Headache Therapy: Update 51st Annual Course in Drug Therapy

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Disclosures

- I have participated in clinical trials underwritten by Novartis

Overview of Headache Therapeutics

- Migraine
  - Prophylaxis and abortive therapy
  - Review of new agents
    - Gepants, Ditans ✓
    - Anti-CGRP ✓
- Tension-type headache
- Cluster headaches
  - New advances ✓
- Post-traumatic headaches
- The slide about cannabis

Migraine facts

- Extraordinarily common (10-22% of population)
- 3000/1,000,000 will have a migraine any given day
  - 12,000 people *today* in Montreal
- Commonly misdiagnosed
  - 'post-concussion' –of those with headache at 5 years, 66% had ICHD2 features of migraine or probable migraine
    - Stacey et al. Journal of Neurotrauma 2017 34:1558-1564
  - 'sinus headaches'– of 100 people who presented with self-diagnosed 'sinus headache'….
    - 52 % had migraine +/- aura, 11% chronic migraine, 23% probable migraine
    - 1% cluster headache,
    - 3% sinusitis (acute or chronic)

      Eross, E. et al. Headache 2007 Feb;47(2):213-24.

Treatment concepts for migraine

- Abortive Treatment
  - Tylenol, NSAIDs
  - Anti-emetics
  - Triptans
  - New Agents
    - Gepants
    - Ditans
- Preventative
  - Episodic vs Chronic Migraine
  - Guideline based
    - The three As
    - Other effective treatments
  - Chronic Migraine
    - OnabotulinumtoxinA
    - Anti-CGRP agents
    - Atogepant
  - The importance of the headache journal

Non-Pharmacological treatments

- Ketogenic Diet
  - Prospective study of VLCKD
  - 96 overweight migraineurs randomized to Ketogenic or Standard Diet
  - Attack frequency -2.9, headache days -4.11 days
    - Di Lorenzo et al. Eur J Neurol 2015
- Randomized Controlled Pilot Trial of Behavioral Insomnia Treatment for Chronic Migraine With Comorbid Insomnia
  - 3--30 minutes biweekly sessions vs standard therapy
  - Reduction in headache frequency 48.9% vs 25% (control group)
    - Smitherman et al. Headache 2016

Migraine Abortive Therapy

- General principles
  - Timing of use: understand gastroparesis/allodynia
  - Cost, and cost effectiveness
  - Monitoring for medication overuse
    - NSAID use >15 days/month
    - Triptan use >10 days /month
- Goals
  - pain free at two hours
  - Maintenance of functional ability, reduce work disability, ED visits

NSAIDs-Evidence

Ibuprofen

2 hr pain-free of 25%, 28% and 29% for 200, 400, and 600mg vs 13% for placebo

Kellstein et al Cephalalgia 2000: 20; 233-243

Naproxen (250-1100mg/D)

