MIGRAINE TREATMENT UPDATE:CURRENT AND PIPELINE

Soma Sahai, MD

Clinical Professor of Neurology

Director, Neurology Clinics

Program Director, Headache Fellowship

Division Chief, Headache and Neuralgia

Disclosures

Previously:

Consultant for Amgen, Allergan

Speaker Bureau for Teva and Eli Lilly

Outline

1. Recognize the global disability from migraine
2. Understand that migraine is a brain disorder
3. Learn about the current and future abortive treatments for Migraine headache
4. Recognize current and future preventative treatments for migraine

Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015

GBD 2015 Neurological Disorders Collaborator Group*

Lancet Neurol 2017; 16: 877–97

Summary

Background Comparable data on the global and country-specific burden of neurological disorders and their trends are

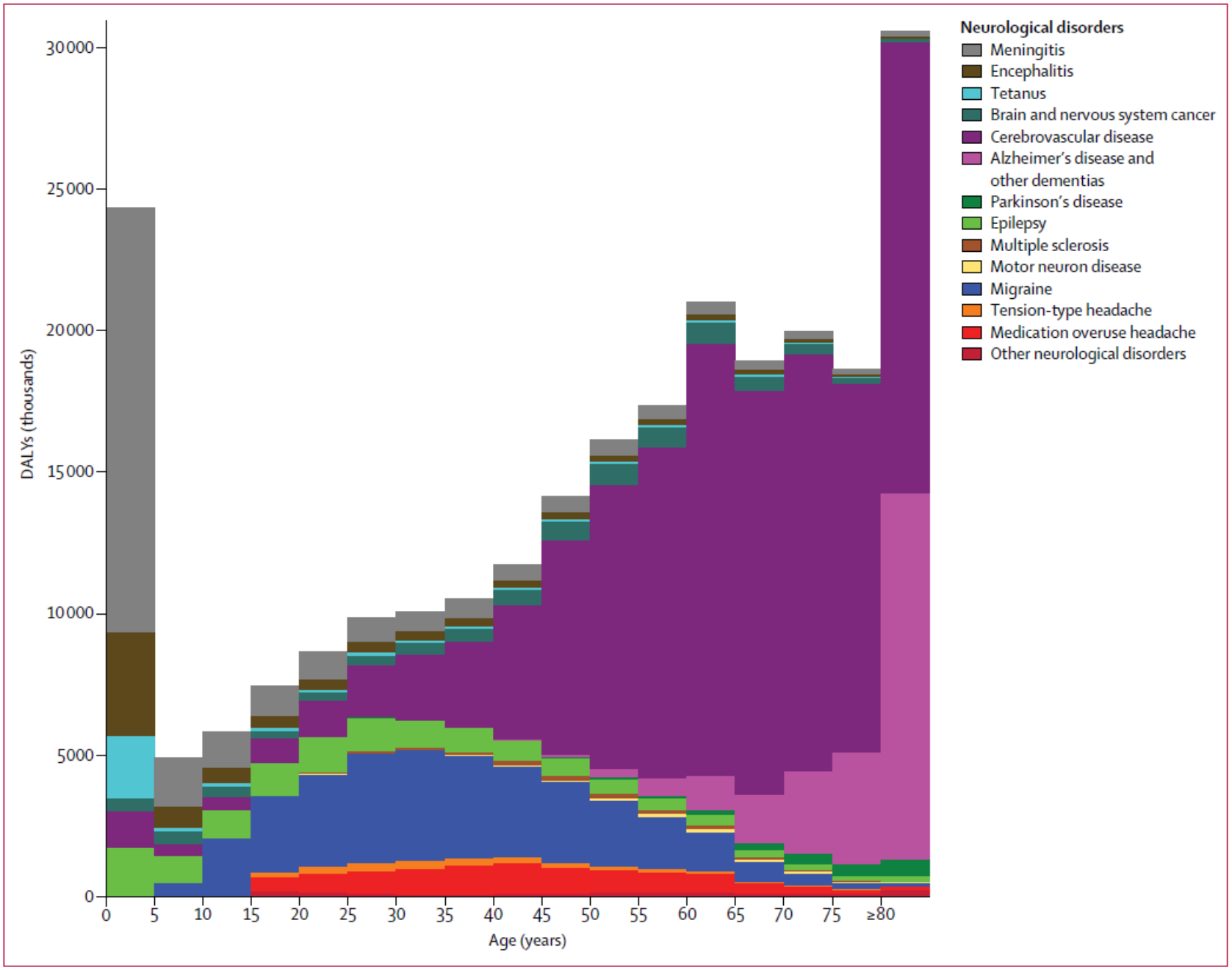
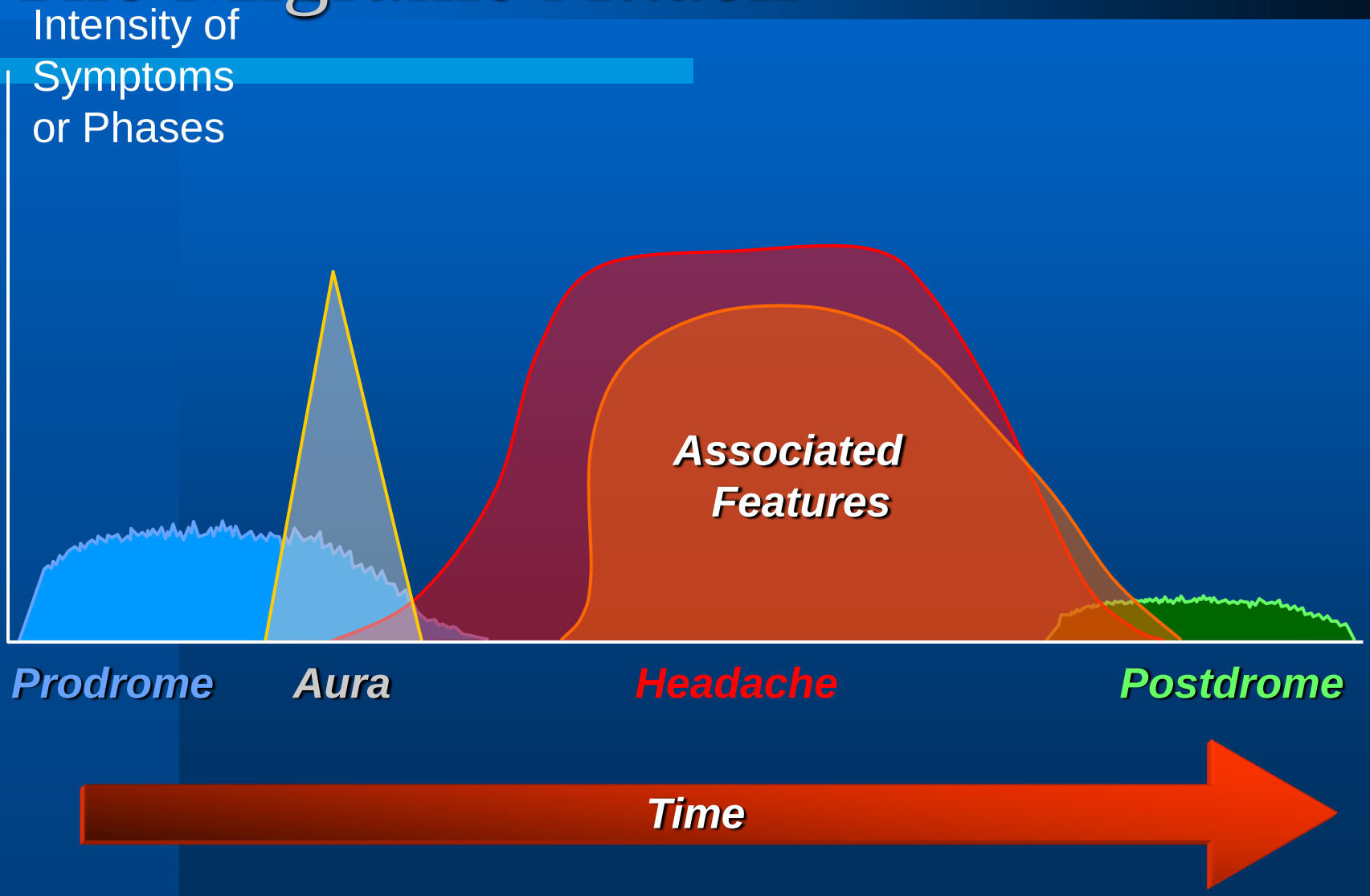


Figure 1: Global DALYs by age and neurological disorder in 2015
DALYs=disability-adjusted life-years.

The Migraine Attack



MIGRAINE

- Migraine in not “just a headache”.
- Migraine is an inherited neurological disorder characterized by an underlying state of increased responsiveness of cortical and subcortical networks that amplify the intensity of sensory stimuli.
- It is a “syndrome” characterized by disturbances of sensory function, affect, cognitive and autonomic function.

Why is Migraine a brain disorder?

