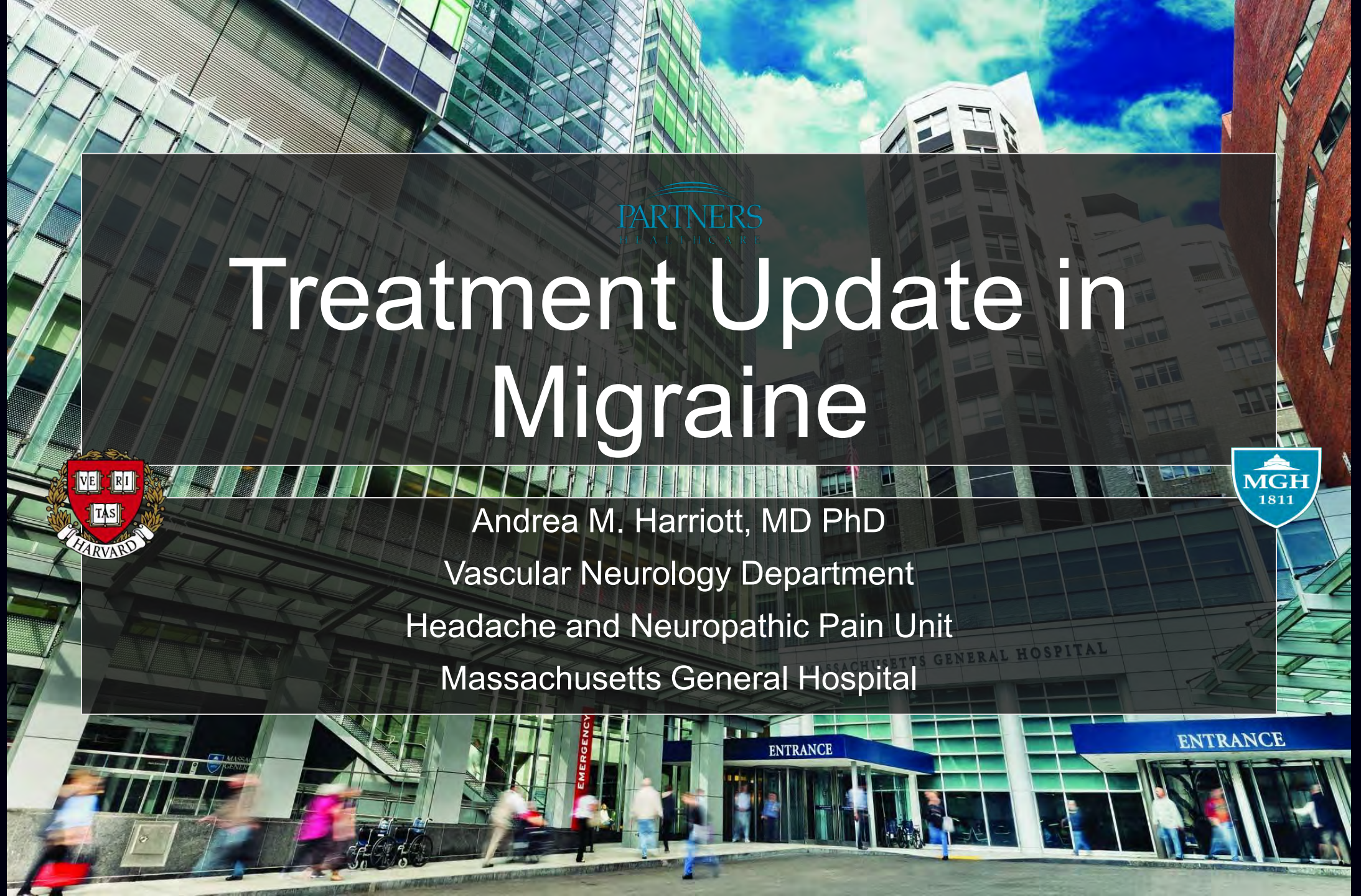

Treatment Update in Migraine

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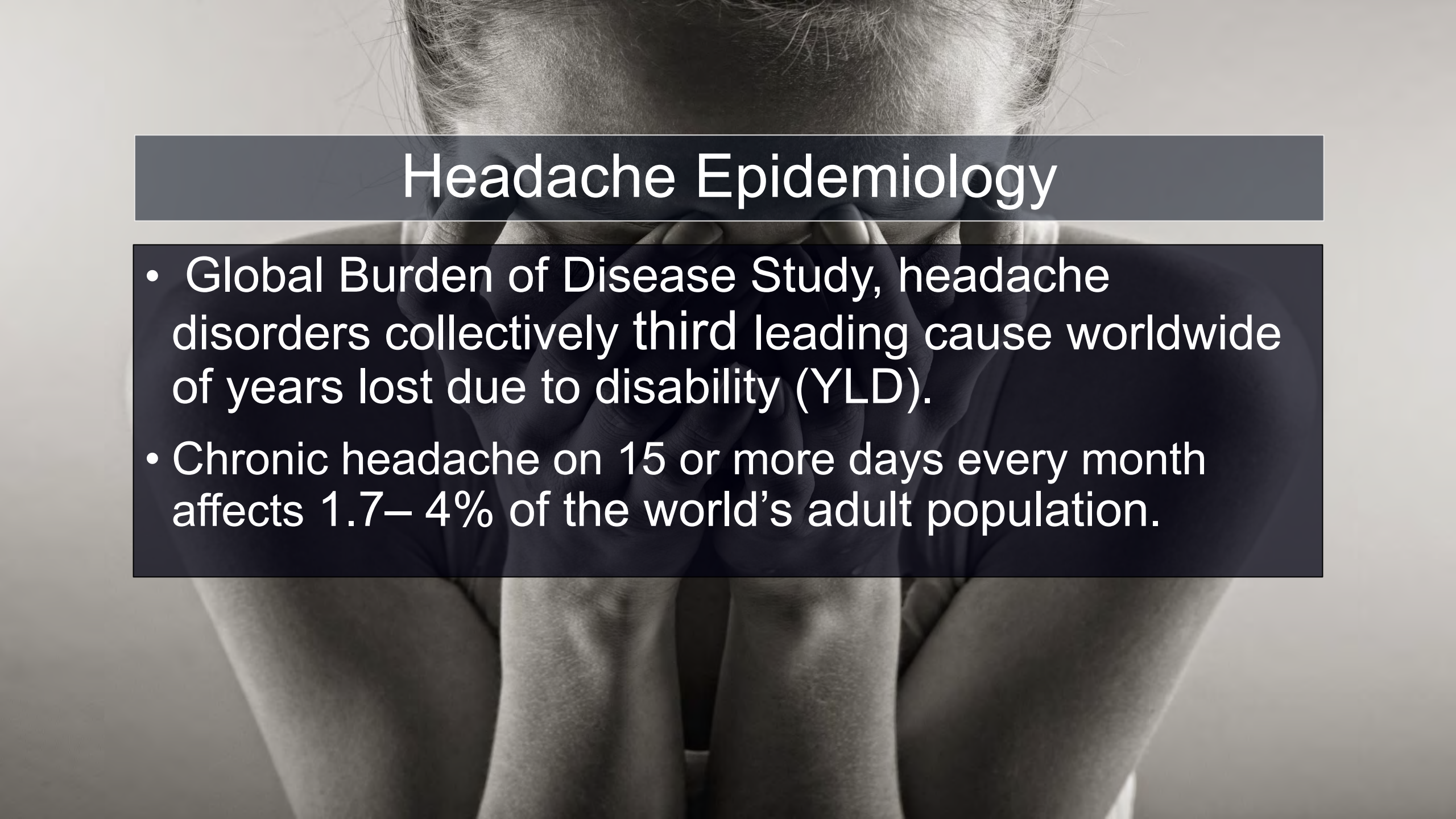
DISCLOSURES

