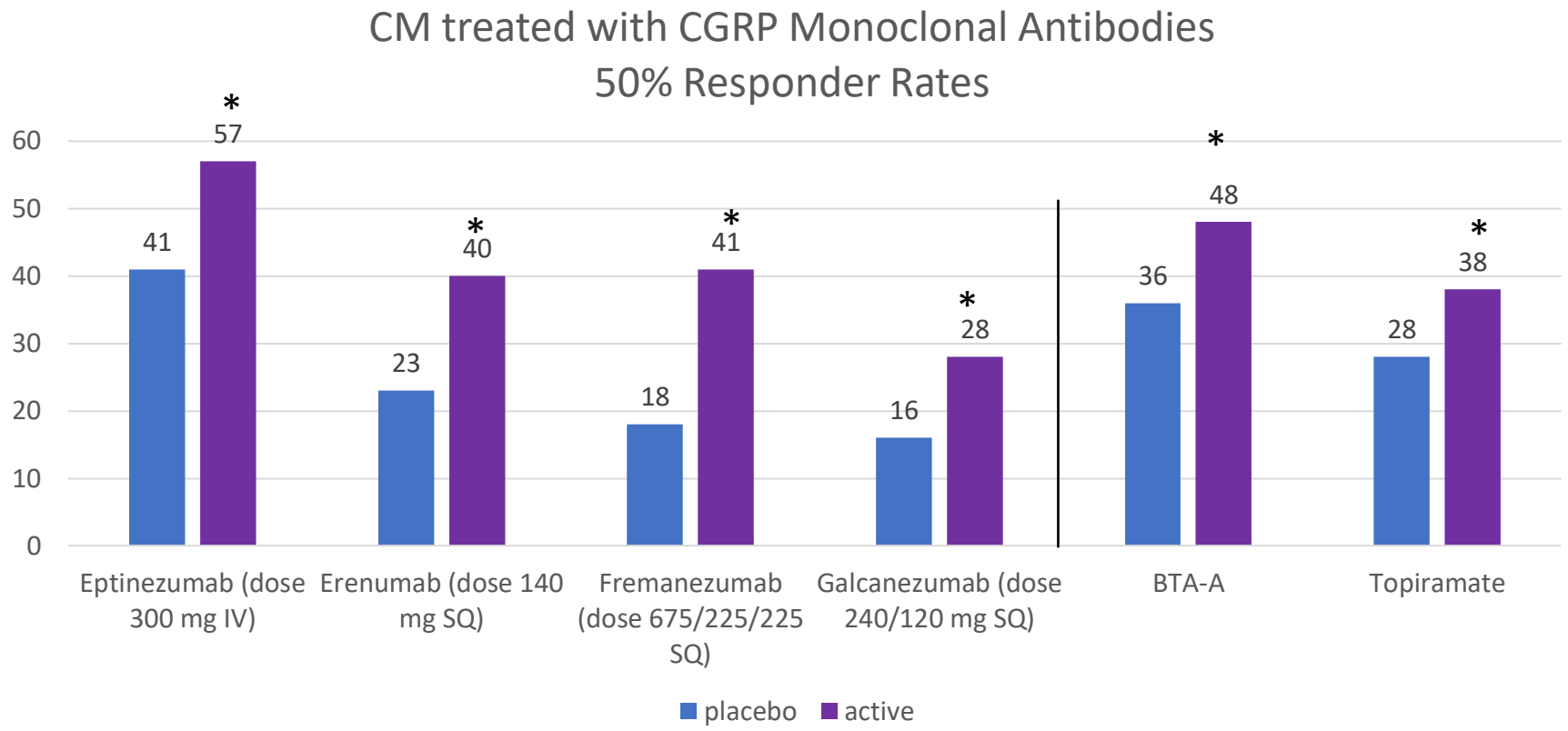


[a] Statistically significant difference vs placebo.

