Current migraine prevention and management

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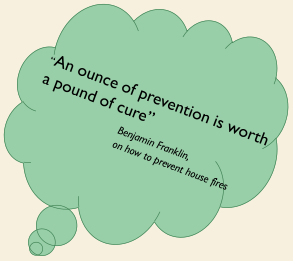


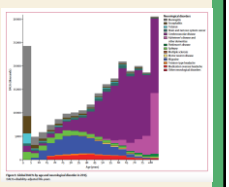
MIGRAINE IS COMMON

- No reliable specific migraine data for Australia
- Population of 24.64 million (2017)
- Assuming mean prevalence of 11.2, then 2.76 million Australians have migraine.

Ref: 1. Steiner TJ et al. Lifting the Burden

EVEN WORSE, MIGRAINE IS DISABLING

- Results from the Global Burden of Disease Study 2015:
  - Migraine is the second most disabling disease overall
  - It is the greatest cause of disability adjusted life years (DALY), under the age of 50
- Migraine impairs ability to function, work and maintain relationships
- There is an increased rate of anxiety, depression and other comorbidities
- We routinely measure headache days, but aura, premonitory and postdromal symptoms also impair people.



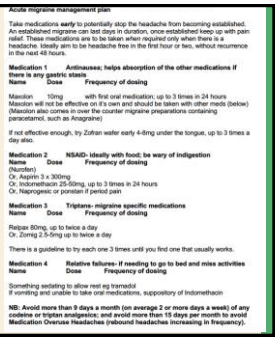
PRINCIPLES OF MIGRAINE MANAGEMENT

- Goals[1-3] include improvement in headache burden by reducing:
  - Headache days
  - Headache duration
  - Headache intensity and severity
- Benefits occur over time and cannot be expected immediately[3]
- Acute treatment: "when needed"
  - Aim to be headache free within 1-2 hours and back to usual activities within 4 hours
  - Secondary aim to not have recurrent headache within 48 hours
- Prophylactic treatment:
  - Aim to reduce the frequency of attacks & the degree of disability

Ref: 1. Dodick DW, Silberstein SD. *Pract Neurol.* 2007;7:383-393. 2. Zeeberg P et al. *Neurology.* 2006;66:1894-1898. 3. Silberstein SD et al. *Clin Ther.* 2006;28:1002-1011.

ACUTE TREATMENT

- If nauseated, need absorption of other oral medications- antiemetic
- NSAIDs
- Triptans
- "Relative failures"- not appropriate to use narcotics regularly; but some need strong analgesics or suppositories on *rare* occasions


Acute migraine management plan

Take medications **early** to potentially stop the headache from becoming established. An established migraine can last days in duration, once established keep up with pain relief. These medications are to be taken when required only when there is a headache. Ideally aim to be headache free in the first hour or two, without recurrence in the next 48 hours.

Medication 1 Antinausea; helps absorption of the other medications if there is any gastric stasis
Name Dose Frequency of dosing

Maxolon 10mg with first oral medication; up to 3 times in 24 hours
Maxolon will not be effective on it's own and should be taken with other meds (below)
(Maxolon also comes in over the counter migraine preparations containing paracetamol, such as Anagraine)

If not effective enough, try Zofran wafer early 4-8mg under the tongue, up to 3 times a day also.

Medication 2 NSAID- ideally with food; be wary of indigestion
Name Dose Frequency of dosing
(Nurofen)
Or, Aspirin 3 x 300mg
Or, Indomethacin 25-50mg, up to 3 times in 24 hours
Or, Naprogesic or ponstan if period pain

Medication 3 Triptans- migraine specific medications
Name Dose Frequency of dosing

Relpax 80mg, up to twice a day
Or, Zomig 2.5-5mg up to twice a day

There is a guideline to try each one 3 times until you find one that usually works.

Medication 4 Relative failures- if needing to go to bed and miss activities
Name Dose Frequency of dosing

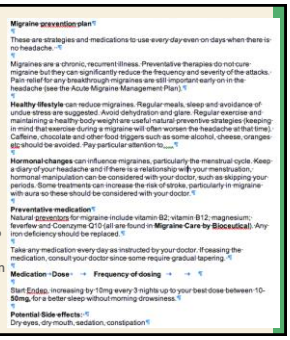
Something sedating to allow rest eg tramadol
If vomiting and unable to take oral medications, suppository of Indomethacin

NB: Avoid more than 9 days a month (on average 2 or more days a week) of any codeine or triptan analgesics; and avoid more than 15 days per month to avoid Medication Overuse Headaches (rebound headaches increasing in frequency).