I have no relevant financial relationships to disclose.

Objectives

- Basic approach to treatment
- Migraine abortive treatments
- Migraine preventive treatments
- The pipeline



Headache Epidemiology

- Global Burden of Disease Study, headache disorders collectively third leading cause worldwide of years lost due to disability (YLD).
- Chronic headache on 15 or more days every month affects 1.7– 4% of the world's adult population.

Introduction to Acute Migraine Treatments

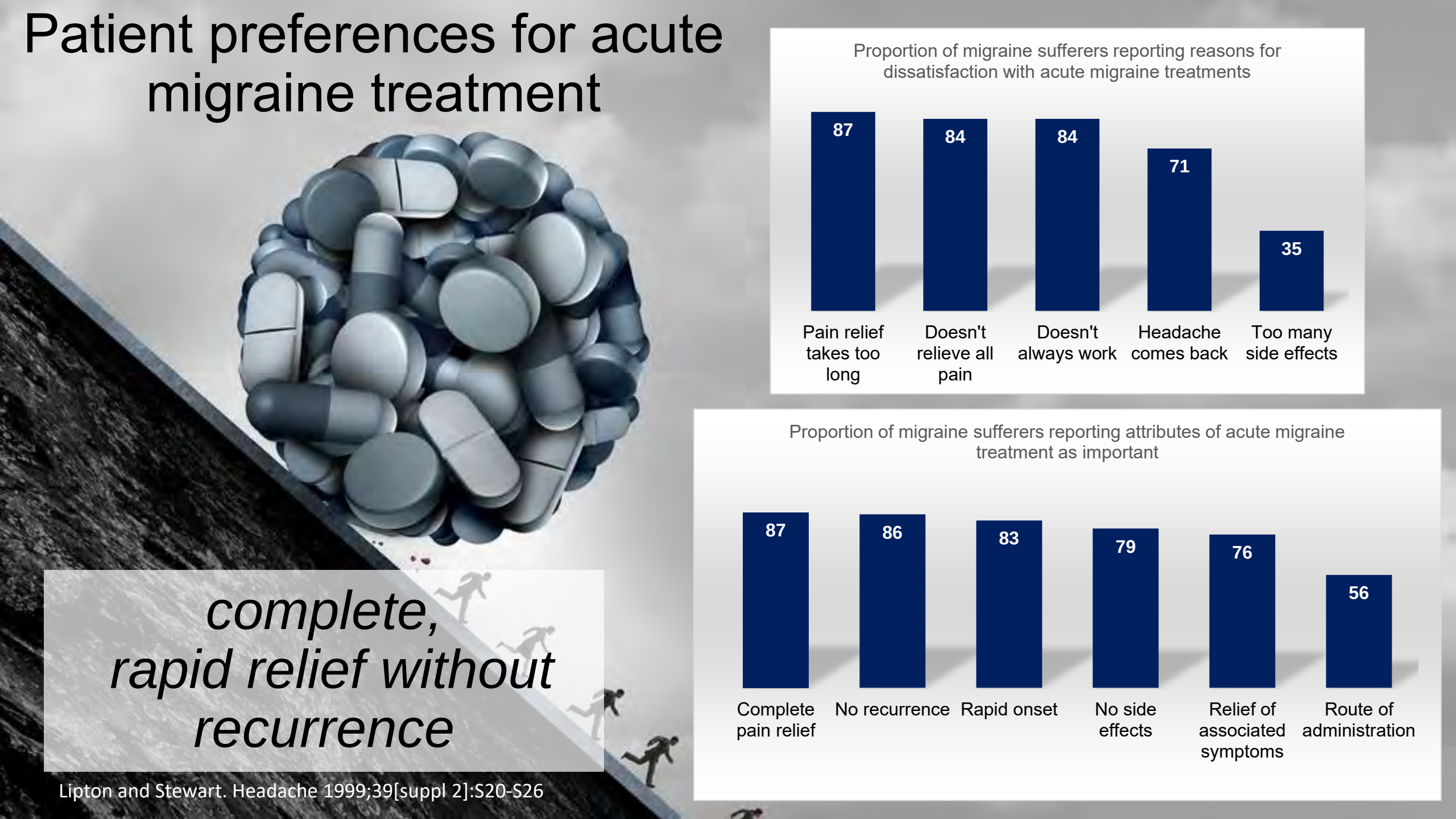
- Center around individual migraine sufferers
- Contextualized by comorbidities and daily activities
- Understanding individual wants and expectations
- Meeting the challenge with compassion and an earnest desire to achieve pain freedom
- Interconnect concepts with measurable terms (quality of life, impact)

