Migraine & Primary Care

Physiology, Diagnosis, Pitfalls, & Treatment

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DISCLOSURE

Christopher Rhyne, MD.

Has received honoraria for serving on the speakers' bureau for:

- Abbvie
- Lilly
- Amgen
- Theranica
- Lundbeck
- Teva
- Biohaven

All of the relevant financial relationships listed have been mitigated.

Migraine Headache for Primary Care Education Goals:

Better understand The Epidemiology of Migraine Headache and this relationship to Primary Care.

Better understand strategies for making an appropriate Diagnosis of Migraine Headache.

Better understand Treatment and barriers to treatment of Migraine Headache in Primary Care.

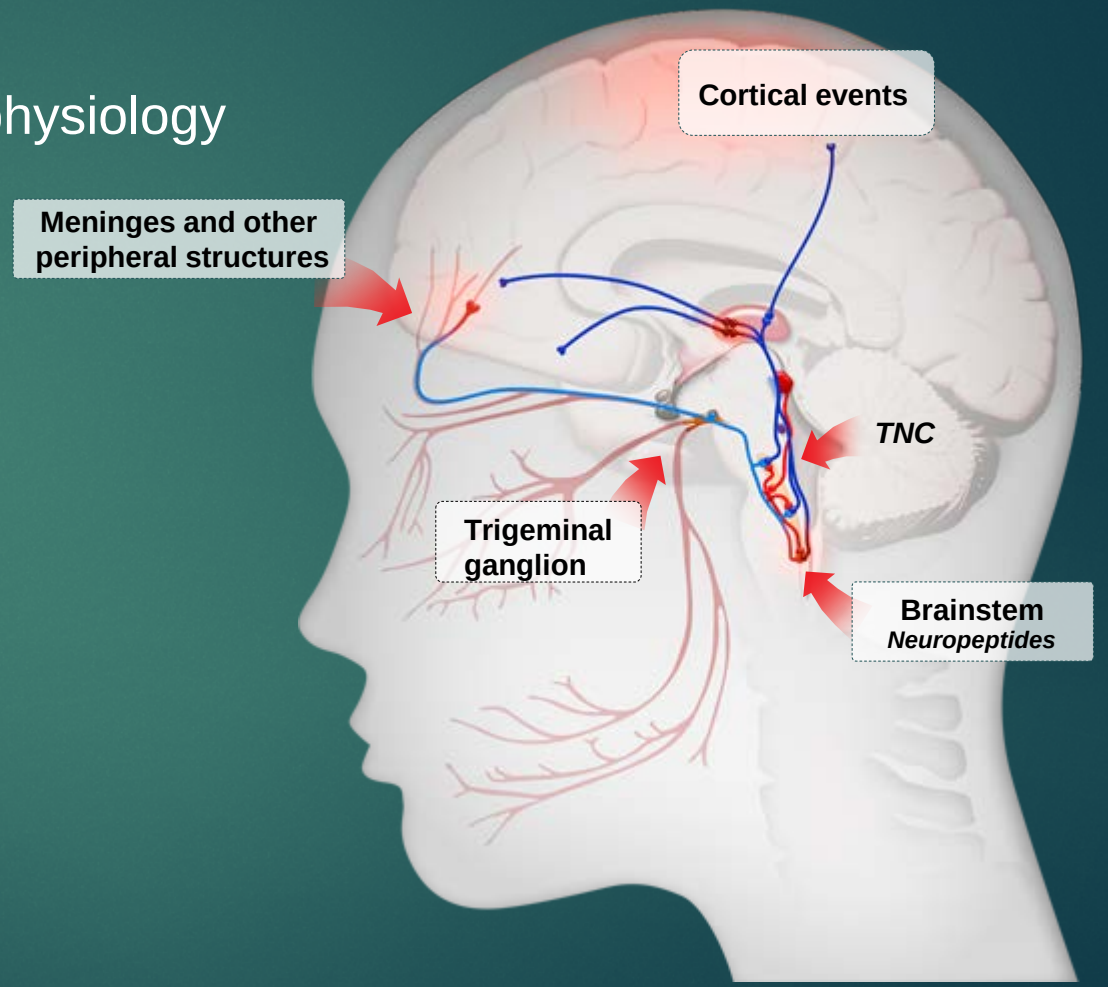
Migraine Diagnosis

- *Headaches last 4-72 hrs and have no other cause.
- Adapted from Headache Classification Committee of the IHS. Cephalalgia. 2018;38(1):1-211.

Headache Description *(Any 2)*	**Associated Symptoms** *(Any 1)*
Unilateral	Nausea or vomiting
Throbbing	Photophonia and photophobia
Worse with exertion	
Moderate to severe intensity	

What is Migraine

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

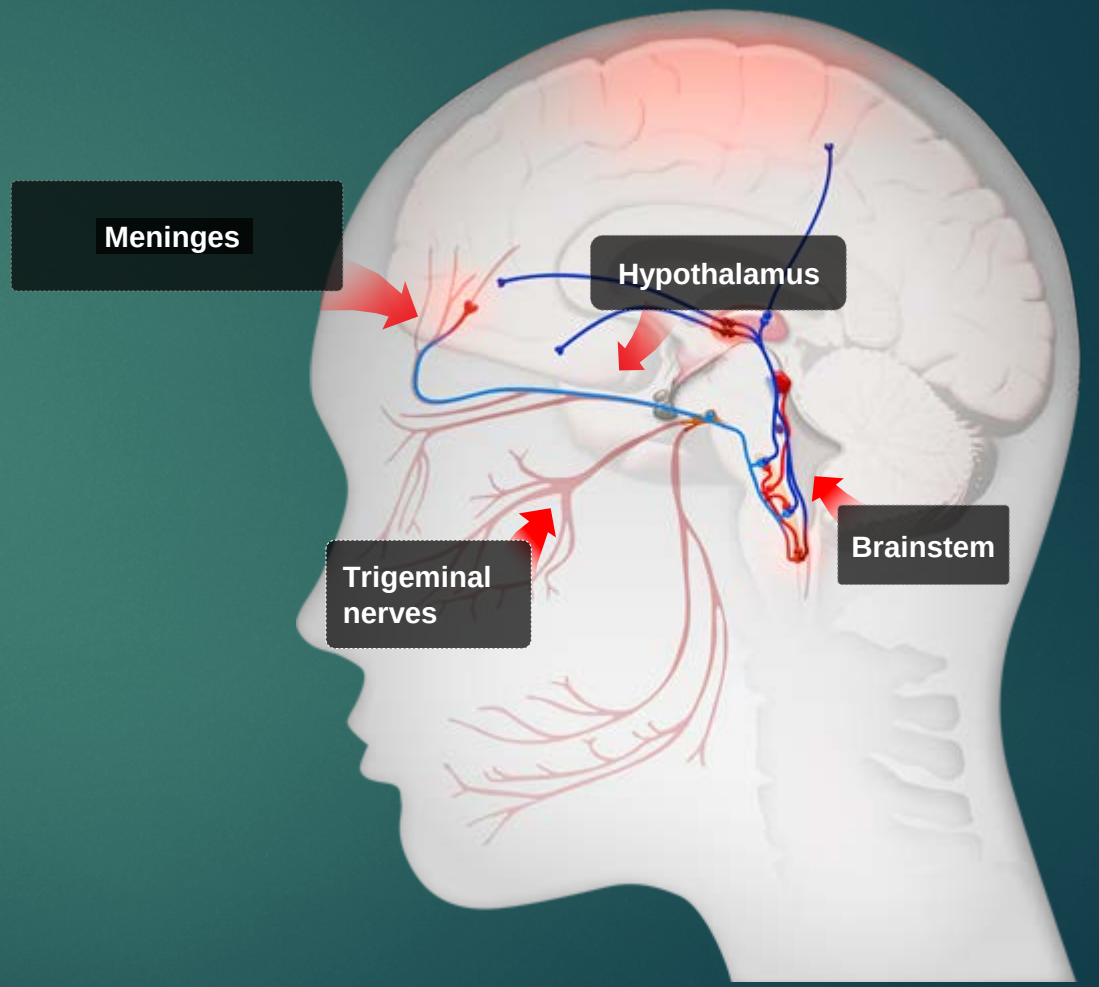


TNC = trigeminal nucleus candalis.

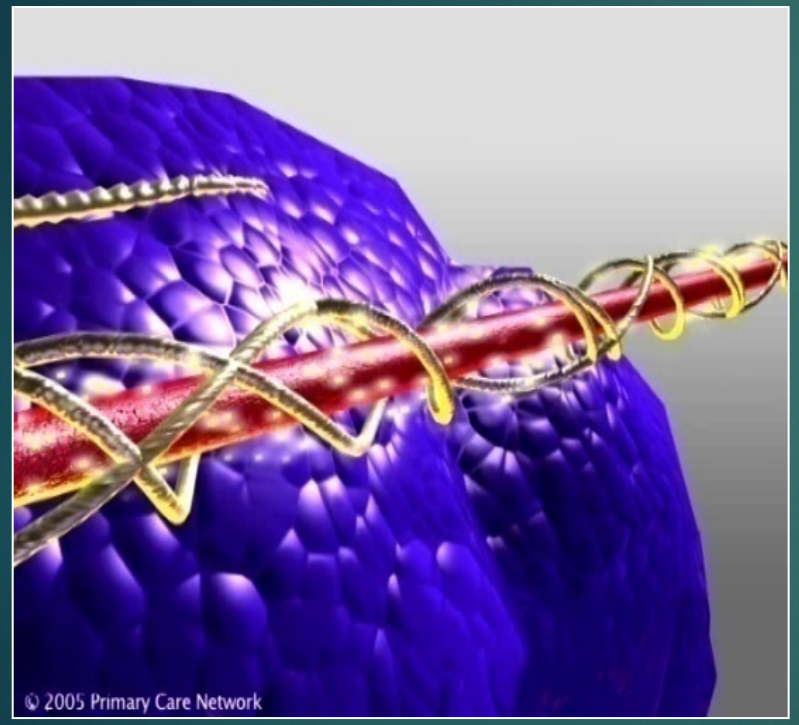
Bigal ME, et al. *Neurology*. 2008;71:848-855. Brandes JL. *Headache*. 2008;48:430-441. Coppola G, et al. *Cephalalgia*. 2007;27:1429-1439. Goadsby PJ, et al. *N Engl J Med.* 2002;346:257-270. Haut SR, et al. *Lancet Neurol.* 2006;5:148-157. Lovati C, et al. *Headache*. 2008;48:272-277. Pietrobon D.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

Head Pain Anatomy

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

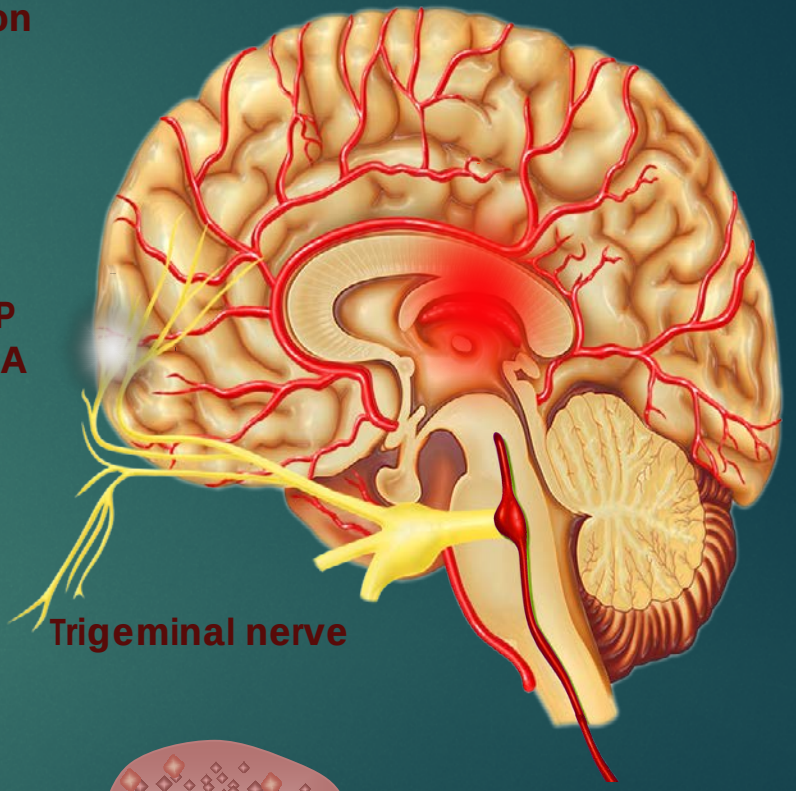


Trigeminovascular Activation in Migraine

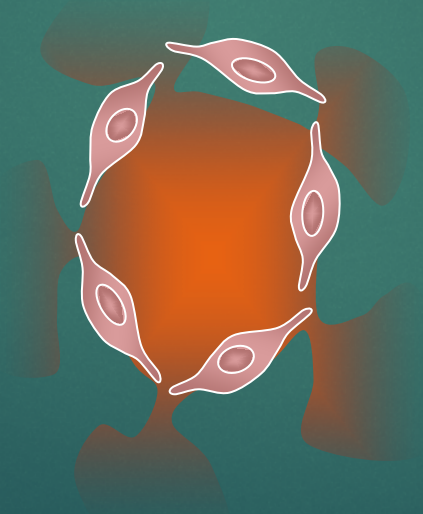


Dilation

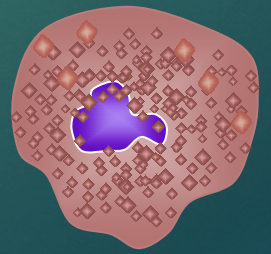
CGRP
Substance P
Neurokinin A



Trigeminal nerve



Blood vessel leakage



Mast cell

Release of histamine granules

 Durham PL, et al. *J Neurosci.* 1999;19(9):3423-3429.