PROPHYLACTIC TREATMENT

- Strategies for every day to decrease the frequency and severity of the migraines
- Consider lifestyle issues to target
- Hormonal management (not first line)
- Nutriceuticals (natural prophylactic medications; check for deficiencies)

- **Medication prophylaxis**
  - If more than 3 *significant* migraines a month
    - Difficult to treat migraines or too frequent
  - Current choices largely dependent on interactions and side effects
  - Current compliance limited by tolerability, interactions and efficacy



Migraine prevention plan

These are strategies and medications to use every day even on days when there is no headache.

Migraines are a chronic, recurrent illness. Preventative therapies do not cure migraine but they can significantly reduce the frequency and severity of the attacks. Pain relief for any breakthrough migraines are still important early on in the headache (see the Acute Migraine Management Plan).

Healthy lifestyle can reduce migraines. Regular meals, sleep and avoidance of undue stress are suggested. Avoid dehydration and glare. Regular exercise and maintaining a healthy body weight are useful natural preventive strategies (keeping in mind that exercise during a migraine will often worsen the headache at that time). Caffeine, chocolate and other food triggers such as some alcohol, cheese, oranges etc should be avoided. Pay particular attention to.....

Hormonal changes can influence migraines, particularly the menstrual cycle. Keep a diary of your headache and if there is a relationship with your menstruation, hormonal manipulation can be considered with your doctor, such as skipping your periods. Some treatments can increase the risk of stroke, particularly in migraine with aura so these should be considered with your doctor.

Preventative medication

Natural preventors for migraine include vitamin B2; vitamin B12; magnesium; feverfew and Coenzyme Q10 (all are found in **Migraine Care by Bioceutical**). Any iron deficiency should be replaced.

Take any medication every day as instructed by your doctor. If ceasing the medication, consult your doctor since some require gradual tapering.

Medication - Dose → Frequency of dosing → →

Start Endep, increasing by 10mg every 3 nights up to your best dose between 10-50mg, for a better sleep without morning drowsiness.

Potential Side effects:

Dry eyes, dry mouth, sedation, constipation

REALISTIC EXPECTATIONS: WHAT IS HALF OF A LOT?

- Diary for objective measurement, as important for the patient as for the doctor
- Ideally captures frequency *and* severity in a simple to read way

Acknowledgement: Dr Paul Spira, Aspen Headache Diary

"NOTHING WILL WORK"

Consider:

1. Diagnosis is incomplete or incorrect
2. Important exacerbating factors have been missed
3. Pharmacotherapy has been inadequate
4. Non-pharmacologic treatment has been inadequat
5. Other factors, including unrealistic expectations and comorbidities

Ref: Lipton RB, Silberstein SD, Saper JR, Bigal ME, Gaodsby PJ. Neurology April 2003

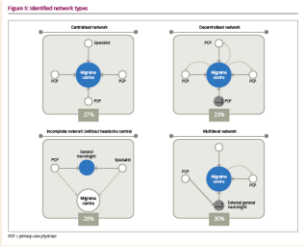
MIGRAINE MANAGEMENT IN AUSTRALIA: PRIMARY CARE

- BEACHES study in 2007, regarding GP management[1]:
  - Migraine is recognised frequently in Australian general practice
    - Prevalence was 14.9% in females and 6.1% in males.
    - Majority had one or fewer attacks per month (77.1%). 12.3% had three or more per month
  - Use of acute medication often follows published guidelines
    - 60.6% of the acute medications were recommended; but opioids were 38% of acute medications
  - Prophylactic medication appears to be underutilised, especially in patients with frequent migraine
    - Only 8.3% (54/648) of migraine patients were currently taking prophylactic medication.
  - A limited range of therapeutic options for migraine prophylaxis
    - The most common prophylactic agents used were pizotifen and propranolol; others were rarely used
  - Some GPs used inappropriate drugs for migraine prevention
    - inappropriate use of acute medications accounted for 9% of "prophylactic treatments"

