South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurology

MEDICINE REVIEW:

1. Executive Summary

Date: 14 June 2018
Medicine (INN): Valproic acid, Topiramate, Carbamazepine, Propanolol, Atenolol and Amitriptyline
Medicine (ATC): N03AG01 /N03A11/C07AA05
Indication (ICD10 code): Prophylaxis in adults experiencing >5 migraine attacks per month.
Patient population: Adults needing migraine prophylaxis
Level of Care: Adult Hospital level (secondary and regional level)
Prescriber Level: Doctors
Current standard of Care: Amitriptyline, carbamazepine
Efficacy estimates: (preferably NNT): No significant difference in efficacy between: valproic acid, topiramate, propranolol, and atenolol NNT= 7 to achieve > 50% reduction on migraine frequency. >50% reduction in monthly migraine frequency in 200-400 patients per 1000 treated.[1] Carbamazepine of doubtful efficacy[3].
Motivator/reviewer name(s): Dr Anastasia Rossouw, Dr Andrew Black
PTC affiliation: East London Hospital Complex PTC

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Anastasia Rossouw
Secondary reviewer: Dr Andrew Black

3. Author affiliation and conflict of interest details

Primary reviewer (AR):

Affiliation: PTC East London Hospital Complex Pharmacy Therapeutics Committee; Adult Hospital Level Committee (2017-2020).
Conflict of interest: Sanofi Aventis: Honorarium received for conducting workshop-training sessions.

Secondary reviewer (AB):

Affiliation: Helen Joseph Hospital, Gauteng, Adult Hospital Level Expert Review Committee (2017-2019).
Conflict of interest: Astra Zeneca - Attendance and accommodation to attend industry funded Pulmonology Update; Pfizer - Sponsorship to attend Pneumococcal weekend summit; Bristol Meyers Squib Foundation - Pro rata fee for training on Lung Cancer screening and diagnosis, as part of a Lung Cancer screening and Diagnosis grant.

4. Indication:

Migraine prophylaxis in patients who has episodic migraine not responding to acute management strategies.

5. Introduction/ Background

Migraine is common with a global prevalence ranging between 8-18%. It preferentially affects more women than men, aged between first to fourth decade of life.[1] Migraine prophylaxis is warranted when abortive acute oral medications fail to provide symptomatic relief with recurrent, typically more than five attacks per month (Internal Headache Society Classification).
The current STG includes carbamazepine as a treatment option for migraine prophylaxis. The efficacy of carbamazepine for this condition was questioned and an alternative agent suggested.

This review was carried out to
a) determine the efficacy of carbamazepine for this condition;
b) review the evidence for efficacy of the three major classes of medicines used for migraine prophylaxis (Anti epileptics, B blockers and tricyclic anti-depressants); and
c) assess if any of the medicines with established efficacy are superior.

6. **Purpose/Objective** : To assess the efficacy and safety of medications used as migraine prophylaxis.

Population: adults presenting with recurrent migraine attacks (>5 attacks per month)
Intervention: agents indicated for migraine prophylaxis (propranolol, atenolol, topiramate, valproic acid)
Comparison: amitriptyline, carbamazepine
Outcomes: reduction in migraine attacks (>50% reduction in headache frequency)

7. **Methods:**
   a) **Data sources and search strategy**
   Pubmed and Cochrane

   ("anticonvulsants"[All Fields] OR "anticonvulsants"[MeSH Terms] OR "anticonvulsants"[All Fields] OR ("antiepileptic"[All Fields] AND "drugs"[All Fields]) OR "antiepileptic drugs"[All Fields]) AND (("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]))
   926 records were retrieved. The titles as well as the reference lists were screened and 3 records were included for this review.

- **Meta-analysis:** *Jackson et al*[i] conducted a network meta-analysis comparing the effectiveness and side effect profile of migraine prophylactic medications.[1] This was a recent meta-analysis of good quality and no later literature relevant to this review was found in the search.

