Neurology ECHO Network

Session 1

17/02/2022

Didactic: Headaches and Migraines

Case presentation: Dr Lena Derkatch

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Contributing partners:

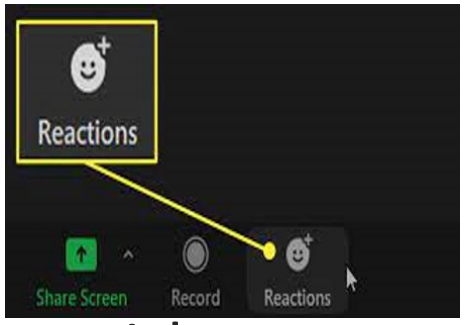
phn COUNTRY SA An Australian Government Initiative

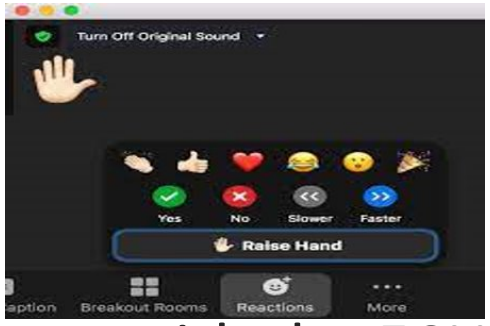
phn ADELAIDE An Australian Government Initiative

sapmea where knowledge + health meet

ECHO Etiquette

- Please remain on ‘Mute’ except when speaking.
- Ask questions or make comment by raising your hand (in ‘Reactions’)





- Use ‘Chat’ if you wish to communicate with the ECHO Coordinator.
- Please maintain confidentiality.

Migraine Echo Presentation

ANDREW MOEY

NEUROLOGIST

LYELL MCEWIN HOSPITAL & SA GROUP OF SPECIALISTS (CALVARY ADELAIDE HOSPITAL)

Outline

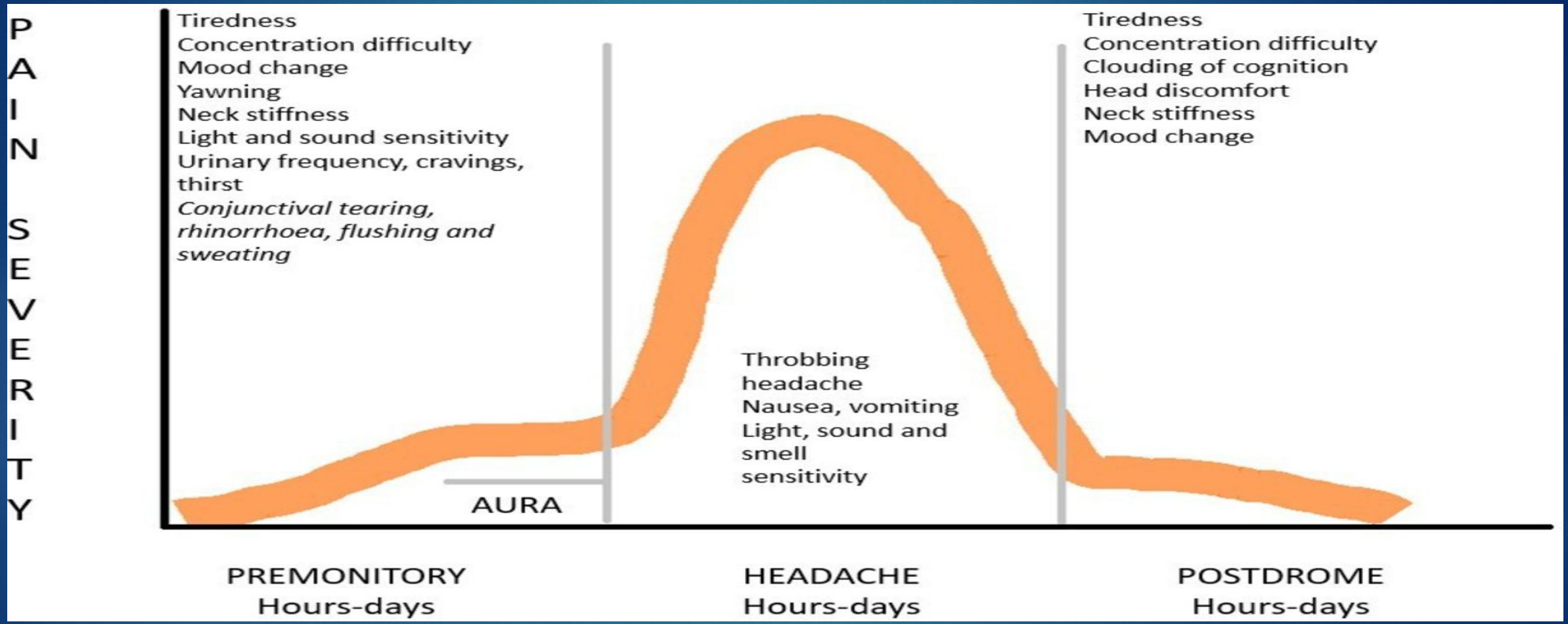
- Migraine
  - What is it
  - Clinical implications and treatment options
  - When to refer
- Cluster headache and TACs
- Medication overuse headache
- PBS approved migraine treatments
- Practical aspects migraine management

