WCN2019 Teaching Course

Migraine Preventative Therapy

A/Prof Richard Stark
Van Cleeff Department of Neuroscience,
Alfred Hospital & Monash University
Richard.stark@monash.edu

Disclosures

- Advisory Board &/or Lecture Fees from:
  - Allergan
  - Novartis
  - Teva
  - Eli Lilly
  - Biogen

Learning objectives:
Understand the importance of

- Brief discussion of Diagnosis
- Triggers, Lifestyle factors & Acute treatments
- Preventive treatments
  - Traditional first line & second line therapies.
  - “Natural” remedies
  - Newer oral therapies: Topiramate, candesartan, lamotrigine
  - New Injectables: Botox, CGRP antibodies
  - Neurostimulation
  - Management of Chronic Migraine & Medication Overuse

Migraine tends to be underdiagnosed

Severe recurrent headache is usually migraine

ID Migraine: 3 question screen for migraine

- In the last three months, has a headache interfered with your activities on at least one day?
- When you have a headache, do you feel nauseated (sick)?
- When you have a headache, does light bother you?

Be alert to dual pathology:

This causes diagnostic difficulty

There may be a treatable aggravating factor for migraine

- There are many potential triggers or aggravating factors in individuals susceptible to migraine
- Most are well known: hormonal factors, diet, stress, sleep disruption
- Any significant **pain around the head or neck can be a potent migraine trigger**
  - Hence, pain arising from neck, TMJ, sinuses or other structures may trigger migraine
- If cervicogenic/TMJ/sinus headaches have migrainous features they should be treated from both angles:
  - Treat the underlying disorder
  - Also treat the migraine

Migraine: acute treatment
Classes of effective drugs

- NSAIDs
  - Includes aspirin, diclofenac, naproxen etc
- $5HT_{1B,1D}$ agonists
  - Triptans. Ergotamines probably also.
- Dopamine antagonists
  - Chlorpromazine, prochlorperazine etc
  - (appear to have migraine-lytic effect as well as anti-emetic)
- Analgesics
  - (last resort)

Excellent evidence base for all of these

Prophylaxis: 2 big questions

- **When** to opt for prophylaxis
  - Usual advice is to consider it if there are >3 migraine days per month
  - But individual circumstances vary
    - Losing a day from work once a month may persuade some patients to opt for prophylaxis
- **Which** to choose
  - There are MANY options
  - But GPs often restrict themselves to 1 or 2 drugs

Options for migraine prevention

- Traditional first line therapies — *Propranolol, pizotifen, amitriptyline*
- Older second line therapies — *Valproate, cyproheptadine, clonidine, verapamil*
- Newer oral therapies — *Topiramate, candesartan, lamotrigine*
- “Natural” remedies — *Magnesium, Vit B2, Feverfew etc*
- New Injectables — *Botox, CGRP antibodies*
- Neurostimulation
- Mini-prophylaxis for menstrual migraine

Some general principles of migraine prophylaxis

- Patients are anxious about side effects
  - Avoid obviously inappropriate treatments
- Patients may be non-compliant
- Benefits tend to be cumulative
- Benefits tend to be dose related
- Side effects tend to be dose related
- It is a balancing act: Benefit vs adverse events
- Be aware of Medication Overuse Headache (MOH)

PROPHYLAXIS: type	Generic name	Trade name	Main problems	TGA	CM
β blockers	Propranolol / metoprolol	Inderal / Betaloc	Asthma, Raynaud's	Y	
	Other more selective β blockers may be less effective (evidence is equivocal)				
Serotonin antagonists	pizotifen	Sandomigran	Weight gain, drowsiness	Y	
	cyproheptadine	Periacten		Y	
	methysergide	Deseril	Retroperitoneal fibrosis (unavailable)	Y	
Anticonvulsants	valproate	Epilim	Weight gain, hair loss, lethargy		
	topiramate*	Topamax	↓ appetite, drowsiness, tingle, dysphasia	Y	Y
	lamotrigine	Lamictal	Only for migraine with aura, rash		
	pregabalin	Lyrica	Very little data		
	gabapentin*	Neurontin	Very little data (but some in CM)		Y
Ca channel block	verapamil	Isoptin	Limited efficacy		
	flunarizine	Sibellium	Not available everywhere. Weight gain, dry mouth		
Other anti H/T inser	clonidine	Catapres	Limited efficacy	Y	
	candesartan	Atacand	High dose required, drops BP		
Tricyclics	amitriptyline / nortriptyline	Endep / Allegron	Dry mouth, drowsiness, weight gain		
MAOIs	phenelzine	Nardil	Cheese effect		
SSRIs: there is little evidence of efficacy					
Other	botulinum toxin	Botox	Limited to CM	Y	Y
Supplements	Mg++, Vit B2, etc		Limited efficacy		