As effective as DHE in acute migraine

Treves et al. Headache 2005:32; 280-282

Aspirin and Acetomenophen

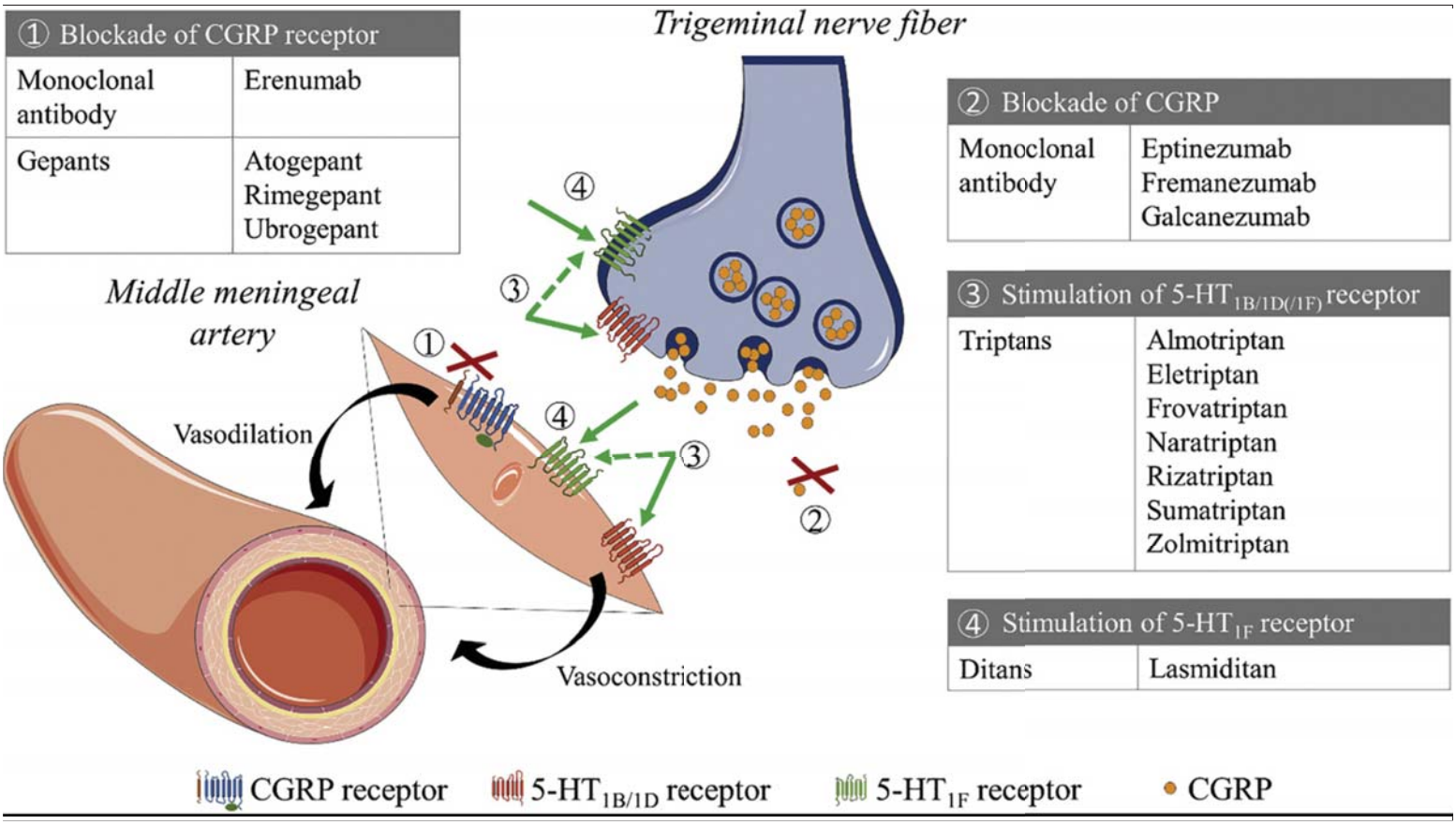
- ASA--Cochrane review: April 14, 2010
  - 13 studies (4222 participants) compared ASA 900-1000mg + metoclopramide with placebo or active agents (mostly Sumatriptan 50mg or 100mg)
  - ***Aspirin 1000mg is as effective as sumatriptan 50mg or 100mg with fewer side-effects***
- Acetomenophen
  - 1000mg acetaminophen vs placebo
  - 2 hour response rate of 57.8% vs. 38.7% for placebo
  - Pain free at 2 hours 22.4 vs 11.3%
    - Lipton et al. Arch Intern Med 2000; 160; 3486-92

Triptans

- Mechanism of action
  - 5-HT1b and 1d agonists
  - Inhibition of pro-inflammatory neuropeptide release
- Vasoconstriction
  - Theoretically increase risk in patients with coronary artery disease
- Serotonin syndrome
  - Fever, autonomic changes

Triptans... Choice

- Sumatriptan 50-100mg oral, 20 mg IN, 6 mg sc
- Naratriptan 2.5 mg oral→ long half-life
- Zolmitriptan 2.5 mg (po/IN)
- Almotriptan 12.5 mg oral
- Rizatriptan 10mg oral
- Eletriptan 40mg oral
- Frovatriptan 2.5mg oral → long half-life



New Agents—abortive treatments

Gepants

- Antagonists of CGRP
- Rimegepant 75 mg
  - Pain free at 2 hours 58.1% vs 42.8%
- Ubrogepant 50/200mg
  - 20% pain freedom at 2 hours
  - No head-to-head data with triptans/NSAIDs

Ditans

- Serotonin 5HT-1F agonist
- Lasmiditan 200 mg
  - 2-hour pain-freedom
  - 38.8% vs 25% placebo
  - No head-to-head vs triptan or NDAIDs

Practice Improvements

- Improve Reporting/Recording
  - Patients often under-report attacks
    - Office visits, ED visits, missed work-days, limited activity
  - Make a migraine calendar **mandatory**
    - Overcomes recency bias
    - Always informative
    - Allows MDs and patients to make more rational decisions
    - Several apps allow for recording of headaches and other migraine symptoms unrelated to headache

Practice Improvements

- Understand the phases of migraine
  - Treat early: encourage patients to carry meds.
  - Understand role of allodynia in reducing triptan effectiveness
    - Early treatment
- Failure of NSAID/tylenol alone doesn't mean that it needs to be abandoned—consider step therapy.
  - NSAID or Tylenol
  - Triptan +/- NSAID or tylenol
  - Triptan +/- NSAID or tylenol +/- Maxeran

Abortive therapy. The Bottom Line.