Ref: 1. Stark RJ, Valenti L, Miller GC. "Management of migraine in Australian general practice" *MJA*, 2007; 187(3): 142-6

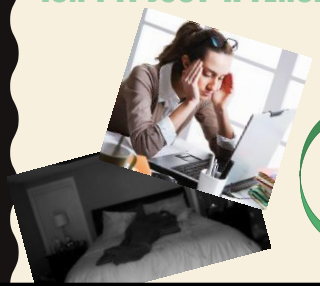
"MOST" PROJECT

- 28 health care networks, mainly in Europe and 3 in Australia
- Different models (right image)
- Findings:
  - New patients waited more than 3 months in 61%
  - Average waiting time was 6 months for initial appointment (even >12 months)
  - Follow ups waited more than 3 months in 36%.
- Recommendations included:
  - a "network" approach to bridge different levels of care
  - Consistency in practice amongst specialised headache clinics
  - Integration with primary care



Ref: Kainth P et al. "management of migraine and the accessibility of specialist care- findings from a multi-national assessment of 28 healthcare networks" *European Neurological Review*. 2018; 13(2): Epub ahead of print

ISN'T IT JUST A TENSION HEADACHE?



Episodic migraine

Diagnostic criteria:

A. At least five attacks[2] fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Only needs 2 of the features (C), Only needs one or more of the associated features (D)

DIFFERENTIATING TENSION TYPE HEADACHE FROM MIGRAINE

Chronic migraine

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days/month for >3 months, fulfilling any of the following[2]:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.[3 5]

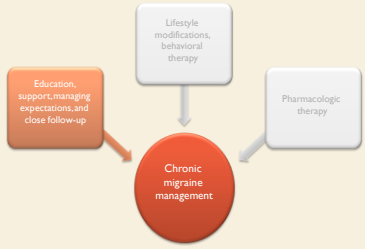
Tension type headache

Diagnostic criteria:

A. At least 10 episodes of headache occurring on <1 day/month on average (<12 days/year)
B. Lasting from 30 minutes to 7 days
C. At least two of the following four characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. no nausea or vomiting
   2. no more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.[3]

Ask about preference to rest, vs exercising for distraction

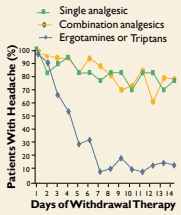
MULTIFACETED APPROACH TO THERAPY



Ref: Dodick DW. *N Engl J Med.* 2006;354:158-165.

MANAGEMENT OF MEDICATION OVERUSE

1. Patient education
2. Withdrawal of overused medication
   Abrupt better than gradual
3. Bridging therapy for withdrawal headache (4 days for triptans, 10 days for opiates)
   Outpatient: NSAID (eg naproxen SR 750mg or prednisolone)
   Inpatient infusions
4. Prophylactic
   Best timing not yet clear
5. Monitor for relapse



Diener HC, Limmroth V. *Lancet Neurol.* 2004;3:475-483.

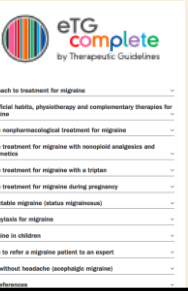
PREVENTIVE TREATMENT MIGRAINE

- Preventive treatment can reduce migraine headache days, severity, and disability[1]
- Initiate preventive treatment[2]
  - In Germany, only 7% of individuals were treated with preventive therapy[2];
  - AAN working group found 13% of expected 38% were treated with prophylactics
- Individualize drug selection[2]
  - Comorbid and coexistent illness/disorders
- Select preventive drug based on evidence when possible[2]
- Combining 2 preventive drugs may be useful in selected cases[2]
- A diary and/or disability measure are important to monitor response to therapy

Ref: 1. Dodick DW, Silberstein SD. *Pract Neurol.* 2007;7:383-393.2. Katsarava Z. et al. Submitted.3. Vargas BB, Dodick DW. *Neurol Clin.* 2009;27:467-479.