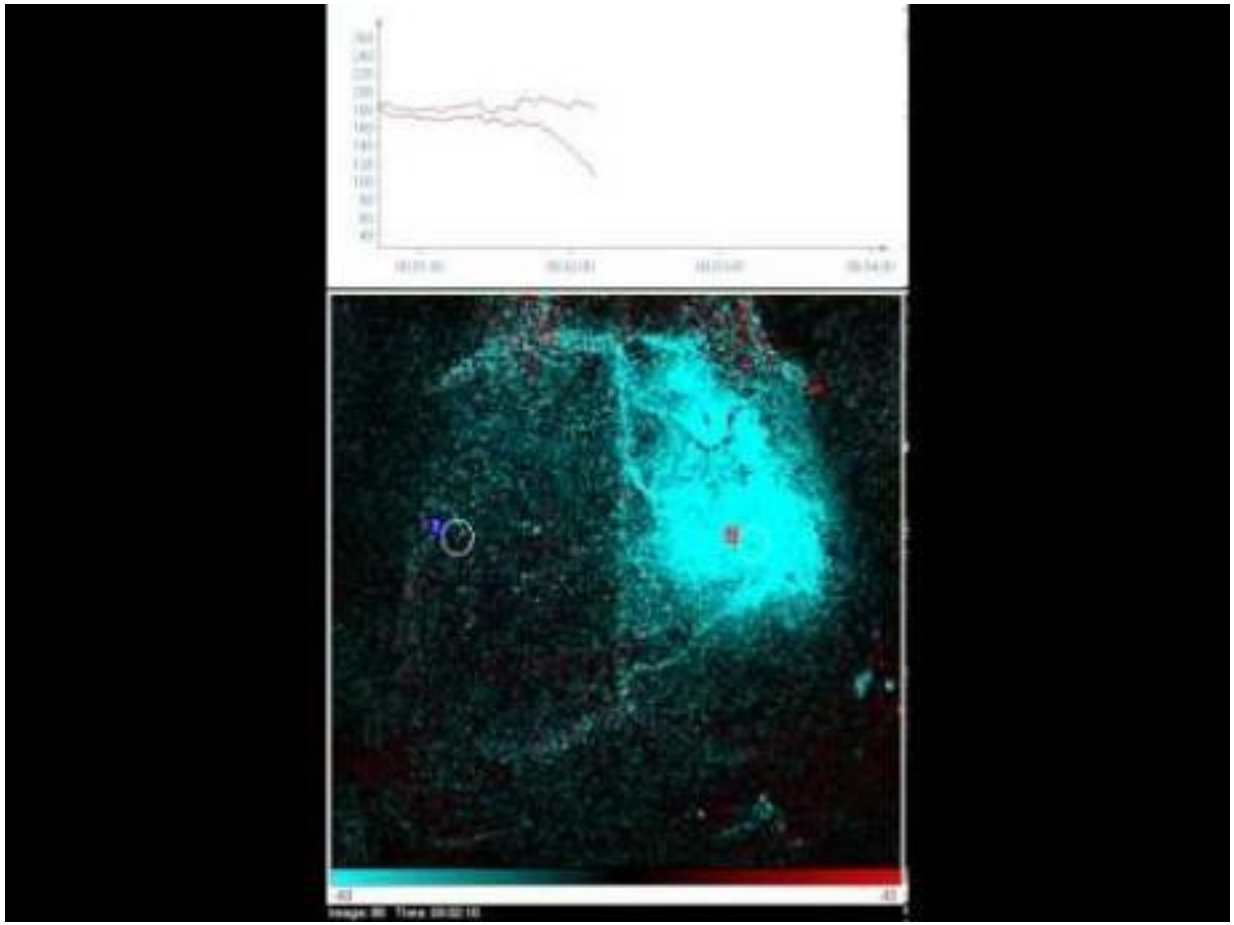
Neurovascular

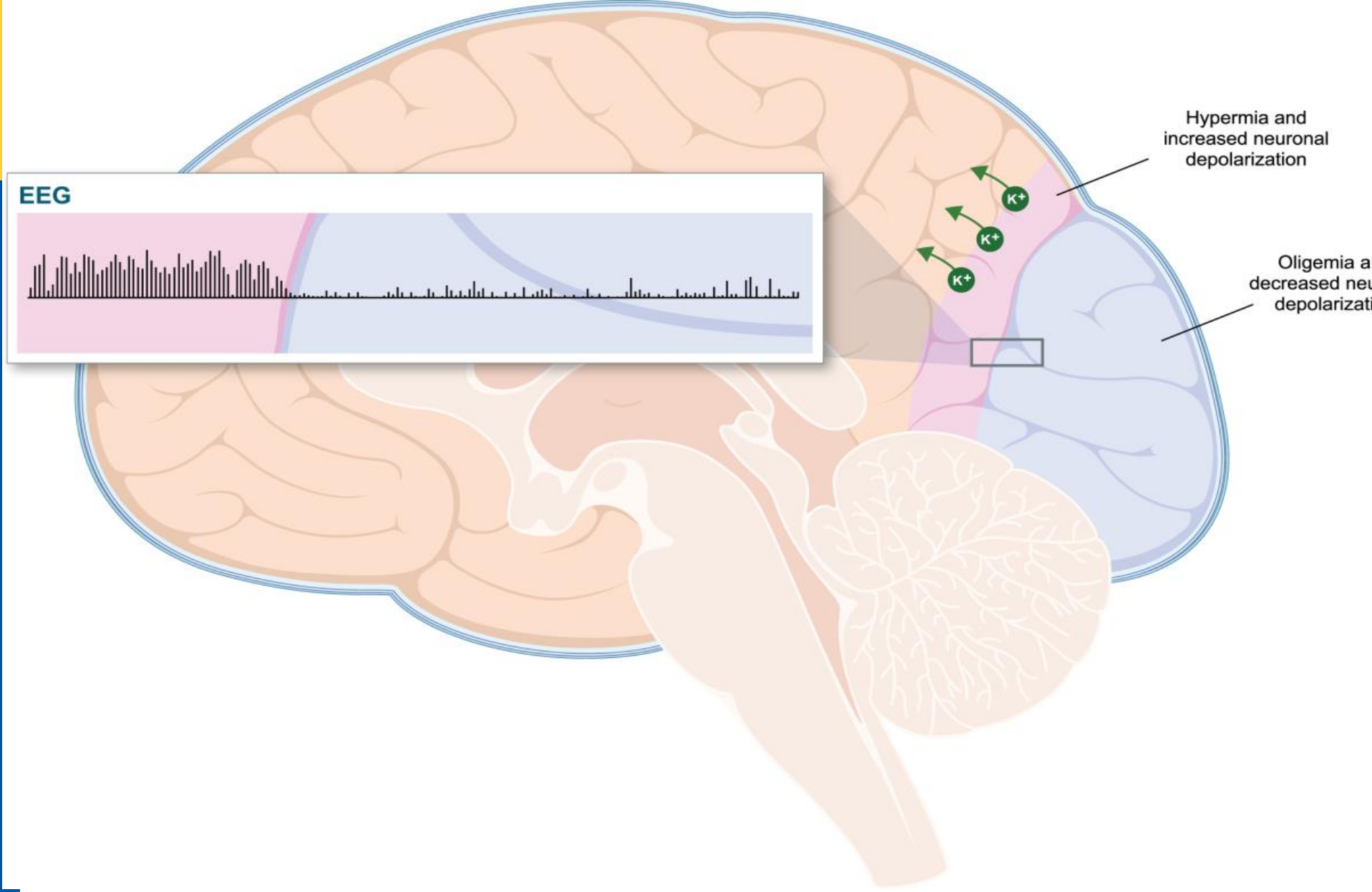
Neuronal hyperexcitability, esp. occipital cortex…

…makes brain susceptible to migraine attacks

MIGRAINE Aura……

- ……is an electrical event in the brain
- This event is called *Cortical spreading depression ; a* wave that spreads at the rate of 2-6 mm/min on the surface of the brain
- There is change in chemical flow within the neurons---resulting in changes in electrical signaling---which leads to change in local blood flow.

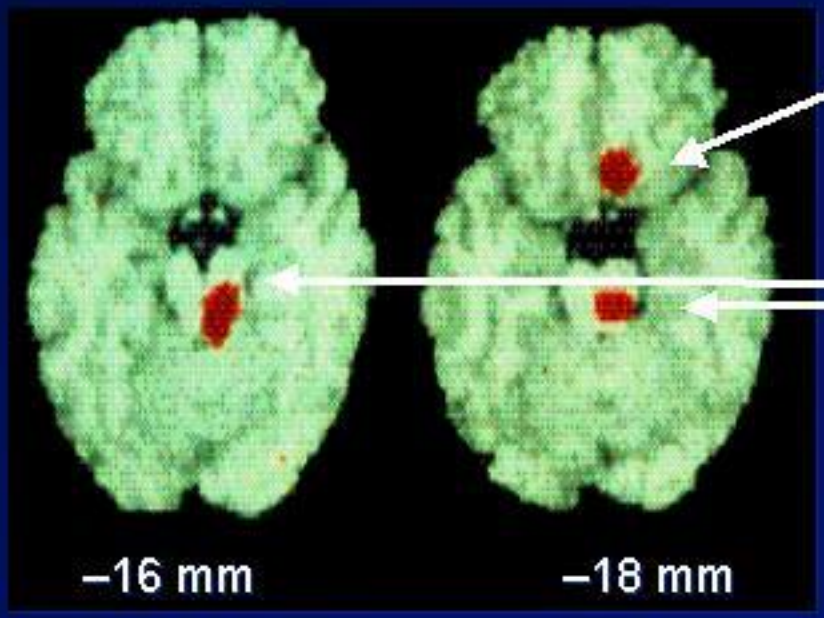




Headache: The Journal of Head and Face Pain, Volume: 58, Issue: S1, Pages: 4-16, First published: 26 April 2018, DOI: (10.1111/head.13300)