- **Systematic review:** *Mullener et al*[ii] conducted a an up dated systematic review of their 2013 review in 2015comparing the efficacy of various anticonvulsants in the treatment of migraine prevention[2].

- **Randomised controlled trials**: Rompel double blind cross over study of carbamazepine and placebo[3]

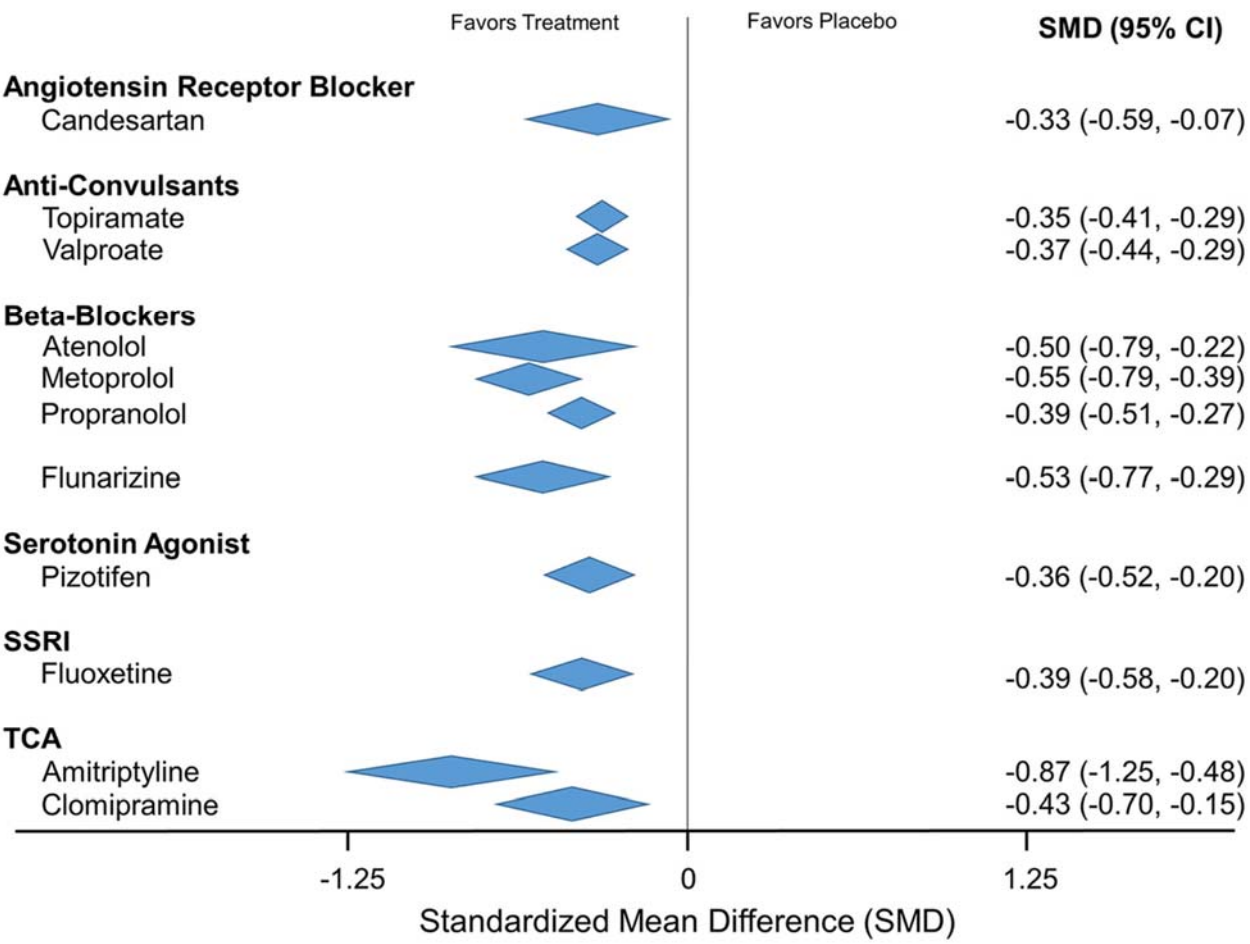
  10 additional RCTs were identified that compared the medicines under review head to head
  2 compared Topiramate to valproate
  1 compared Topiramate to propranolol
  1 compared Topiramate to propranolol to placebo
  2 compared amitriptyline to topiramate
  1 compared amitriptyline to valproate
  2 compared amitriptyline to propranalol to placebo
  1 compared propranolol to atenolol to placebo
  As all these trials were included in the metaanalysis, they were not reviewed individually for this review.