Prophylaxis not tolerated

- Need to pin down details
  - What dose did they get to?
  - How long were they on it?
  - Did they actually have the reported side-effect or did they read it in the PI and assumed they would get it?

- Be aware that patients frequently do not persist with treatment
  - For example in one US study, persistence with the initial oral prophylactic was 25% at six months and 14% at twelve months.

Why do patients reject prophylaxis or why does it fail: Solutions

PROBLEM	SOLUTION
Patient reluctance “I am allergic to everything”	Listen, explain
	Choose least threatening options first for these
Unacceptable side-effects	Be aware of S/E in advance
	Choose drug suitable for individual
Poor compliance	Prefer once daily drugs
	Prefer infrequently injected treatments Botox, CGRP
Inadequate efficacy	Follow diary to get real data
	Better drugs!

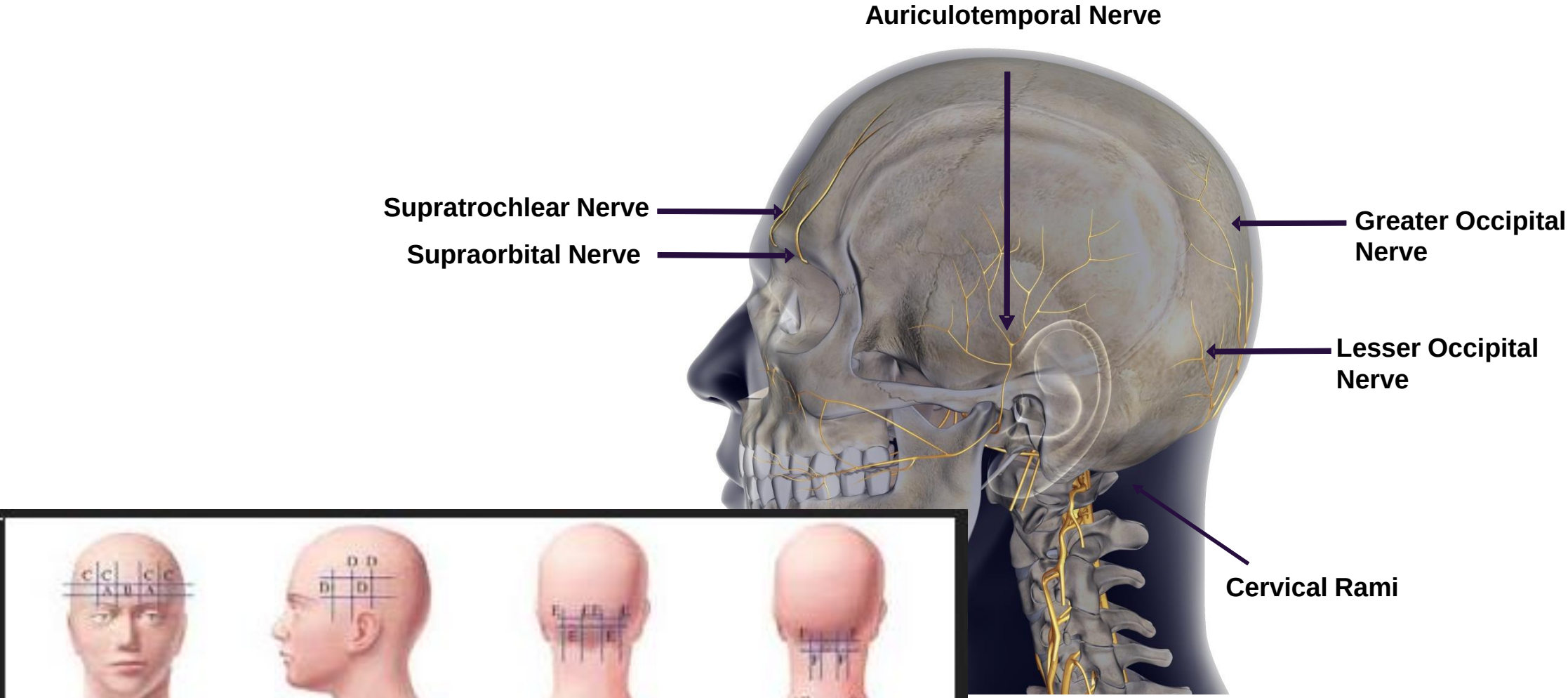
The results of the Topiramate study are typical of many migraine prophylactics