What exactly is migraine?

- Migraine without aura
  - A) At least 5 attacks with criteria B-D
  - B) Duration 4-72 hrs (untreated)
  - C) At least 2 of:
    1) Unilateral
    2) Pulsating
    3) Moderate or severe pain
    4) Aggravated by physical activity
  - D) At least one of:
    1) Nausea and/or vomiting
    2) Photo/phonophobia
  - E) Not better accounted for by another diagnosis

- Migraine with aura
  - A) At least 2 attacks with criteria B and C
  - B) One or more of:
    1) Visual
    2) Sensory
    3) Speech and/or language
    4) Motor
    5) Brainstem
    6) Retinal
  - C) At least 3 of:
    1) Gradual spread over >5 mins
    2) 2 or more aura in succession
    3) Duration aura 5-60 mins
    4) At least one unilateral
    5) At least one positive (scintillations, paraesthesia)
    6) Aura associated with (of followed within 60 mins) by headache
  - D) Not better accounted for by another diagnosis

Current view of the migraine attack.



Nazia Karsan, and Peter J Goadsby Pract Neurol 2021;21:475-480

Not migraine? Red flags for secondary headache

- $SNOOP_4$
- S = systemic symptoms (fever, weight loss, night sweats, chills)
  = secondary disease (cancer, immunosuppression, chronic infection)
- N = Neurologic symptoms/signs – confusion, focal neurology, visual obscuration, pulsatile tinnitus, diplopia
- O = Onset – thunderclap
- O – Older (>50 yrs) – new onset, persistent/progressive headache
- P1 = positional (orthostatic, recumbent, worse with change in position)
- P2 = Prior history (new onset, change to persistent daily headache)
- P3 = pregnancy/postpartum new onset
- P4 = precipitated by Valsalva – cough, sneeze, bending, straining

Migraine preventive treatment

- Antiepileptic – valproate, topiramate, gabapentin
- Antidepressant – amitriptyline, venlafaxine
- Beta blocker – propranolol, metoprolol, timolol
- Other antihypertensives – verapamil, lisionpril, candesartan
- Neurotoxins – Botox
- Calcitonin gene-related peptide mAbs – erenumab, fremanezumab, galcanezumab, eptinezumab