- No triptan/ ditan/ gepant has been shown to be superior to NSAIDs/ Tylenol in head-to-head trials
- Triptans/ Ditans/ Gepants have similar results vs Placebo
- Gepants/ Ditans have less frequent CV side effects compared to triptans

Migraine Prophylactic Therapy

- General principles
  - Initiate with the lowest dose
  - Give treatment adequate time (2-3 months)
  - Long-acting or once-a-day formulations improve compliance
  - Discuss rationale and goals (50% reduction in headache frequency, missed time from work,etc)
  - Address expectations
  - **Headache diary**

When to use prophylaxis

- Significant impact (missed work) despite appropriate use of abortive therapy
- A frequency requiring use of abortive therapy associated with side-effects/MOH
- 3 or more headaches/ month unresponsive to abortive therapy
  - Pryse-Phillips CMAJ; 1997; 156:1273-87
- *Depends on the agent, depends on the patient*

General categories-the 4 As

- Tricyclic ***A***ntidepressants
  - Amitriptyline…..Venlafaxine*
- ***A***ntihypertensives
  - Beta-blockers, Atacand, Lisinopril
- ***A***nticonvulsants
  - Valproic Acid, Topamax, Neurontin
- '***A***lternative therapies' **
  - Riboflavin, Coenzyme Q10, Magnesium

Antidepressants

- Amitriptyline (10-75mg/D)
  - OR of 2.41 for a 50% reduction over placebo
- Venlafaxine 150mg
  - OR 1.81 for 50% reduction over placebo
- SSRIs not typically used—often increase frequency of migraine

Anticonvulsants

- Valproic Acid (500-1500mg/D)
  - OR of 2.74 for 50% reduction over placebo
    - Freitag et al. Neurology 2002;58:1652-9
    - NNT: 3.5
- Topamax (100mg/D)
  - OR of 2.44 for 50% reduction over placebo
  - Similar efficacy to Propranolol, Valproate
- Gabapentin (900mg-3600mg/D)*
  - OR of 4.51 for 50% reduction over placebo
    - Mathew et l. Headache 2001;41:119-28

Anticonvulsants—Topiramate & Valproate

Topiramate

- 6 studies-2 'good', 3 'fair', 1 'poor'
- Comparison to Amitriptyline (Dodick)
  - Topiramate 100mg had similar redection in monthly migraines
- Placebo comparison in 2 studies (Gupta)
  - 50mg produced 2.03 OR of 50% reduction in migraine frequency

Valproate

- 3 parallel group studies and 2 crossover studies
- Meta-analysis of parallel studies possible
- Daily doses of 500-1500mg used
- Odds ratio for 50% reduction 2.74
- 27% of VPA treatment patients stopped because of side effects

Anticonvulsants...side effects

- Valproic acid
  - Significant teratogenicity. Weight gain, hair loss and tremor
- Topamax
  - Paresthesia, renal stones, glaucoma, word finding difficulty, mood change

Antihypertensives

- Propranolol vs placebo
  - OR of 1.94 for 50% compared to placebo
  - 'High-dropout rates'
- Head-to-head metanalysis:
  - Nadolol vs. Propranolol-slight advantage to nadolol
  - Metoprolol vs. Propranolol-no difference
- Candesartan (8 and 16mg) , Lisinopril (20mg) both shown benefits in single, well-conducted studies

Propranolol compared with ARB

- 72 patients, 2 or more migraines per month
  - 80 ➔ 160 propranolol
  - 8 ➔ 16 mg candesartan (atacand)

  Primary endpoint: 50% reduction in headache
  - 23% placebo
  - 43% candesartan
  - 40% propranolol

Magnesium, CoQ10, Riboflavin

- Magnesium Citrate 600mg/d
  - Superior to placebo
  - Diarrhea in 19% , low dropout rate
    - Peikert et al. Cephalalgia 1996;16: 257-63
- Coenzyme Q10 (300mg /D)
  - OR of 5.4 for 50% reduction
    - Sandor et al Neurology 2005;64: 713-5
- **Riboflavin 400 mg daily**
  - **OR of 5.6 for a 50% reduction vs. Placebo**
  - **Few side-effects, low cost**
    - **Schoenen et al Neurology 1998**

Drug	NNT for 50% reduction	NNH	Major side-effects
A	5.2	4	Fainting, depression, sexual dysfunction
B	5	14	Fainting
C	2.3	32	Yellow urine, GI upset
D	3.3-6.2	4.3	Weight gain, mood change
E	3.5-4.1	5	Kidney stones, mood change, cognitive changes
F	3.1	2.4	Weight gain, hair loss, tremor
G	4.1-8	6	Weight gain, fatigue

Which agent would you select? Which agent would your patient select?

Drug	NNT for 50% reduction	NNH	Major side-effects
Propranolol 160	5.2	4	Fainting, depression, sexual dysfunction
Candesartan 16	5	14	Fainting
Riboflavin 400mg	2.3	32	Yellow urine, GI upset
Gabapentin 2400	3.3-6.2	4.3	Weight gain, mood change
Topiramate 100mg	3.5-4.1	5	Kidney stones, mood change, cognitive changes
Valproate 250mg BID	3.1	2.4	Weight gain, hair loss, tremor
Amitriptyline 10mg	4.1-8	6	Weight gain, fatigue

Which agent would you select? Which agent would your patient select?

