WCN2019 Teaching Course

Migraine Preventative Therapy

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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\textsubscript{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

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

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

Cumulative hours of headache at baseline: 295.9 ± 4.5 BoNTA group vs 281.2 ± 4.4 placebo group, p=0.021.

*Statistically significant between-group difference: favors BoNTA vs placebo.
CGRP mAbs in Development for Migraine Prevention
Availability will vary between countries

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab</th>
<th>Erenumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody-IgG</strong>[^a]</td>
<td>1κ</td>
<td>2λ</td>
<td>2κ</td>
<td>4</td>
</tr>
<tr>
<td><strong>Type[^a]</strong></td>
<td>Humanized</td>
<td>Human</td>
<td>Humanized</td>
<td>Humanized</td>
</tr>
<tr>
<td><strong>Target[^a]</strong></td>
<td>CGRP</td>
<td>CLR/RAMP1</td>
<td>CGRP</td>
<td>CGRP</td>
</tr>
<tr>
<td><strong>T₁/₂ (days)^[a]</strong></td>
<td>31</td>
<td>21</td>
<td>40-48</td>
<td>28</td>
</tr>
<tr>
<td><strong>Route/frequency of administration[^a]</strong></td>
<td>iv (quarterly)</td>
<td>sc (monthly)</td>
<td>sc (monthly/quarterly)</td>
<td>sc (monthly)</td>
</tr>
</tbody>
</table>
Results of Studies of CGRP mAbs in CM 50% Responder Rates

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

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*)


• Aurora SK, 2011. *Headache* 51:1358-1373. (*PreEmpt Trial Botulinum toxin in CM pooled data*)


• Schoenen J; et al. *Neurology.* 80(8):697-704, 2013 (*Cefaly trial*)

• Katsarava et al. *Neurology* 2001;57:1694 – 1698 (*Patterns of MOH*)