CNS Activation During Migraine

Dysfunction of brain stem pain and vascular control centers



Pain Perception*

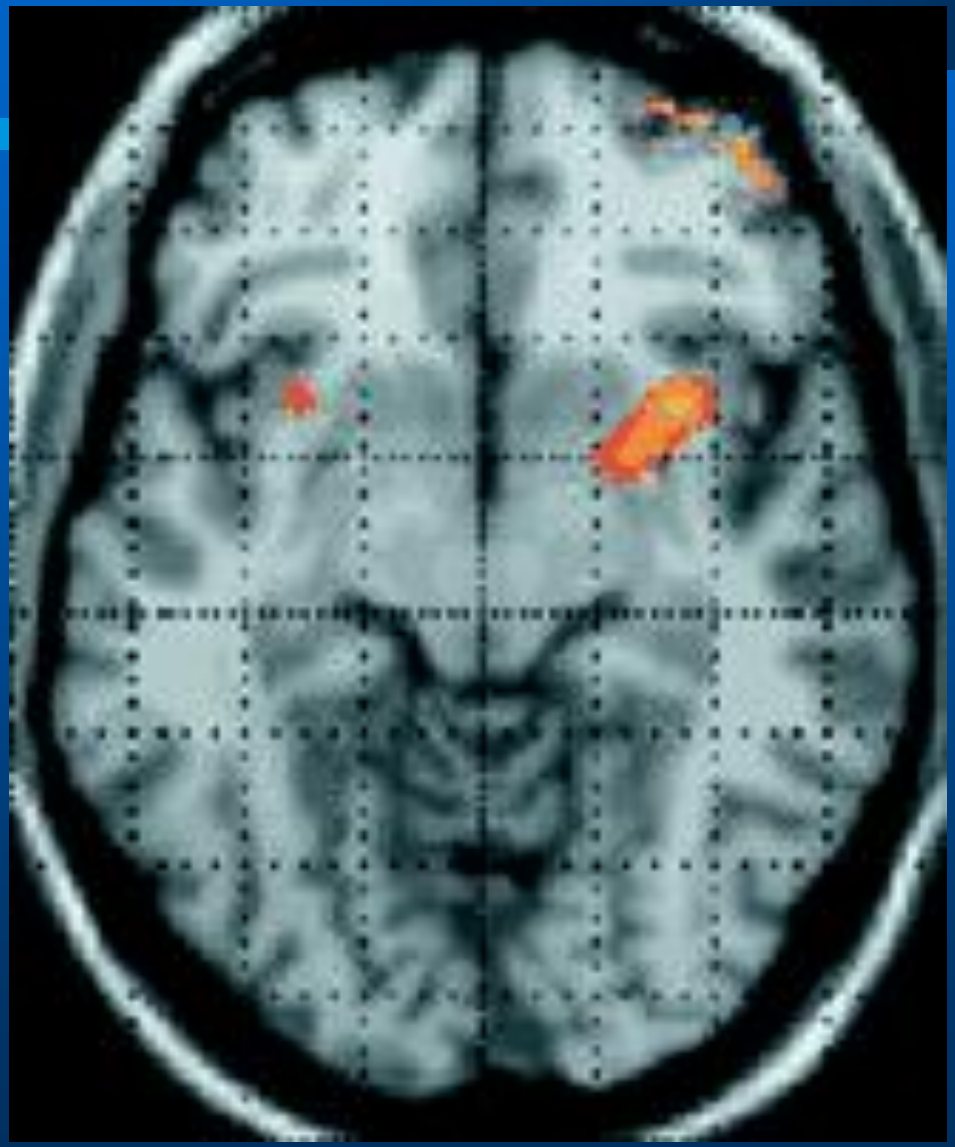
- Anterior cingulate corte

"Migraine Generator"*

- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

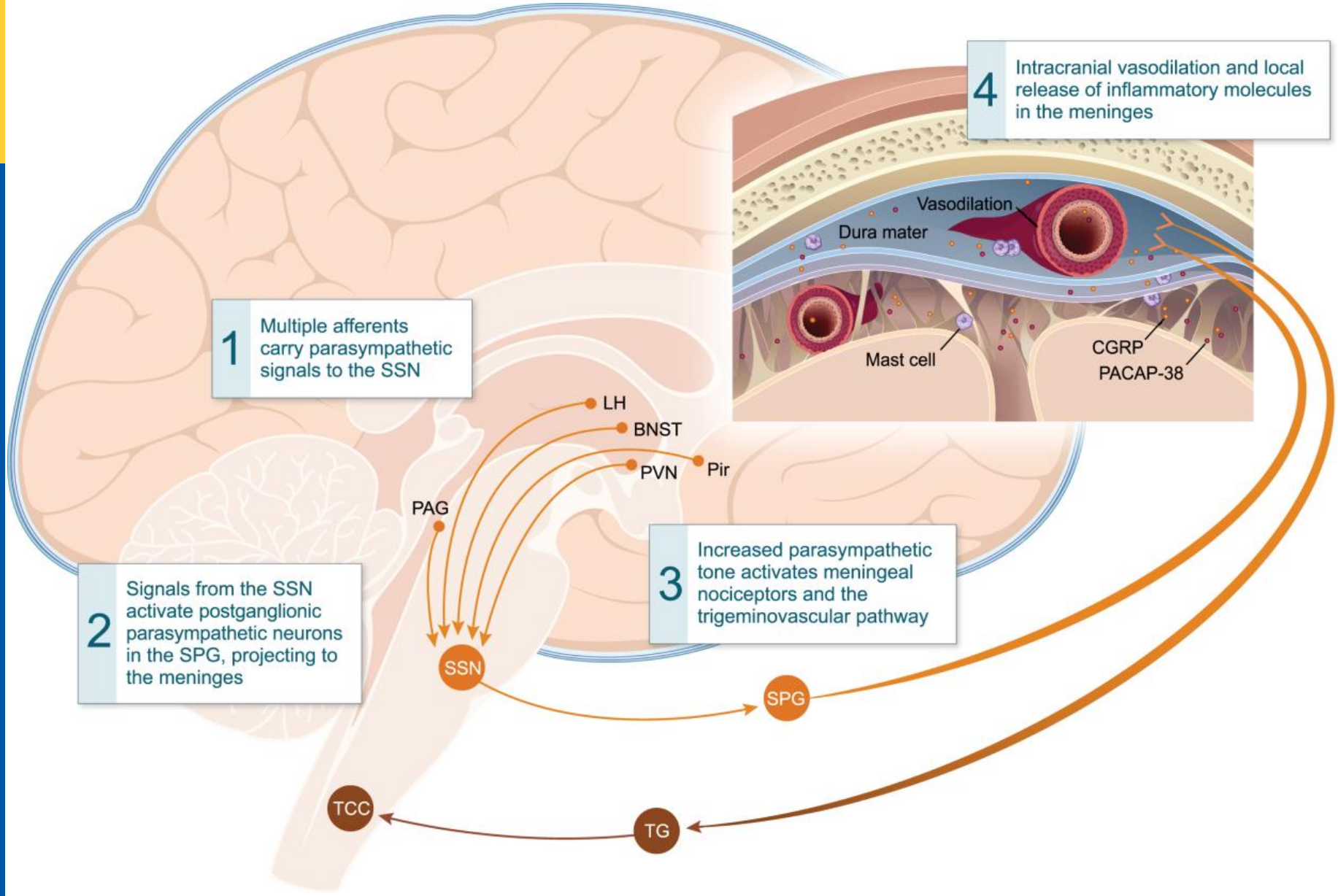
*Areas of red indicate cerebral blood flow increases ($P < 0.001$).
(Weiller et al. 1995)

PET scan in experimentally induced pain



Phase 1: prior to migraine attack

- Upto 3 days prior to migraine
- Fatigue, mood changes, food cravings, yawning, muscle tenderness.
- Points to involvement of Hypothalamus as a potential origin of migraine attack.
- Other areas of activation include brainstem, limbic(emotional) system and cortical (executive, speech, language) areas.



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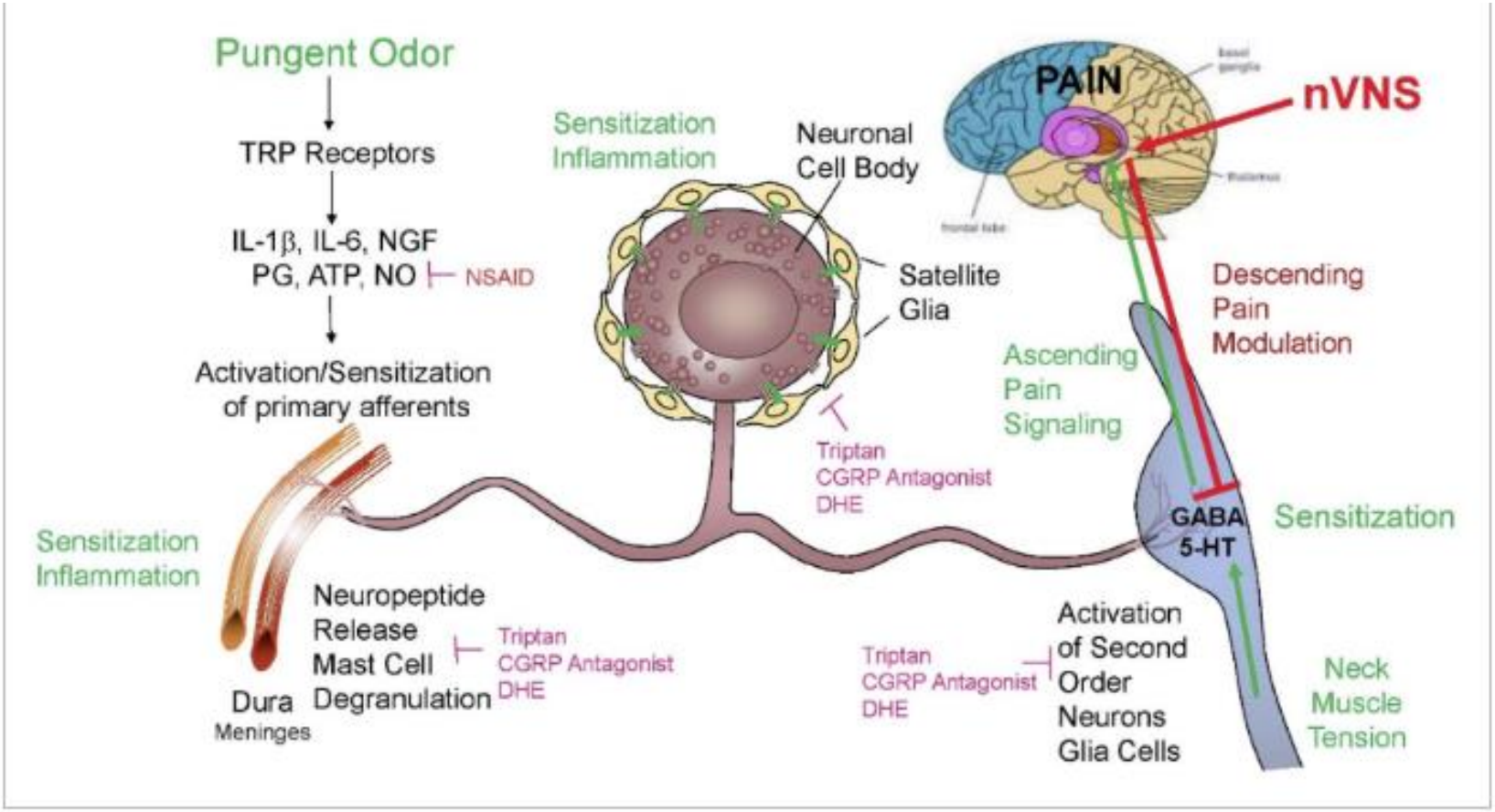
Multiple mechanisms of Migraine:
Many pathways/receptors and chemicals



Migraine headaches: Acute abortive treatment

Which is the best treatment to stop an acute migraine attack ?

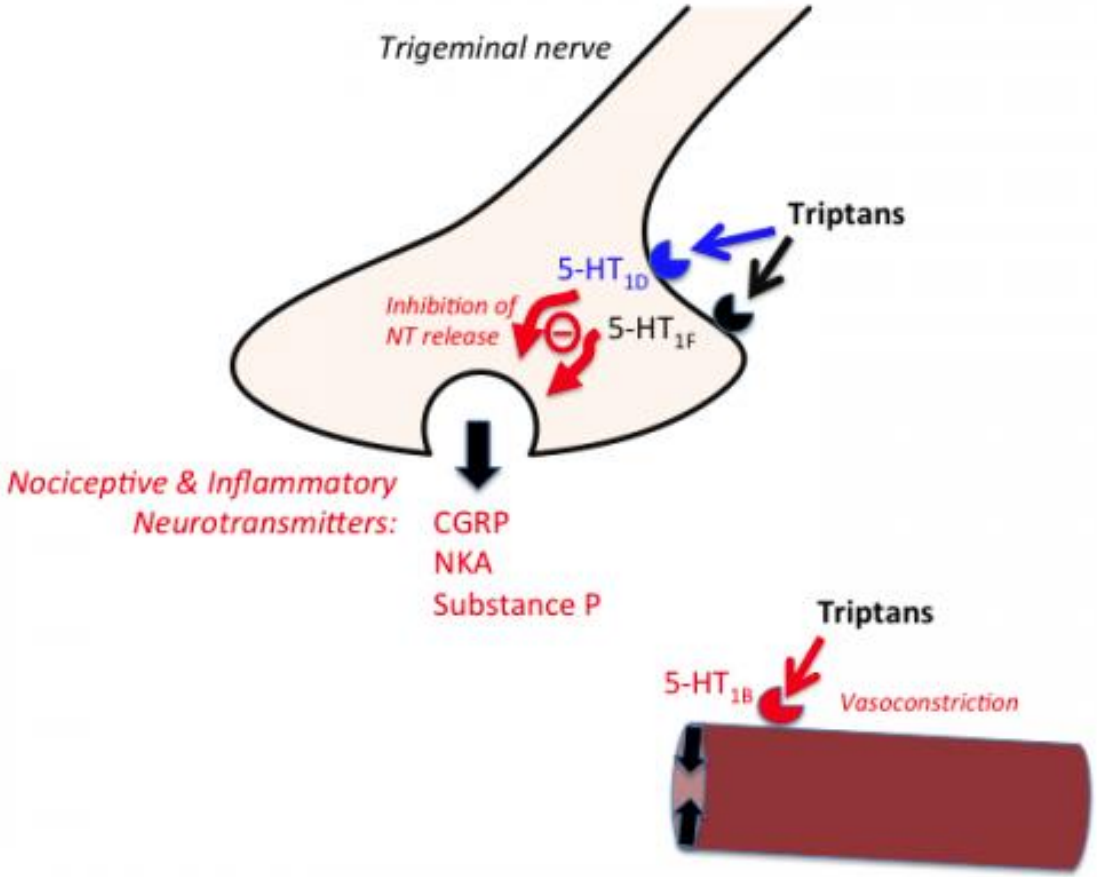
1. to decrease pain intensity by 50% or more
2. to stop or decrease nausea/vomiting
3. to stop or decrease other symptoms
   (light or noise sensitivity)