Introduction to Acute Migraine Treatments

GOALS

- Alleviate suffering
- Provide fast relief of pain and associated migraine related symptoms
- Restore function
- Reduce disability
- Optimize self-care
- Minimize side-effects

Patient preferences for acute migraine treatment



complete, rapid relief without recurrence

Lipton and Stewart. Headache 1999;39[suppl 2]:S20-S26

Migraine treatments

- Abortive or acute treatment
  - ✓ Used to alleviate the pain when it starts
  - ✓ Think of these as pain killers
  - ✓ Should be used as needed
  - ✓ Should not be overused

- Preventive treatment
  - ✓ 4 to 6 headache days per month
  - ✓ Infrequent but severe/disability attacks
  - ✓ Used to decrease headache frequency
  - ✓ Daily medications
  - ✓ Can take time to become effective

Treating migraine attacks

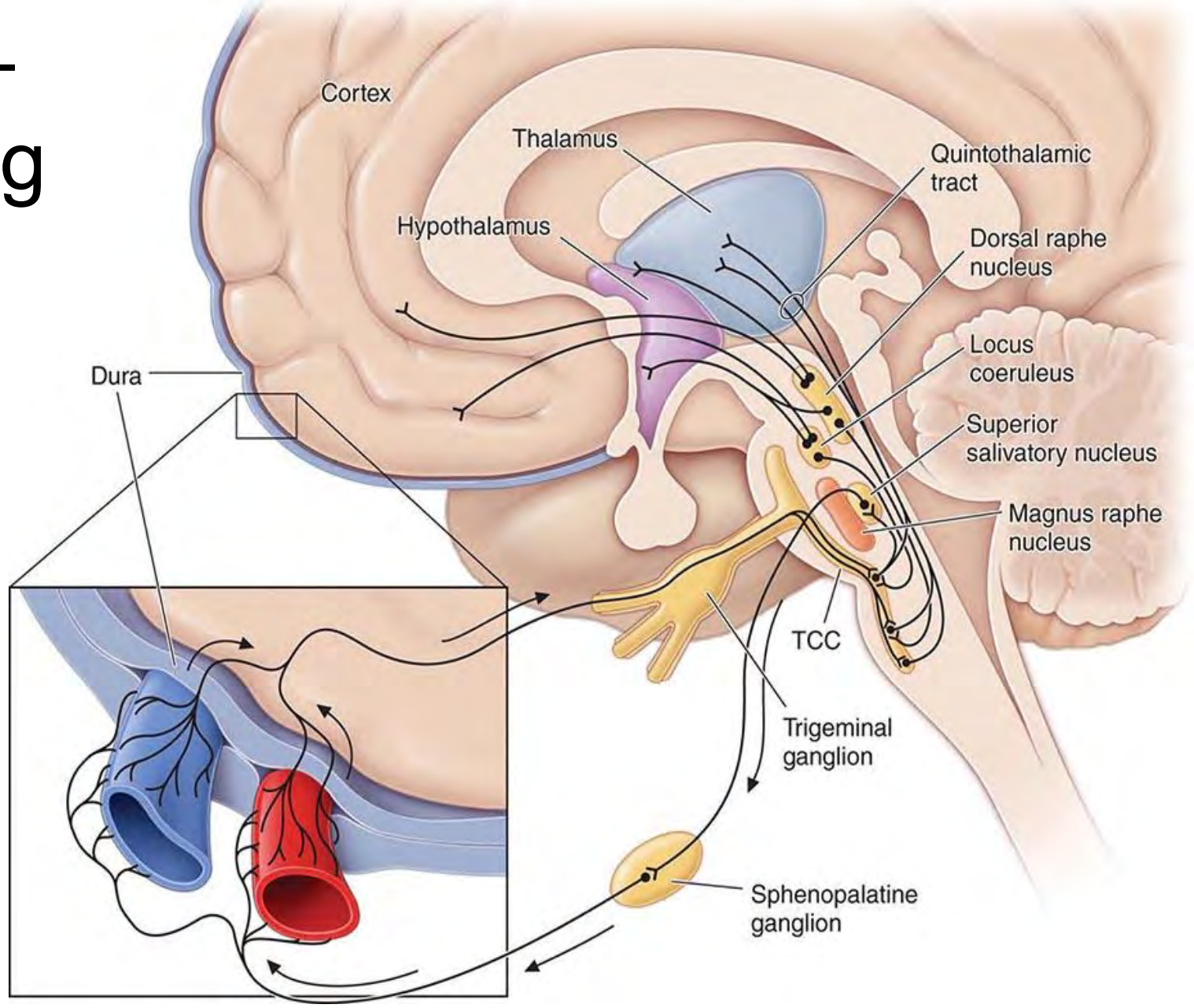
Principles in treating migraine attacks

- **Treat attacks early**
- **Choose treatment based on attack severity**
- **Combine acute treatments when needed (triptan + antinausea medication)**
- **Consider preventive strategies (medication and non-medication) when headache days per month are increasing or infrequent attacks are very disabling**

Lipton et al JAMA. 2000; 284(20):2599-2605

Migraine treatment – what are we targeting

- Brain excitability
- Neurotransmitters and areas of the brain that may be activated during migraine
- Activation nerves that signal pain from the head and neck
- Inflammation around the coverings of the brain
- Release of pain signaling proteins like Calcitonin Gene Related Peptide or CGRP



Acute Migraine Treatments

Less specific

- NSAIDs
- Combination meds
- Anti-nausea meds (Reglan, Zofran etc)
- Antihistamines

More Specific

- DHE
- Triptans
- Ditans
- Gepants

Nonsteroidal Anti-inflammatory Drugs

- Reduce inflammation
- Can cause stomach irritation, bleeding, and kidney dysfunction if used too much
- Some are over the counter
- Can be used in combination with triptans