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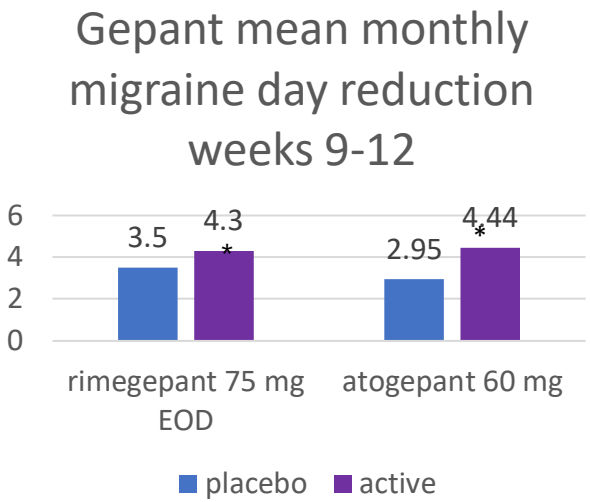
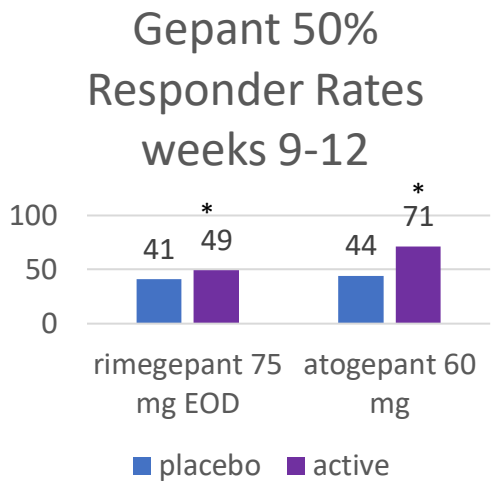
Smith et al. Headache 2017; 57:130; Silberstein et al. New Engl J Med 2017; 377:2113; Aurora et al. Headache 2011; 51:1358; Tepper et al. Lancet Neurol 2017;16:425; Detke et al. Headache 2017;57:1336-1337; Silberstein et al. Headache 2006;46:838; Brandes et al. Headache 2017;57:197; Bigal et al. Lancet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

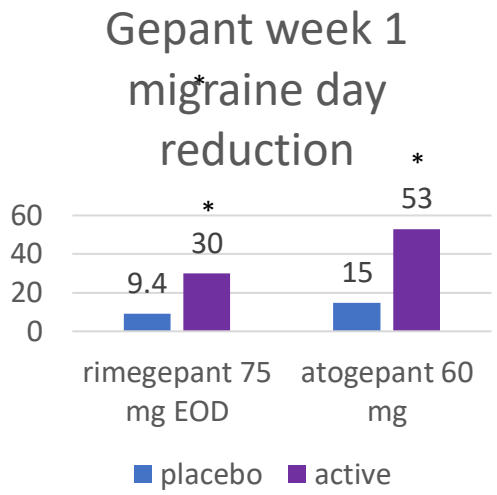
Gepants

- 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), Zavegepant 10 mg NS (acute)

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.

Acute Treatment

Medication Overuse Headache

- Headache >15 days per month
- Regular overuse for >3 month
- Examples:
  - **15+** days of simple analgesia
  - **10+** days of triptans, opioids, butalbital, or combo meds
    - Likely less for opioids and butalbital*

IHS (2018). "The International Classification of Headache Disorders, 3rd edition." Cephalgia **38(1): 1-211.**

Acute Treatments

NSAIDs

Triptans

Gepants

Ditans

Devices

Triptans

~40-75% 2h pain relief

Sumatriptan	PO= 25mg, 50mg,100mg IN= 10mg *(Tosymra)*;11mg *(Onzetra)*; 5 & 20mg SC = 3mg *(Zembrace)*; 4 & 6mg	Oldest High A/E rate
Almotriptan	6.25 - 12.5mg po	Fast, low A/E
Eletriptan	20 - 40mg po	Fast, mod A/E
Frovatriptan	2.5mg po	Long, low A/E
Naratriptan	1 – 2.5mg po	Long, low A/E
Rizatriptan	5 – 10mg po/ODT	Fast, mod A/E
Zolmitriptan	2.5 – 5mg po/OD/IN Pending = Qtrypta patch *(microneedles)*	Fast, mod A/E
Suma + Naproxen	Sumatriptan 85mg + Naproxen 500mg	Combo med
Riza + Meloxicam	Pending = AXS-07	New & Faster

Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, Peterson J, Coyle D, Skidmore B, Gomes T, Clifford T, Wells G. Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis. Headache. 2015 Jul-Aug;55 Suppl 4:221-35.