SR and AB retrieved, reviewed and analysed the data and reached consensus. Duplicate studies were removed.

b) Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Outcomes: primary and secondary	Effect sizes	Comments
Jackson et al, meta-analysis, 2015[i]	Meta-analysis including 179 RCTs: 9 alpha blockers 3 Angiotensin Converting Enzyme Inhibitors(ACE) 3 Angiotensin Receptor Blockers (ARB) 33 anticonvulsants 39 beta blockers 12 calcium channel blockers 7 flunarizine 6 SSRIs 1 SNRIs 9 serotonin agonists 9 TCA 2 compared amitriptyline to topiramate 1 compared amitriptyline to valproate 2 compared amitriptyline to Propranolol to placebo 1 compared propranolol to atenolol to placebo	6765	Patients presenting with episodic migraines (> 5 attacks per month)	Placebo or other medicine	Primary outcome: reduction in the frequency or severity of migraine headaches of at least 4 weeks duration using the HIS classification i.e. 1) headache frequency, 2)a headache index that included frequency, 3)severity or 4)duration	**Anticonvulsants** (n=8529) with topiramate (n=12) and valproic acid (n=6) the two agents most frequently investigated *Topiramate*: pooled mean difference showed efficacy at all-time points (4 to24 weeks) and at all doses (50, 100 and 200mg/day), with higher doses being more effective over a shorter period of time. At 4 weeks, patients on topiramate experienced pooled RR=2.4 (95 % CI 1.3 to 4.2) vs RR=1.8 (95% CI 1.5 to 2.2) at 26 weeks *Valproic acid:* pooled mean difference at varying time points (4,8 and 12 weeks) showed efficacy at all doses (500 to1500mg). Patients using Valproate had twice the chance of experiencing at least a 50% reduction in headaches, pooled RR 2.1 (95% CI 1.5 to3.0). A response was not see with incremental dosing (dose-response p = 0.83). **Beta blockers** (n=2019), a total of 38 trails comparing to placebo over an average of 11 weeks. Numerous studies but atenolol (n=3), metoprolol (n=4) and propranolol (n=19) showed efficacy in reducing HA/month by >50%. Propranolol was more likely to reduce headache by more than 50%, pooled RR: 2.1 (1.6 to 2.9). **Tricyclic antidepressants (TCAs)** (n=1570), a total of 8 trails over an	Overall studies were heterogeneous and varying in duration (4-16 weeks), participant numbers and headache severity (no. of headaches per month). Included quality of studies ranged from moderate to good quality. List of individual included studies and risk of biases table provided. Assessment for publication bias was performed. The majority of the trials compared medicine to placebo. 10 RCT's compared the medicines under review head to head: 2 compared Topiramate to valproate 1 compared Topiramate to propranolol 1 compared Topiramate to propranolol to placebo Indirect comparisons of individual medicines using meta-regression suggested that amitriptyline was more effective than propranolol (p = 0.009), topiramate (p = 0.005) and valproate (p = 0.009). And no different to atenolol (p = 0.20). In direct comparison amitriptyline was no more effective than topiramate or propranolol. Propranolol was equivalent to atenolol and topiramate. Topiramate was equivalent to valproate. Overall all the medicines were found to be of equal efficacy and no individual agent was found to be superior. The authors have no support or funding to report; and have declared that there are no competing interests.