CGRP Receptor: Location and Function

Vascular smooth muscle cells

- Relaxation of vessels; increase blood flow

Mast cells

- Degranulation—release of inflammatory molecules

Second-order neurons

- Activation—pain transmission

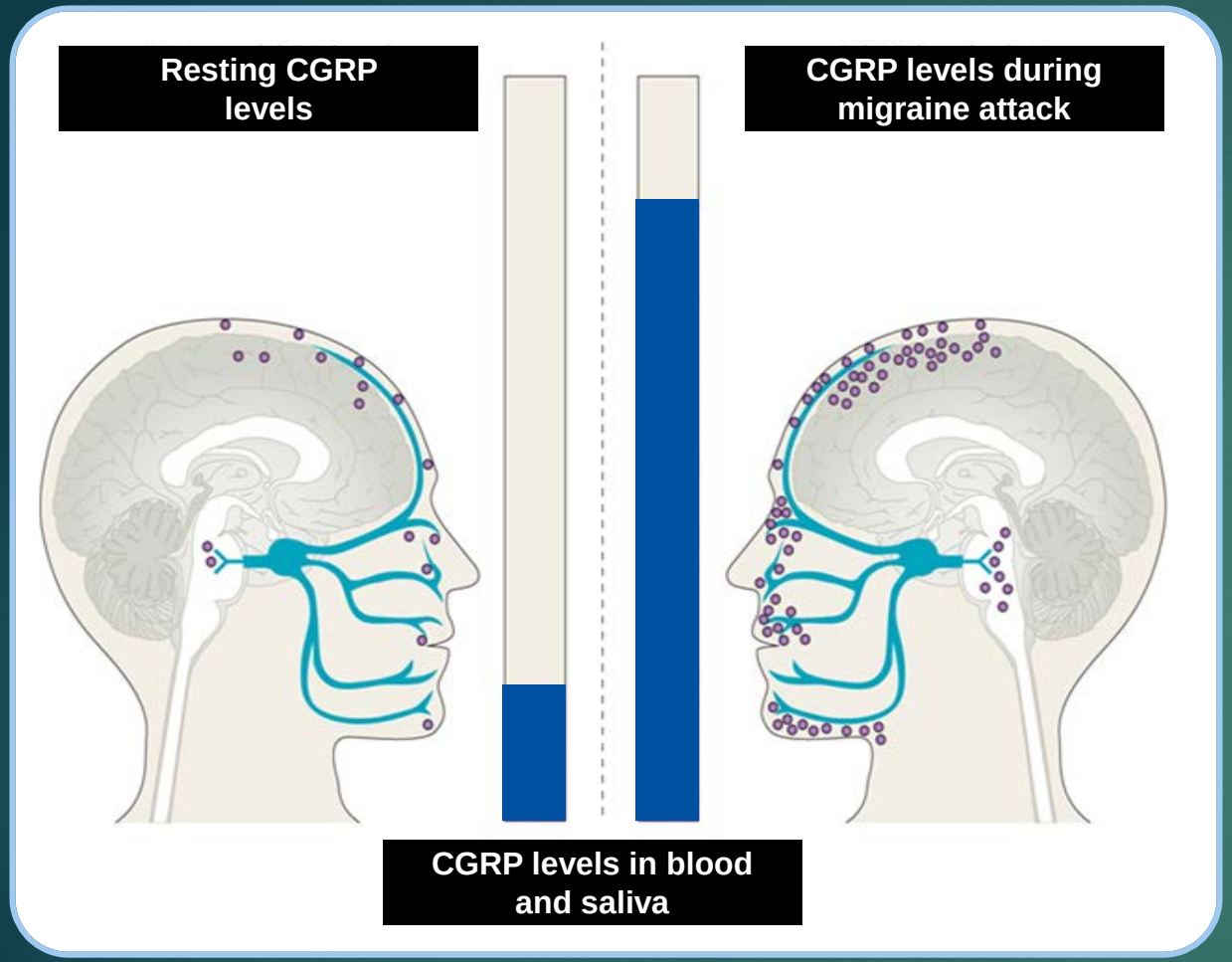
Neuronal cell bodies and glia within trigeminal ganglion

- Autoregulation—promote further CGRP release
- Excitation of satellite glial cells—release of inflammatory molecules (NO, cytokines)

NO = nitric oxide.

Durham PL. *N Engl J Med*. 2004;350(11):1073-1075.

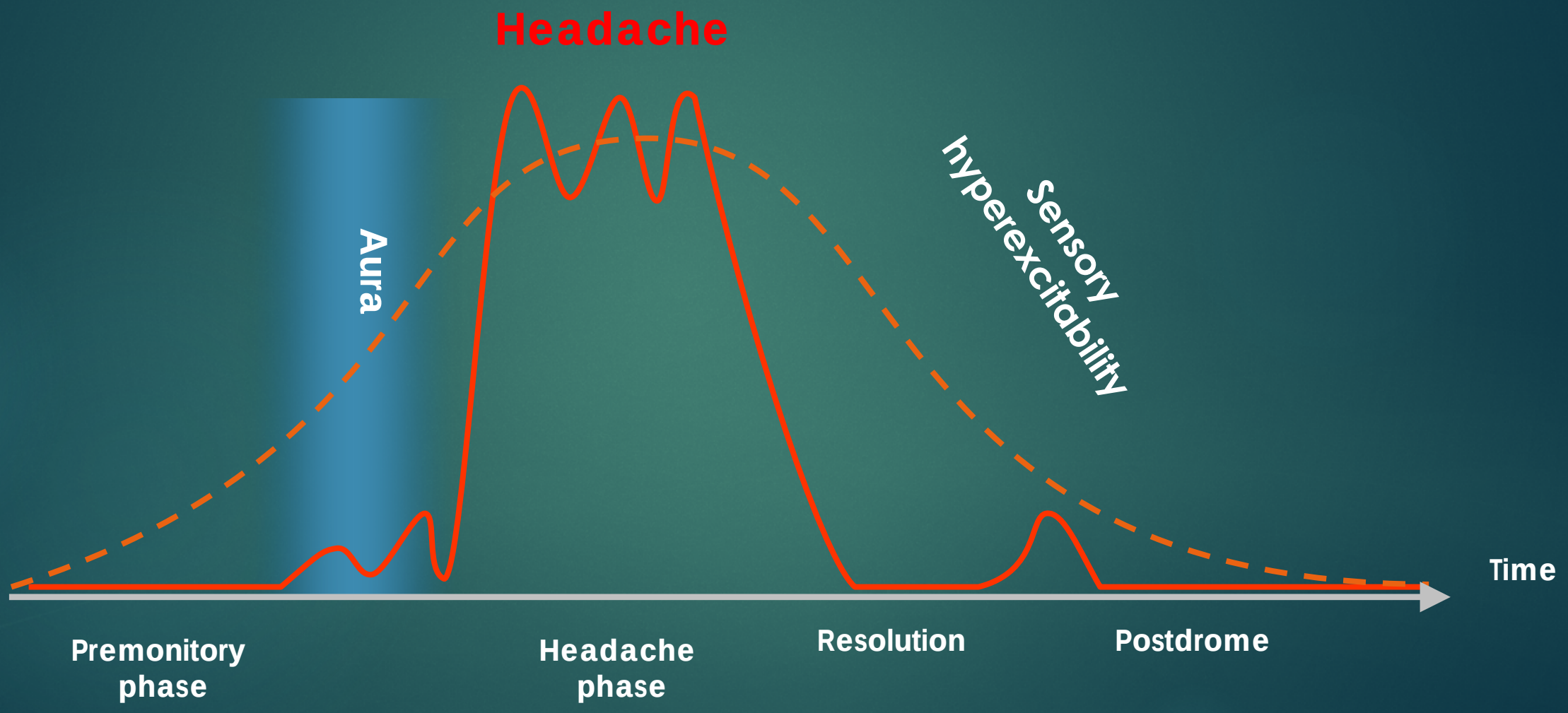
CGRP and Migraine Connection



- Serum CGRP levels are elevated in migraine
- CGRP infusion evokes migraine

Edvinsson L, et al. *J Cereb Blood Flow Metab*. 1987;7(6):720-728. Edvinsson L, et al. *Neurosci Lett*. 1985;58(2):213-217. McCulloch J, et al. *Proc Natl Acad Sci USA*. 1986;83(15):5731-5735. Edvinsson L. *Trends Neurosci*. 1985;8:126-131. Lassen LH, et al. *Cephalalgia*. 2002;22(1):54-61. Goadsby PJ, et al. *Brain*. 1994;117(Pt 3):427-434. Olesen J, et al. *N Engl J Med*. 2004;350(11):1104-1110. Ho TW, et al. *Neurology*. 2008;70(16):1304-1312. Voss T, et al. *Cephalalgia*. 2016;36(9):887-898. Tso AR, et al. *Curr Treat Options Neurol*. 2017;19(8):27.

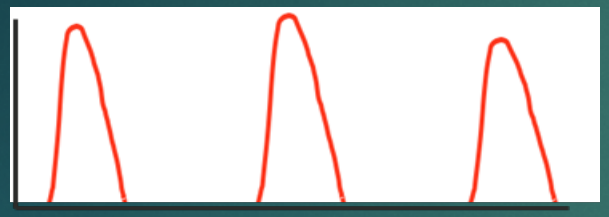
The Natural Course of a Typical Migraine Attack



Adapted with permission from Linde M. *Acta Neurol Scand*. 2006;114:71–83.

Migraine Frequency: A Continuum

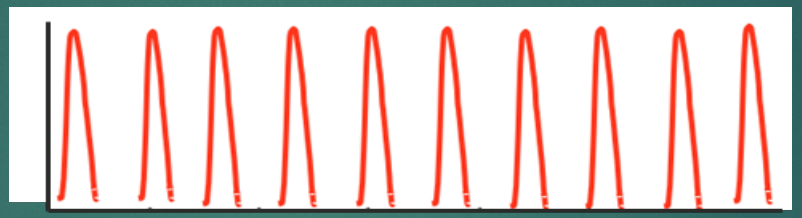
1-6 days/month
Episodic
Low frequency



Intermittent headaches, lots of headache-free days

Low frequency
80%

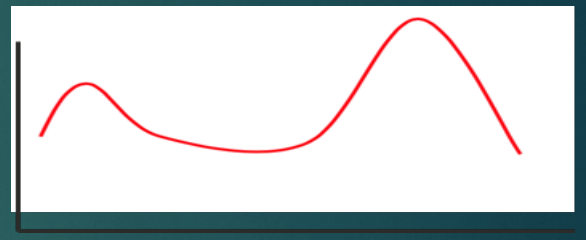
7-14 days/month
Episodic
High frequency



Frequent headaches, still headache-free days

High frequency
14.5%

15-30 days/month
Chronic migraine
High disability



Rare headache-free days, may be daily with exacerbations

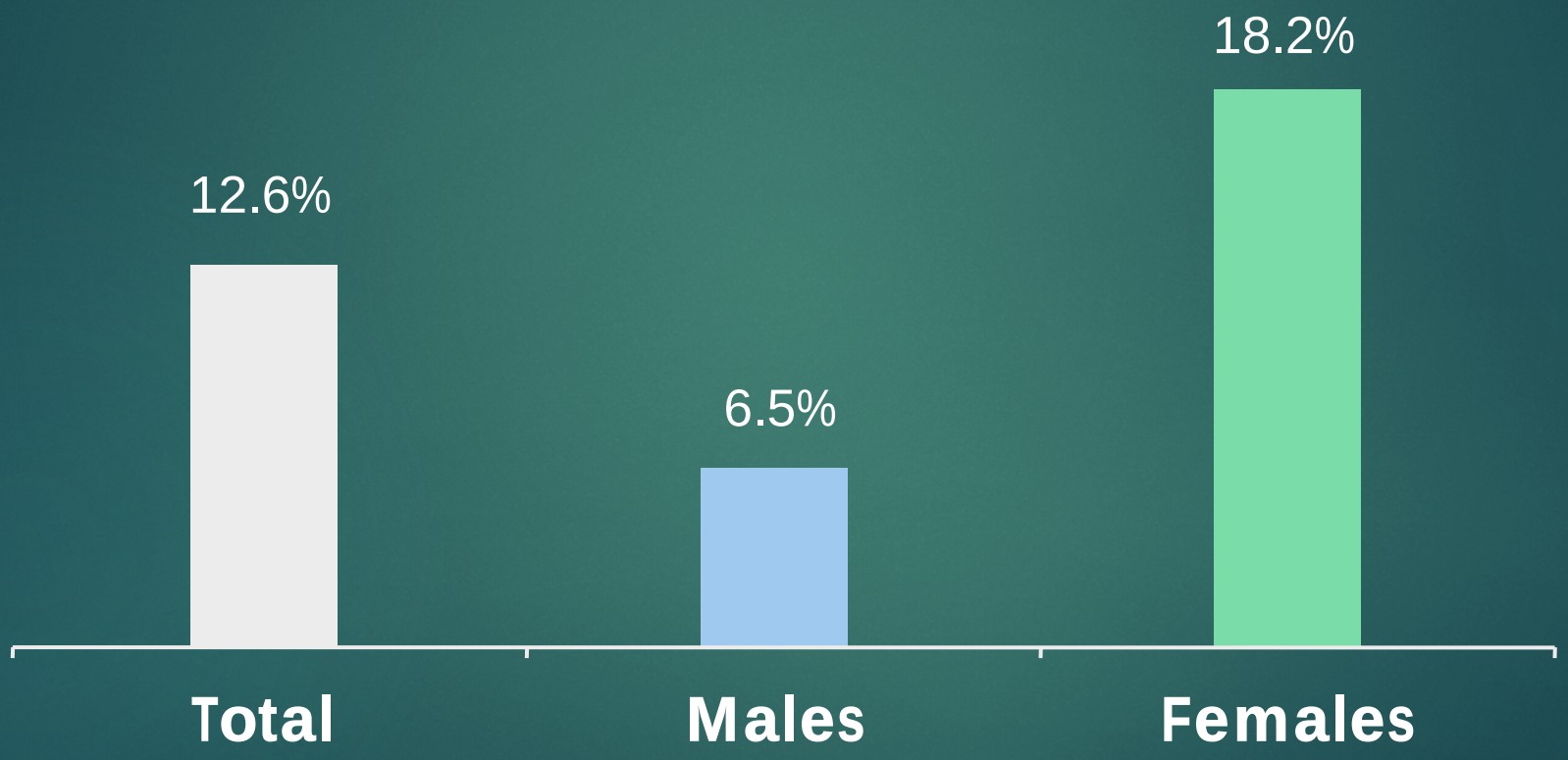
Chronic
5.5%

Over a lifetime, a person can experience attacks that vary in frequency and severity.

Blumenfeld AM, et al. *Cephalalgia*. 2011;31(3):301-15.

Migraine Prevalence in the US

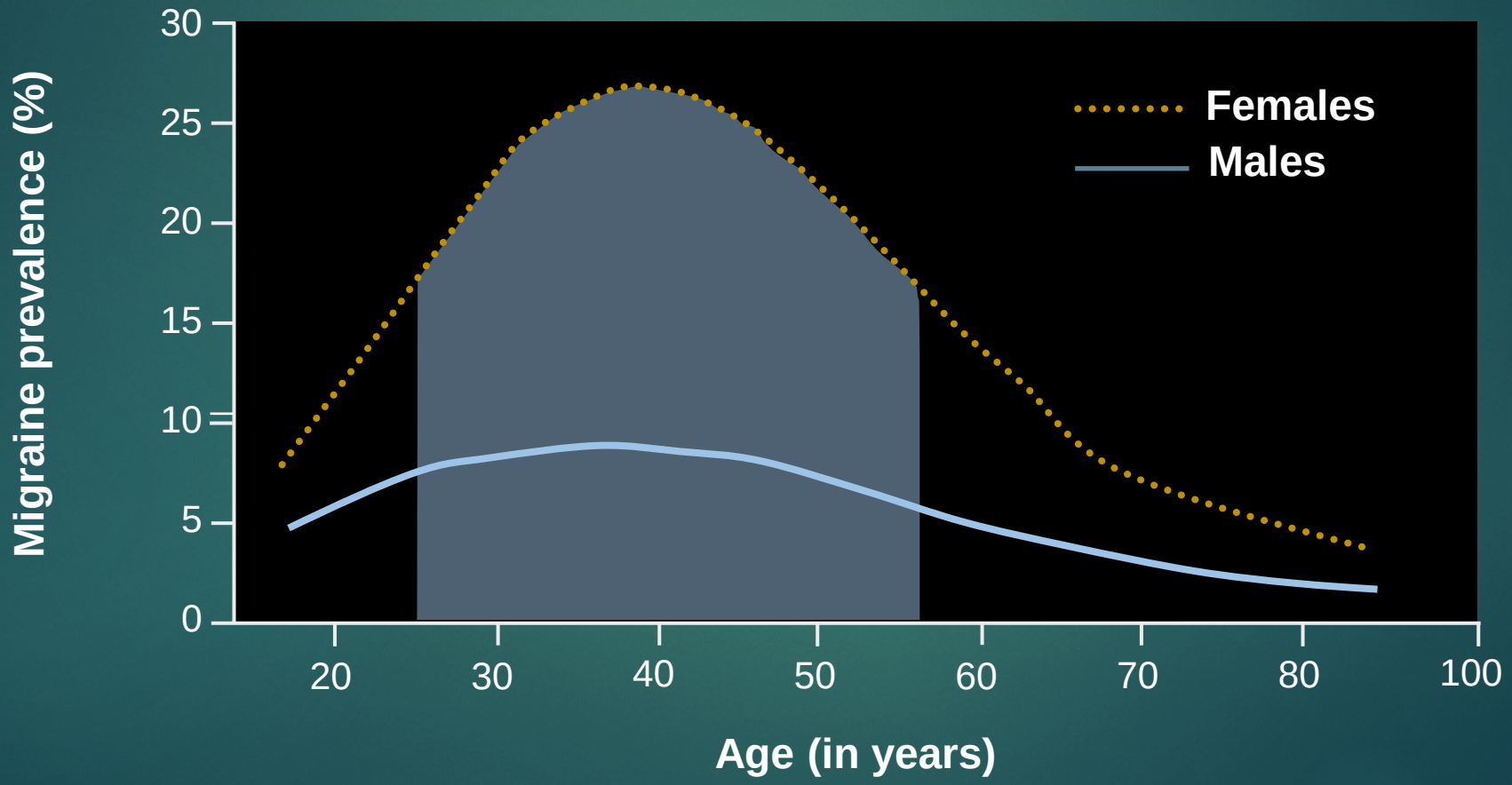
- 39 million Americans Suffer with Migraine Headache Disease.