- There is a large placebo effect
- There is a better response with higher doses
- There is cumulative benefit over time
- The optimum dose reflects a balance between efficacy and dose-dependent side effects
- The optimum dose may vary between individuals

Some relatively recent additions to our options for prophylaxis

- Candesartan
  - Two good trials show its effectiveness
  - Similar effect to (but better tolerated than) propranolol
  - Not clear if the benefit is a class effect for all A2 inhibitors or specific to candesartan
- Lamotrigine
  - Benefit in patients with aura
  - No benefit in migraine without aura
  - Usually well tolerated (but beware allergic rash)
  - May be helpful for unusual “aura-like” symptoms such as visual snow

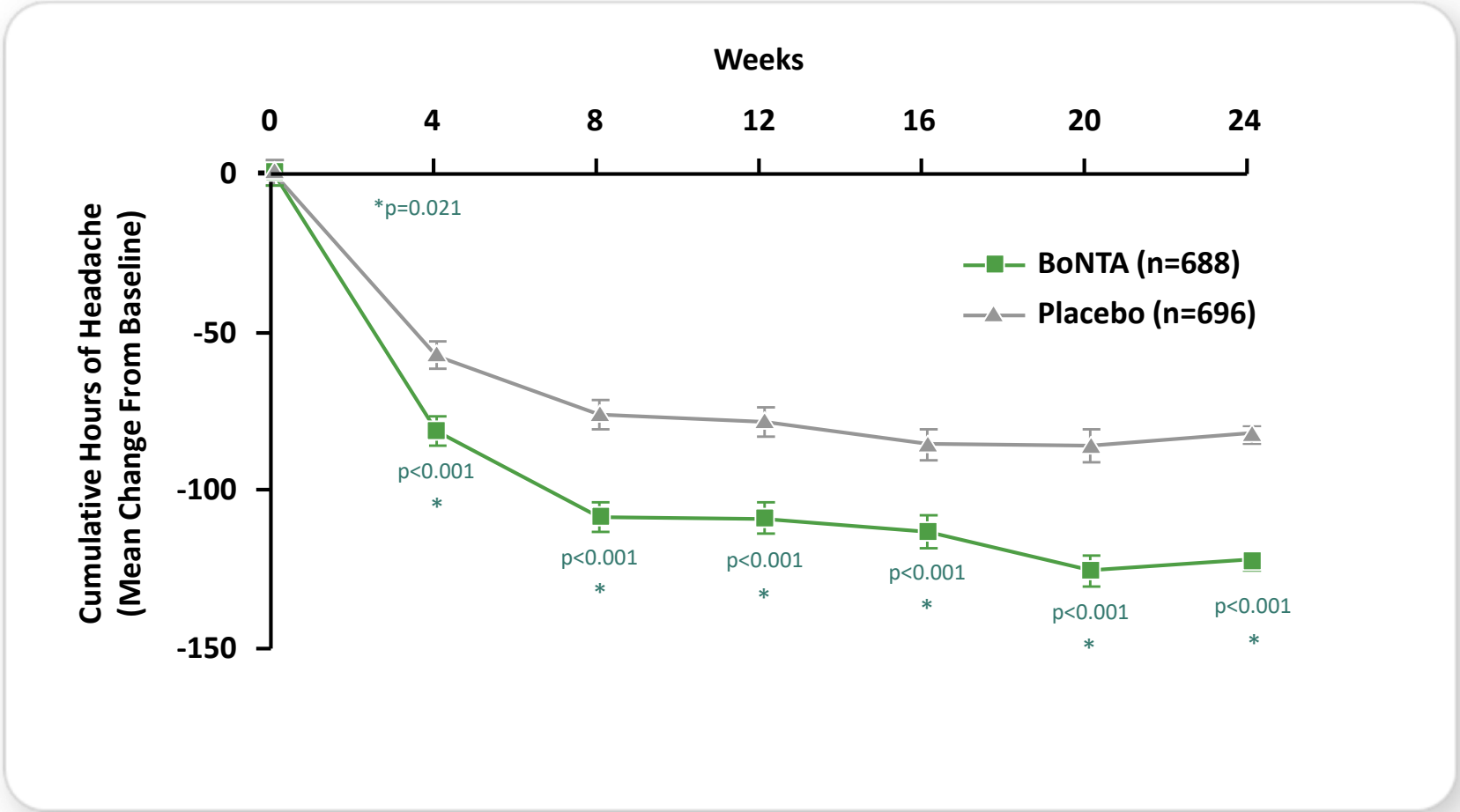
Botulinum toxin may work in CM by reducing CGRP release from pain fibres
Anatomical Injection Sites Follow Distributions & Areas Innervated by the Trigeminal Sensory System