When to stop prophylaxis

- No good evidence-based recommendations
- 75% of those who stop experience recurrence within 3 months
  - Woeber et al Cephalalgia 1991; 11:251-6
- Often, agents are tapered to see if they are still needed

Chronic Migraine --Definition-ICHD 3

- Diagnosis of migraine +/- aura
- ≥ 8 migraine days / month ≥ 15 overall headache days/ month
- Chronic migraine more resistant to treatment
  - Abortive and preventative
  - Higher association with medication overuse
- Useful interventions
  - OnabotulinumtoxinA
  - antiCGRP monoclonal antibodies
  - gepants

Headache
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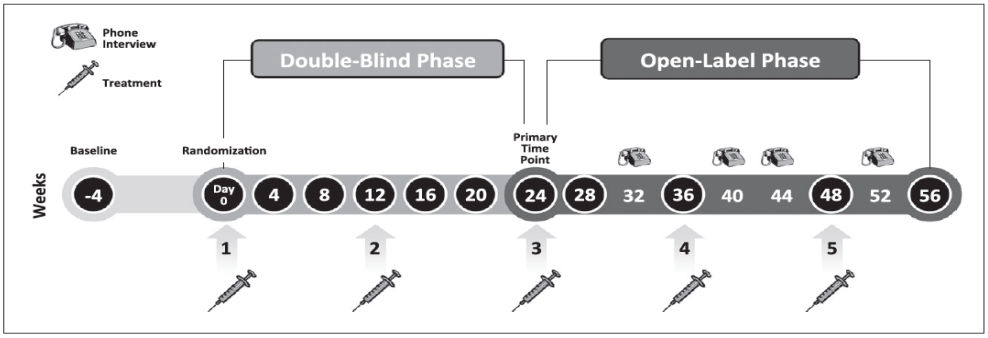
Research Submissions

OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program

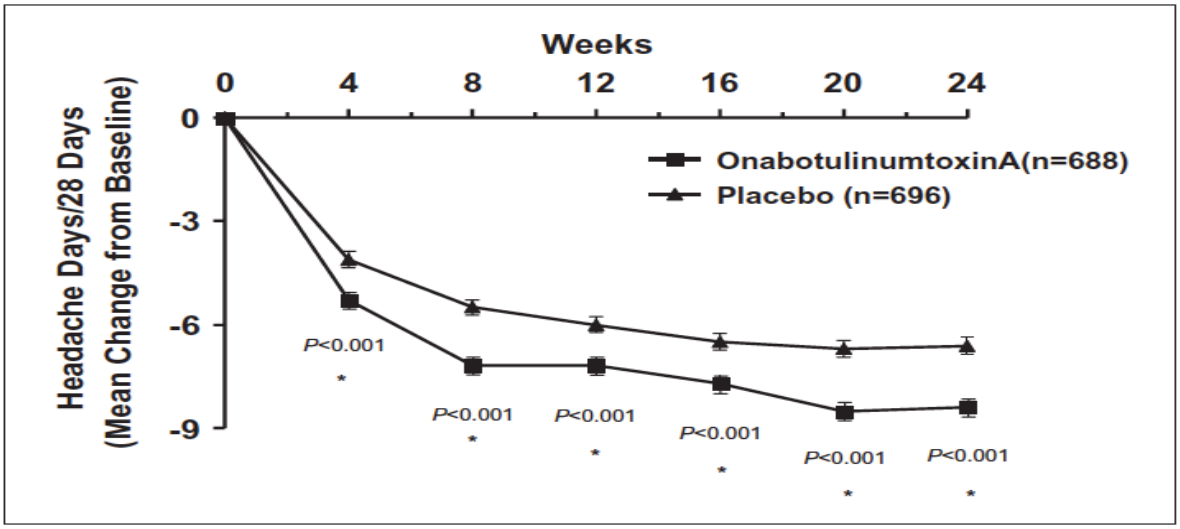
David W. Dodick, MD; Catherine C. Turkel, PharmD, PhD; Ronald E. DeGryse, MS; Sheena K. Aurora, MD; Stephen D. Silberstein, MD; Richard B. Lipton, MD; Hans-Christoph Diener, MD; Mitchell F. Brin, MD, on behalf of the PREEMPT Chronic Migraine Study Group

Objective.—To assess the efficacy, safety, and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.