  - Naproxen sodium 500-550mg, tablet
  - Diclofenac potassium 50mg, tablet, sachet
  - Ibuprofen 400mg, tablet, solubilized
  - Indomethacin 25mg, tablet, PR
  - Flurbiprofen 100mg
  - Ketoprofen 100mg
  - Acetylsalicylic Acid 975-1000mg, effervescent and tablet

Triptans

- Core of acute migraine treatment
- Migraine-specific medications
- Multiple clinical trials demonstrate effectiveness
- Differences in how fast and long they act
- Differences in the formulation (pill, injection, nasal spray)

Triptans

Vs Sumatriptan 100mg	2Hr Relief	Sustained Pain-free	Consistency 2 of 3	Tolerabilty
Sumatriptan (50 mg)	=	=	=/–	=
Zolmitriptan (2.5 mg)	=	=	=	=
Naratriptan (2.5 mg)	–	–	–	++
Rizatriptan (10 mg)	+	+	++	=
Eletriptan (80 mg)	+(+)	+	=	–
Almotriptan (12.5 mg)	=	+	+	++

- inferior, =/- possibly inferior, = no difference, + better, +(+) possibly much better, ++ much better compared to 100 mg sumatriptan

Lancet. 2001 Nov 17;358(9294):1668-75.

Lasmiditan (Reyvow)
controlled substance

option for people with vascular disease

doi:10.1093/brain/awz134 BRAIN 2019: 142; 1894–1904 | 1894

BRAIN
A JOURNAL OF NEUROLOGY

CLINICAL TRIAL

Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine

Peter J. Goadsby,[1] Linda A. Wietecha,[2] Ellen B. Dennehy,[2,3] Bernice Kuca,[4] Michael G. Case,[2] Sheena K. Aurora[2] and Charly Gaul[5]

- Dosing 50, 100mg tablets Q24Hr PRN
- Centrally- penetrant, highly selective 5-HT1F receptor agonist without vasoconstrictive activity
- Serotonin syndrome were reported in patients treated with REYVOW
- Has abuse potential
- CNS depression, sedation, driving impairment

E-mail: wietecha_linda_a@lilly.com

Keywords: lasmiditan; migraine; phase 3; efficacy; safety/tolerability

Abbreviations: MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Score; TEAE = treatment emergent adverse event

Received October 3, 2018. Revised February 26, 2019. Accepted March 14, 2019. Advance Access publication May 27, 2019
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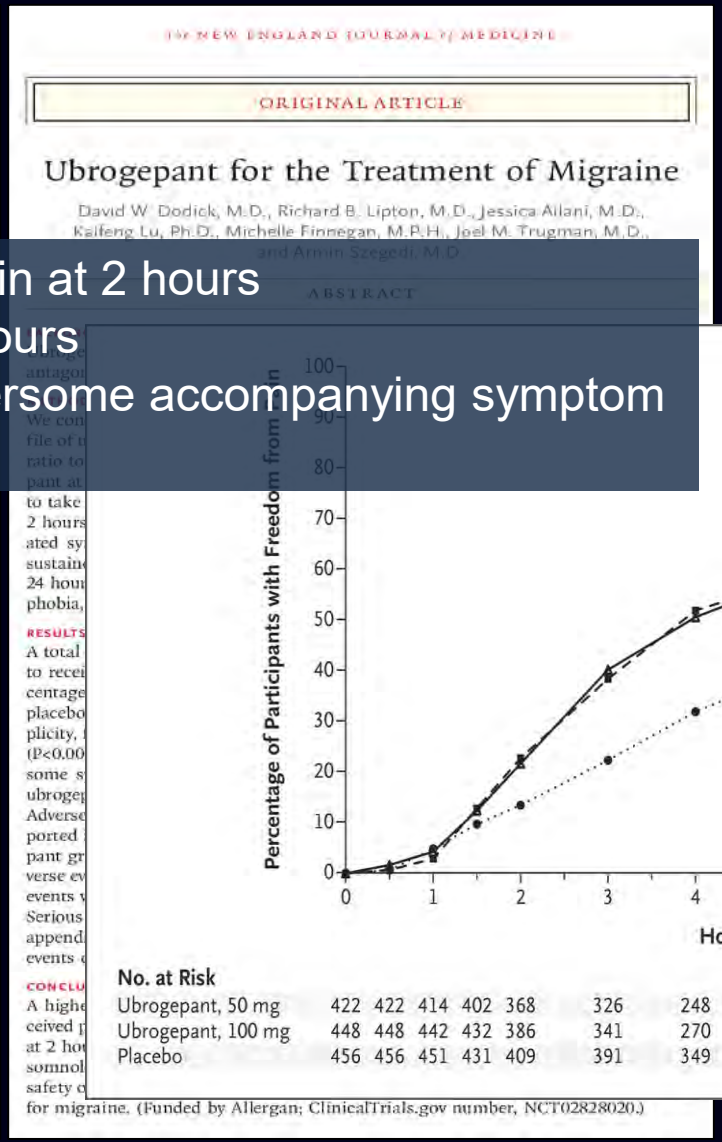
Small molecule CGRP Receptor Blockers

- **Rimegepant (Nurtec)**
  75mg Q24 hr PRN

- **Ubrogepant (Ubrelvy)**
  50mg and 100mg, PRN pain, can re-dose in 2 hours

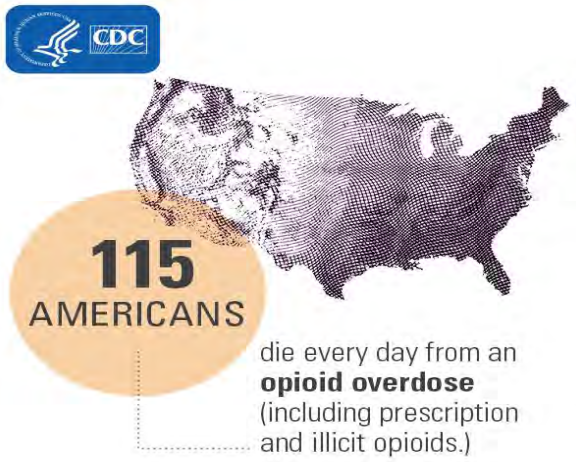
- Increased freedom from pain at 2 hours
- Increased pain relief at 2 hours
- Improvement in most bothersome accompanying symptom
- Continued 24 hours relief