NSAIDS

Combo with triptans =
60-80% 2h headache relief

Naproxen

- 500mg prn

Indomethacin

- 25-75mg prn

Diclofenac po or Cambia (powdered diclofenac)

- 50mg prn

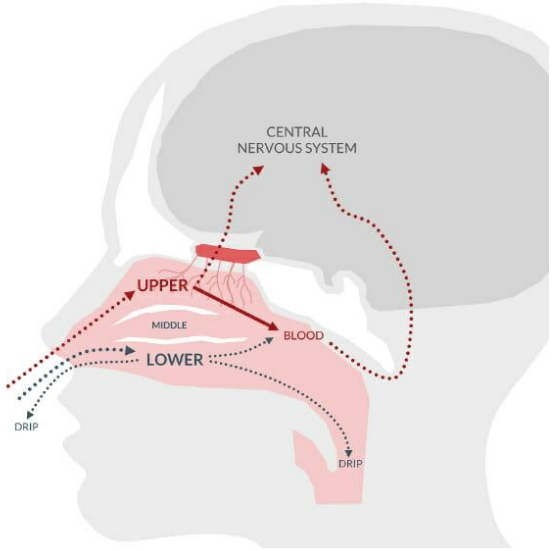
Ketorolac

- 10mg po; 15.75mg IN; 30-60mg IM

Dihydroergotamine (DHE)

~40% 2h Pain freedom*

- **Nasal**
  - Old = Migranal
  - New POD device = TRUDHESA
    - Drug levels similar to IV
    - AE: nasally-related
- **Parenteral**
  - 1mg SC/IM
  - 1mg IV q8h or continuous IV
  - AE: Nausea
- NOT within 24h of a triptan



https://clinicaltrials.gov/ct2/show/NCT03557333

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Gepants

- Ubrogepant
  - 50, 100 mg po
  - Repeat after 2h (max 200 mg/24h)
- Rimegepant
  - 75mg ODT (max 75 mg/24 h)
  - Acute and preventive
- Zavegapent NS
  - 10 mg NS (max 10 mg/24h)
- Pipeline: FE 205030 sc

~20% 2h Pain freedom*

*Placebo was about 11-14%

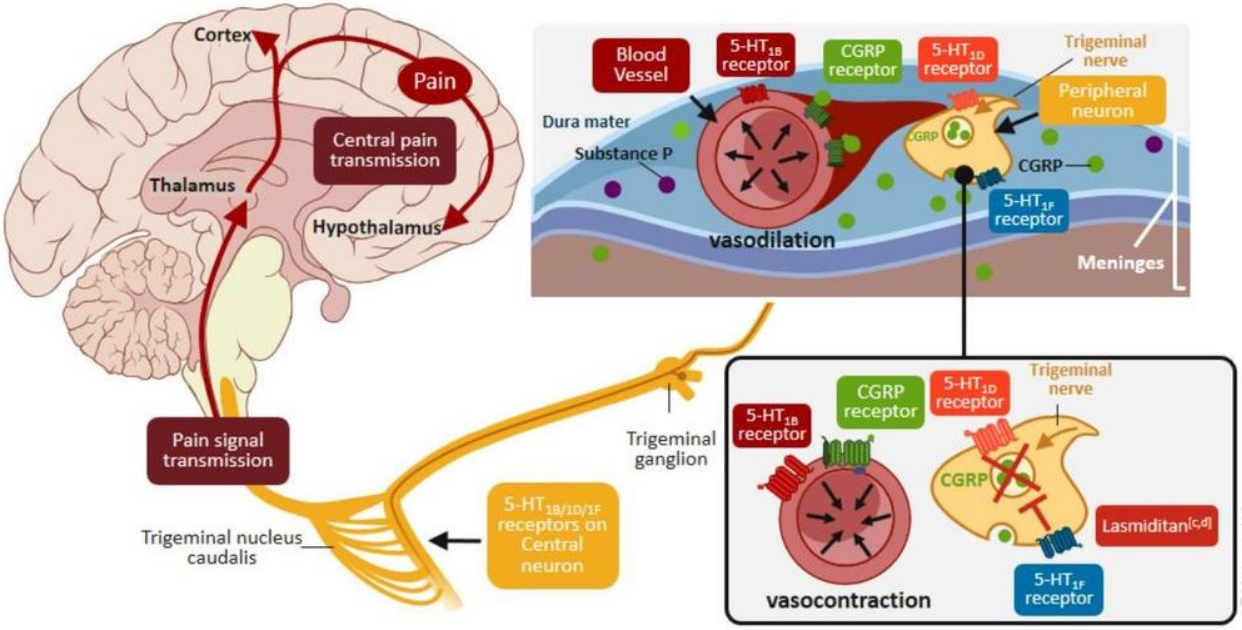
Ditans

- Triptans = 5HT-1B/1D agonist
  - Vasoconstriction due to 1B

~30-40% 2h pain freedom

- Ditans = 5HT-1F agonist
  - No vasoconstriction

- Lasmiditan
  - Once daily PRN
  - Can repeat after 24h
  - 8h driving restriction
  - Schedule 5 med