Lipton RB. *Headache*. 2001;41(7)646-57.

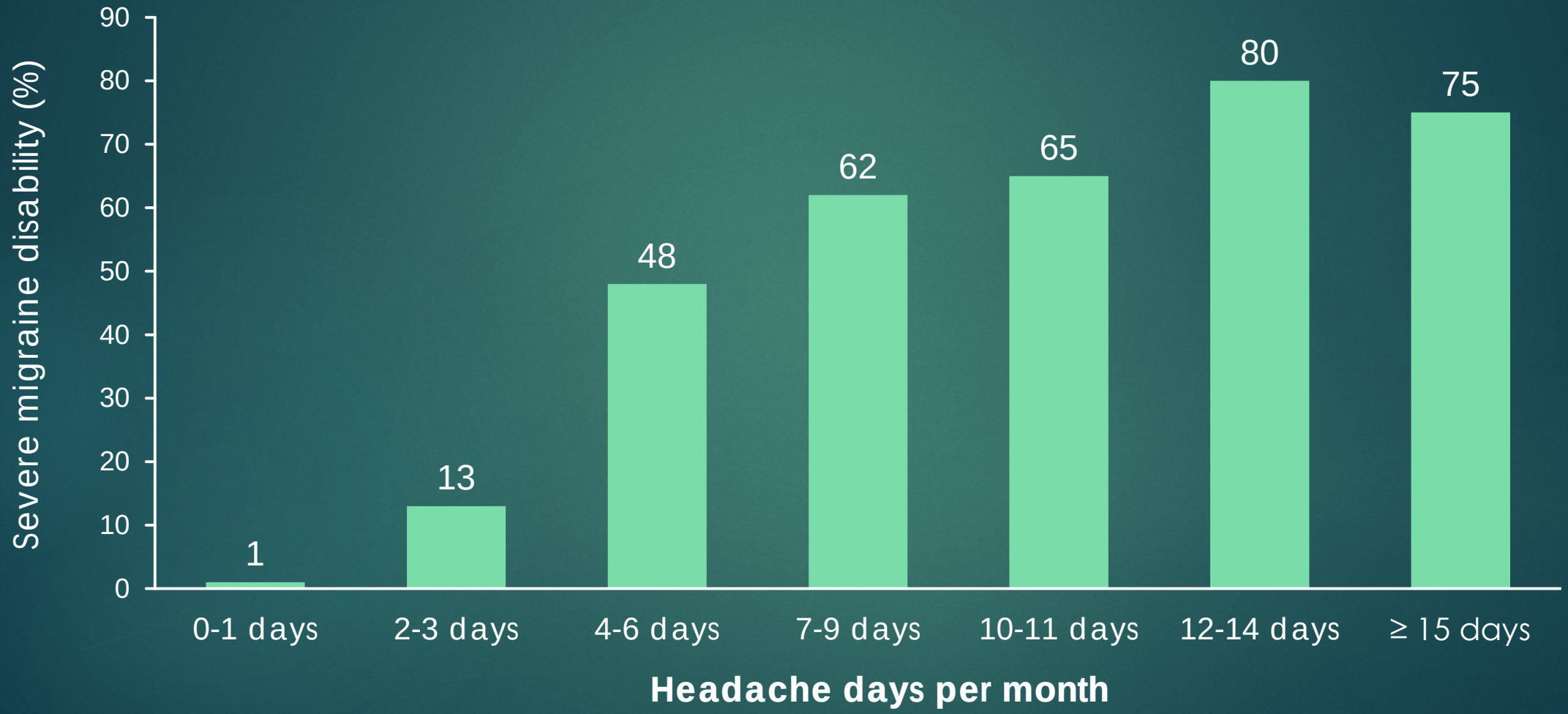
Prevalence by Age

- Greatest Prevalence between 25-55 years of age.



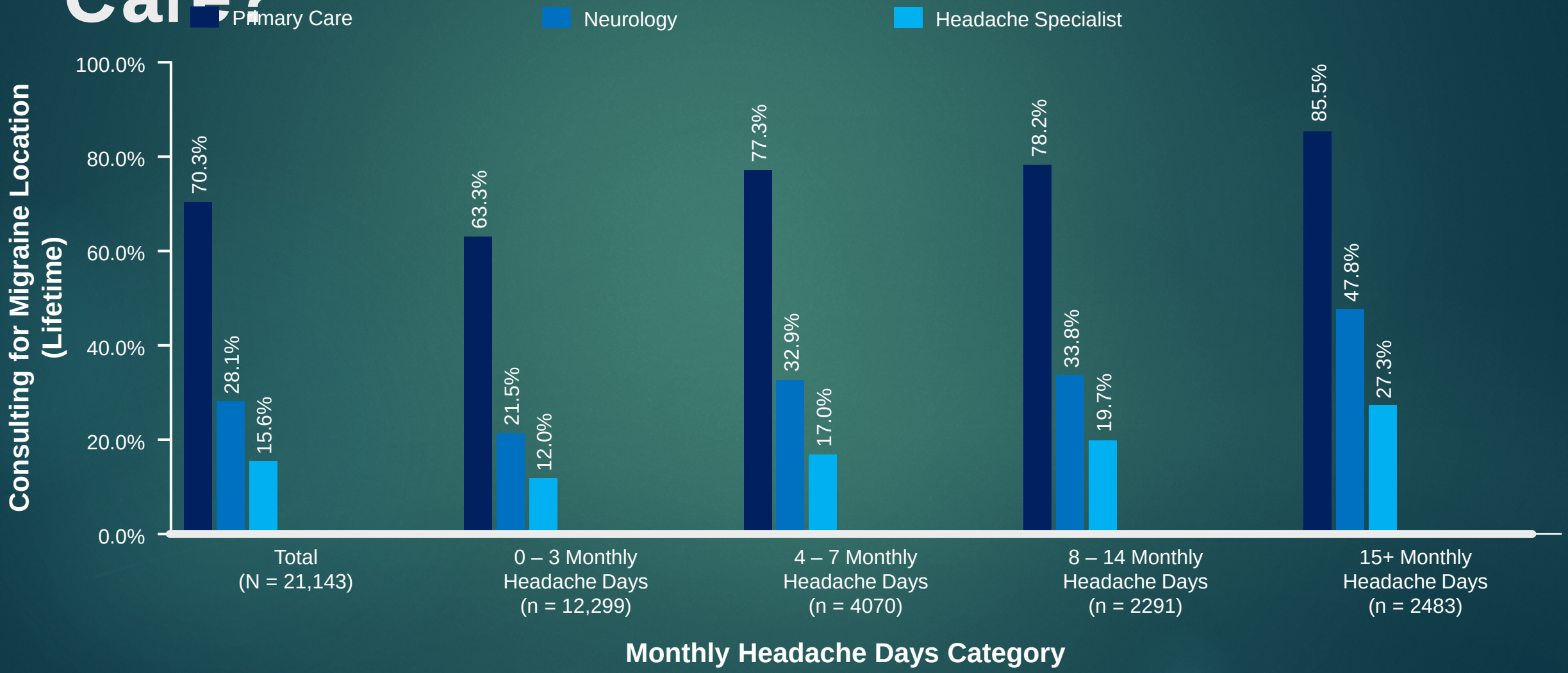
Stewart WF, et al. *JAMA*. 1992;267(1):64-69.

Disability Based on Migraine Headache Days:



Blumenfeld AM. *Cephalalgia.* 2010;31(3):301-315.

Where do Headache Patients Seek Care?



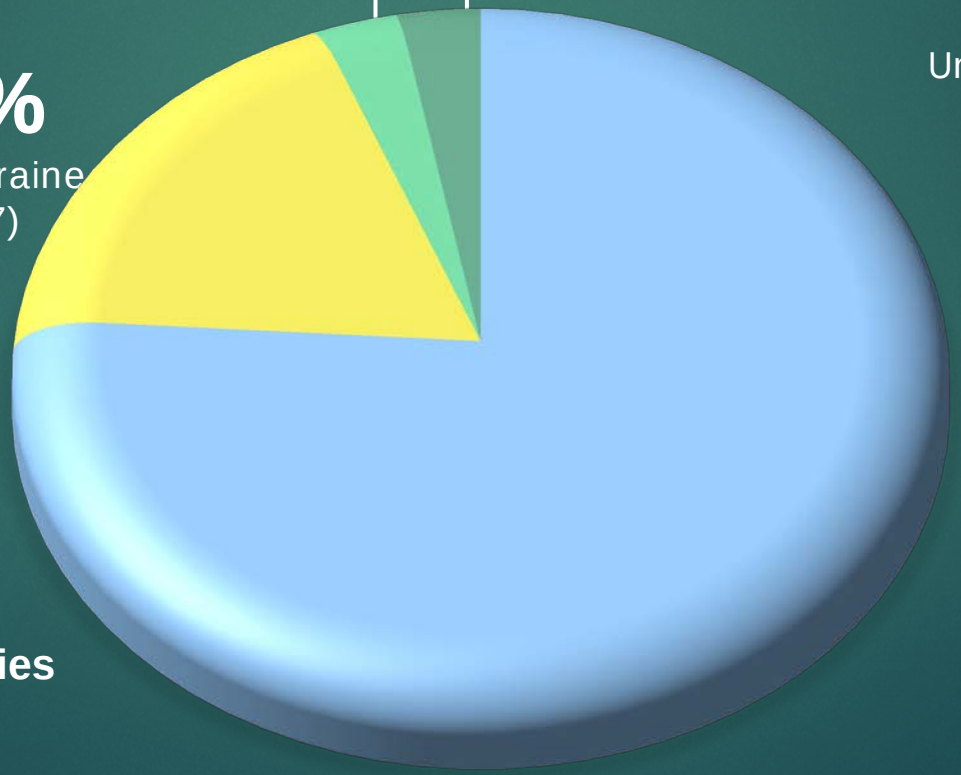
Lipton RB. *Headache.* 2022;62(2);122-140.

Prevalence in Primary Care Waiting Rooms

Prevalence of migraine is 33% in primary care waiting rooms

Tepper S. *Headache*. 2004;44(9):856-864

Global Prevalence of Episodic Headache Presenting to PCP Based Upon Expert Panel Diary Review



3%
Tension
(N=11)

18%
Prob migraine
(N=67)

3%
Unclassifiable
(N=11)

76%
Migraine
(N=288)

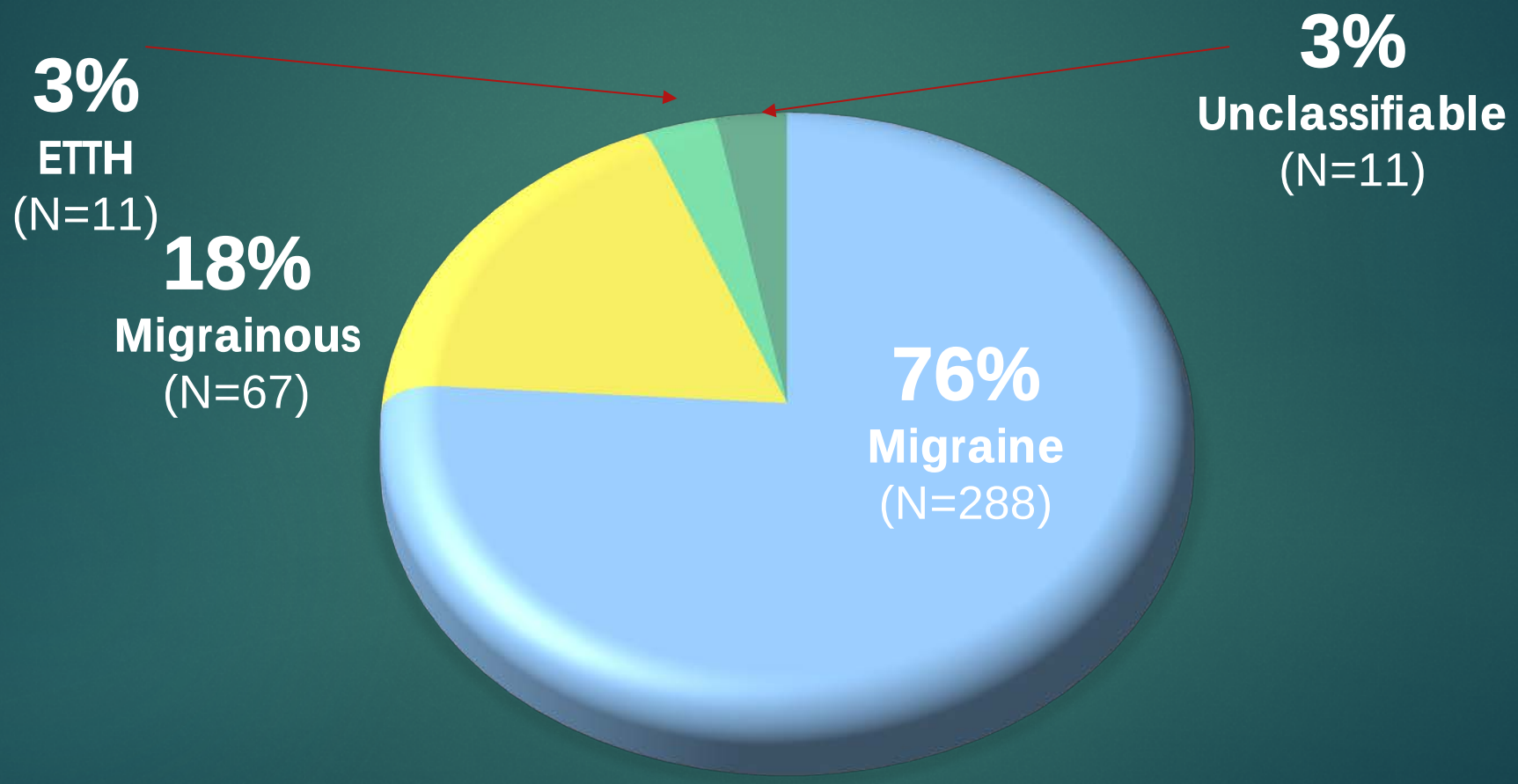
94%
migraine/probable migraine

n=377 patients who returned diaries

PCP = primary care provider.