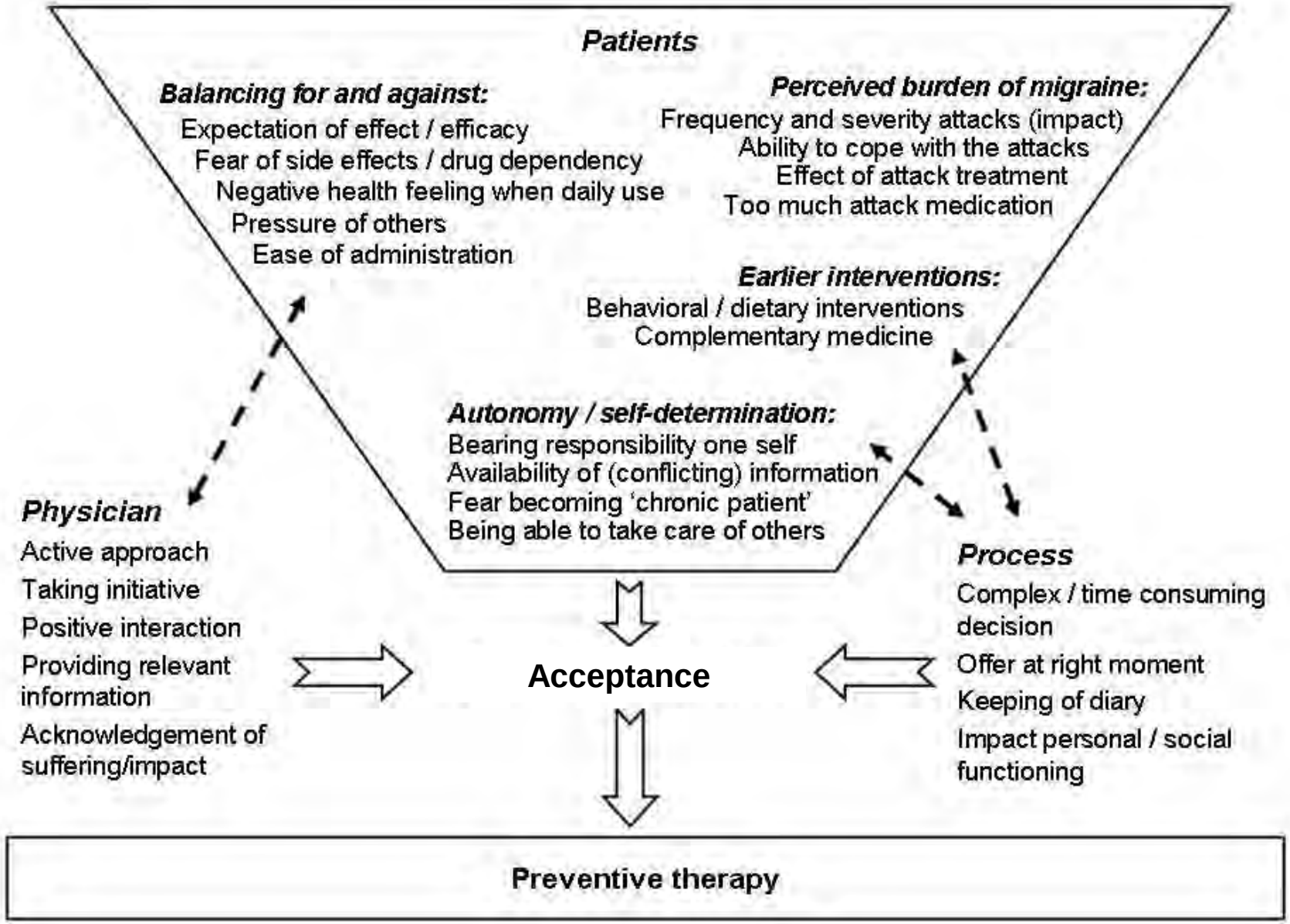
The other options

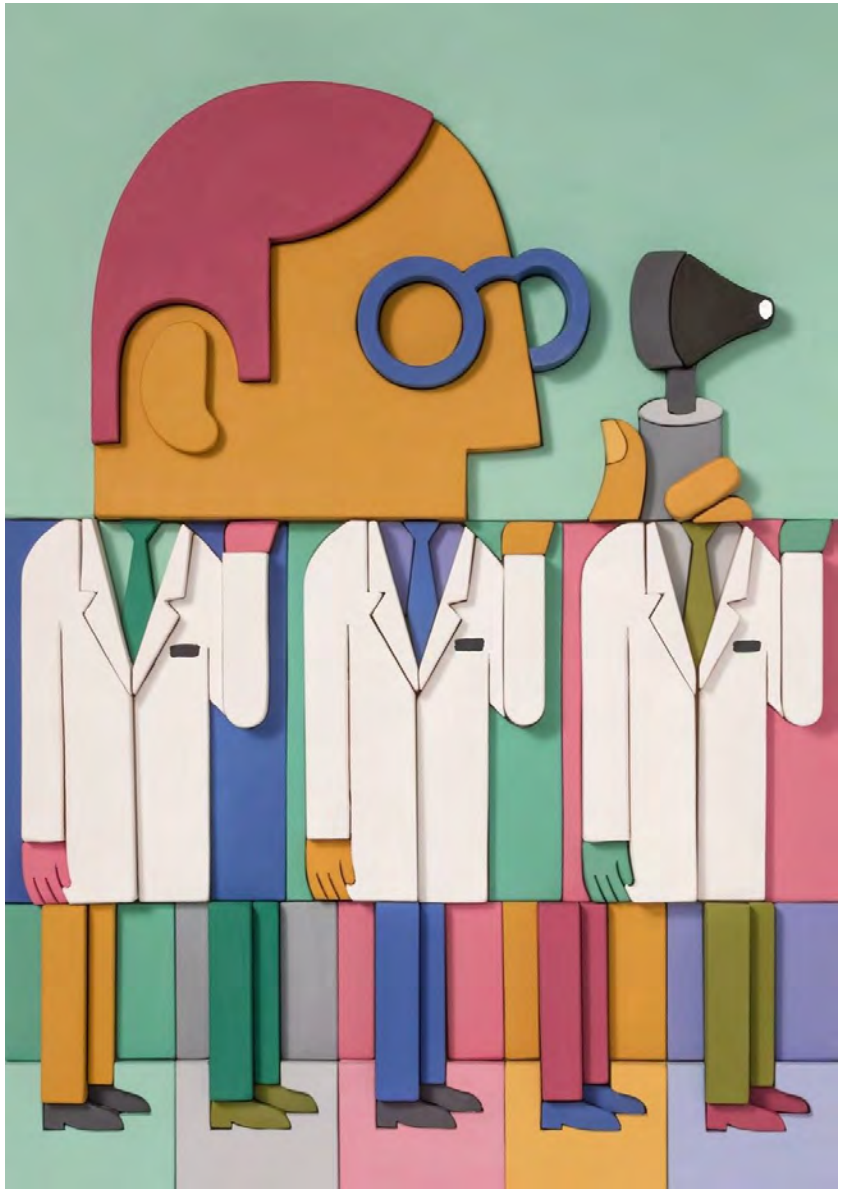
- Opioids and barbiturates can cause sedation, respiratory and cardiac depression, opioid induced hyperalgesia, and dependency