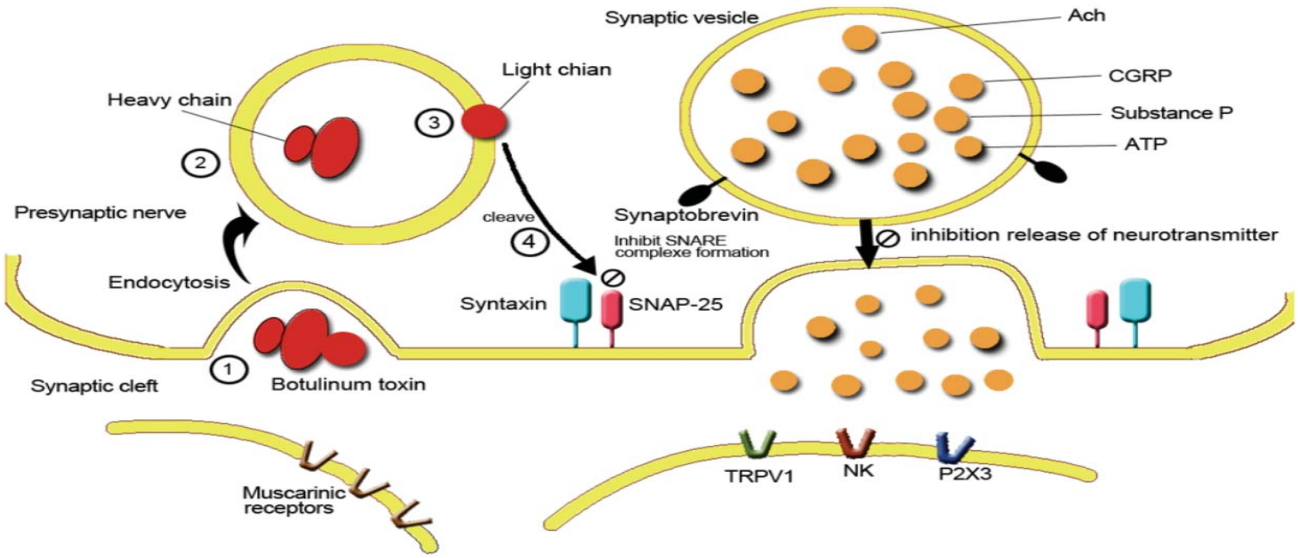
Background.—Chronic migraine is a prevalent, disabling, and undertreated neurological disorder. Few preventive treatments have been investigated and none is specifically indicated for chronic migraine.



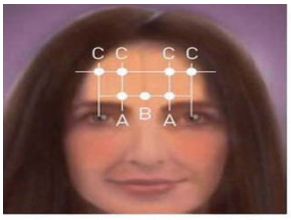
PRREMPT Results



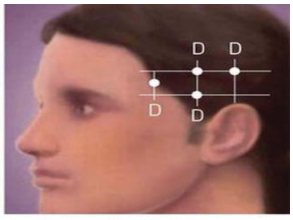
BoNT-A Mode of action



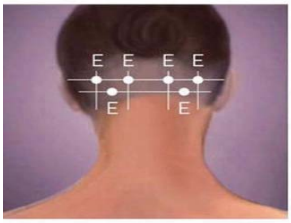
PREEMPT Protocol



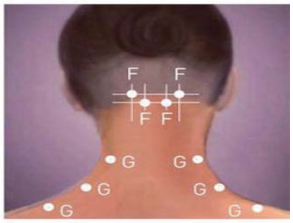
A. Corrugator: 5 Units each side
B. Procerus: 5 Units (1 site)
C. Frontalis: 10 Units each side