Migraine headaches: Acute abortive treatment

Acute/Abortive Examples

NSAIDs/ Analgesics	Ergot Alkaloid Derivative	Triptans	Combination/Other	Calcitonin Gene-Related Peptide Antagonists (small molecules)
Acetaminophen	Ergotamine	Almotriptan	Acetaminophen/aspirin/caffeine	UBRELVY™
Aspirin	Dihydroergotamine (DHE)	Eletriptan	Butalbital/acetaminophen/caffeine	Nurtec™
Diclofenac		Frovatriptan	Butalbital/aspirin/caffeine	
Ibuprofen		Naratriptan	Butorphanol	
Naproxen		Rizatriptan	Ergotamine/caffeine	
		Sumatriptan	Sumatriptan/naproxen	
		Zolmitriptan		

Proposed Mechanisms for Triptan Effect on Migraine



Prophylactic Examples

Antidepressants	Antiepileptics/ Anticonvulsants	Beta-blockers	Calcium Channel Blockers	Angiotensin-Converting Enzyme (ACE) Inhibitors/ Angiotensin II Receptor Blockers (ARB)	Calcitonin Gene-Related Peptide Antagonists (mAbs)
Amitriptyline	Divalproex sodium	Atenolol	Diltiazem	Candesartan	Aimovig®
Citalopram	Gabapentin	Metoprolol	Nifedipine	Enalapril	Emgality®
Doxepin	Topiramate	Nadolol	Nimodipine	Irbesartan	Ajovy®
Fluoxetine	Valproic acid	Propranolol	Verapamil	Lisinopril	Vyepti™
Fluvoxamine		Timolol		Losartan	
Mirtazapine				Olmesartan	
Nortriptyline				Ramipril	
Paroxetine				Valsartan	
Protriptyline					
Sertraline					
Venlafaxine					

Preventative treatment

Neuronal membrane Stabilizers
Prevent spontaneous depolarization

Antiepileptics
Valproic Acid
Topiramate
Zonisamide
Lamotrigine
Antidepressants
Amitriptyline
Nortriptyline
SNRIs
Venlafaxine Wellbutrin
Muscle relaxants Tizanidine Baclofen

Antihypertensives
Beta-blockers: Propranolol Timolol
Calcium channel blockers
ACE inhibitors/ARBs
Botulinum toxin type A injection
CGRP MABs
Erenumab (Aimovig)
Fremanezumab (Ajovy)
Galcanezumab (Emgality)
Eptinezumab (V