50 mg

100 mg

200 mg
(100 mg x2)

a. Dussor G. *Curr Opin Support Palliat Care*. 2014; 8(2):137-142; b. Vila-Pueyo M. *Neurotherapeutics*. 2018; 15(2):291-303; c. Oswald JC, et al. *J Pain Res*. 2018;11:2221-2227; d. Eli Lilly & Company (2018). [Press release].

*Placebo was about 20%

Kuca, B., et al. (2018). "Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study." Neurology **91(24): e2222-e2232.**

NOT Recommended:

OPIOIDS & BULTALBITAL

↓Treatment Response

Risk of Chronic Daily Headache

Tolerance, Withdraw, Abuse, Overdose

Increased sensitization

Loder E, Weizenbaum E, Frishberg B, Silberstein S; American Headache Society Choosing Wisely Task Force. Choosing wisely in headache medicine: the American Headache Society's list of five things physicians and patients should question. Headache. 2013 Nov-Dec;53(10):1651-9.

When an Acute Treatment Fails…

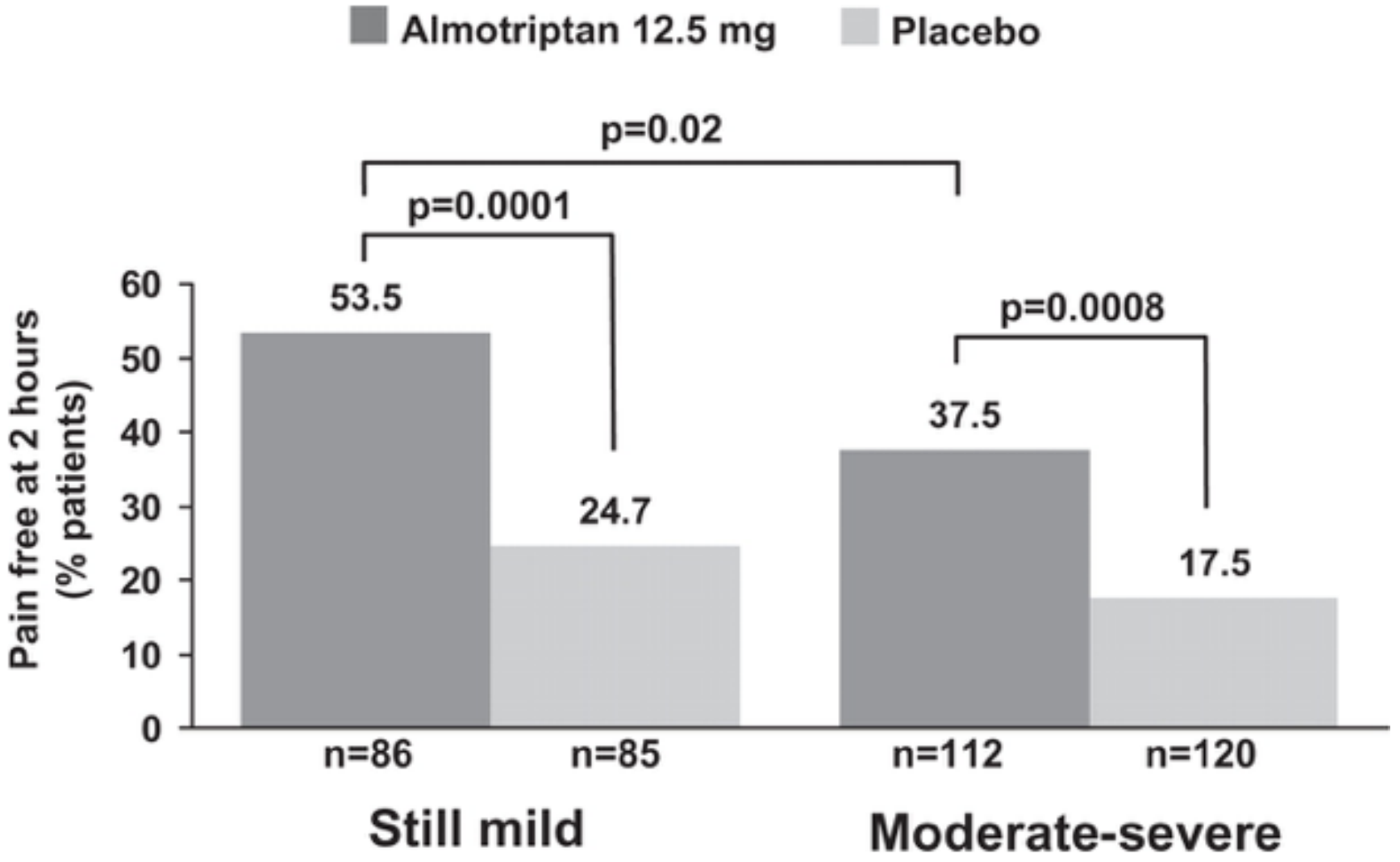
- Treat at least three different attacks