D. Temporalis: 20 Units each side



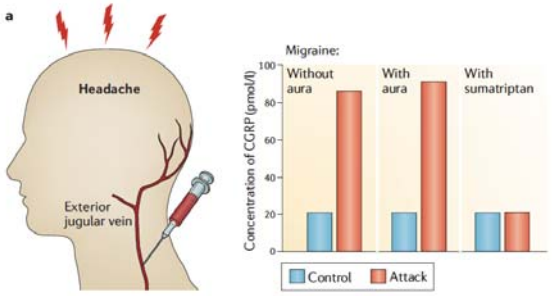
E. Occipitalis: 15 Units each side



F. Cervical paraspinal: 10 Units each side
G. Trapezius: 15 Units each side

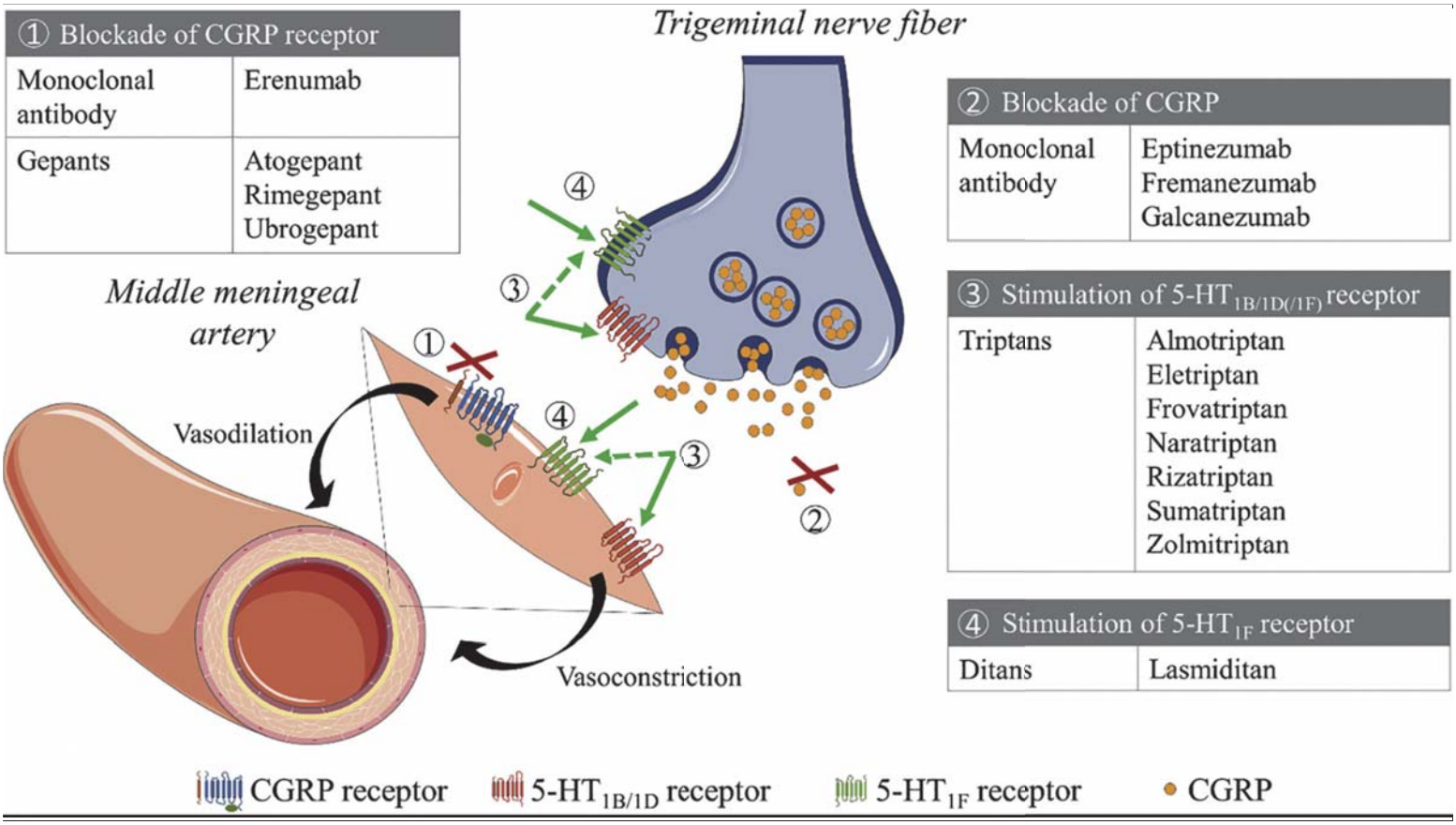
Evidence for CGRP's role in Migraine

- Goadsby (1990) shows elevated CGRP levels during attacks
- Exogenous CGRP causes headache
- Triptans prevent CGRP release at the same time as aborting attacks



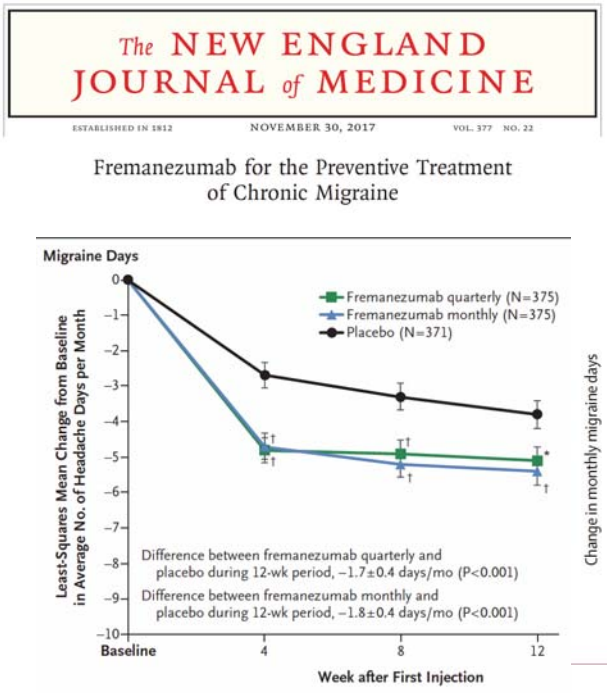
antiCGRP monoclonal antibodies

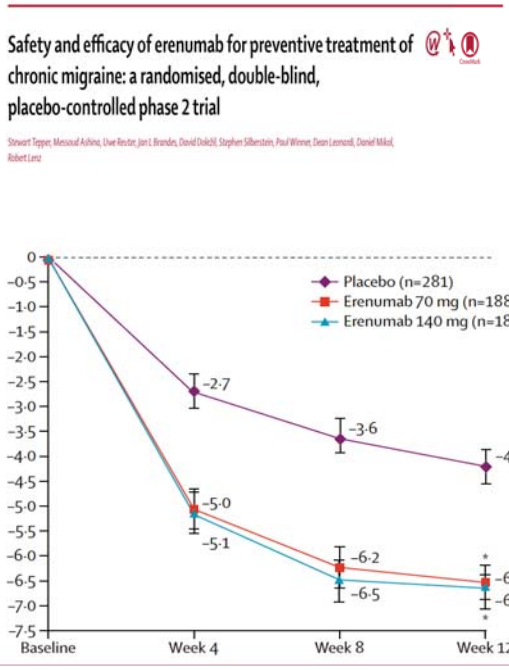
- Discovered in 1980s but used to localize and quantify CGRP and its receptor
- Between 2005 and 2017 interest grew in use of monoclonal antibodies as potential anti-migraine agents
- Between 2017-2018 four agents have reported phase III clinical trial results for prevention of episodic and chronic migraine