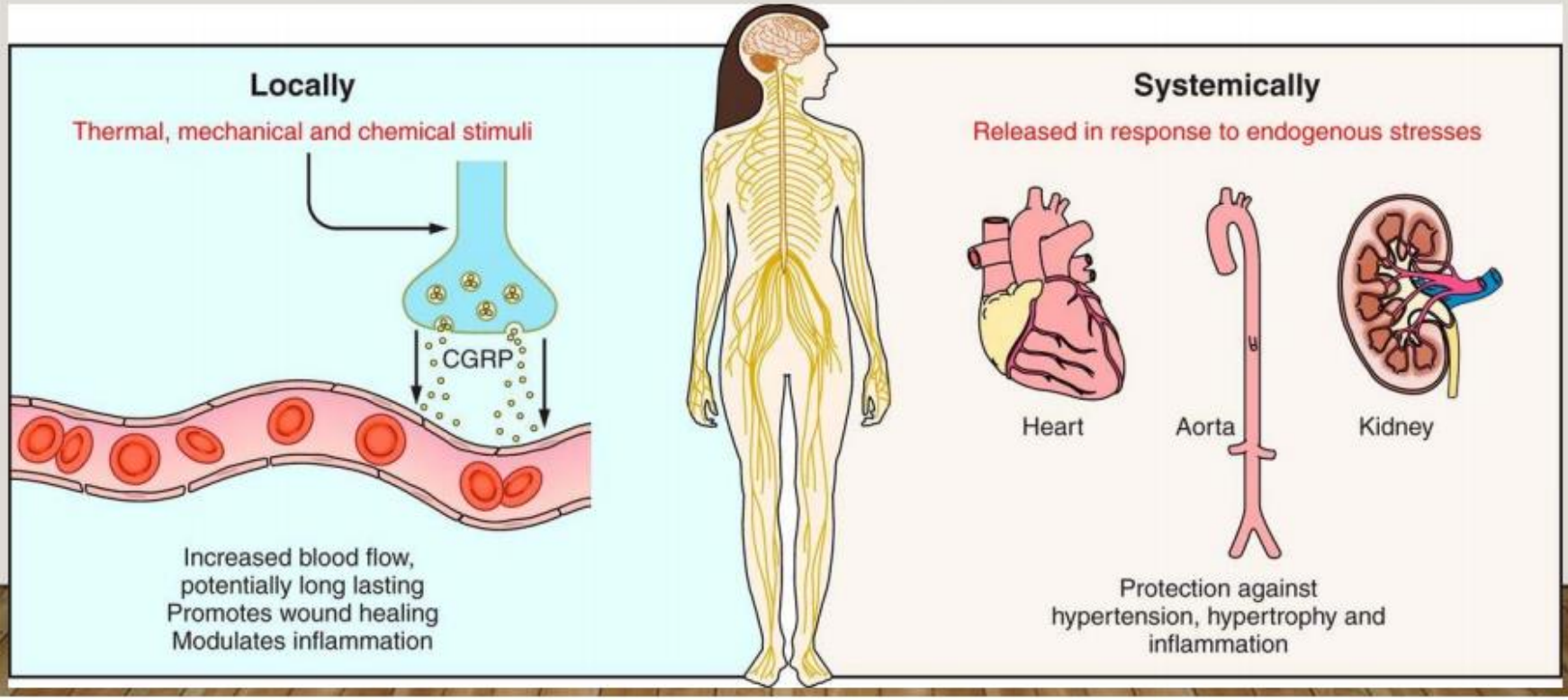
Preventative treatment

NEUTRACEUTICALS
ALTERNATIVE MED

MAGNESIUM
VITAMIN B2
COENZYME Q10
BUTTERBUR
FEVERFEW
MELATONIN
TURMERIC

YOGA
BIOFEEDBACK
ACUPUNCTURE
MEDITATION

CALCITONIN GENE-RELATED PEPTIDE (CGRP): EFFECTS ON THE BODY



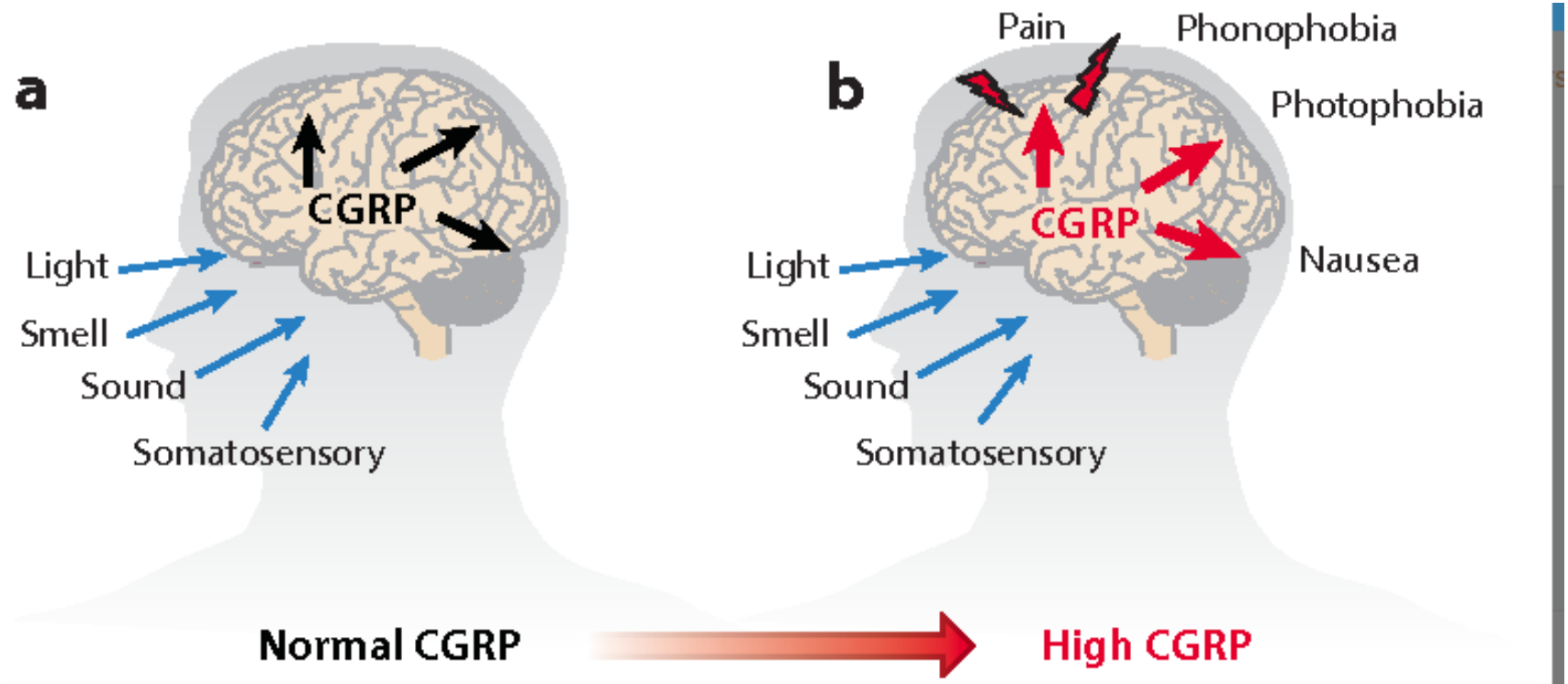


Figure 3

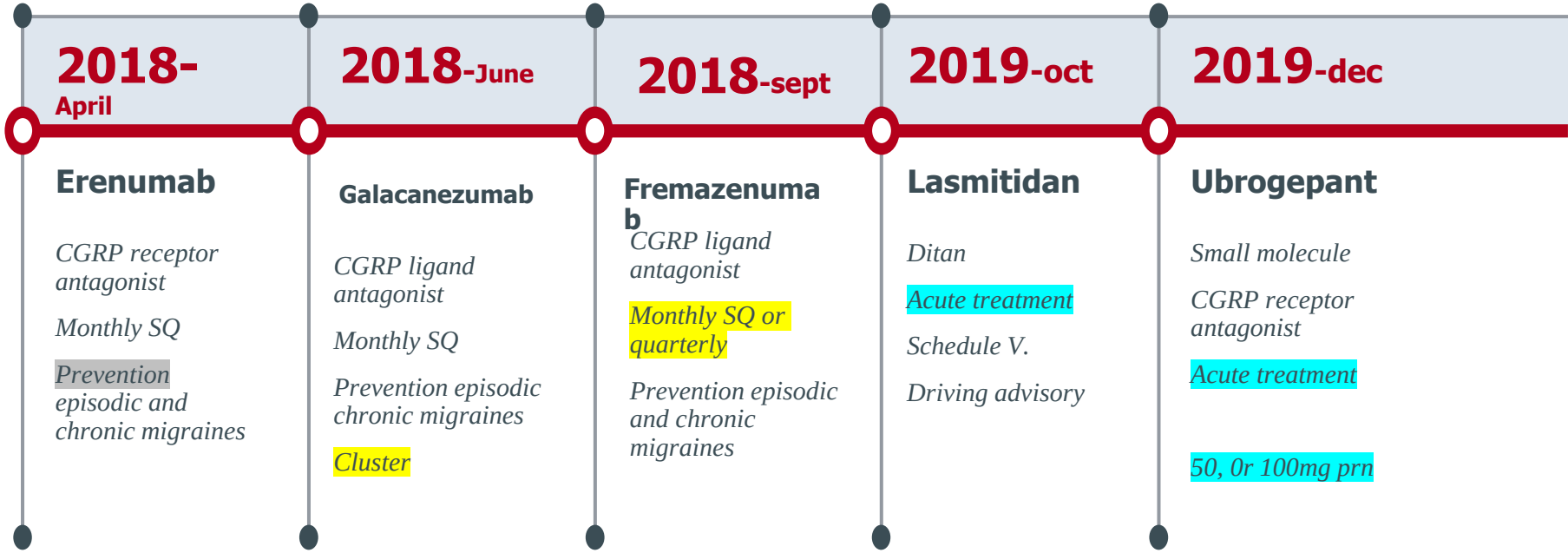
Published in Annual review of pharmacology and toxicology 2015

Calcitonin gene-related peptide (CGRP): a new target for migraine.

Andrew F Russo

Migraine bonanza

Timeline Tagline



Migraine bonanza

Timeline Tagline

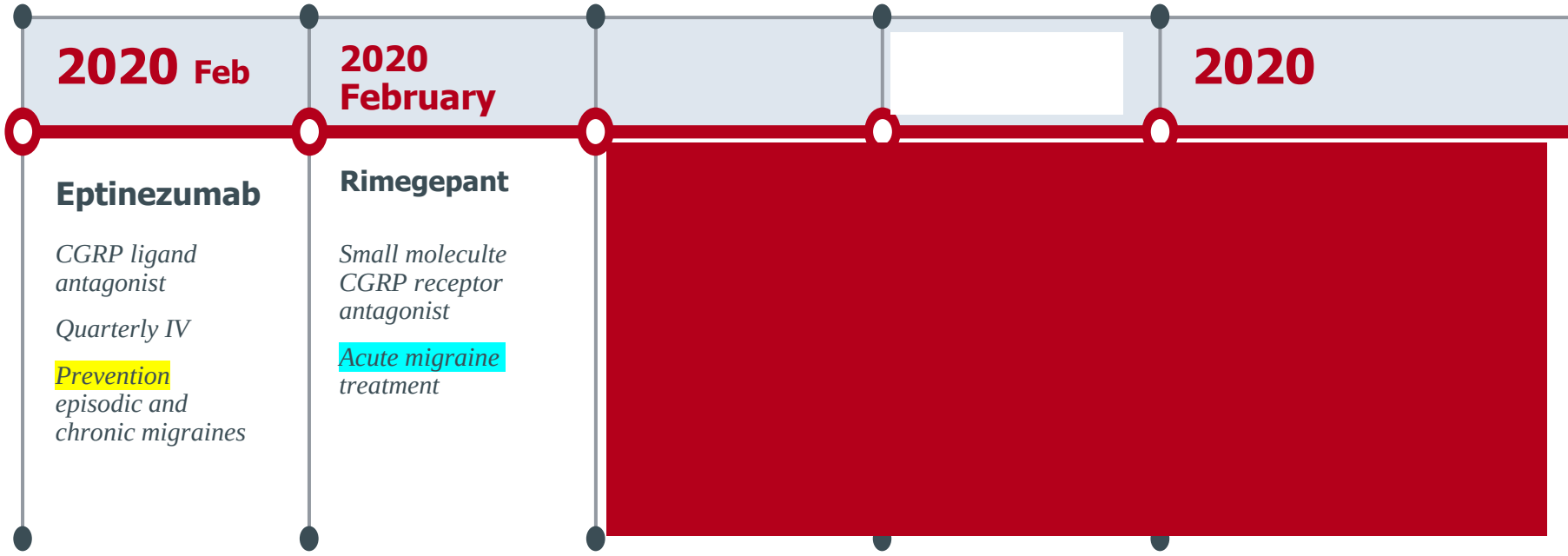
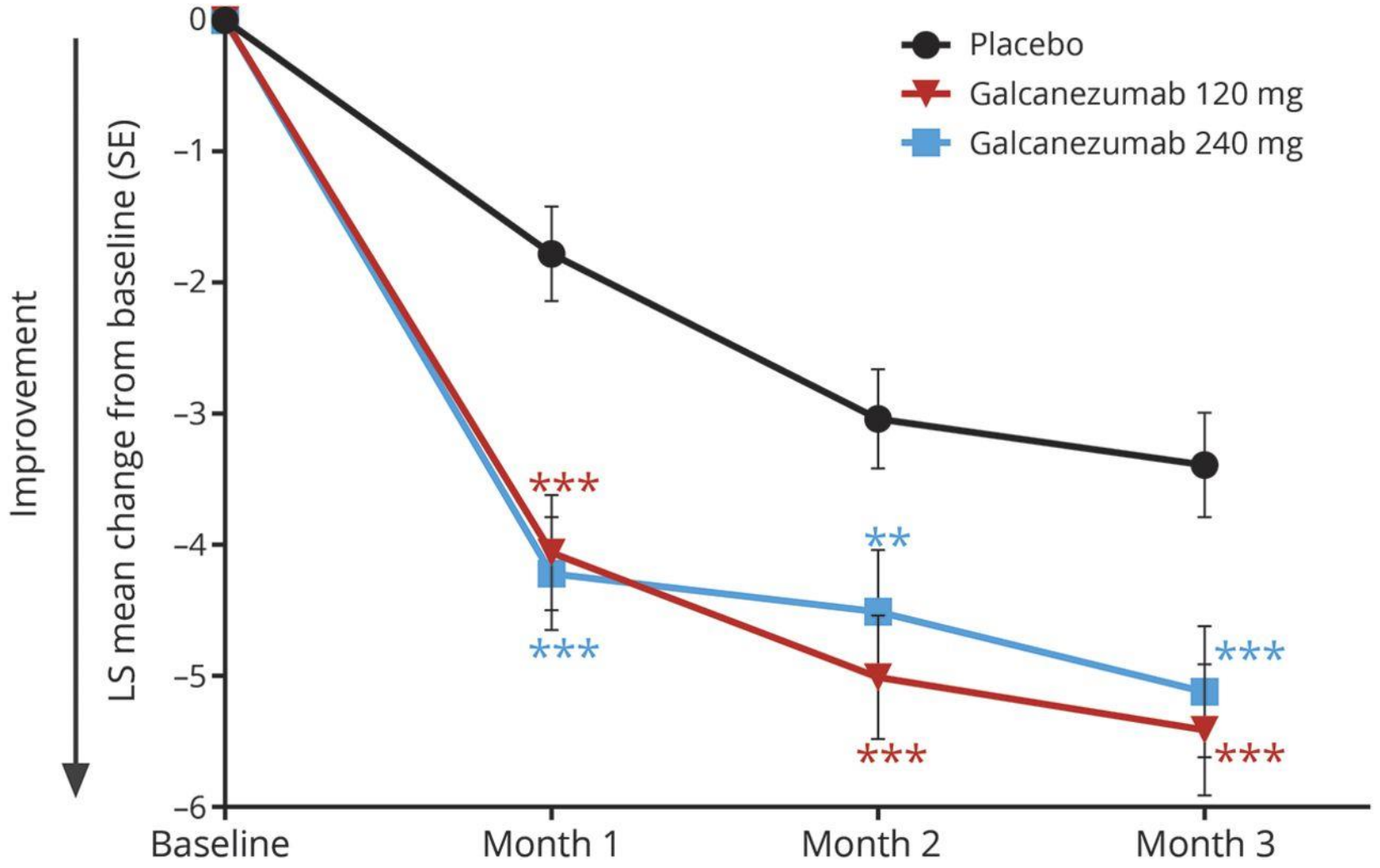


Table 1: Anti-CGRP Therapies for EPISODIC Migraine: Phase III Results

DRUG NAME	DOSING	FREQUENCY	TRIAL	COMMON SIDE EFFECTS
Erenumab (AMG 334)	Subcutaneous injection	Monthly	ARISE 70 mg STRIVE 70 mg 140 mg	• Runny/stuffy nose • Upper respiratory tract infection • Injection site pain
Galcanezumab (LY2951742)	Subcutaneous injection	Monthly	EVOLVE-1 120 mg 240 mg EVOLVE-2 120 mg 240 mg	• Injection-site reaction and pain • Upper respiratory tract infection • Abdominal pain
Fremanezumab (TEV-48125)	Subcutaneous injection	Monthly or quarterly	HALO EM 225 mg (monthly) 675 mg (quarterly)	• Injection site pain
Eptinezumab (ALD403)	Intravenous infusion	Every 12 weeks	PROMISE 1 100 mg	• Upper respiratory tract infection • Urinary tract infection