When an Acute Treatment Fails…

- Treat at least three different attacks
- If treatment is ineffective
  - Treat early

When an Acute Treatment Fails…

Figure 2 Pain-free data at 2 h in the Act when Mild (AwM) analysis demonstrating a significant benefit for treatment with almotriptan 12.5 mg when taken early, within 1 h, and when pain is still mild compared with when pain is moderate or severe.



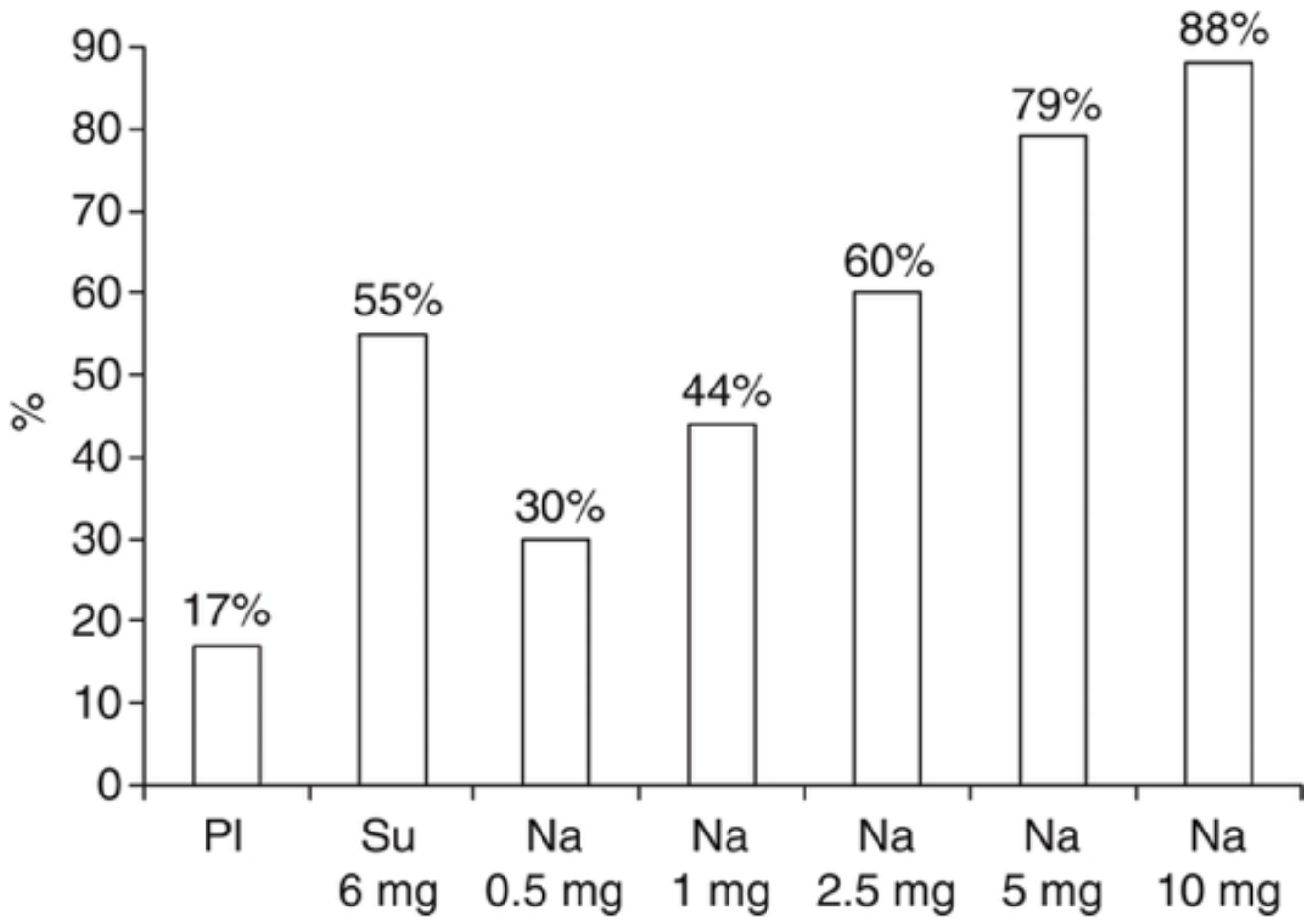
Goadsby P et al. Cephalalgia 2008;28:383-391