Medication	Target dosing[a]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Divalproex sodium	250-500 mg 2 times a day or 500-1000 mg delayed release once daily	A	May cause thrombocytopenia or hepatotoxicity; monitoring is required; contraindicated during pregnancy; use limited by side effect burden despite efficacy
Topiramate	100 mg once daily or 50 mg 2 times a day	A	May cause weight loss, which some patients find beneficial; contraindicated in patients with nephrolithiasis
Metoprolol	50 mg 2 times a day	A	Unlikely to worsen asthma (highly cardioselective)
Propranolol	60 mg once daily or 2 times a day	A	Contraindicated in people with asthma; evidence that beta-blockers worsen depression has been challenged in recent years
Eptinezumab	100-300 mg IV every 3 months	N/A	Faster onset because of IV administration
Erenumab	70 mg or 140 mg subcutaneous monthly	N/A	Constipation, hypertension, hypersensitivity reaction
Fremanezumab	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	N/A	
Galcanezumab	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly	N/A	
OnabotulinumtoxinA	155 units subcutaneous monthly	A	Lack of systemic side effects and drug interactions makes this a high-priority option for patients with chronic migraine
Amitriptyline	50 mg nightly	B	Generally better tolerated when started at lower doses and increased slowly
Venlafaxine	75-225 mg extended release once daily	B	May worsen headaches in some patients; withdrawal syndrome can be prolonged and bothersome
Candesartan	8-16 mg once daily	C	Generally well tolerated
Lisinopril	10-40 mg once daily	C	Generally well tolerated
Cyproheptadine	4-8 mg once daily or divided 2 times a day	C	Use limited by sedation and weight gain
Gabapentin	900-3600 mg total daily dose, divided 3 times a day	U	Frequently used despite lack of clinical trial data; dose amounts and frequency have high variability
Verapamil	120-240 mg once daily	U	Frequently used despite lack of clinical trial data, likely because of the benign side effect profile
Memantine	10 mg 2 times a day	None	Generally well tolerated
Duloxetine	60 mg once daily	None	Used in place of venlafaxine because of decreased risk of withdrawal syndrome; better evidence for use in pain conditions globally
Levetiracetam	500-1000 mg 2 times a day	None	Recent evidence suggests possible benefit[11]
Nortriptyline	50 mg once daily	None	Used in place of amitriptyline because of decreased anticholinergic effects
Pregabalin	25-75 mg 3 times a day	None	Used if gabapentin is effective but not tolerated or loses efficacy

AAN = American Academy of Neurology; AHS = American Headache Society; IV = intravenous; N/A = not available.
[a] Many patients with migraine respond to lower doses of preventive medication, whereas others may need higher doses.

Migraine acute treatment

- Paracetamol 1000mg (Level A)
- Aspirin 500mg, diclofenac 50-100mg, ibuprofen 200-400mg, naproxen 500-550mg (Level A)
- Triptans – rizatriptan, sumatriptan, eletriptan, zolmitriptan (Level A)
- Codeine, tramadol (Level B, medium to weak evidence)

Non-pharmacological migraine treatment

- Lifestyle modifications
  - Adequate sleep
  - Good hydration
  - Well-balanced frequent meals
  - Avoid alcohol
  - Modest morning caffeine
  - Regular physical activity
  - Stress management
- Herbal/nutritional supplements
  - Magnesium (B)
  - Riboflavin (B)
  - Coenzyme Q10 (C)
  - Melatonin
  - Feverfew (B)

Non-pharmacological migraine treatment

- Behavioural, mind-body
  - Yoga, meditation
  - Cognitive behavioural therapy
  - Relaxation training
- Physical
  - Acupuncture – difficult to validate – different treatment paradigms
- Neuromodulation
  - External trigeminal nerve stimulation device
  - Single-pulse transcranial magnetic stimulation device

Cluster headache (and other TACs)

- Trigeminal autonomic cephalalgias (TACs)
- Cluster headache
  - Severe unilateral orbital, supraorbital, temporal pain, 15-180mins
  - At least one of, ipsilateral to headache:
    - Conjunctival injection/lacrimation
    - Nasal congestion/rhinorrhea
    - Eyelid edema
    - Forehead/facial sweating
    - Miosis/ptosis
  - Restlessness/agitation
  - Frequency – one alt die to 8/day

Other TACs

- Short lasting unilateral neuralgiform headache attacks (SUNHA)
  - 1-600s
  - Up to 100s per day
  - Preventive – lamotrigine, topiramate, gabapentin, indomethacin
- Paroxysmal hemicrania
  - 2-30mins
  - 1-40 per day
  - Preventive: indomethacin
- Hemicrania continua
  - Continuous pain, superimposed attacks
  - 20-50 per day
  - Preventive: Indomethacin