PREEMPT 1 & 2 Pooled Analyses of Efficacy:

Mean Change From Baseline in Cumulative Hours of Headache

Botox in Chronic Migraine



*Statistically significant between-group difference: favors BoNTA vs placebo.
Cumulative hours of headache at baseline: 295.9 ± 4.5 BoNTA group vs 281.2 ± 4.4 placebo group, p=0.021.

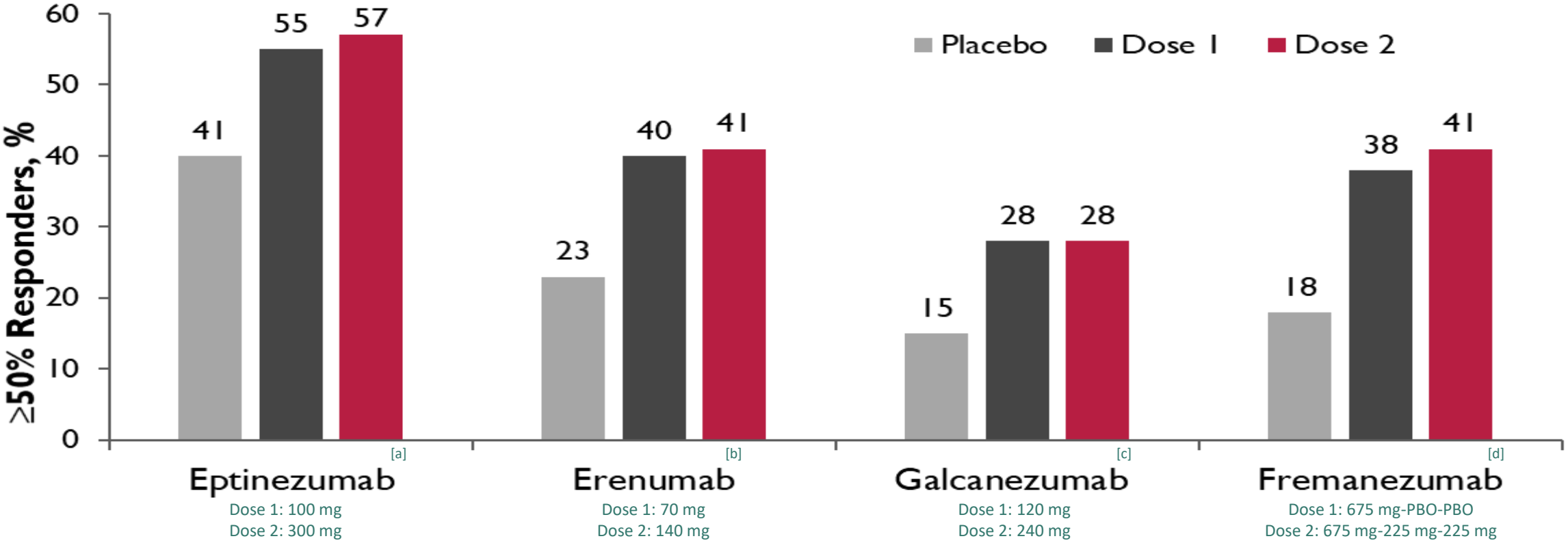
CGRP mAbs in Development for Migraine Prevention