- Considering opioid induced hyperalgesia, abuse/addiction issues, and some evidence that opioids render migraine-specific abortive medications less effective, it is recommended that opiates/opioids ***not be used as first-line therapy for migraine pain***



Influences on preventive therapy





We devote vast resources to surgeons and the like, while starving the physicians whose steady, intimate care helps many more.

THE NEW YORKER

The Heroism of Incremental Care
By Atul Gawande

> “There is rarely a single, immediate remedy, she said, whether it was a drug or a change in diet or an exercise regimen. Nonetheless, she wanted her patients to trust her. Things would take a while—months, sometimes longer. Success would be incremental.”

- Diet, exercise, adequate hydration
- Sleep hygiene
- Avoiding triggers if present (typically stress reduction techniques and sleep management)
- Food diaries can be tedious
- Unclear if specialized diets (including modified Atkins) help
- Mindfulness based meditation
- Cranial sacral massage
- Can start with nutritional supplements
    - Magnesium
    - Riboflavin
    - Feverfew
    - Avoid Butterbur

Migraine headache prevention

- Start low and go slow
- Adequate trial is 3mo
- Monitor with HA calendar
- Consider comorbidities
- Consider combo Rx
- Re-evaluate at regular intervals

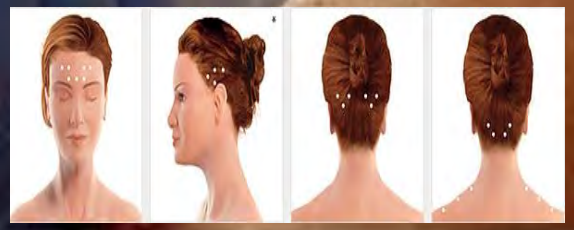
Evidence Level	Medication ✓ = FDA Indication	Usual Daily Dose	Comments
B	Atenolol	50-100 mg	? Avoid in migraine w aura
A	Propranolol ✓	80-240 mg	? Avoid in migraine w aura
A	Metoprolol	50-150 mg	? Avoid in migraine w aura
U	Verapamil	180-480 mg	Cluster, migraine w prolonged aura, vestibular migraine
A	Divalproex sodium✓	250-1500 mg	FDA pregnancy category D
U	Gabapentin	300-1800 mg	Downgraded, favorable AE profile
A	Topiramate✓	25-150 mg	FDA pregnancy category D
B	Amitriptyline	10-150 mg	Downgraded but clinically strong
B	Venlafaxine	37.5-150 mg	Well tolerated, not sedating
C	Cyproheptadine	2-8 mg	Pediatric population, sedating

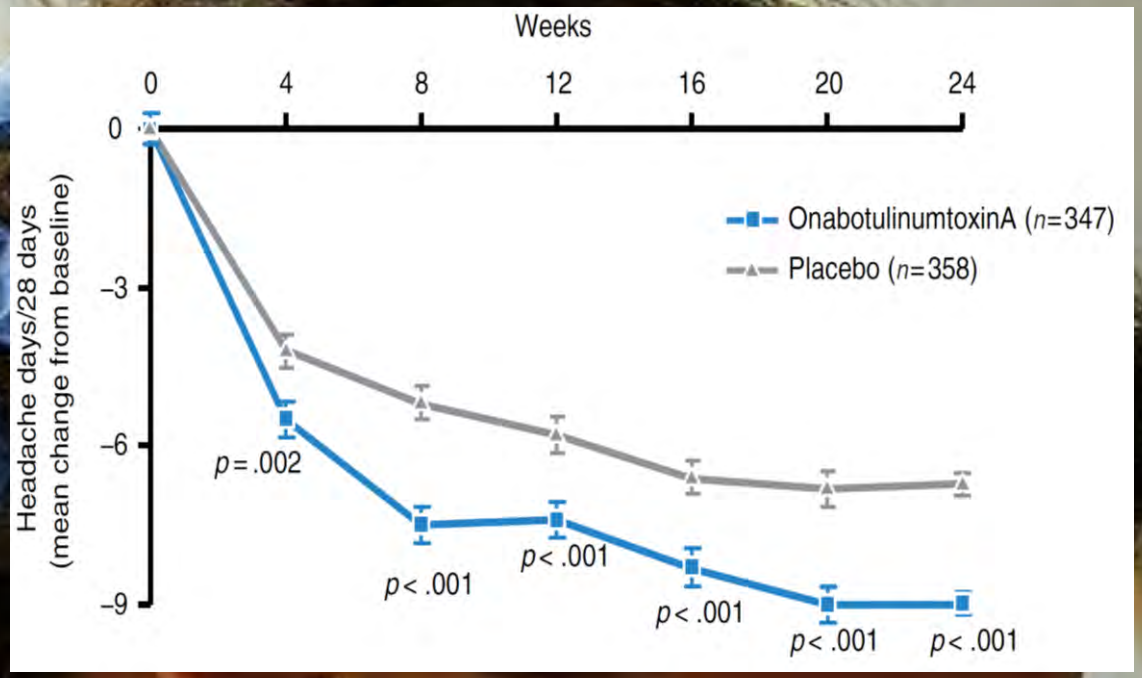
Non-prescription (magnesium, COQ10, feverfew, riboflavin), Lisinopril, Candesartan, Lamotrigine (migraine aura), devices, biofeedback and behavioral therapies