Migraine vs cluster headache

- Migraine
  - Location: Variable, unilateral in 60%
  - Duration: Hours to days
  - Autonomic: Sometimes
  - Migrainous features: Always
  - Triggers: Menses, pregnancy, menopause, stress, exercise, bright lights
- Cluster headache
  - Location: Unilateral frontal/temporal/periorbital
  - Duration: Minutes to hours
  - Autonomic: Always
  - Migrainous: Sometimes
  - Triggers: Alcohol, sleep

When to refer a migraine patient?

- Disabling migraine headaches despite trials of at least 2 first line migraine preventive medications without improvement
- a third prophylactic agent should be commenced while awaiting review)
- Common preventive oral agents:
  - Propranolol 40mg bd
  - Topiramate 50mg nocte
  - Amitriptyline 50mg nocte
  - Valproate 200mg bd
  - Sandomigran 1.5mg nocte
- Address medication overuse headache (paracetamol, NSAID, codeine, triptans)

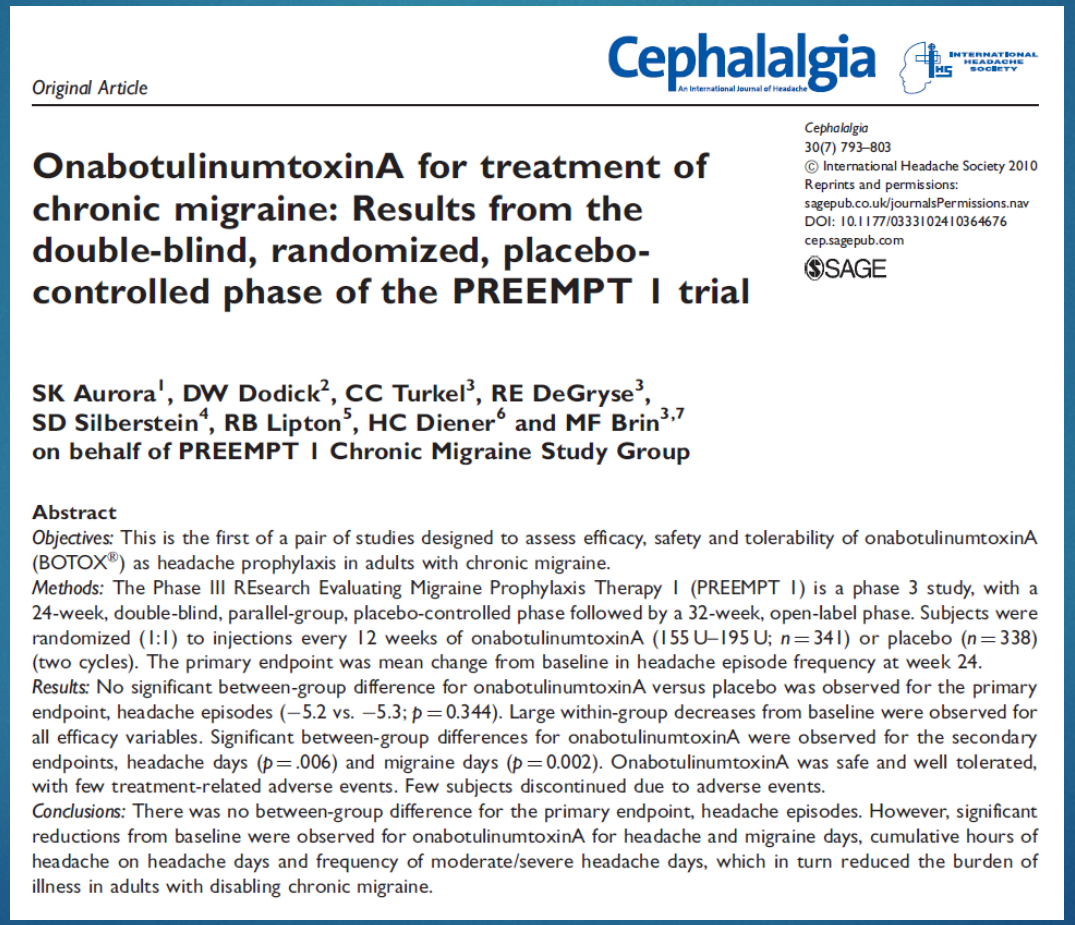
Medication overuse headache

- Headache >15 days/month in patient with headache disorder
- Regular overuse for >3 months of 1 or more acute treatment drugs
  - Panadol +/- codeine
  - NSAIDS
  - Opioids – tramadol, mersyndol
  - Triptans
- Screening questions:
  - Do you have headache >15days/month?
  - Do you take treatment:
    - >10 days/month?