OUR CLINICAL PRACTICE IN AUSTRALIA: USEFUL RESOURCES

- Electronic Therapeutic Guidelines, updated November 2017
  - Printable sheets
  - Diagnosis tips and red flags
  - Pharmacological management
  - specifics such as medication dosing and safety are all considered



HEADACHE THERAPEUTIC GUIDELINES

- Offers multiple options, without being an exhaustive list
- Dosing and titration are included.
- States reasonable trial is 8-12 weeks; and if several medications are not effective then refer for expert advice

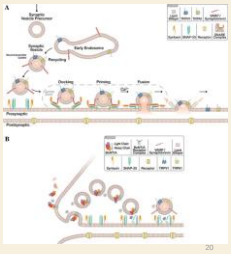
MIGRAINE: PREVENTATIVE DRUG TREATMENT

- Individualised choice largely on comorbidities, interactions and potential side effects

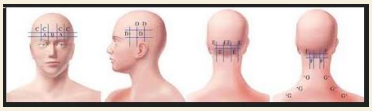
Class	Generic name	Trade Name	Main Problems
ß blockers	propranolol	Inderal	Asthma, Raynaud's
Anti Serotonin	pizotifen	Sandomigran	Weight gain, drowsiness
	cyproheptadine	Periacten	Weight gain
Anticonvulsants	valproate	Epilim	Weight gain
	topiramate	Topamax	Reduced appetite, cognitive effects
Ca ch blocker	verapamil	Isoptin	Variable efficacy
Other anti H/T	clonidine	Catapres	Variable efficacy
	candesartan	Atacand	High dose required, hypotension
Tricyclics	amitriptyline	Endep	Dry mouth drowsiness

BOTULINUM TOXIN

- Not dependent on muscle relaxation in Chronic Migraine
- Acts by modulating neurotransmitters
- Authority in Australia depends on having >15 days of headache a month; and failed 3 preventors.



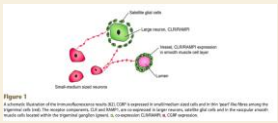
PREEMPT PROTOCOL OF BOTOX FOR CHRONIC MIGRAINE



155 units injected in 31+ sites over the course of nerves, such as supraorbital, supratrochlear, auriculotemporal and occipital nerves

EMERGING TREATMENTS

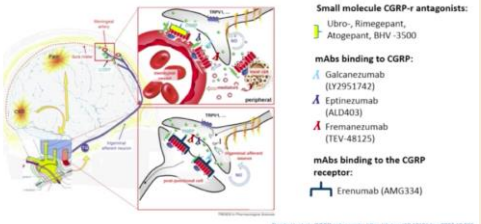
- CGRP monoclonal antibodies
  - Erenumab recently approved by TGA (PBS status pending); Galcanezumab, Fremanezumab, Eptinezumab



- SCI or IV administration
- All phase II/III trials have been +ve in EM and CM, including primary endpoint of >50% response rate
- Steeper response curve, compared to usual slow response (still worth 3 months trial)
- No significant side effects
- No known interactions.
- No short term safety issues, with limited data up to 3 years

Ref: Edvinsson L et al

CGRP: Monoclonal antibodies (mAbs) & small molecules for migraine therapy



Small molecule CGRP-r antagonists:
Ubro-, Rimegepant, Atogepant, BHV -3500

mAbs binding to CGRP:
Galcanezumab (LY2951742)
Eptinezumab (ALD403)
Fremanezumab (TEV-48125)

mAbs binding to the CGRP receptor:
Erenumab (AMG334)

Also small molecule CGRP antagonists under development

SUMMARY

The important components of migraine management:

- Accurate diagnosis[1]
- Patient education[2]
- Nonpharmacological strategies including trigger management, lifestyle modification, and behavioral therapy[1,3]
- Management of overuse of acute medications[2]
- Use of both symptomatic and prophylactic drugs[4]
- Headache diary and disability instrument can help to monitor response to treatment[3,5]

1. Silberstein SD, Lipton RB. In: Silberstein SD, et al., eds. *Wolff's Headache and Other Head Pain*. 8th ed. New York: Oxford University Press; 2008:315-377.
2. Dodick DW. *N Engl J Med*. 2006;354:158-165.
3. Gallagher RM, Cutrer FM. *Am J Manag Care*. 2002;8:558-573.
4. Vargas BB, Dodick DW. *Neurol Clin*. 2009;27:467-479.
5. Kosinski M et al. *Qual Life Res*. 2003;12:963-974.