Tepper SJ, et al. *Headache*. 2004;44:856-864.

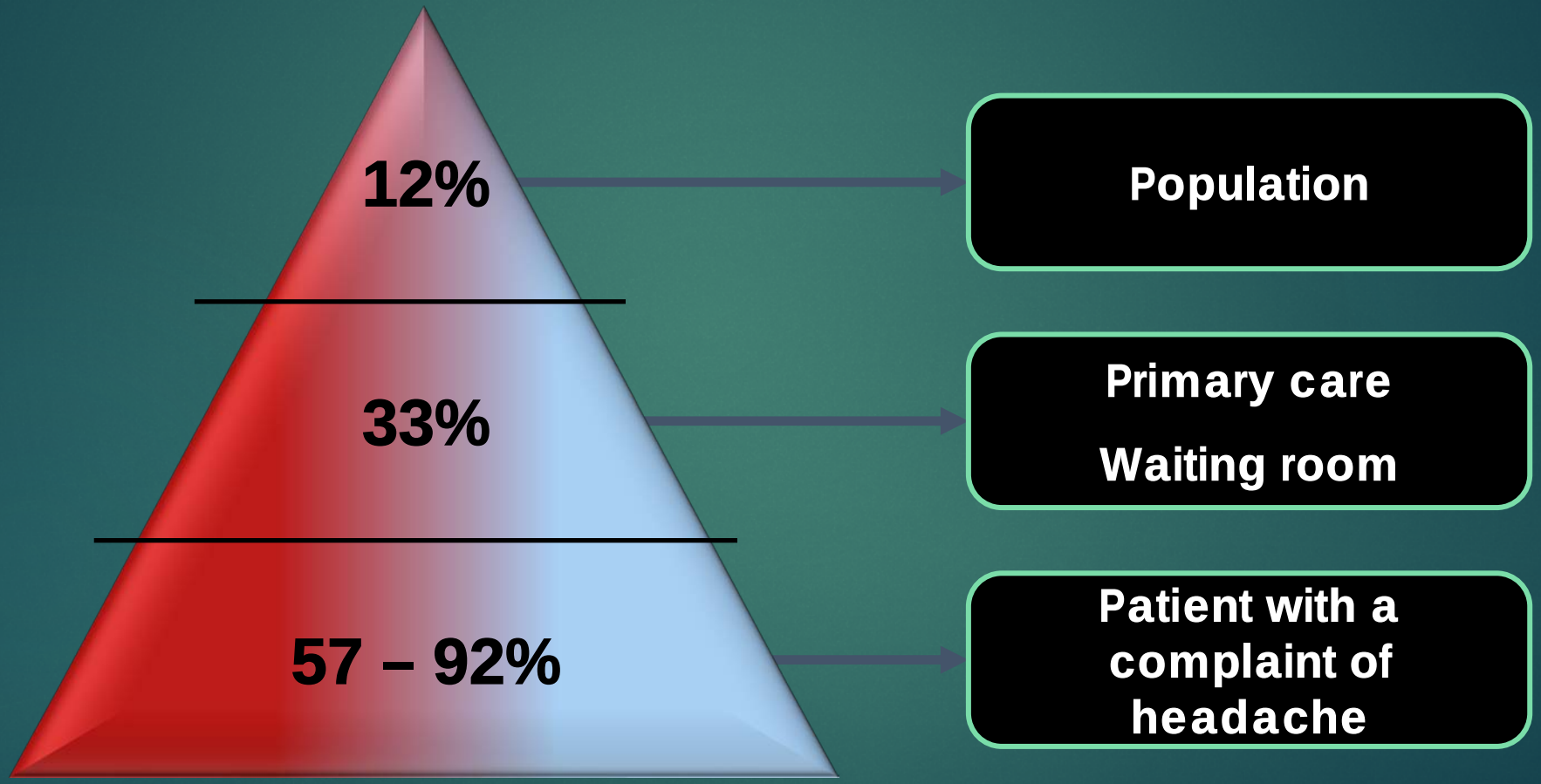
Most Likely Diagnosis in Patients with Complaint of Headache!



ETTH = episodic tension-type headache.

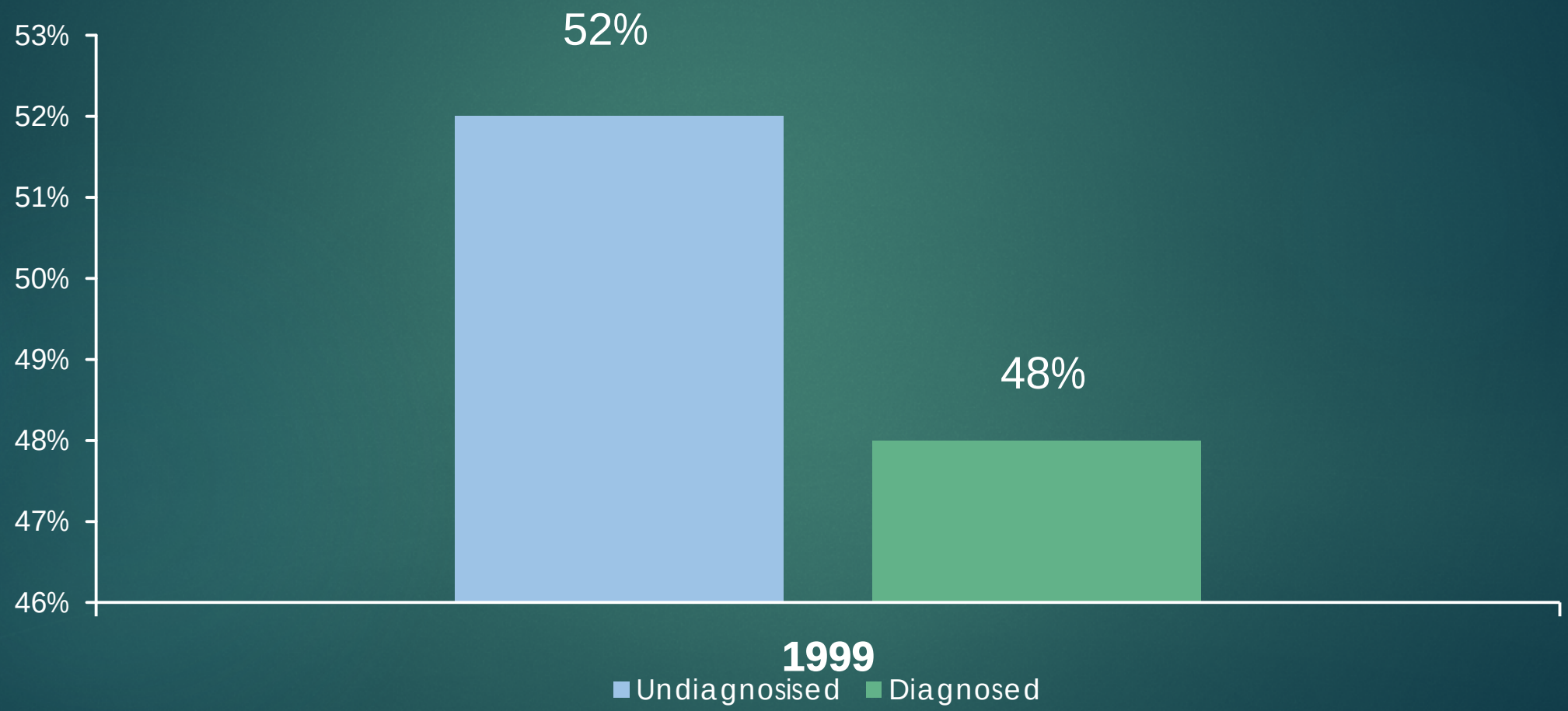
Tepper S. *Headache.* 2004;44(9):856-864

The Prevalence of Migraine in Primary Care



Stang PE, et al. *Headache.* 1994;34(3):138-142. Tepper S. *Headache.* 2004;44(9): 856-864.

Migraine Is Underdiagnosed



Lipton RB. *Headache.* 2001;41:646-657.

Why do we miss the diagnosis?

Time

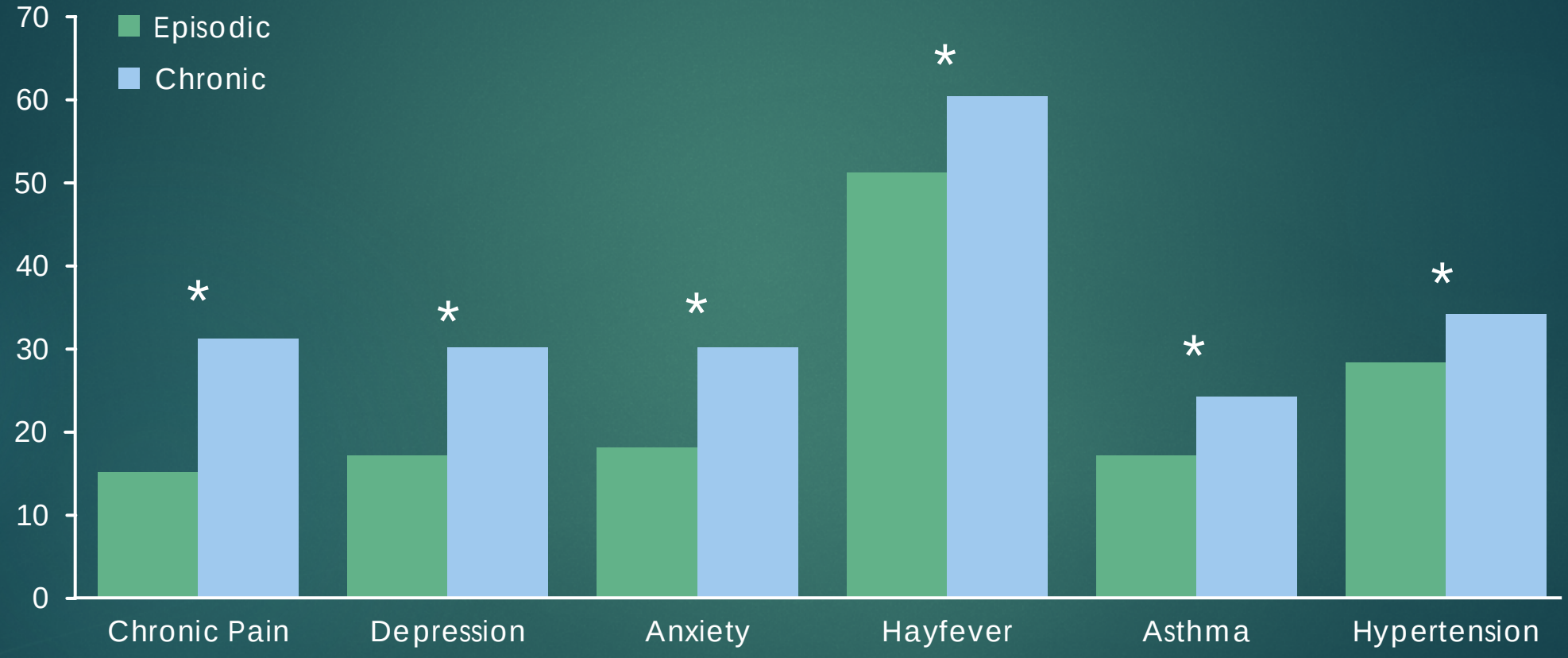
Multiple Complaints at any one visit

Comorbid issues common with migraine

Lack of Experience in Identifying Migraine vs other Primary headache types

Lack of experience with appropriate treatment

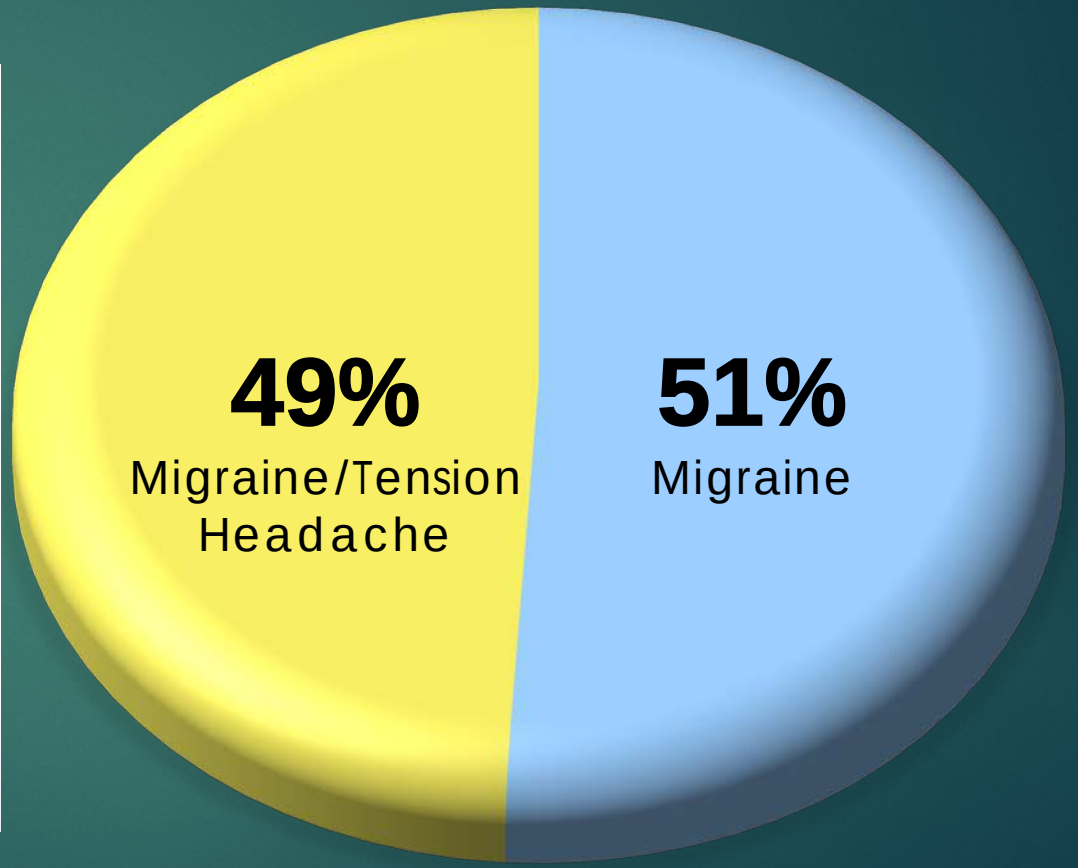
Comorbid Medical and Psychiatric Disorders Common!!



*P<0.05

Buse D. *J Neurol Neurosurg Psychiat.* 2010;81:428-432.

One Head with Different Headaches



Stang PE. *Headache.* 1994;34(3):138-42.

Primary vs Secondary Headache Disorders

Primary

- Migraine
- Tension-type headache
- Cluster headache
- Other primary headache disorders

Secondary

Headaches that arise as a result of another disorder

Approaching Headaches With Directed Exams

DIRECTED INTERVIEW

DIRECTED EXAM

MAKE THE CALL

DECIDE ON ADDITIONAL WORK UP AND TREATMENT

The Interview Questions

Location

Laterality

Quality (throbbing)

Severity

Frequency (days/week or days/month)

Associated symptoms

- Nausea, vomiting, photo/phonophobia

Neurological symptoms

- Visual aura symptoms, hemiparesis, hemisensory loss, diplopia, or vertigo

Additional Questions

- Worse on standing
  - Suspicious for “low pressure headaches” secondary to a leak of spinal fluid
- Worse with coughing, bearing down, or sneezing (Valsalva maneuvers) or worse during the morning
  - Suspicious for “high pressure headaches”

Simple Neuro Exam

- Vitals
- Fundoscopic exam
- Cranial nerve assessment
- Muscular strength testing
- Reflexes
- Cerebellar testing

This is exam is typically normal !!