    - For >3 months?
    - Regularly?

PBS criteria for botulinum toxin and CGRP blockers

- Treated by neurologist
- Chronic migraine criteria: >15 headache days/mth, >8 migraine days/mth, over >6 months
- Failed 3 preventives: propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, valproate, topiramate
- Medication overuse headache appropriately managed
- 18 years or older

Botulinum toxin for chronic migraine



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OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial

SK Aurora[1], DW Dodick[2], CC Turkel[3], RE DeGryse[3], SD Silberstein[4], RB Lipton[5], HC Diener[6] and MF Brin[3,7] on behalf of PREEMPT 1 Chronic Migraine Study Group

Abstract

Objectives: This is the first of a pair of studies designed to assess efficacy, safety and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.

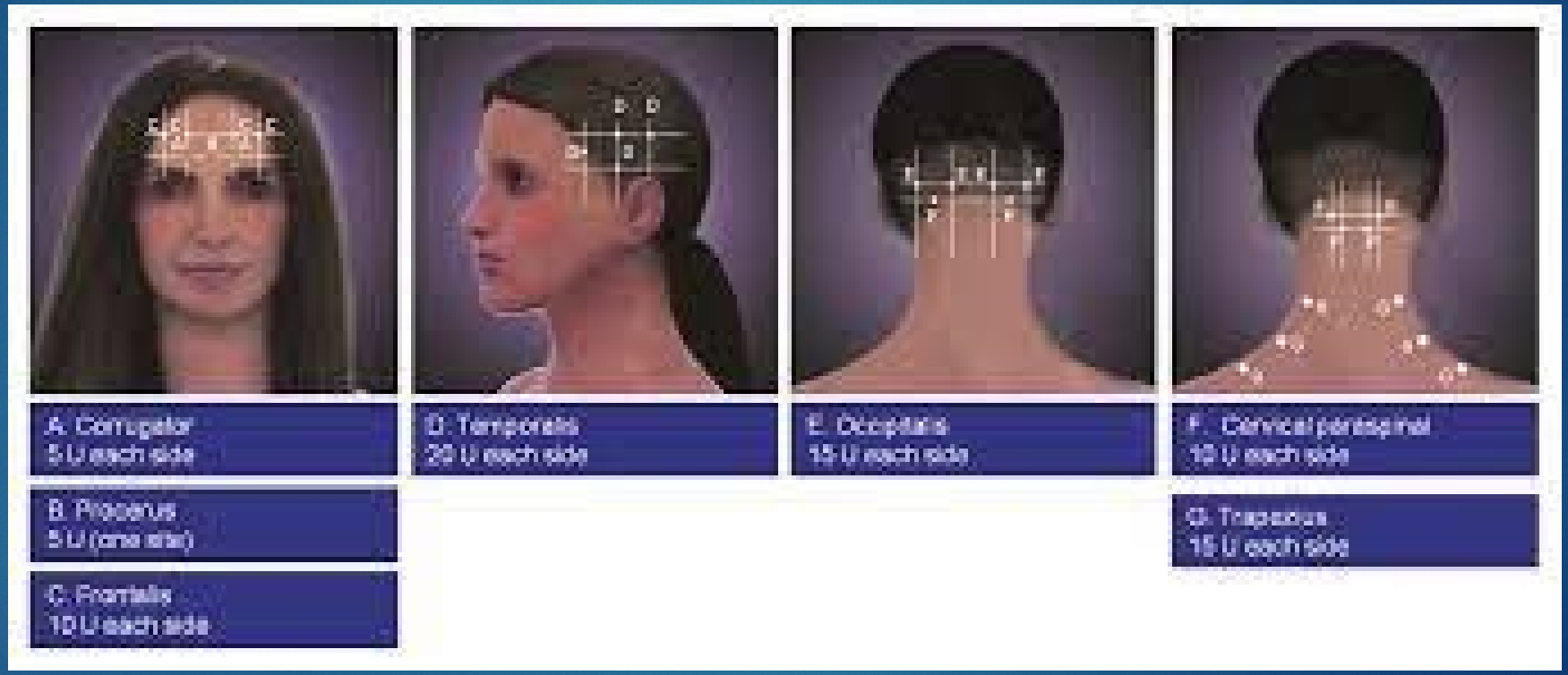
Methods: The Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1 (PREEMPT 1) is a phase 3 study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Subjects were randomized (1:1) to injections every 12 weeks of onabotulinumtoxinA (155 U–195 U; $n = 341$) or placebo ($n = 338$) (two cycles). The primary endpoint was mean change from baseline in headache episode frequency at week 24.