						average of 10weeks; 5 trails were conducted using Amitriptyline (see Amitriptyline at a dose of 100mgover a shorter period (4weeks) were more likely to reduce headache frequency by 50% as compared to placebo (RR=-0.57 (95 % CI -0.93 to -0.23) vs RR=-1.24 (95% CI -1.66 to -0.82) NNT pooled = 7	
Mulleners et al, SR,2015[2]	SR	53	Patients with episodic migraine			***Topiramate*** (n=20, 10 comparing topiramate with placebo, three comparing different doses of topiramate and seven comparing topiramate to another active intervention), dose range 50 to200mg/day with average of 19 weeks duration (4 to 52 weeks) were three times more likely to experience >50% reduction in headache frequency compared to placebo, OR=3.18 (95% CI 2.10 to 4.82). ***Valproic acid*** (n=10, 4 trials cross over design and 6 parallel-group design), dose 400-1000mg with an average treatment duration of 11weeks showed that patients were four times more likely to have a 50% reduction in headache frequency, OR= -4.31 (95% CI -8.32 to - 0.30)	A priori design clearly stated as well as method of selection of studies and databases. Data extracted by two researchers and attempts were made to find grey literature (books and reference lists were all searched). PRISMA diagram was provided. No list of individual included studies; also no risk of biases table provided. No assessment for publication bias was performed.
Rompel et al, 1970[3].	Double blind cross over	48				***Carbamazepine*** (n=48) showed significant improvement in patients (OR 11.77; 95% confidence interval (CI) 3.92 to 35.32). NNT = 2 (95% CI 2 to 3)	Only one prospective RCT, small number, inadequate data and reporting on methodology and outcomes.



Network meta-analysis from Jackson et al 2015[1]

8. Discussion

There are a large number of treatment options available for the prophylactic treatment of episodic migraines; this review focused on the three medicine classes with the most data, anti-convulsants, beta-blockers, and tricyclic antidepressants (amitriptyline.

Few head-to-head comparisons exist between the many classes/groups of prophylactic treatment options and the decision on which medicine to use should be individualised based on effectiveness and side effect profile of each medicine.

Our decision was largely guided by the Jackson meta-analysis[1]. This was thought to be appropriate as our search did not find any literature of relevance to our PICO published post this meta-analysis, and the Jackson meta-analysis was of good quality. Overall there was no difference in the efficacy or safety between the different medicines.

Overview

Placebo RCTS: Overall, individual medication classes i.e. anticonvulsants (sodium valproate and topiramate), beta-blockers (propranolol, n=19 trials) and tricyclic antidepressants (amitriptyline) were shown to be twice as likely to reduce headache frequency by at least 50% when compared to placebo.[1]

Network meta-analysis did not identify a difference in the efficacy or safety between the different medicines[1].

Carbamazepine: Although carbamazepine was twice as likely to reduce headache frequency as compared to placebo, the study was small (n=48) and information limited[3]; therefore, the recommendation for its use in migraine prevention cannot be applied uniformly and it is recommended that the current recommendation in the EML be removed.

Quality of the studies

Meta-analyses[1]: The overall studies included in the meta-analyses were heterogeneous, varied in duration (4-16 weeks), participant numbers and headache frequency (no. of headaches per month) as well as severity. The studies also varied in quality with only 37% of the included studies scoring >5, using the Jadad criteria.

Systematic review[2i]: For topiramate, nine of the included 20 studies were assessed to have a high risk of bias for randomisation, allocation, performance, detection, attrition and reporting. Similarly, seven trails that were reviewed for valproic acid also found to have a high risk of bias for the same domains as topiramate.