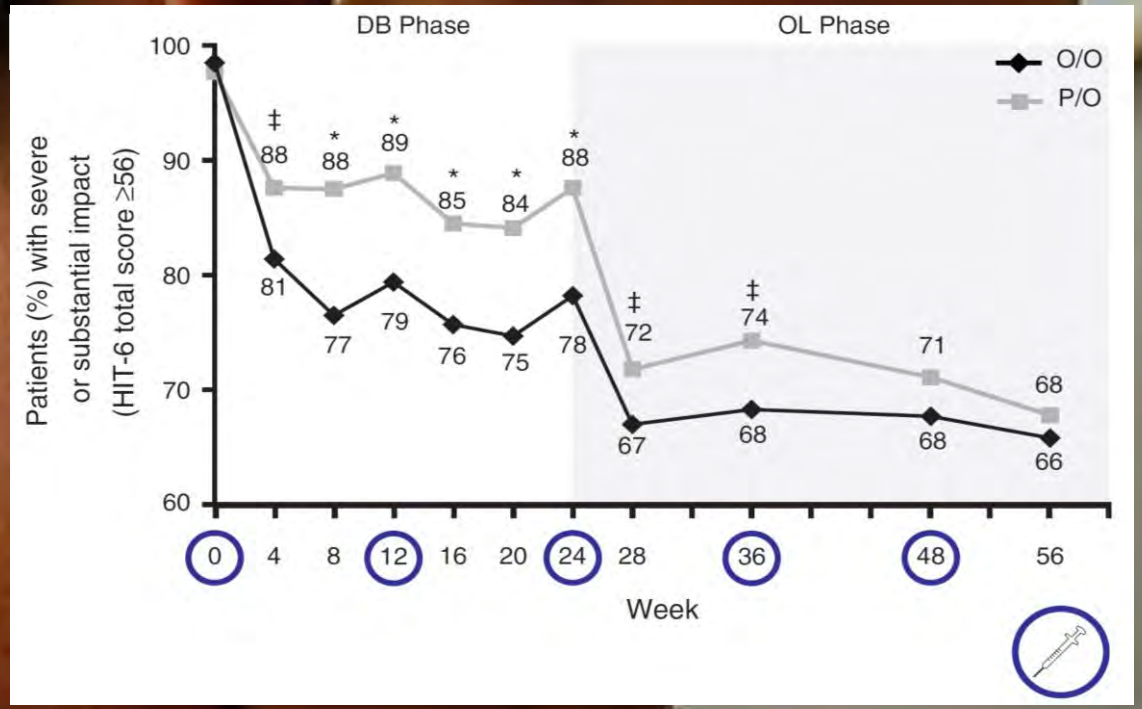
Onabotulinum Toxin A is the only FDA approved medication for the treatment of chronic migraine – PREEMPT trials