Worrisome Headache Red Flags (SNOOP4)

Sign or symptom	
S	Systemic symptoms
N	Neurological signs or symptoms
O	Onset
O	Older
P4	Progression, papilledema, position, precipitated by Valsalva

Dodick DW. *Semin Neurol.* 2010;30(1):74-81.

Causes of Secondary Headache

Etiologies	Examples
Neoplastic	Primary or metastatic brain neoplasms
Infectious	Meningitis, acute sinusitis, brain abscess
Vascular	Subarachnoid hemorrhage, carotid or vertebral dissection, aneurysm, CVA, temporal arteritis
Low- or high-pressure syndromes	Intracranial hypotension or hypertension
Drug-induced	Medication overuse headaches
Idiopathic	Vasculitis, CNS lupus, CNS sarcoidosis

CVA = cardiovascular accident; CNS = central nervous system.

Secondary Headache in Primary Care

	New PCP diagnosis Primary headache disorder (n=21,758 [25%])	**New PCP diagnosis Undifferentiated headache disorder (n=63,921 [74%])**
Brain tumor	0.045%	0.15%
SAH	0.02%	0.14%
Temporal arteritis	0.18%	0.66%
Stroke	0.45%	1.06%
TIA	0.25%	0.43%
Benign space-occupying lesions	0.009%	0.05%
Total	0.95%	2.49%

SAH = subarachnoid hemorrhage; TIA = transient ischemic attack.
Kernick D. *Cephalgia.* 2008;28(11):1188-1195.

Primary Headaches

Diagnosis of Migraine, Tension Headache, and Cluster Headache

Migraine Diagnosis – Let's look at it one more time

Headache Description *(Any 2)*	**Associated Symptoms** *(Any 1)*
Unilateral	Nausea or vomiting
Throbbing	Photophonia and photophobia
Worse with exertion	
Moderate to severe intensity	

***Headaches last 4-72 hrs and have no other cause.**
Adapted from Headache Classification Committee of the IHS. *Cephalalgia*. 2018;38(1):1-211.

Chronic Migraine

Meet diagnostic criteria for migraine with or without aura

≥ 15 days per month of headache

≥ 8 days per month have migraine features

Unilateral, moderate/severe, throbbing, worse with exertion	Nausea, vomiting, photo/phonophobia	w/wo Aura symptoms

Adapted from Headache Classification Committee of the IHS. *Cephalalgia*. 2018;38(1):1-211.

Aura

Neurological Event that Usually Precedes the Headache

15%-30% experience aura

Visual aura
Visual disturbance

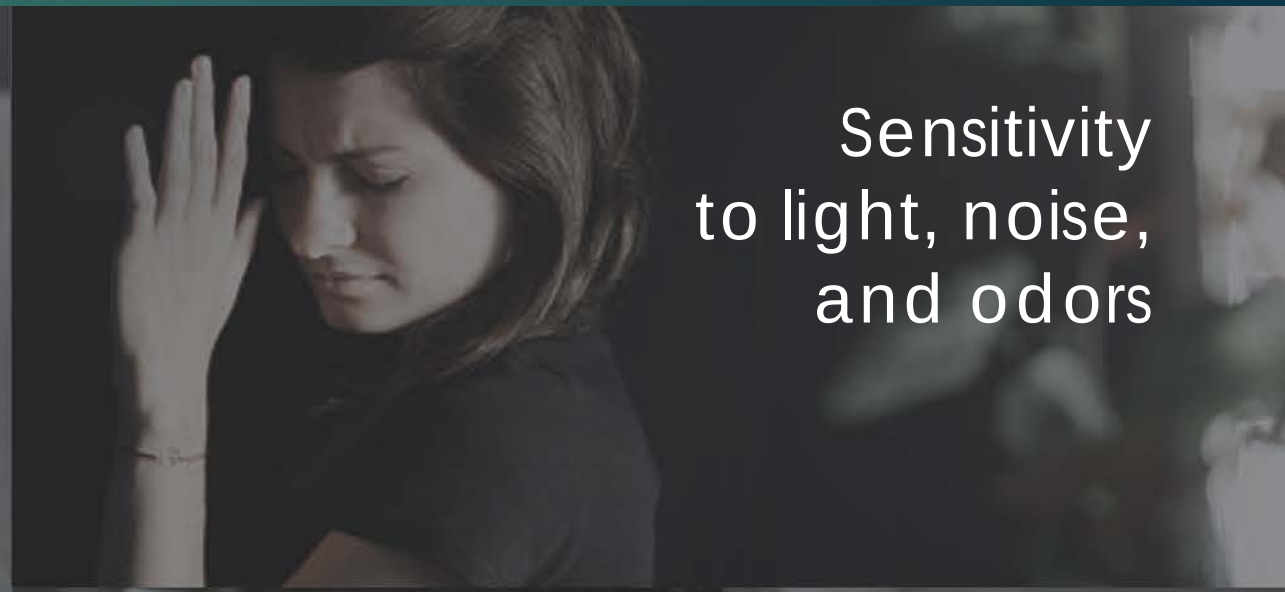
Sensory aura
Numbness of the face
Tingling down arm

Hemiplegic aura
One side of the body

Charles A, et al. *Curr Opin Neurol*. 2015;28(3):255-260. Digre KB. *J Neuroophthalmol*. 2018;38(2):237-243. Lipton RB, et al. *Neurology*. 2007;68:343-349.

Migraine is More than Just a Headache

Moderate to severe headache



Sensitivity to light, noise, and odors

Nausea and or vomiting

Concentration and/or memory troubles

Burch RC, et al. *Headache*. 2015;55(1):21-34. Lipton RB, et al. *Neurology*. 2007;68(5):343-349.

ID Migraine™ Validated Screener

Sensitivity of 0.81 and a specificity of 0.75

During the last 3 months, did you have the following with your headaches

1. **You felt nauseated or sick to your stomach**

   Yes ___ No ___

2. **Light bothered you (a lot more than when you don't have headaches)**

   Yes ___ No ___

3. **Your headaches limited your ability to work, study, or do what you needed to do?**

   Yes ___ No ___

2/3 "Yes" = Positive Screen

Lipton RB, et al. *Neurology*. 2003;61(3);375-382.

Tension vs. Migraine Type Headache

Two of the following

- Mild to moderate intensity
- Bilateral
- Pressure, band-like and non-pulsating
- Not aggravated by exertion
  - often improved

Both of the following

- No nausea or vomiting
- No phonophobia or photophobia (one allowed)

Adapted from Headache Classification Committee of the IHS. *Cephalalgia.* 2018;38(1):1-211.

Cluster Headache

- Severe headaches with psychomotor agitation
- Unilateral
- Duration: 15 minutes to 3 hours
- Cranial autonomic symptoms
  - Ipsilateral rhinorrhea, lacrimation, nasal congestion, or eyelid edema
  - Miosis or ptosis
- Can occur up to 8X per day

CLINICAL SYMPOSIA. 1981;33(20):13.

Acute Treatment Options For Migraine

How Do We Decide What to Use?

What do we need to understand about the evidence?

What do we need to know about patient migraine characteristics?

What are potential barriers for prescribing?

Acute Migraine Treatment Options

Traditional therapies

- Migraine-specific
  - Triptans
  - Ergots/DHE
- Non-specific
  - Acetaminophen
  - NSAIDS
  - Anti-dopamine agents (metoclopramide, prochlorperazine, chlorpromazine)
  - Butalbital
  - Combination analgesics

Newer therapies
Gepants
Ditans
Neuromodulation

DHE = dihydroergotamine.

Acute Migraine Treatment Options cont…

Previous non-specific acute therapies

- NSAIDs
- Dopamine receptor agonists

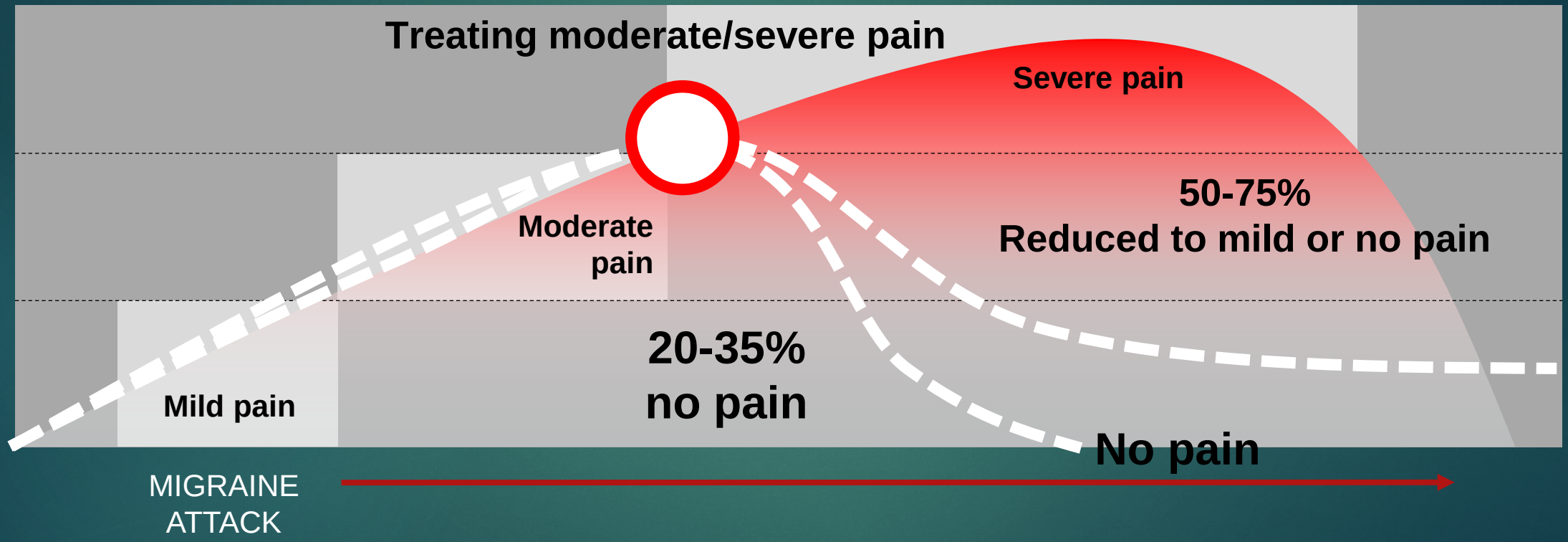
Previous [illegible]ecific [illegible]herapies

- Seda[illegible]
- Opioids

Numerous adverse events

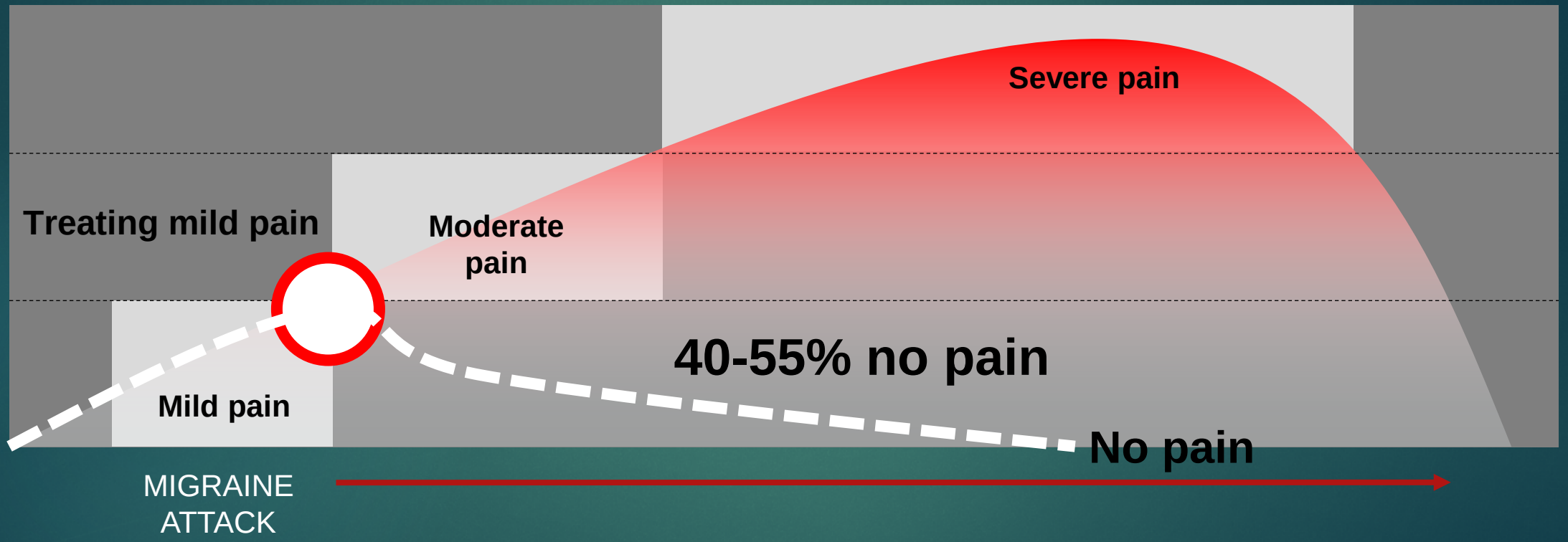
Non-specific therapy led to complications related to the medication

Realistic Expectations of Oral Therapies



Valade D. *Cephalalgia*. 2009;29 (Suppl 3):15-21. Foley KA, et al. *Headache*. 2005;45(5):538-545. Antonaci F, et al. *SpringerPlus*. 2016 ;5:637. Antonaci F, et al. *J Headache Pain*. 2008(4):207-213.

Realistic Expectations of Oral Therapies



Valade D. *Cephalalgia*. 2009;29 (Suppl 3):15-21. Foley KA, et al. *Headache*. 2005;45(5):538-545. Antonaci F, et al. *SpringerPlus*. 2016 ;5:637. Antonaci F, et al. *J Headache Pain*. 2008(4):207-213.