Anti-CGRP monoclonal antibodies

	Dosing	Target	Molecular format	indications
ERENUMAB	70mg/140mg s.c. monthly	CGRP receptor	Human IgG_2	Migraine
FREMANEZUMAB	675 mg, then 225 mg s.c. monthly	CGRP	Humanized IgG_2	Migraine
GALCANEZUMAB	240mg, then 120 mg monthly	CGRP	HumanizedIgG_4	Migraine and Cluster
EPTINEZUMAB	300mg every three months	CGRP	Humanized IgG_1	Migraine





Anti CGRP mabs in Chronic Migraine –The One Slide Summary of Studies

antiCGRP Monoclonal Antibodies in Chronic Migraine						
Compound	**Dose/ Frequency**	**Headache days/ Month reduction**	**≥ 50% reduction**	**NNT**	**>75% reduction**	**NNT**
Erenumab	70mg q month 140mg q month	70 mg -6.6 v. -4.2 140mg -6.6 v. -4.2	40 vs. 23% 41 vs. 23%	5.8 5.5	n/a	
Fremanezumab	375mg q3m 375mg q month	-4.9 v. -3.2 -5.0 v. -3.2	38 v. 18% 41 v. 18%	5 4.3	n/a	
Galcanezumab	120mg q month 240mg q month	120mg -4.8 v. -2.7 240mg -4.6 v. -2.7	27 v.15% 27 v. 15%	8 8	7.0 v.4.5% 8.8 v. 4.5%	40 23.2
Eptinezumab	100mg IV q 3m 300mg IV q3m	-7.7 v. -5.6 -8.2 v -5.6	58 v. 39% 61 v. 39%	4.5 4.6	26.7 v. 15 33 v. 15	8.5 5.55

Anti-CGRP monoclonals—the bottom line

- All agents give a similar response, usually within 2 doses
- Lack of response to one agent doesn't predict lack of response to other agents
- Benefits seen for patients who failed other therapies
- Touted for episodic headache but not widely used in this regard

Atogepant—anti-CGRP for prevention

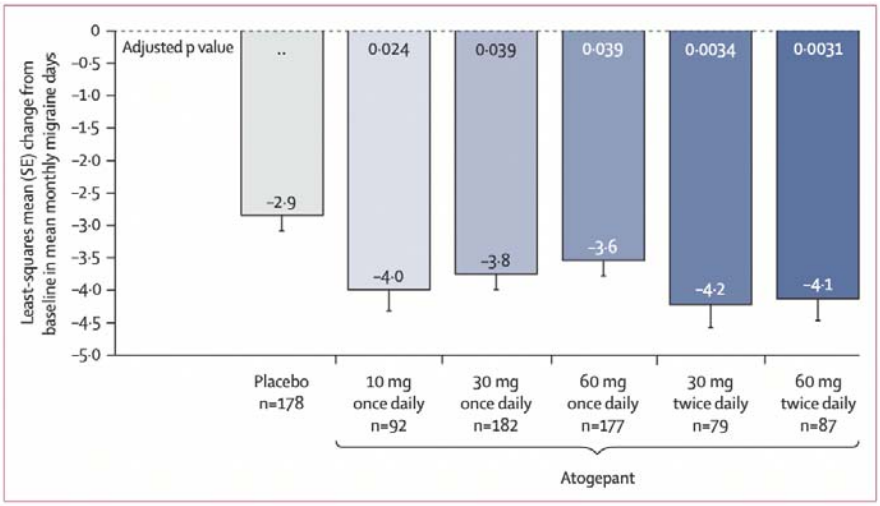


Figure 2: **Change from baseline in mean monthly migraine days across the 12-week treatment period in the modified intention-to-treat population**

50% frequency reduction

Placebo	40%
Atogepant 10 mg	58%

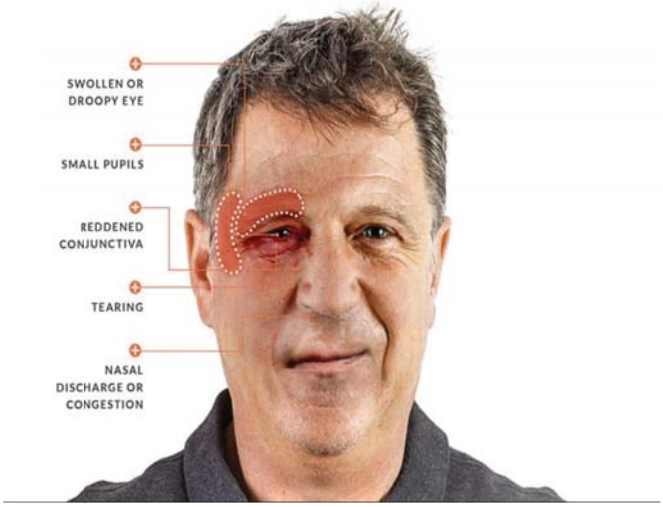
Peter J Goadsby, David W Dodick, Jessica Ailani, Joel M Trugman, Michelle Finnegan, Kaifeng Lu, Armin Szegedi

www.thelancet.co/neurology **Vol 19 September 2020**

Tension-Type Headache

- Amitriptyline 10mg-50 mg reduced headache frequency 30% compared to placebo
  - Mirtazipine 30mg, Venlafaxine 37.5mg similarly effective
    - Bendsten et al Eur J Neurol. 17 (11) 2010. 1318-13-25
- Tizanidine 6 mg daily superior to placebo
  - Placebo controlled double-blind crossover
  - 11.2% absolute reduction in headache days
    - Fogelholm, R Headache 32(10) 1992. 509-513