Figure 3 Reduction in MHDs at each month



Holland C. Detke et al. Neurology 2018;91:e2211-e2221

AMERICAN ACADEMY OF NEUROLOGY

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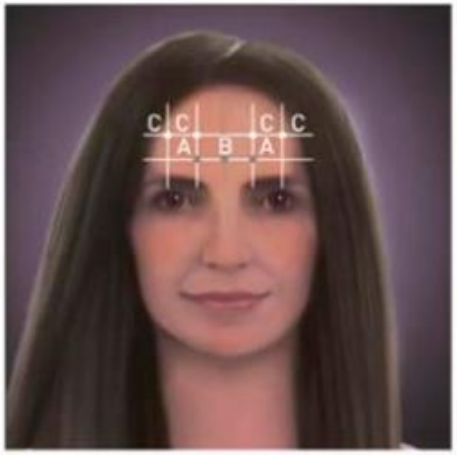
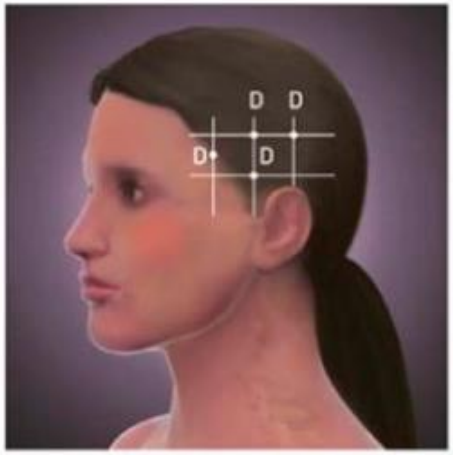


A. Corrugator
5 U each side

B. Procerus
5 U (one site)

C. Frontalis
10 U each side



D. Temporalis
20 U each side

E. Occipitalis
15 U each side

F. Cervical paraspinal
10 U each side

G. Trapezius
15 U each side

Headache Currents

Multidisciplinary Team Treatment Approaches to Chronic Daily Headaches

Soma Sahai-Srivastava, MD; Erica Sigman, DPT; Ashley Uyeshiro Simon, OTD, OTR/L, MSCS; Lyssa Cleary, DPT; Lori Ginoza, DPT

Table 2.—Topics That Occupational Therapists Can Address on an Interdisciplinary or Multi

Headache self-management	Logs, journals, increasing patient self-efficacy[a,b,c]
Exercise routines	Frequency, type, and duration of exercise[p]
Eating routines	Regularity, blood sugar management, dietary H/A
Sleep routines	Regularity, quantity, and quality; sleep hygiene; hea
Stress management	Stressor identification and remediation, coping stra
Medication management	Medication overuse headache prevention, complian
Weight management	Weight loss or weight gain
Ergonomics	Limit physical or environmental triggers, prescribe schedules[k]
Body mechanics	Posture, proper mechanics for activities[l,m]
Activity pacing & energy conservation	Taking breaks, preventing flare-ups[n,o]
Lifestyle balance	Preventing overexertion throughout the day/week[n]
Cognition	Memory, concentration, focus[n,p]
Communication	Assertiveness, communication strategies[n,p]
Community integration	Minimize triggers in the community, socialization,

Ashley Uyeshiro Simon, OTD, OTR/L & Lindsey Reeves, OTD, OTR/L

Outcomes of the program development study for quality improvement:

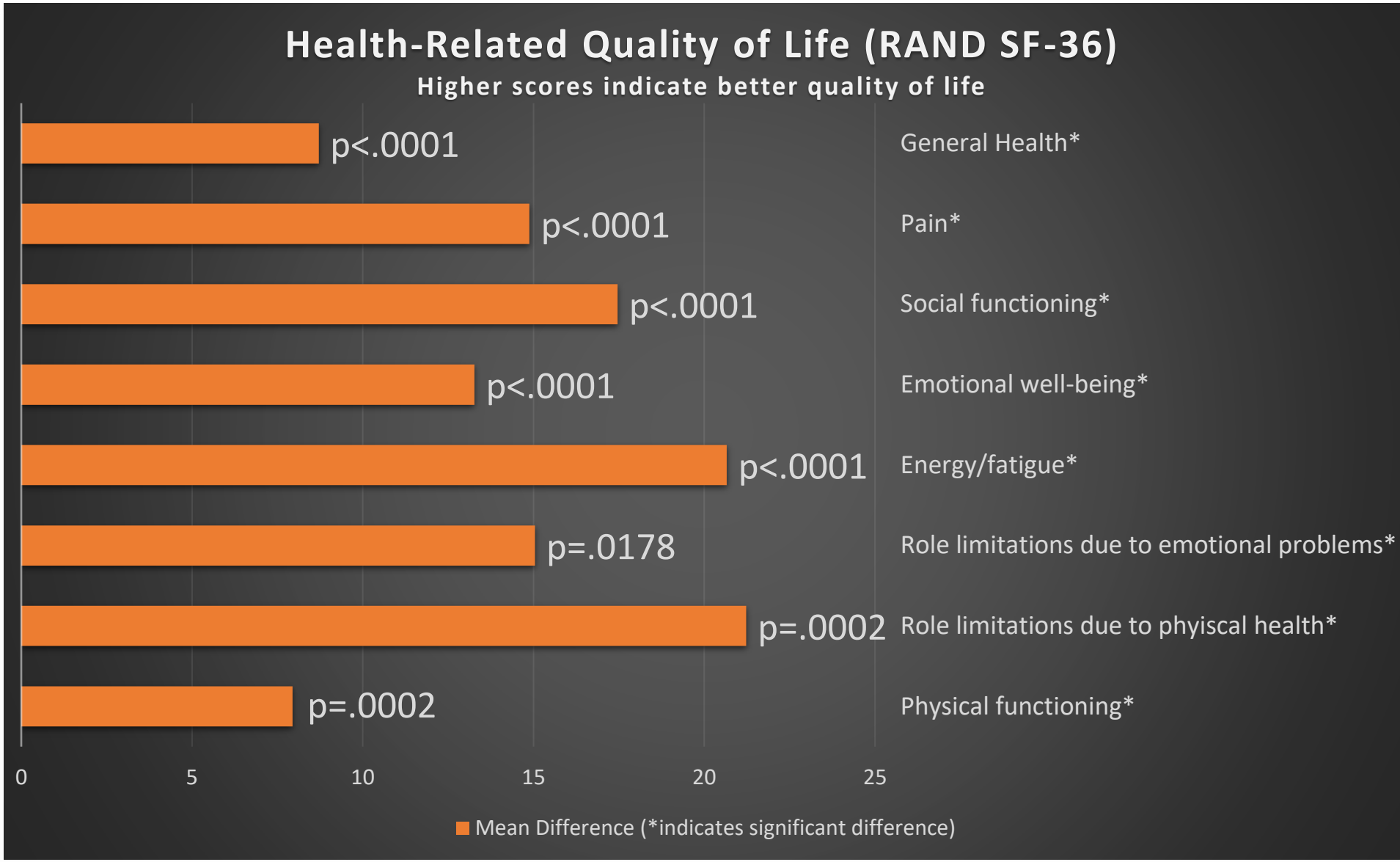
N= 322 patients

Completers = 157 patients (met the inclusion criteria of completing 4 or more OT sessions.

Non- completers= 165 did not meet this criteria ("non-completers").

average number of sessions attended 4.95

Figures 4-9: Outcome Measure Results



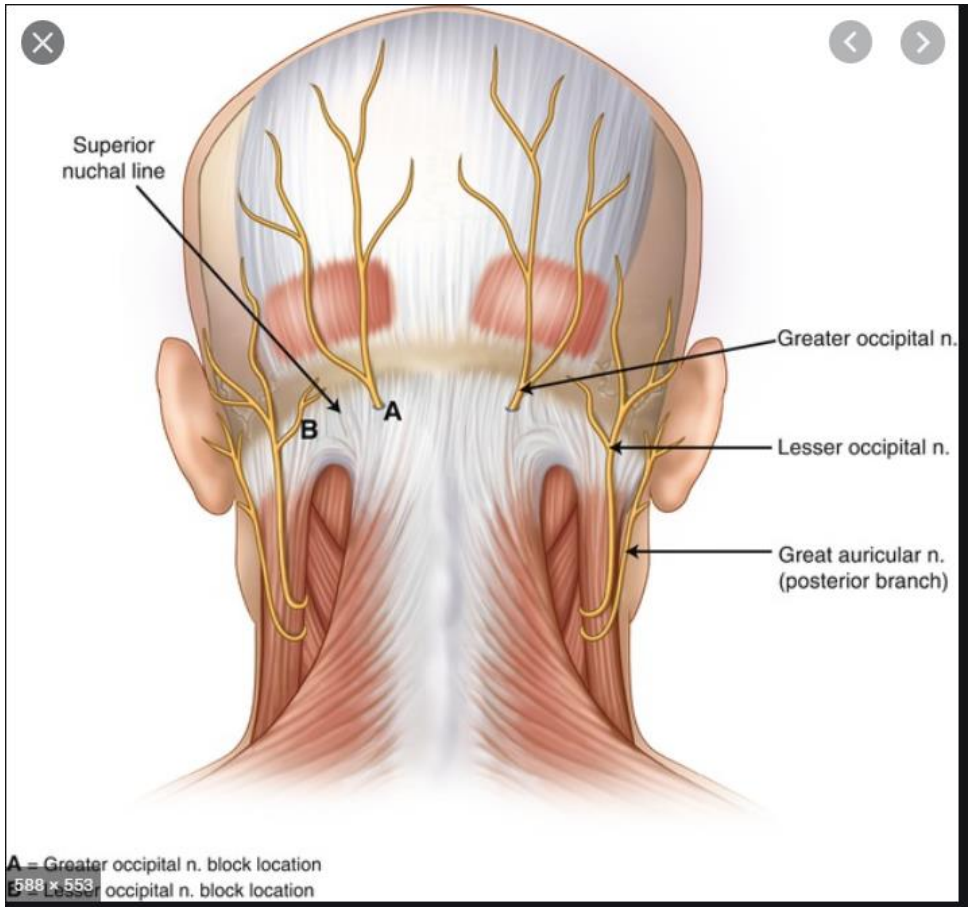
Physical Therapy Treatment

- Ergonomics and postural education
- Patient education
  - Strategies to manage musculoskeletal triggers
  - Strategies to modify response to headaches/pain
  - Sleep hygiene (sleep positions)

- Exercises to improve:
  - Muscle strength and endurance
    - Cervical muscles, scapula-thoracic muscles, abdominal muscles
  - Muscle-length deficits
  - Cervical spine ROM
  - Thoracic mobility
  - Postural deficits
- Modalities
  - TENS, Laser light, ice pack, moist heat
- Manual therapy

Peripheral nerve blocks

- Novacaine
- Low risk, quick, high yield
- Success depends on experience of injector
- Lasts 4-6 weeks