Availability will vary between countries

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Antibody-IgG[a]	1κ	2λ	2κ	4
Type[a]	Humanized	Human	Humanized	Humanized
Target[a]	CGRP	CLR/RAMP1	CGRP	CGRP
$T_{1/2}$ (days) [a]	31	21	40-48	28
Route/frequency of administration[a]	iv (quarterly)	sc (monthly)	sc (monthly/quarterly)	sc (monthly)

Results of Studies of CGRP mAbs in **CM**
50% Responder Rates

- Outcomes of selected trials for the preventive treatment of chronic migraine



- a. Smith J, et al. *Headache.* 2017:57 Suppl 3:130; b. Tepper S, et al. *Lancet Neurol.* 2017;16:425-434; c. Detke HC, et al. *Cephalalgia.* 2017;37:338; d. Silberstein SD, et al. *N Engl J Med*. 2017;377:2113-2122.

Approach to treating Chronic migraine

- Is there medication overuse? If so,
  - Deal with this first
  - Treatments for the underlying condition are often ineffective when the rebound cycle is established, but become effective later
- Then manage the underlying condition

Treating MOH

- Patient must see the point and want treatment
- Withdraw & withhold offending drugs
- Psychiatric assessment
- Manage inevitable withdrawal headache
- Abrupt withdrawal is best
- Outpatient options
  - NSAIDs or Steroids
- Inpatient options
  - Just observe (Katsarava & Diener group)
  - DHE or Lignocaine

Is MOH the same condition whether the medication is opioid, Triptan, paracetamol or NSAID?

No!!

- Anecdotally:
  - **opioids** are worse than
  - **ergotamines** which are worse than
  - **triptans** which are worse than
  - **simple analgesics**; and
  - **NSAIDs** are not much of a problem
- In Australia **codeine** has been a major concern

Headache:
Take Home Messages (1)

- Migraine is currently under-recognised and under-treated in the community.
- Migraine treatment may include lifestyle measures, acute therapies and prophylaxis
- There are many options for prophylaxis
- Being aware of potential side-effects and reasons or patient resistance to treatment is vital

Headache:
Take Home Messages (2)

- There are new and exiting treatments emerging
- These include “re-purposing” existing drugs
- Botox has revolutionised the treatment of chronic migraine
- CGRP antibodies are very promising
- Neurostimulation shows some promise too
- Specific approaches to menstrual migraine and MOH

Some references

- Stark RJ, Valenti L, Miller GC.. *Medical Journal of Australia* 2007; 187:142-146 (**Management of migraine in Australian general practice**)
- Silberstein et al *Arch Neurol. 2004;61:4* (**Topiramate**)
- Tronvik et al, JAMA 2003:289:65-69 (**Candesartan**)
- Lampl C, et al. *J Neurol Neurosurg Psychiatry 2005; 76: 1730–32*.(**Lamotrigine in migraine with aura***)*
- Aurora SK, 2011. Headache 51:1358-1373. (**PreEmpt Trial Botulinum toxin in CM pooled d**ata)
- Smith, J et al Headache, 2017. 57(53): p. 130. (**Eptinezumab in CM***)*
- Tepper, S., et al. Lancet Neurol, 2017. 16(6): p. 425-434. (**Erenumab in CM**)
- Silberstein, S.D., et al.,. N Engl J Med, 2017. 377(22): p. 2113-2122. *(***Fremanezumab in CM)**
- Detke HC, et al. *Cephalalgia.* 2017;37:338; (**Galcanezmab in CM**)
- Schoenen J; et al. *Neurology. 80(8):697-704, 2013* (**Cefaly trial**)
- Katsarava et al. *Neurology 2001;57:1694 – 1698* (**Patterns of MOH)**