Cluster Headaches



- Cluster headache
  - 15-180 minutes, 0.5-8 attacks
  - Autonomic symptoms/signs
    - Ptosis
    - Tearing
    - Conjunctival injection
    - Nasal congestion
  - Previous treatments
    - Verapamil 120-480 mg
    - Oxygen
    - Triptans for attack

Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial

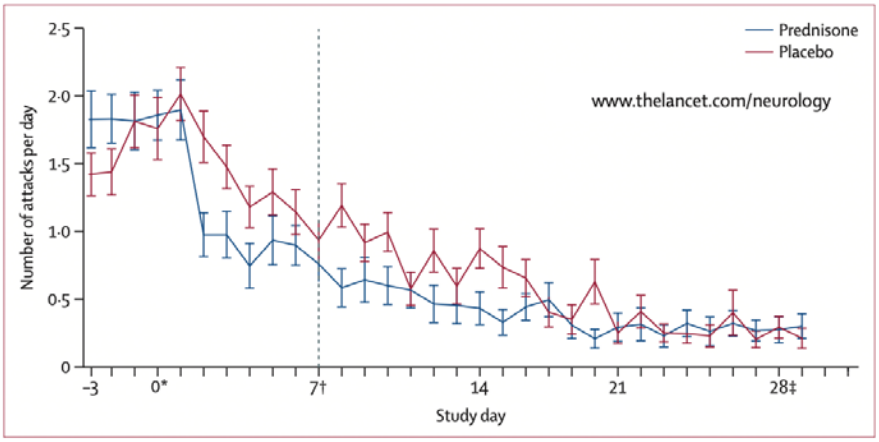


Figure 2: **Mean number of cluster headache attacks per day with prednisone treatment compared with placebo**

www.thelancet.com/neurology **Published online November 24, 2020**

Pred 100 mg per day for 3 days, the reduced 20 mg every 3 days

35% of prednisone group had stopped at day 7 vs 7% of placebo group

FDA NEWS RELEASE

FDA approves first treatment for episodic cluster headache that reduces the frequency of attacks

More Press Announcements

Press Announcements

For Immediate Release: June 04, 2019

The U.S. Food and Drug Administration today approved Emgality (galcanezumab-gnlm) solution for injection for the treatment of episodic cluster headache in adults.

Content current as of:
06/04/2019

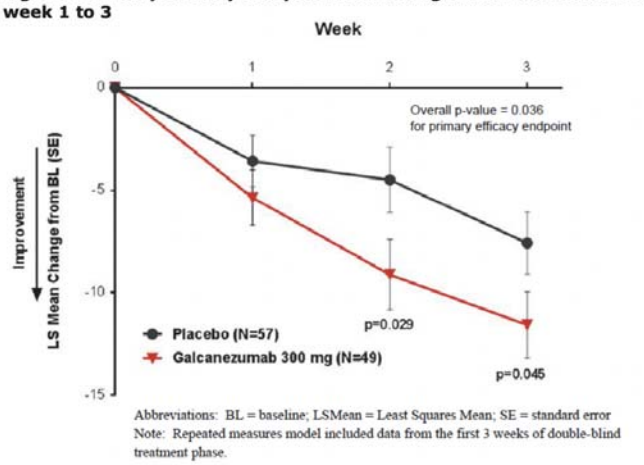
Regulated Product(s)
Drugs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Galcanezumab in Prevention of Episodic Cluster Headache

Figure 6 Primary efficacy analysis: Mean change from baseline at weekly intervals from week 1 to 3



Abbreviations: BL = baseline; LSMean = Least Squares Mean; SE = standard error
Note: Repeated measures model included data from the first 3 weeks of double-blind treatment phase.

Personal experience:

7 patients treated

All experienced reduction of number of headaches and duration of 'typical cluster cycle duration'

5/7 had cessation within 96 hours

4/7 had cessation within 36 hours

Post-Traumatic Headaches

- There are no randomized prospective trials for post-traumatic headache.
- Patients with a premorbid history of a primary headache disorder (migraine, cluster, tension type) are at higher risk of persistent headache 3 months post injury
  - Identify the primary headache disorder
  - Treat the primary headache disorder

Cannabis

- 1 prospective study
- Medication overuse headache
  - Ibuprofen vs nabilone 0.5 mg—nabilone superior
  (criticism--ibuprofen treatment may provoke MOH)
  Pini LA et al. J Headache Pain 2012