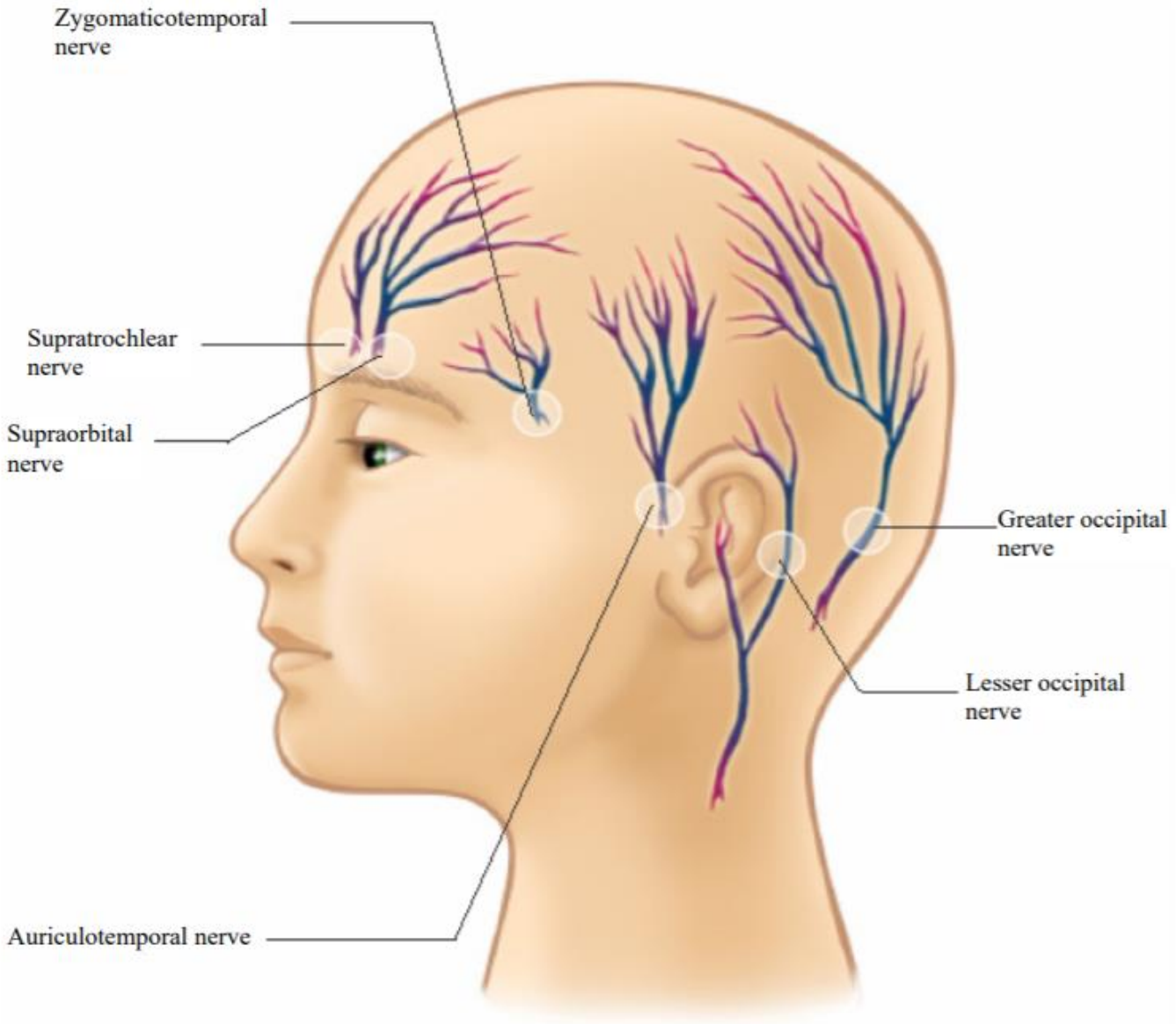


Figure 1. Schematic of scalp block nerves in a pediatric patient.

Nerivio

- Self-administration at home
- Battery powered, non-rechargeable
- Placed on upper arm and produces electrical signals to inhibit migraine pain
- An App is installed on a smartphone to control and monitor the treatment

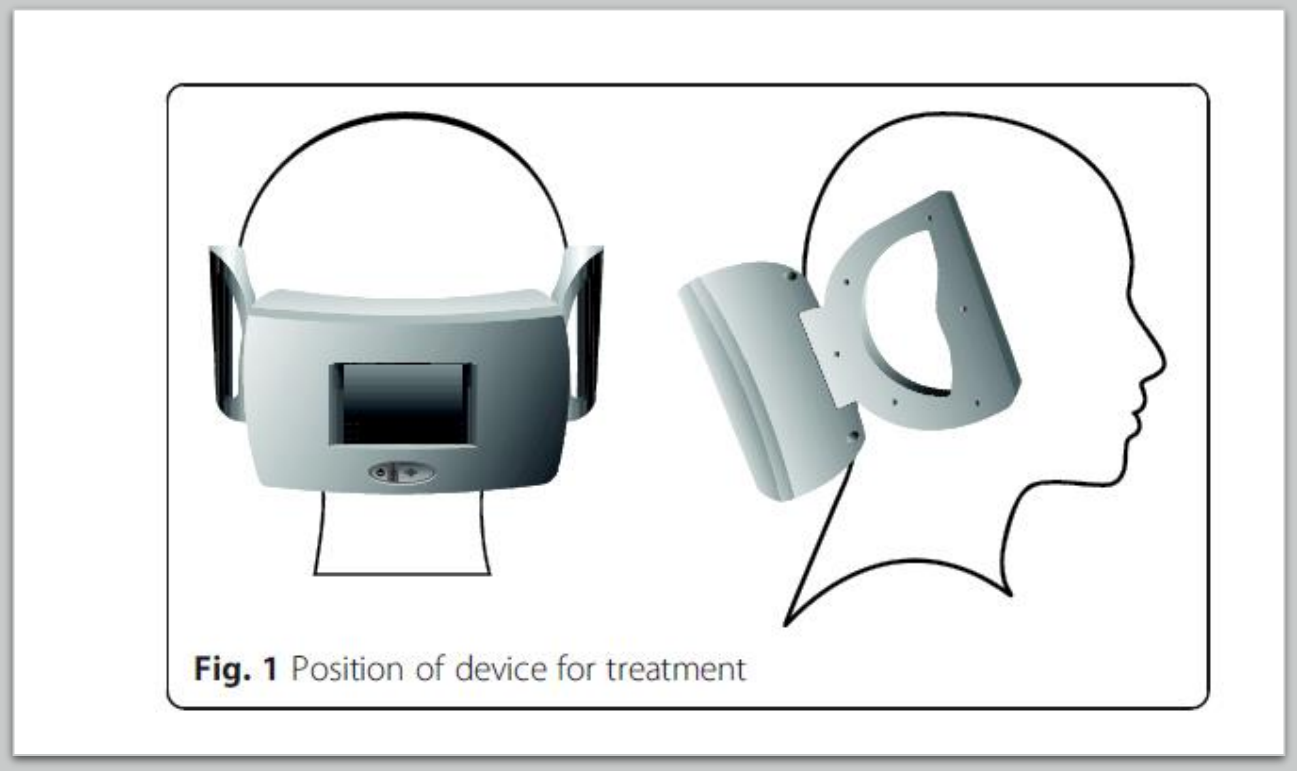
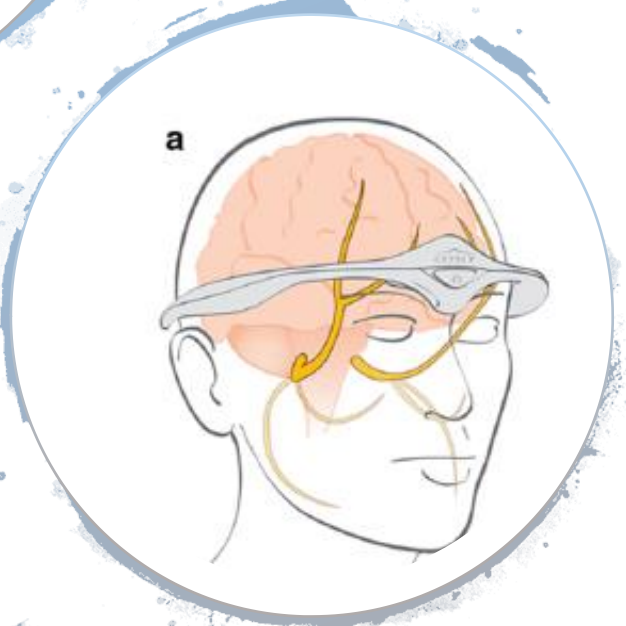