Chronic migraine = 15 or more headache days per month for 3 or more months

155 Units, 31 injection sites



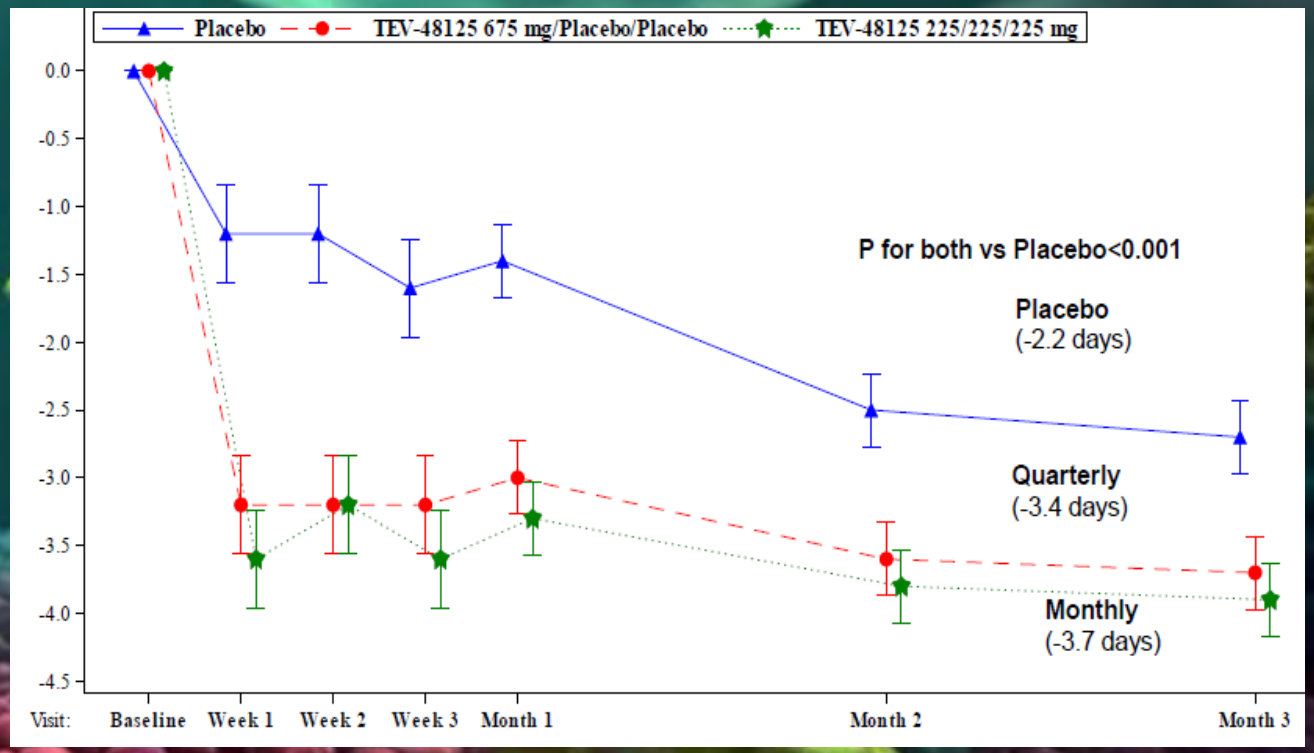




Cephalalgia. 2016 Aug;36(9):899-908.

CGRP Antibodies for the treatment of episodic and chronic migraine

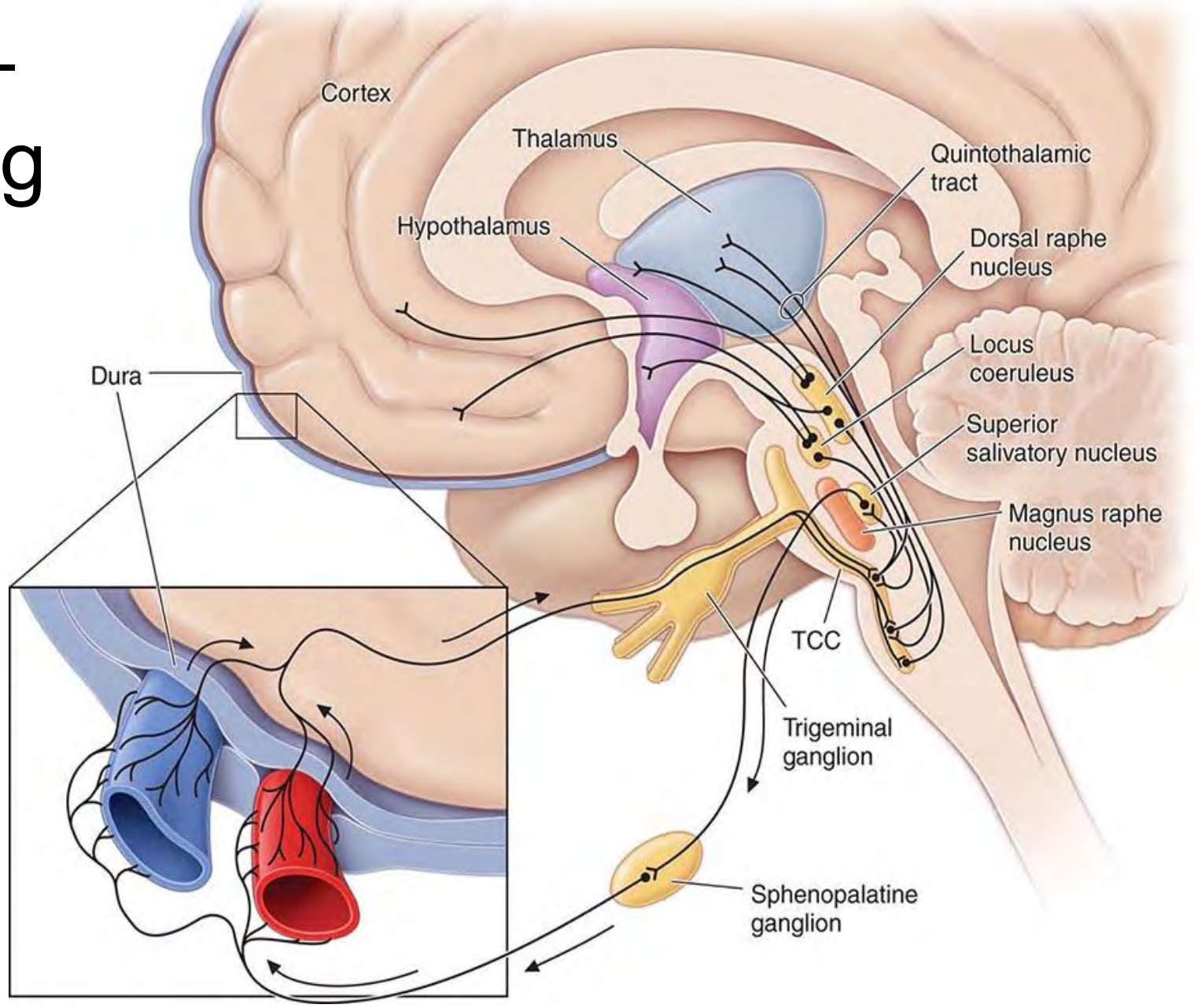
	Eptinezumab ALD 403	Galcanezumab LY29517542	Erenumab AMG 334	Fremanezumab TEV-49125
CGRP Target & IgG	Ligand(α&β) (~90% humanized) $IgG1_{kappa}$(yeast)	Ligand(α&β) (~90% humanized) IgG4a	Receptor (human) $IgG2_{lamda}$ XenoMouse®	Ligand(α&β) (fully humanized) $IgG2a_{kappa}$
T1/2	~32 days	25-30 days	21 days[3] PK modeling for 70mg/70kg	~45 days[1]
Dosing	IV Q 3 months (SQ monthly)	SQ monthly	SQ monthly 70mg dose levels detectable ≥100 days[3]	SQ monthly
Median Tmax			3-14 days throughout dose range & all cohorts	
			CGRP receptor binding 5000 fold > AMY_1, AM	



Br J Clin Pharmacol 2015;79:886.

Migraine treatment – what are we targeting

- PACAP
- Insulin like growth factor 1 nasal spray
- CGRP blocker nasal spray (Zavegepant)
- Neuromodulation



Thank you