When an Acute Treatment Fails…

- Treat at least three different attacks
- If treatment is ineffective
  - Treat early
  - Increase dose

When an Acute Treatment Fails…

Figure 1 Pain-free response after 2 h for placebo, subcutaneous sumatriptan (Su) 6 mg and subcutaneous naratriptan (Na) 0.5–10 mg (6).



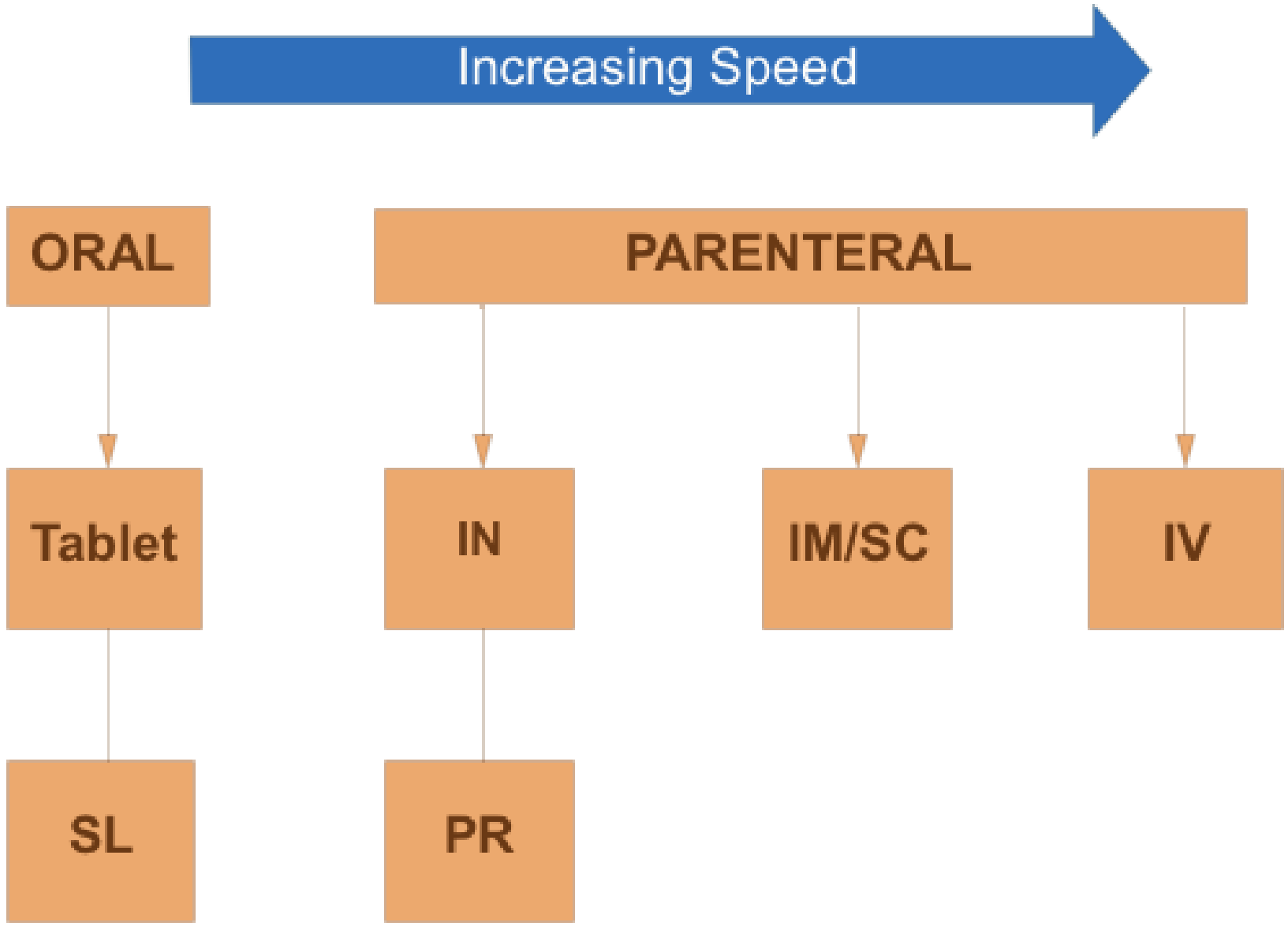
Tfelt-Hansen P Cephalalgia 2008;28:767-768