Evidence Assessment for Abortive Medications

Level of evidence	Examples
Level A	
Analgesics	Acetaminophen 1000 mg
Ergots	DHE nasal spray 2 mg
NSAIDS	ASA 500 mg, diclofenac 50/100 mg, ibuprofen 200/400 mg, naproxen 500/550 mg, celecoxib oral solution*, diclofenac powder*
Combinations	Acetaminophen/ASA/caffeine 500/500/130 mg, sumatriptan/naproxen 85/500 mg
Gepants*	Rimegepant*, ubrogepant*, zavegepant (pending FDA approval)
Ditans*	Lasmiditan*
Triptans	Almotriptan 12.5 mg, eletriptan 20/40/80 mg, naratriptan 1/2.5 mg, rizatriptan 5/10 mg, sumatriptan 25/50/100 mg tabs, 20 mg NS, 4/6 mg sq, zolmitriptan 2.5/5 mg tabs, 2.5/5 mg NS

*** Not reviewed in 2015 review.**
ASA = acetylsalicylic acid; NS = nasal spray.
Marmura MJ, et al. *Headache.* 2015;55: 3-20

Potential Side Effects May Guide Choice

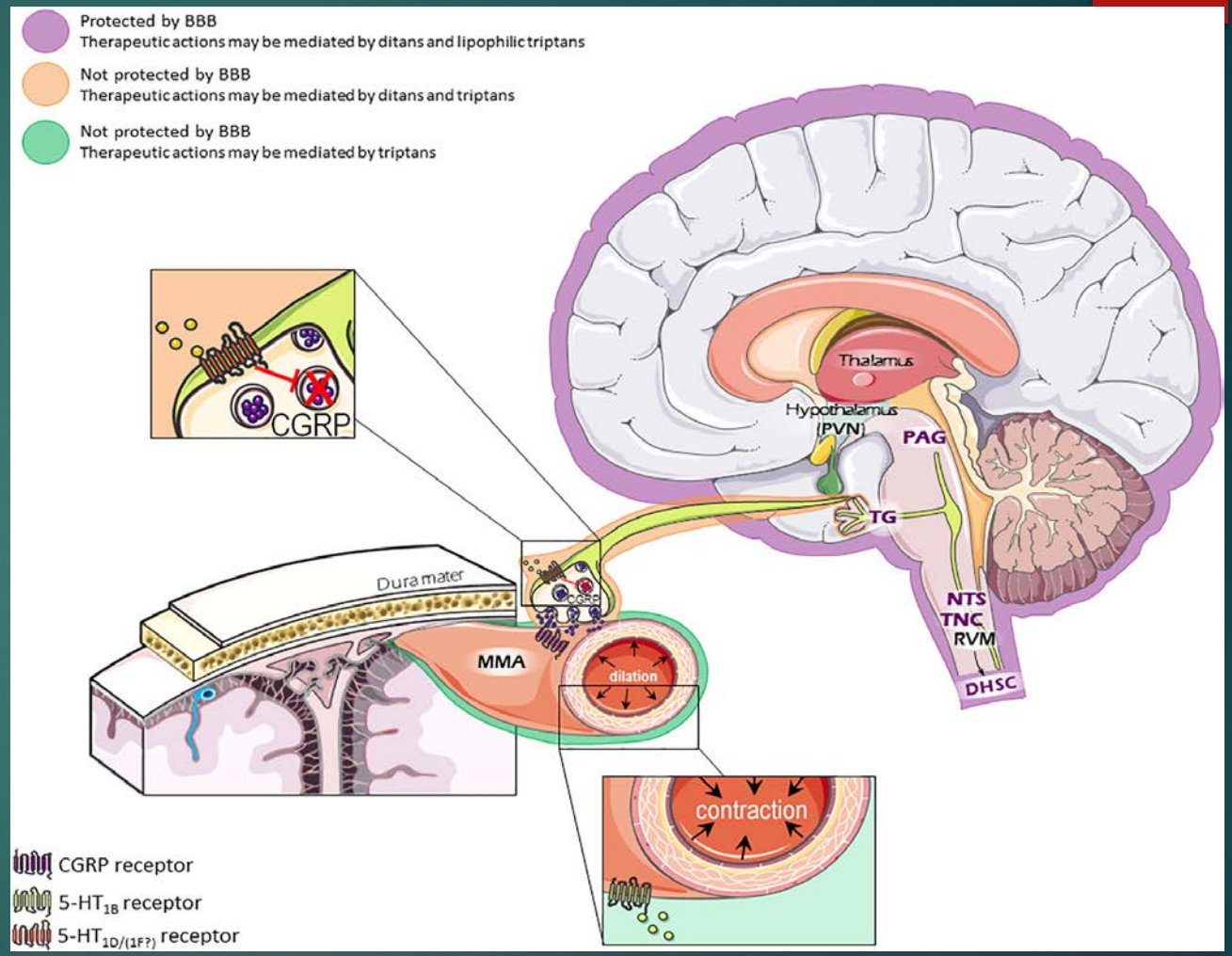
Med class	Side effects	Cautions	Drug interactions
NSAIDS	Gastritis, PUD	CRF, CV disease	MTX, immunosuppressives
Triptan	Triptan side effects	CV disease	SSRIs, SNRIs?
Gepants	Nausea, somnolence	None No CV contraindication	CYP3A4 inhibitors*
Ditans	Dizziness, somnolence, paresthesia	Driving restriction No CV contraindication	
Ergots	Nausea, vomiting	CV disease	CYP3A4 inhibitors*

***Potent CYP3A4 include itraconazole, fluconazole, erytho/clarithromycin, protease inhibitors.**
PUD = peptic ulcer disease; CRF = chronic renal failure; CV = cardiovascular; MTX = methotrexate; CYP3A4 = cytochrome P450 family 3 subfamily A member 4.

Triptan MOA

Standard of care

- Mechanism of action
  - Serotonin 5-HT1B agonist
  - Serotonin 5-HT1D agonist
- Clinically effective
- Peripheral-acting
- Vasoconstricting
- Adverse events
  - Chest pain/tightness
  - Neck/throat discomfort



PVN = paraventricular nucleus; PAG = periaqueductal gray; TG = trigeminal ganglion; NTS = nucleus tractus solitarius; TNC = trigeminal nucleus caudalis; RVM = rostral ventromedial medulla; DHSC = dorsal horn of the spinal cord; MMA = middle meningeal artery.

Contraindications to Triptans

- History of stroke, aneurysm, or myocardial infarction

- Uncontrolled hypertension

- History of ischemic bowel disease or severe peripheral vascular disease

- Serotonin syndrome?

Overall, triptans are very safe!

Standard of care for migraine

Ditan -

- 5HT1F receptor agonist
  - Lasmiditan
  - Highly efficacious in clinical trials
  - Adverse events reflect CNS activity

    Dizziness/driving restriction (Schedule V)
  - No vasoconstriction
  - Mechanism of action
    - Peripheral reduction of CGRP

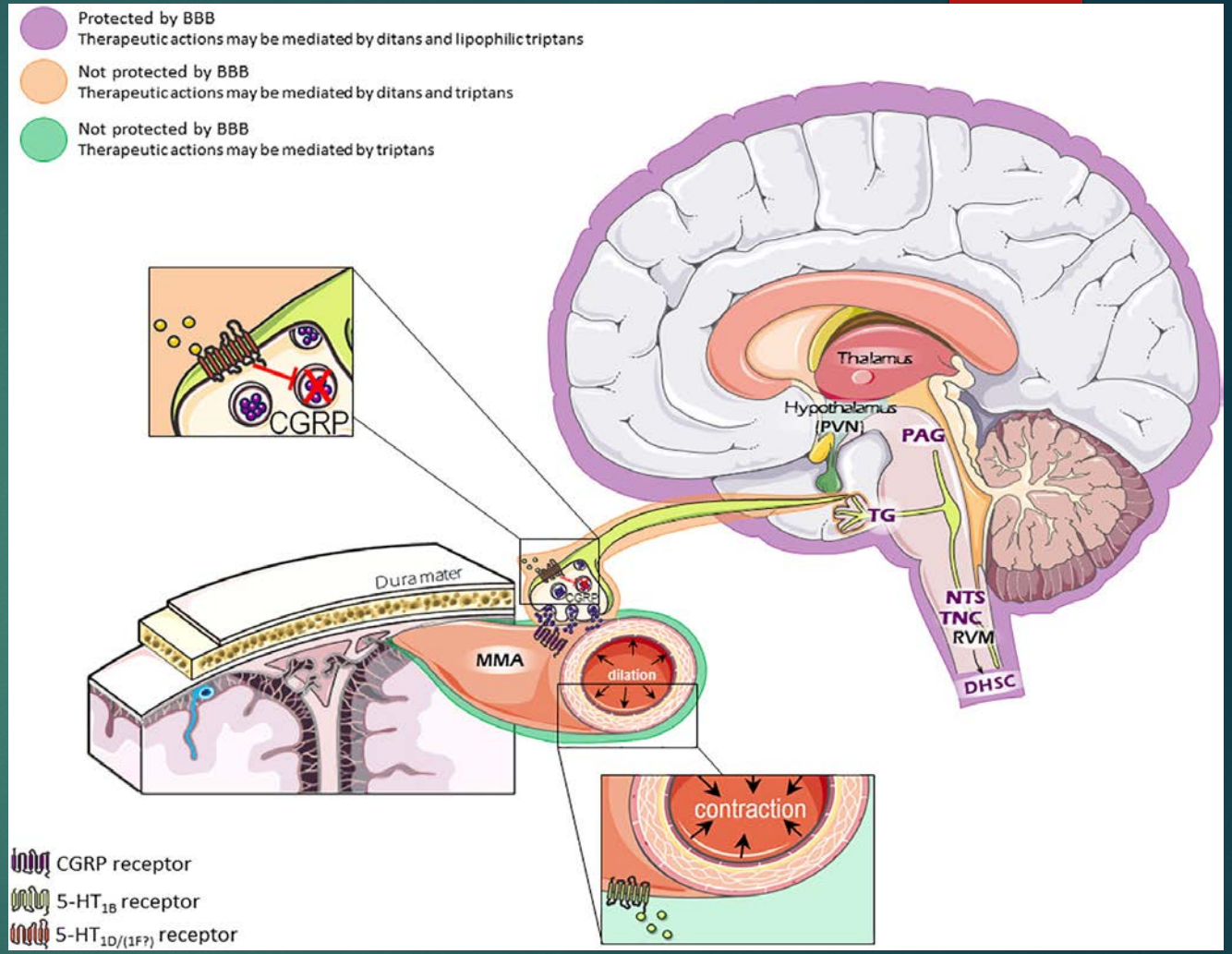
    Central 5HT1F receptors
    at key areas of migraine

    Hypothalamus

    Thalamus

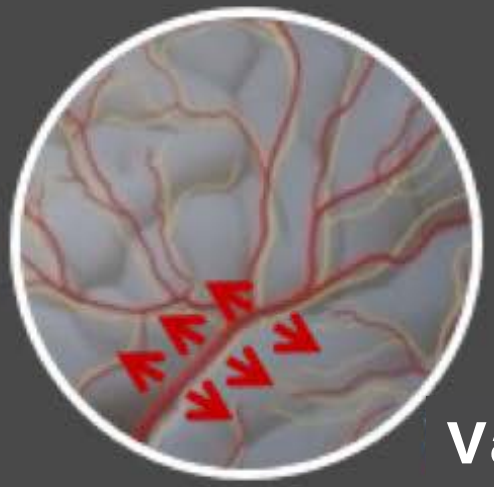
    Trigeminal nucleus caudalis

    Periaqueductal gray



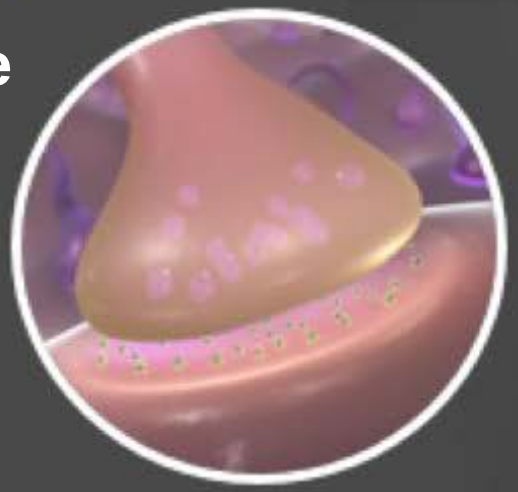
CNS = central nervous system.
Rubio-Beltrán E, et al. *Pharmacol Ther*. 2018;186:88-97.

CGRP(Calcitonin Gene-Related Peptide)



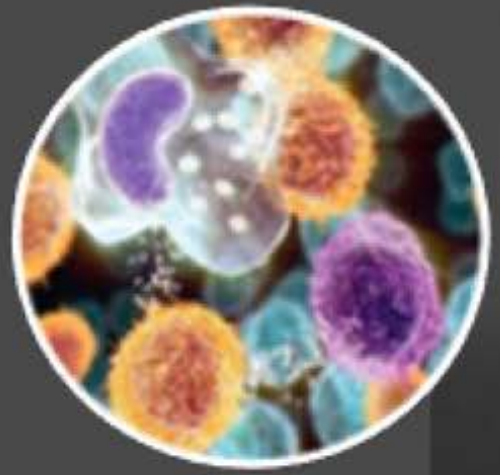
Vasodilation

Neuropeptide Release



Nociceptor Sensitization

Inflammation



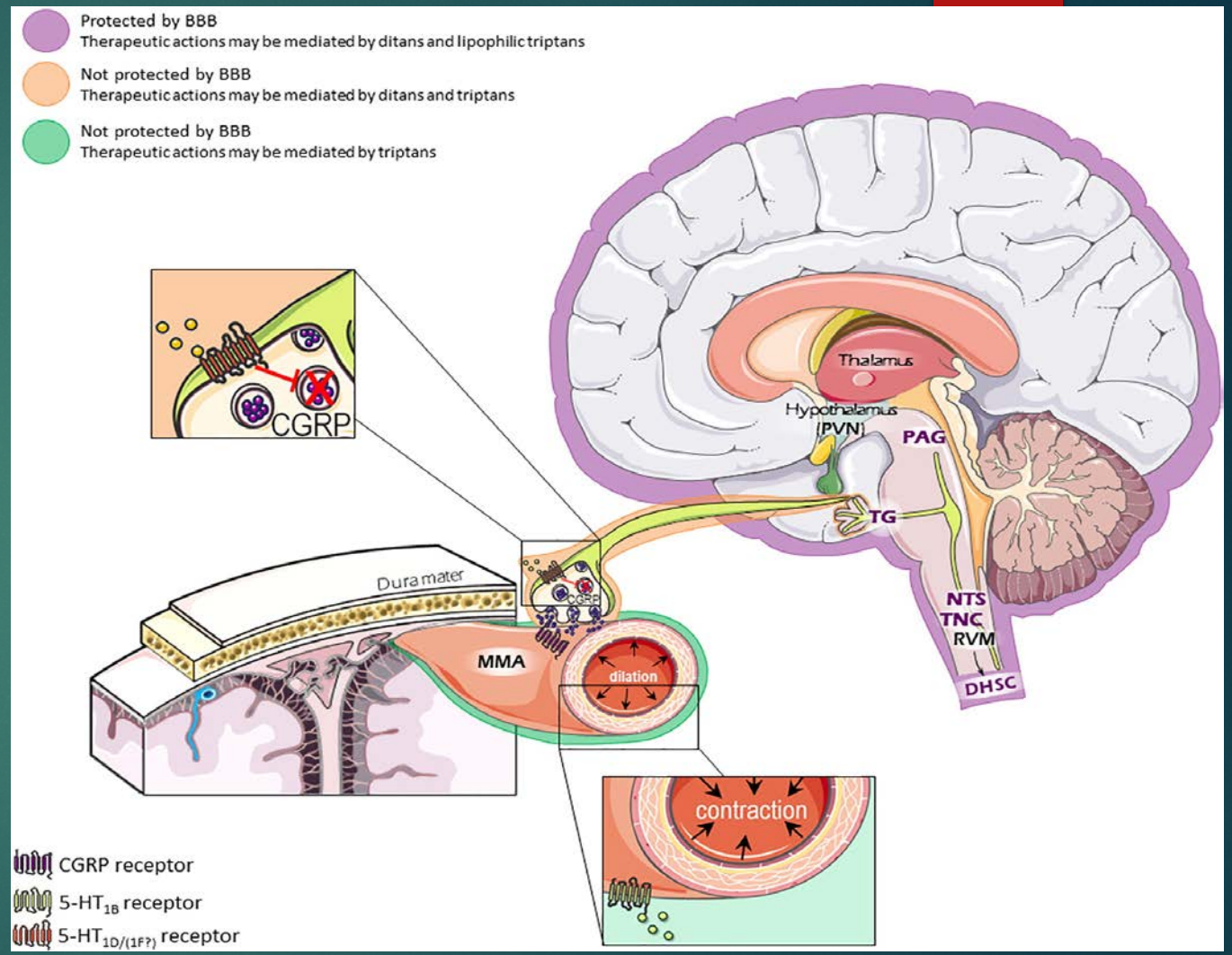
Gepants -

- "Gepants"
  - Ubrogepant 50 mg, 100 mg tablets

    Max 200 mg per day
  - Rimegepant 75 mg ODT

    Max 75 mg per day
  - Clinical trials very impressive
  - Minimal adverse events
  - No vasoconstriction
  - Mechanism of action