Safety and side effect profiles

Patients receiving prophylactic treatment were more likely than those receiving placebo to experience side effects (RR: 1.27, 95% CI: 1.19 to 1.37) and to withdraw from treatment (RR: 1.18, 95% CI: 1.08 to 1.29). Network meta-analysis and direct comparisons found no difference in likelihood of experiencing "any" side effect or in the rate of withdrawing from studies[1]. The side effect profile does however differ between the medicines.

There is a concern regarding potential teratogenicity with valproate and topiramate and the use of these medications is best avoided in pregnancy [4].

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	On average, across the effective prophylactic medications, migraine sufferers had about twice the chance of experiencing at least a 50% reduction in headaches as those receiving placebo with a pooled risk reduction (ARR: 0.15, 95% CI: 0.09–0.21) suggesting that 7 people would need to be treated to produce 50% reduction in headache burden in one subject.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	The use of anticonvulsant agents in the prevention of episodic migraine should only be considered if all other agents had proven to be ineffective. Even then the use of anticonvulsants agents should be monitored and stopped once the patient falls pregnant.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the outcomes?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	
RESOURCE USE	**How large are the resource requirements?** More intensive [x] Less intensive [ ] Uncertain [ ]	Limited data available about the burden of disease in SA. **Cost of medicines/ month (28 days):** Amitriptyline 25 to 75 mg/day — 3.912 to 11.737* Propranolol 80 to 240 mg/day — 8.138 to 24.414** Atenolol 50 mg 12 hrly — 4.876*** Valproic acid 500 mg/day* — 26.61**** Topiramate 100 mg 12 hourly — 21.79***** *Contract circular HP09-2016SD: Weighted average price R 0.140 ** Contract circular HP09-2016SD: Weighted average price R 0.145. *** Contract circular HP09-2016SD: Weighted average price R 0.087 **** Contract circular HP09-2016SD: Weighted average price R0.950 ***** Contract circular HP09-2016SD
EQUITY	**What would be the impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	

	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative(s)	We suggest using the option	We recommend the option
Type of recommendation	☐	☐	☒	☐	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends retaining amitriptyline and replacing carbamazepine with a beta-blocker atenolol or propranolol for the prophylactic treatment of episodic migraine. Consider beta-blockers when amitryptiline is not tolerated or contra-indicated. Although carbamazepine was twice as likely to reduce headache frequency as compared to placebo, the study was small (n=48) and information limited[3]; the recommendation for its use cannot be applied uniformly and it is recommended that the current recommendation for carbamazepine in the EML be removed.

Rationale: The evidence for carbamazepine is limited to a single small study of low quality. For the medicines reviewed, no evidence was found to demonstrate consistent superior efficacy of one medicine over the other for the prophylactic treatment of migraine. While side effect profiles differed, no medicine was found to have less side effects than the other medicines. In view of the teratogenic effects of valproic acid and possibly topiramate and given the relatively high costs of these medicines, beta-blockers recommended as an alternative to the amitriptyline. Network meta-analysis found amitriptyline to be better than several other medications including propranolol and no different than atenolol.

Level of Evidence: I Network meta-analysis, Systematic Review, RCT (low quality), Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm/safety	Price reduction
X	X	

VEN status: (T&Q EML)

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 6 DECEMBER 2018 AND 21 FEBRUARY 2019:

The NEMLC accepted the Adult Hospital Level Committee's proposal, recommending a beta-blocker therapeutic group (i.e. atenolol and propranolol) for migraine prophylaxis where there is a poor response or where the use of amitriptyline is contraindicated.

M & E considerations:

Research priorities : Burden of disease estimation, Quality of Life impact studies. Direct head to head trials with longer duration of follow up.

References

1. Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS ONE 2015;10(7):1-60.
2. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: An updated Cochrane review. Cephalalgia 2014; 35(1):51–62.
3. Rompel H, Bauermeister P.W. Aetiology of migraine and prevention with carbamazepine (Tegretol) results of a double-blind cross-over study. SAMJ 1970; 44 (4), 75-80.
4. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11:CD010224.