Cephalalgia

When an Acute Treatment Fails…

- Treat at least three different attacks
- If treatment is ineffective
  - Treat early
  - Increase dose
  - Change formulation/route of administration

When an Acute Treatment Fails…



When an Acute Treatment Fails…

- Treat at least three different attacks
- If treatment is ineffective
  - Treat early
  - Increase dose
  - Change formulation/route of administration
  - Change drug

Is There Such a Thing as a Triptan Non-Responder?

- Five clinical studies provide evidence that switching from a triptan that is ineffective to a second triptan can result in positive treatment.
- Strongly suggests triptan non-response may not be consistent.

Stark S, Spierings EL, McNeal S, et al. Headache 2000; 40: 513–520.; Farkkila M, Olesen J, Dahlof C, et al.. Cephalalgia 2003; 23: 463–471.; Mathew NT, Kailasam J, Gentry P, et al. Headache 2000; 40: 464–465.; Diener HC, Gendolla A, Gebert I, Headache 2005; 45: 874–882.Goldstein J, ; Tiseo PT, Albert KS, et al. Headache 2006; 46: 1142–1150.

When an Acute Treatment Fails…

- Treat at least three different attacks
- If treatment is ineffective
  - Treat early
  - Increase dose
  - Change formulation/route of administration
  - Change drug
  - Add adjunct

Quadruple Therapy			
Triple Therapy			
Triptans/Ergots	**NSAIDS**	**Neuroleptics**	**Gepants/Ditans**
Almotriptan 12.5 mg PO	Ibuprofen 600-800 mg PO	Prochlorperazine 10 mg PO/IM	Rimegepant 75 mg ODT
Eletriptan 40 mg PO	Naproxen 500 mg PO	Metoclopramide 10 mg PO/IM	Ubrogepant 50/100 mg PO
Frovatriptan 2.5 mg PO	Ketoprofen 75 mg PO	Promethazine 25 mg PO/IM/IV	Lasmitidan**50/100/200 mg PO
Naratriptan 2.5 mg PO	Piroxicam 20 mg PO	Chlorpromazine* 25 mg	
Rizatriptan 10 mg PO/ODT	Indomethacin 50 mg PO	Olanzapine* 10 mg PO	
Sumatriptan -3/4/6 mg Inj -100 mg PO -20 mg NS	Diclofenac 50 mg PO	Haloperidol* 2.5/5 mg PO	
Zolmitriptan 5 mg PO/NS/ODT			
DHE/Ergotamine -1 mg SC/IM -1.45 mg NS			

*caution with use, high risk of extrapyramidal side effects; EKG recommended to exclude QT prolongation
**caution for serotonin syndrome when used with triptan, studies separated these medications by 24 hours
By mouth (PO), nasal spray (NS), oral disintegrating tab (ODT), subcutaneous (SC), intramuscular (IM)

Summary

The most important tools you have in evaluation of primary versus secondary headaches is a **good history** and **physical examination.** In absence of red flag symptoms, **bet on migraine!**

Migraine is an inherited complex brain disorder that is primarily a disease of **brain hyperexcitability.**

Preventive migraine treatment is under-utilized and may have a significant positive impact on a patient's quality of life.

There are many ways to optimize **acute treatment of migraine** and new medications available with different mechanism of action that may be better tolerated.

Thank You!