Fig. 1 Position of device for treatment

Refractory Headaches: innovative treatments

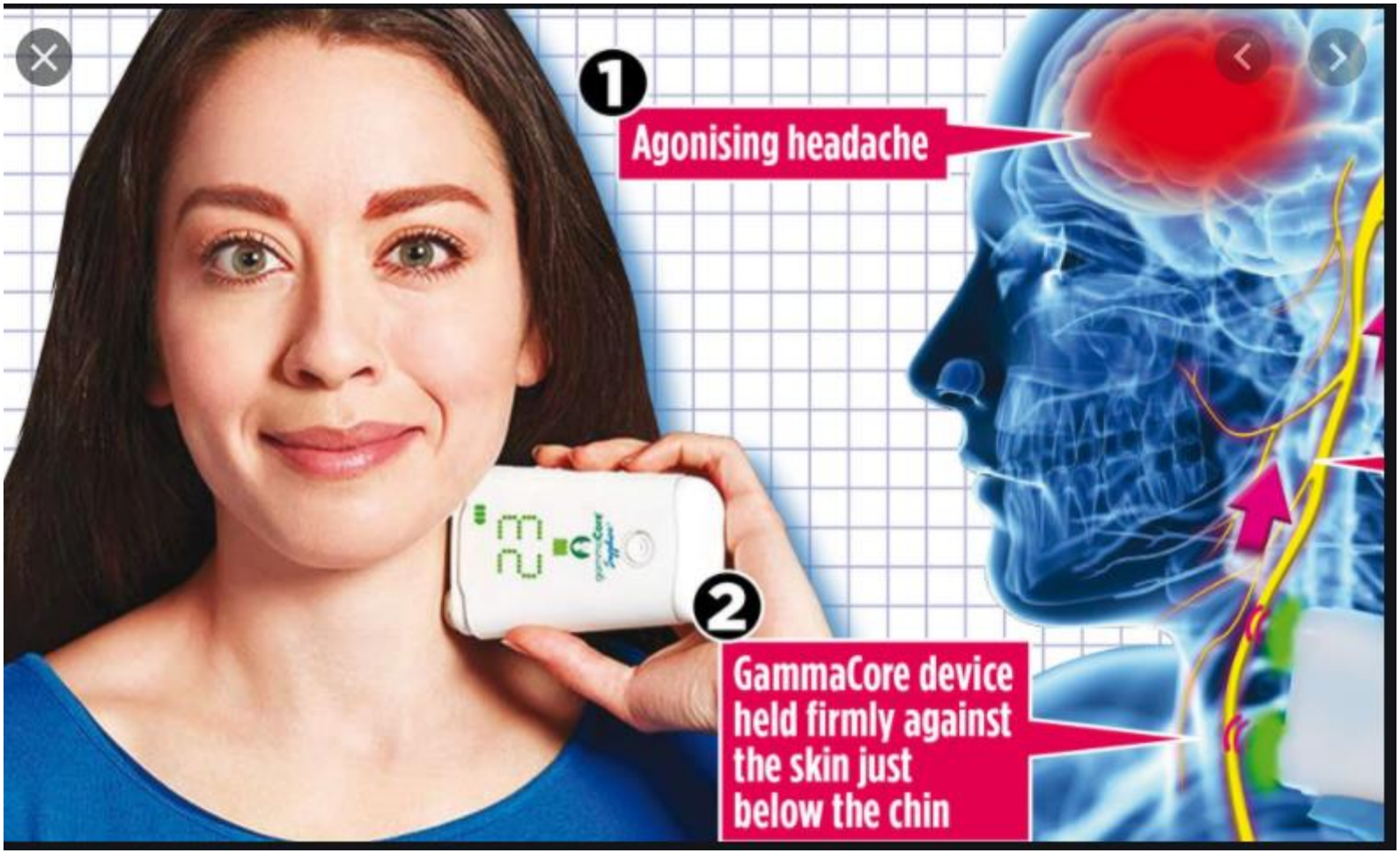
- Transcranial Magnetic stimulation

Refractory Headaches: innovative treatments



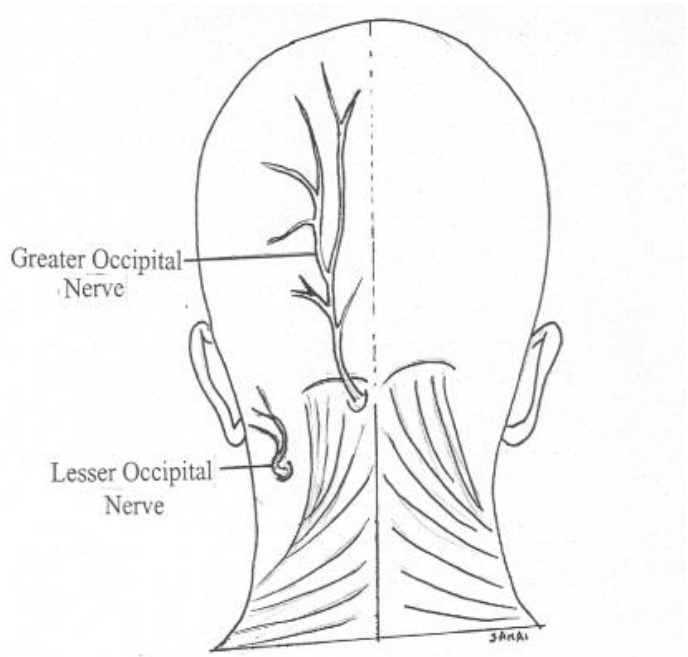
- Peripheral Neurostimulation nerve stimulators
- Cefaly acute, Cefaly prevent and Cefaly DUAL

Gammacore


1
Agonising headache
2
GammaCore device held firmly against the skin just below the chin

Refractory Headaches: innovative treatments

- Peripheral Neurostimulation implanted or percutaneous: Occipital, Supraorbital and Trigeminal nerve stimulators



Refractory Headaches: innovative treatments

- Sphenopalatine Ganglion blocks

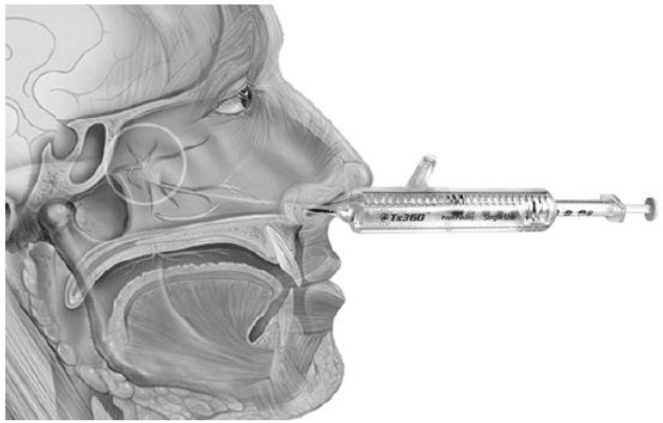


Figure 3. Illustration of Tx360 device anesthetizing the sphenopalatine ganglion.

Refractory Headaches: innovative treatments

- Radiofrequency ablation

Refractory Headaches: innovative treatments

- Occipital nerve decompression surgery

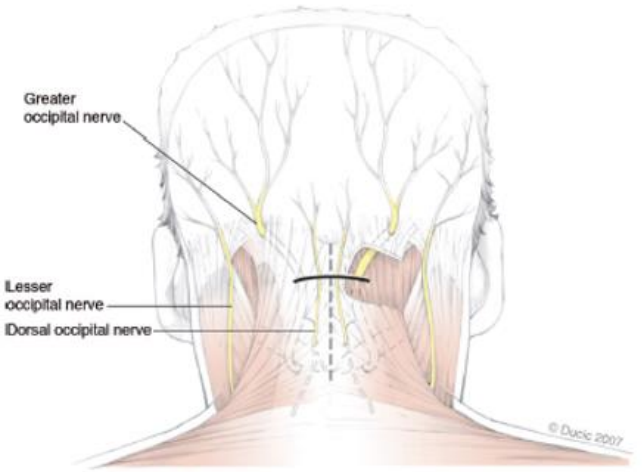


Fig. 1. Recommended incision to access bilateral greater occipital nerves.

Infusion or injections for migraine

Medication
MgSO4
Antinauseants
Steroids
DHE45
Depacon
Propofol
Lidocaine
Levetiracetam
Tramadol
Ketamine
Methocarbamol

SUMMARY

- EACH MIGRAINE IS AS DIFFERENT AS EACH INDIVIDUAL
- THERE IS NO ONE SIZE FITS ALL FOR MIGRAINE TREATMENT
- OFTEN A COMBINATION OF OPTIONS WORK FOR EACH
- FIND YOUR MIGRAINE VILLAGE
- DON’T GIVE UP

Keck Medicine
of USC

USC HEADACHE AND NEURALGIA CENTER

NEUROLOGY (Headache Division):

Soma Sahai, M.D (*Division Chief*)

Lauren Green D.O

Paul Henri Cesar, M.D.

Sandhya Ravikumar, M.D

Ana Gjurgevich, NP

Hawa Mapara, NP

Neuroradiology

Alex Lerner

PHYSICAL THERAPY

Lori Ginoza

Erica Sigman

Max Borroso

OCCUPATIONAL THERAPY

Lindsey Reeves

Malia Sako

PAIN MANAGEMENT

Steven Richeimer, M.D.

PAIN PSYCH0LOGY

Susan Axtell

Faye Weinstein

NEUROSURGERY

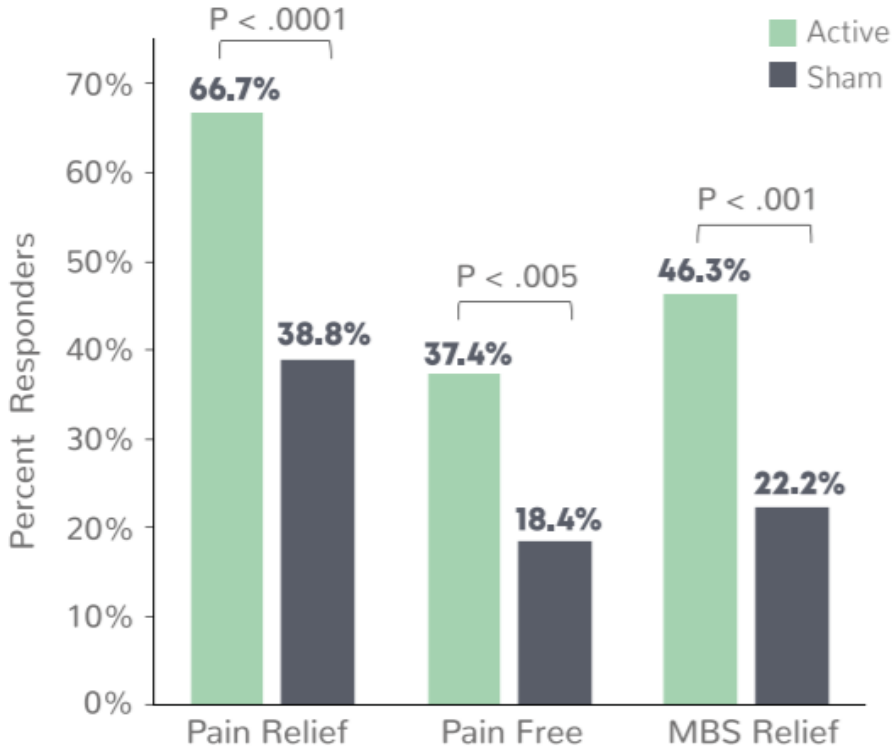
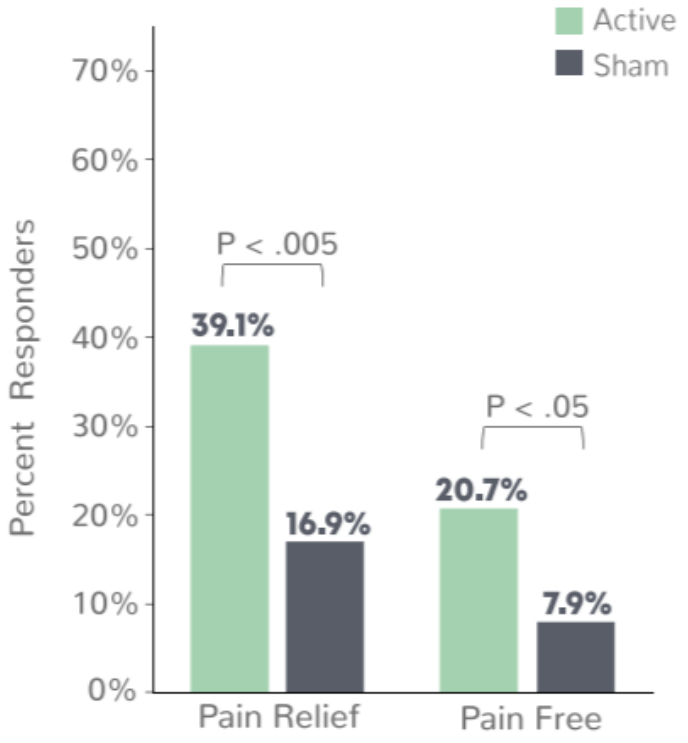
Steven Gioannata,M.D.

Darrin Lee, M.D.

Dawn Fishback , PA

A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (Zavegepant*) Intranasal (IN) for the Acute Treatment of Migraine

Response at 2 hours post-treatment



Sustained response at 48 hours post-treatment