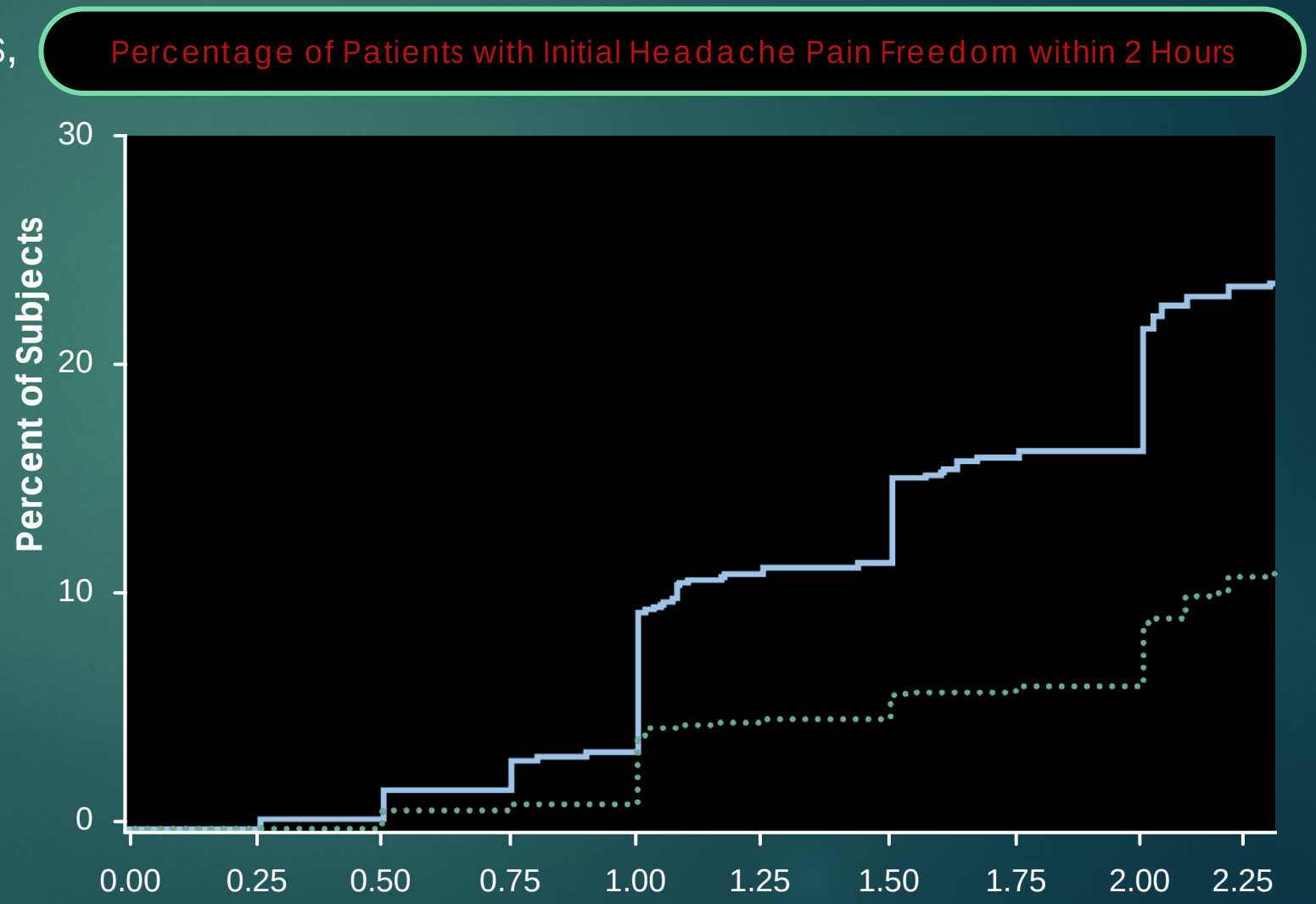
    - Peripheral CGRP blockade



Ceriani CEJ, et al. *Headache*. 2019;59(9):1597-1608.

NSAIDS

- Ketorolac—30 mg IM, 10 mg tablet (consider 20mg q 12 hours, max 2 days per week)
- Indomethacin—50 mg q 8 hours with food
- Meloxicam—15 mg tablet
- Diclofenac—50 mg in crystalized formulation, regular tablet crushed



Targets: Summary

Triptans and ergots prevent CGRP release

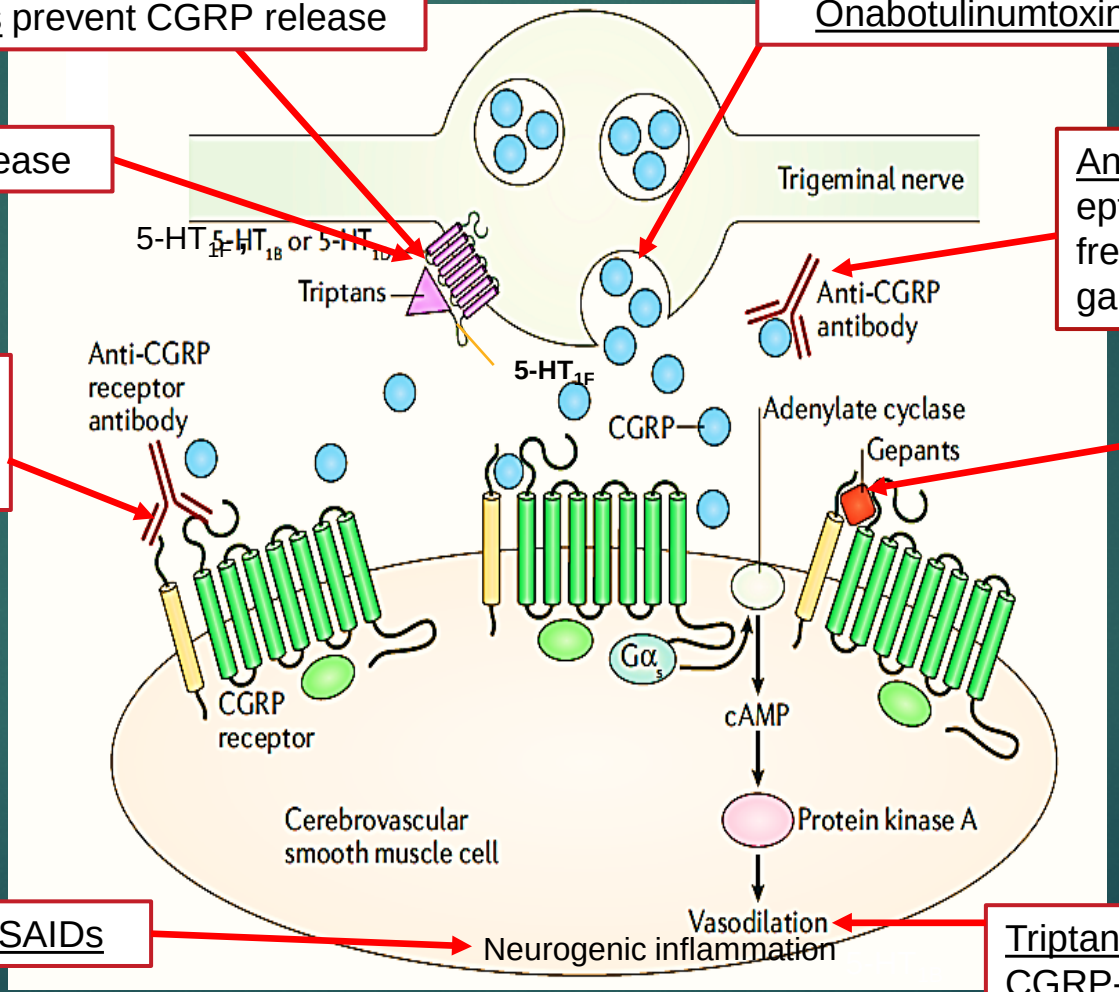
OnabotulinumtoxinA prevents CGRP release

Lasmiditan prevents CGRP release

Anti-CGRP ligand mAbs:
eptinezumab,
fremanezumab,
galcanezumab

Anti-CGRP receptor mAb:
erenumab

CGRP receptor antagonists (gepants):
atogepant*,
rimegepant,
ubrogepant,
zavegepant*



NSAIDs

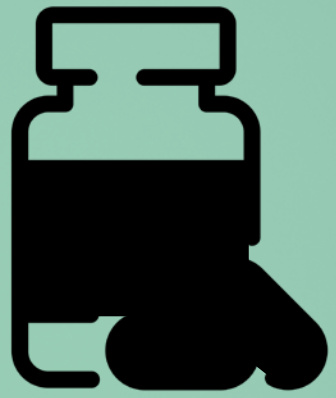
Triptans and ergots constrict CGRP-dilated vessels

***Investigational.**
mAb = monoclonal antibody.
Edvinsson L, et al. *Nat Rev Neurol*. 2018;14(6):338-350.

Preventive Treatment Options For Migraine

When to Start Preventive Medications

4+
headache days



Acute meds
not working (regardless of number of headache days)

Hemiplegic and basilar migraine

Silberstein SD. *Continuum (Minneap Minn).* 2015;21(4Headache):973-989. Dodick DW, et al. *Pract Neurol*. 2007;7:383-393.

Goals of Preventive Migraine Treatment

Reduce
migraine frequency and severity

Improve
function and reduce disability

Silberstein SD. *Continuum (Minneap Minn)*. 2015;21(4Headache):973-989. Silberstein SD. *Neurology*. 2000;55:754-762. Dodick DW, et al. *Pract Neurol*. 2007;7:383-393. American Headache Society. *Headache*. 2019;59(1):1-18.

Traditional Migraine Prevention

Medication Consequences

Limited Use

39%

candidates for migraine prevention

29%

prescribed migraine prevention

12%

using migraine prevention

Prevention Medication Level of Evidence

Level A: Medications with established efficacy (≥ class I trials)	Level B: Medications are probably effective (1 class I or 2 class II studies)	Level C: Medications are possibly effective (1 class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs	**Antidepressants/ SSRI/SNRI/TCA**	**ACE inhibitors**	**Carbonic anhydrase inhibitor**	**Established as not effective**
Divalproex sodium*	Amitriptyline	Lisinopril	Acetazolamide	Antiepileptic drugs
Sodium valproate	Venlafaxine	Antihistamines	Antithrombotics	Lamotrigine
Topiramate*	β-blockers	Cyproheptadine	Acenocoumarol	Probably not effective
β-blockers	Atenolol[a]	α-agonists	Coumadin	Clomipramine[a]
Metoprolol	Nadolol[a]	Clonidine	Picotamide	Possibly not effective
Propranolol*	Triptans (MRM[b])	Guanfacine[a]	Antidepressants SSRI/SNRI	Acebutolol[a]
Timolol[a]*	Naratriptan[b]	Antiepileptic drugs	Fluvoxamine[a]	Clonazepam[a]
Triptans (MRM[b])	Zolmitriptan[b]	Carbamazepine[a]	Fluoxetine	Nabumetone[a]
Frovatriptan[b]		β-blockers	Antiepileptic drugs	Oxcarbazepine
Candesartan		Nebivolol	Gabapentin	Telmisartan
		Pindolol[a]	TCAs	
			Protriptyline[a]	
			β-blockers	
			Bisoprolol[a]	

MRM = menstrually related migraine; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; ACE = angiotensin-converting enzyme.

Traditional Migraine Prevention
Mechanism of Action

Inhibition of cortical spreading depression (CSD)

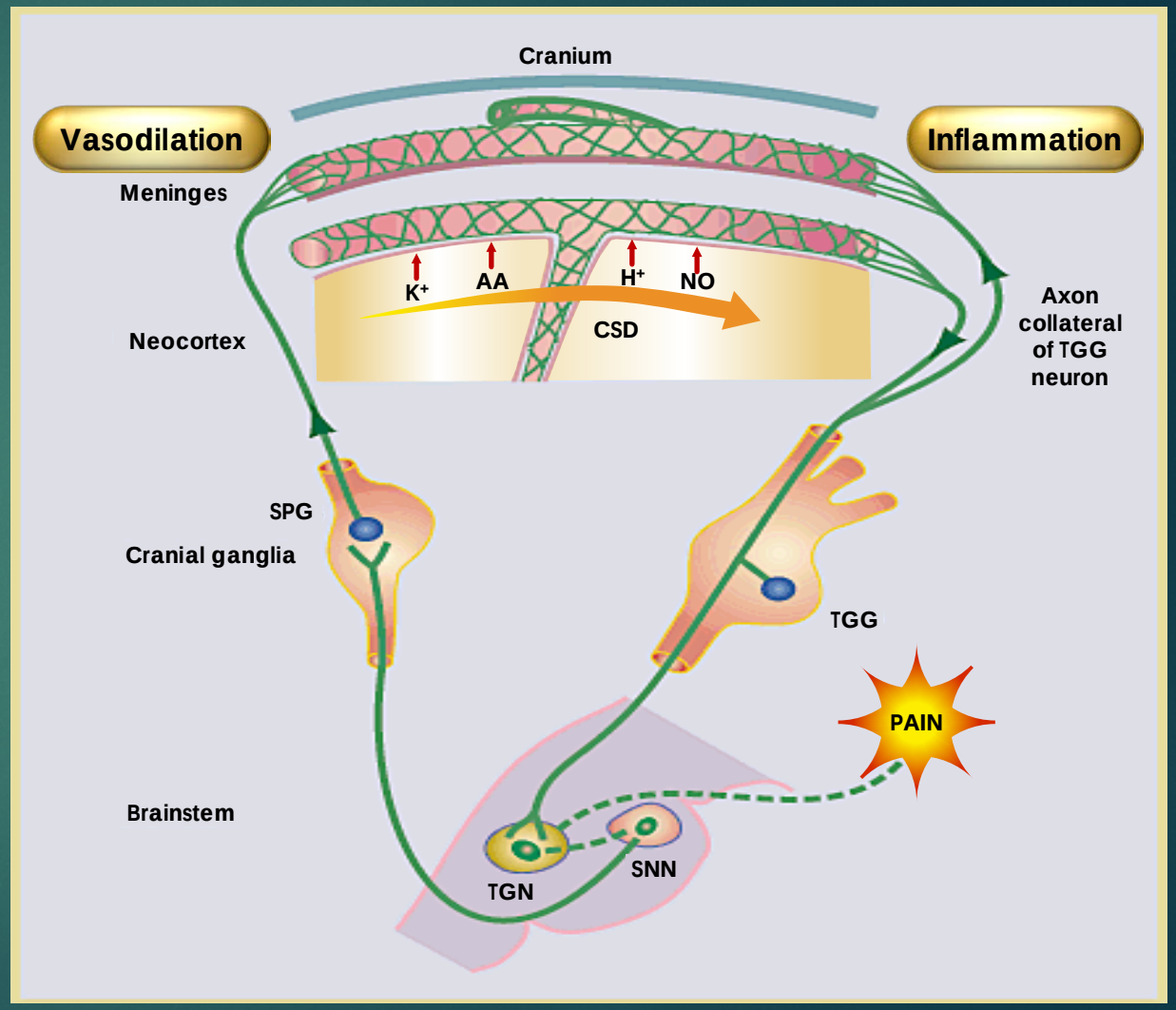
Inhibition of CSD

Conditions favoring CSD increase migraine frequency

- Environmental light
- Hypoglycemia
- Female sex

Many, but not all, traditional migraine preventive agents have been found to inhibit CSD in animal models

- Valproate
- Topiramate
- Amitriptyline
- Propranolol



K+ = potassium; AA = arachidonic acid; H+ = hydrogen; TGG = trigeminal ganglion; SPG = sphenopalatine ganglion; TGN = trigeminal nerve; SSN = suprascapular nerve.