Results: No significant between-group difference for onabotulinumtoxinA versus placebo was observed for the primary endpoint, headache episodes (−5.2 vs. −5.3; $p = 0.344$). Large within-group decreases from baseline were observed for all efficacy variables. Significant between-group differences for onabotulinumtoxinA were observed for the secondary endpoints, headache days ($p = .006$) and migraine days ($p = 0.002$). OnabotulinumtoxinA was safe and well tolerated, with few treatment-related adverse events. Few subjects discontinued due to adverse events.

Conclusions: There was no between-group difference for the primary endpoint, headache episodes. However, significant reductions from baseline were observed for onabotulinumtoxinA for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine.

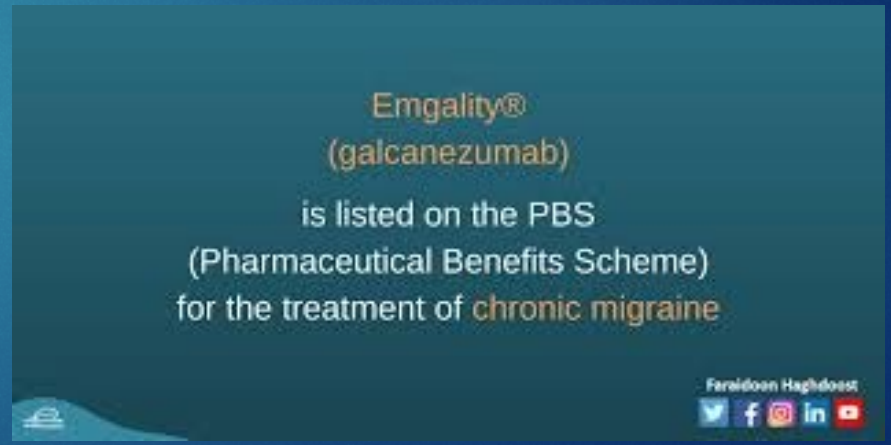
Botox (botulinum toxin) for chronic migraine