Ayata C, et al. *Ann Neurol.* 2006;59:652-661. Zhang X, et al. *J Neurosci.* 2010;30:8807-8814.

Traditional Migraine Prevention
Medication Outcome

Limited efficacy

- 50% reduction in 50% of patients
- Delayed onset—weeks to months

Limited tolerability

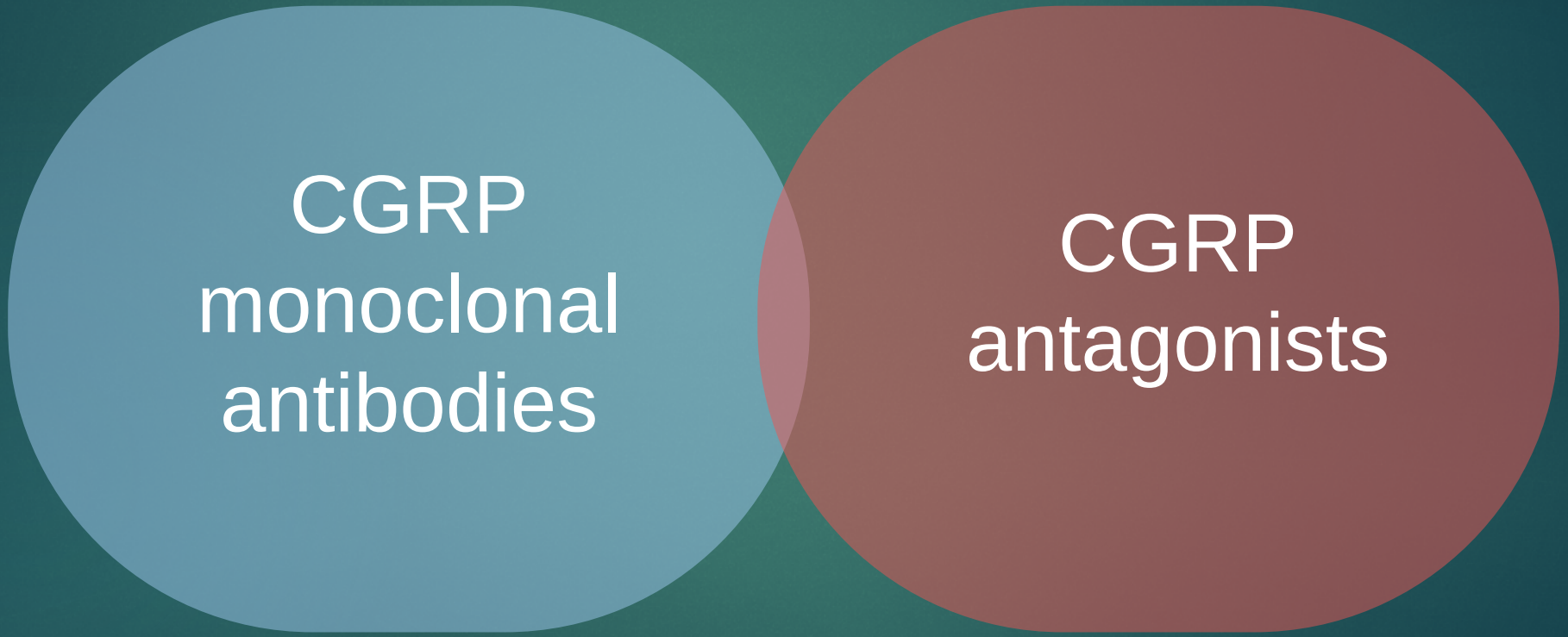
- Most effective agents with multiple side effects
- Interactions with drugs or medical conditions

Limited compliance

- 24% compliance at 6 months, 17% at 12 months

Modern Migraine Prevention

Migraine-Specific Therapies



Anti-CGRP Monoclonal Antibodies

Practical Prescribing

Erenumab

70 mg or 140 mg SC monthly

Fremanezumab

225 mg SC monthly or 675 mg SC quarterly

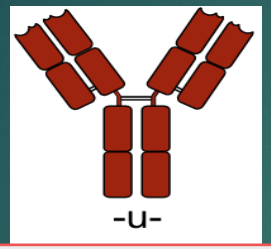
Galcanezumab

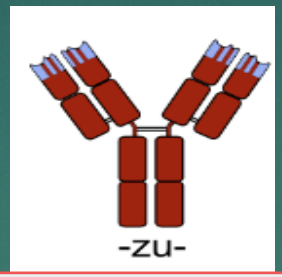
240 mg loading dose, then 120 mg SC monthly

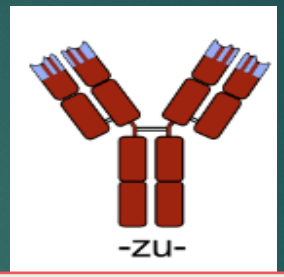
Eptinezumab

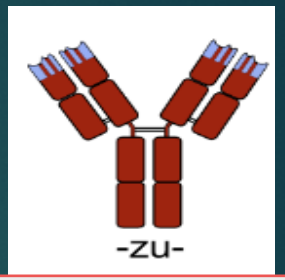
100 or 300 mg IV quarterly

CGRP Monoclonal Antibodies









	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
Dosing	Monthly SC	Monthly SC	Monthly or quarterly SC	Quarterly IV
$T_{½}$ (days)	~28 days	25-30 days	21 days	~27 days
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
Regulatory status 2020	FDA approval migraine 4-30 days per month	FDA approval migraine 4-30 days per month and episodic cluster	FDA approval migraine 4-30 days per month	FDA approval migraine 4-30 days per month

SC = subcutaneous; IV = intravenous; FDA = US Food and Drug Administration.

Charles A, et al. *Lancet*. 2019;394(10210):1765-1774.

Gepants for Migraine Prevention
Additional Modern Prevention Options

Rimegepant QOD for EM/CM Prevention

Baseline: ~7.8 migraine days/month	Rimegepant (n=348)		Placebo (n=347)	
	n	Point estimate (95% CI)	n	Point estimate (95% CI)
Change in mean number of migraine days per month during weeks 9-12, days (primary efficacy outcome)†	348	-4.3 (-4.8 to -3.9)	347	-3.5 (-4.0 to -3.0)

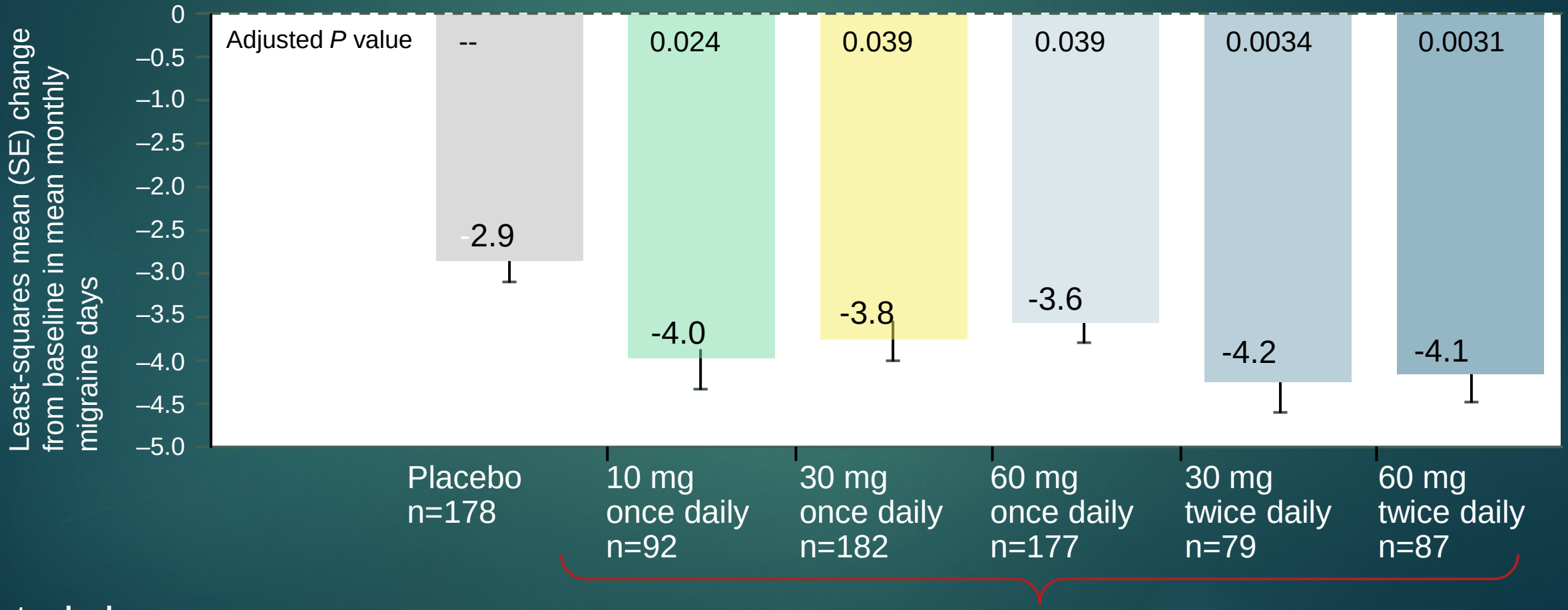
- Placebo-controlled RCT with rimegepant 75 mg BID preventively for 3 months
- Mixed population of episodic and chronic migraine w/ or w/o aura
- Mean baseline migraine frequency: 7.8 days/month
- Placebo reduction weeks 9-12: 4.3 days/month (-3.5 days)

QOD = every other day; CI = confidence interval; RCT = randomized controlled trial.

Croop R, et al. *Lancet*. 2021;397(10268):51-60. FDA [www.accessdata.fda.gov]. Accessed June 30, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212728s006lbl.pdf.

Atogepant Approved for Episodic Migraine Prevention

Change from baseline in mean monthly migraine days across the 12-week treatment period in the modified intention-to-treat population



SE = standard error.

Goadsby PJ, et al. *Lancet Neurol*. 2020;19(9):727-737.

Modern Migraine Prevention *Medication Outcomes*

Improved efficacy

Every primary endpoint, every migraine trial met

- Migraine with and without aura
- Episodic migraine
- Chronic migraine
- Migraine failing multiple preventive medications
- Migraine with and without medication overuse headache

50%, 75%, 100% responder rates

Onset in days to weeks

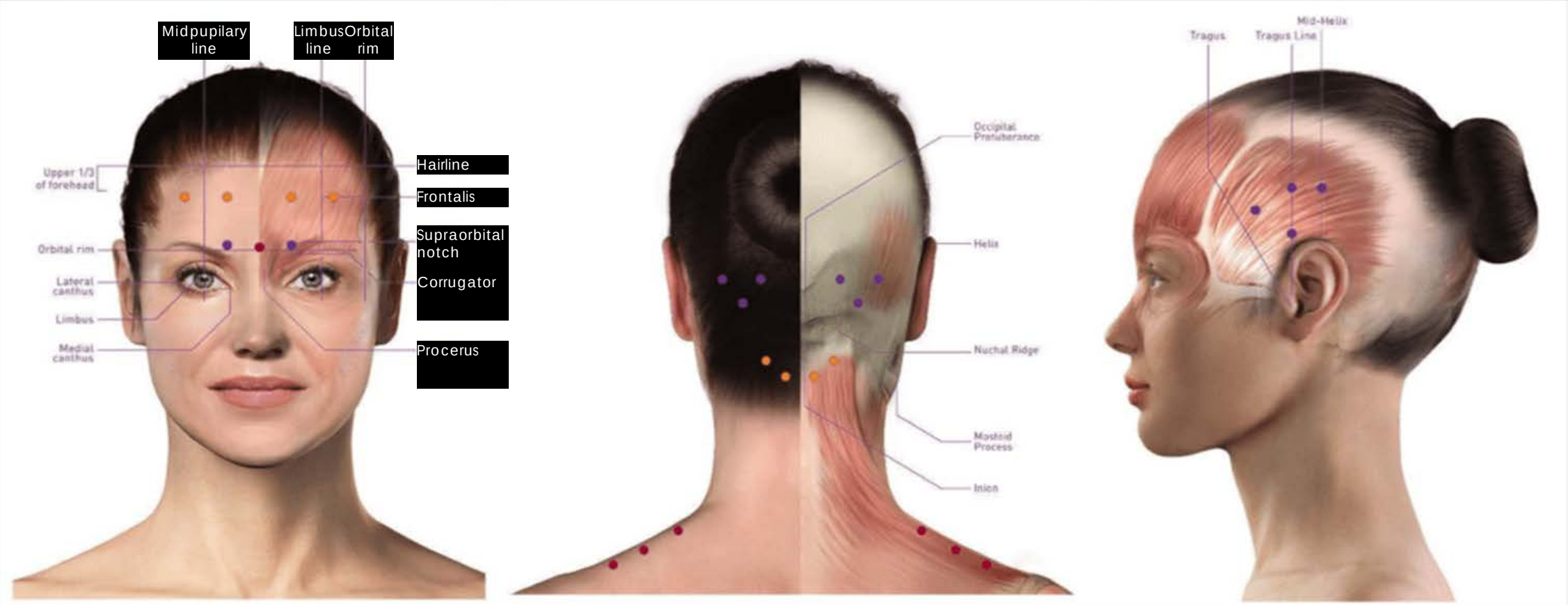
Modern Migraine Prevention *Practical Management Expectations*

- Prior authorization and re-authorization
- Managing injection site reactions
- “Wearing off”
- Impact on triptan response
- Navigating expected migraine variations

Neurotoxin for Migraine Prevention

OnabotulinumtoxinA

Indicated for chronic migraine



Morgan JC, et al. *J Neurol Neurosurg Psychiatry.* 2006;77(1):117-119.

You Can Do This !!!

Primary Care is Uniquely Suited for Headache Care

There is a diagnostic pattern to follow

There is a growing tool set for acute and preventative treatment

Patients deserve our efforts to improve their lives.

You can leverage your continuity

You know the full medical picture

You have closer follow up

You can lead the workup in more effective ways

When do Referral Makes Sense?

KEY PRACTICE POINTS

- Migraine is epidemic.
- Primary care is by far the most common location for patients seeking care.
- Migraine and Secondary headaches have a specific diagnostic criteria.
- There are a vast array of treatment options to manage migraine both for acute rescue and chronic prevention.

Thank You !!

Questions??