- PREEMPT protocol – 155 to 195 U at 31-39 sites, 3 monthly



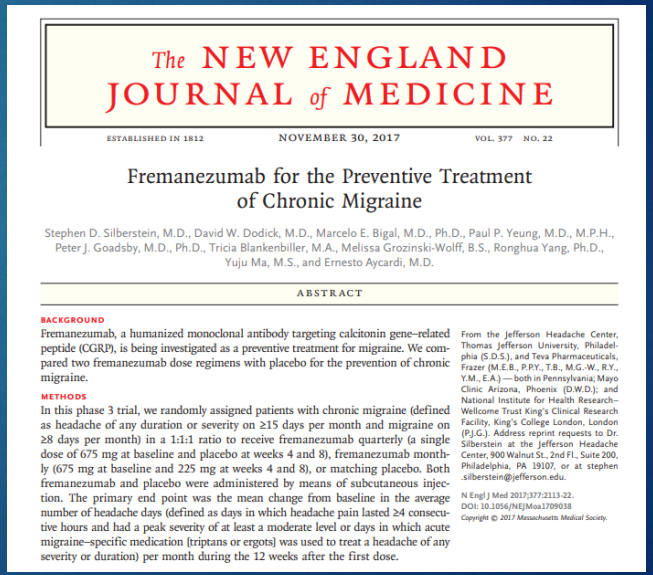
PBS Approved CGRP blocke

- Emgality (galcanezumab)
- Binds to CGRP ligand
- 2 x 120mg loading dose 1st month, then 120mg self-injected per month thereafter
- ADRs:
  - Injection site reaction (rare)
  - Angioedema/anaphylaxis (rarer)



PBS Approved CGRP block

- Ajovy (fremanezumab)
- Blocks CGRP binding to receptor
- 225mg self-administered S/C monthly or 675mg every 3 months
- ADRs
  - Injection site reaction
  - Angioedema/anaphylaxis



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Fremanezumab for the Preventive Treatment of Chronic Migraine

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ABSTRACT

BACKGROUND

Fremanezumab, a humanized monoclonal antibody targeting calcitonin gene–related peptide (CGRP), is being investigated as a preventive treatment for migraine. We compared two fremanezumab dose regimens with placebo for the prevention of chronic migraine.

METHODS

In this phase 3 trial, we randomly assigned patients with chronic migraine (defined as headache of any duration or severity on ≥15 days per month and migraine on ≥8 days per month) in a 1:1:1 ratio to receive fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8), fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8), or matching placebo. Both fremanezumab and placebo were administered by means of subcutaneous injection. The primary end point was the mean change from baseline in the average number of headache days (defined as days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level or days in which acute migraine–specific medication [triptans or ergots] was used to treat a headache of any severity or duration) per month during the 12 weeks after the first dose.

From the Jefferson Headache Center, Thomas Jefferson University, Philadelphia (S.D.S.), and Teva Pharmaceuticals, Frazer (M.E.B., P.P.Y., T.B., M.G.-W., R.Y., Y.M., E.A.) — both in Pennsylvania; Mayo Clinic Arizona, Phoenix (D.W.D.); and National Institute for Health Research–Wellcome Trust King's Clinical Research Facility, King's College London, London (P.J.G.). Address reprint requests to Dr. Silberstein at the Jefferson Headache Center, 900 Walnut St., 2nd Fl., Suite 200, Philadelphia, PA 19107, or at stephen.silberstein@jefferson.edu.

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New migraine treatments

- Acute migraine treatment
  - Ditans (Lasmiditan tablet)
    - Selective 5-HT1F (serotonin) receptor agonist
    - Act on trigeminal system
    - Does not cause vasoconstriction, safe in patients with vascular RFs
    - Equivalent to triptan, without cardiovascular risk
    - Side effects: dizziness, fatigue, paraesthesia, sedation
  - Gepants (rimegepant, ubrogepant tablets)
    - Block CGRP
    - Use for acute treatment when triptans failed, or unacceptable triptan side effect
    - May also be useful for prevention (without long half-life of CGRP monoclonal antibodies)

Practical aspects of migraine management

- When to take acute medication
- Adequate trial of preventive (minimum 2 months), don't titrate too fast (avoid side effects)
- Headache diaries – realistic goals (most migraine trials endpoint 50% reduction in frequency episodes)
- Hormonal aspect – perimenstrual migraine
  - Mini-prevention: Naproxen 500mg bd for 5 days
- OCP with migraine:
  - Migraine with aura – use alternative to OCP
  - Migraine without aura – can use OCP but monitor for other stroke RFs (>35yrs, hypertension)