Review

Preventive pharmacologic treatment of migraine in adults

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Introduction

Migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours[1]. Episodic migraine has a female predilection affecting 17% of women and 6% of men[2-5]. Episodic migraine is characterized by < 15 days of headache per month and chronic migraine by > 15 headache days per month[1]. Migraine headaches may be moderate to severe or debilitating. Migraine affects the physical, psychological and social well being of patients and can restrict daily activities resulting in lost work time and diminished productivity[6]. Forty percent of adults with episodic migraine and all patients with chronic migraine might benefit from preventive medication, however only 12% of adults take preventive medication[2]. Several drug classes are used as preventive treatment in episodic migraine and they affect various aspects of migraine pathophysiology[7,8].

Several classes of drugs are used for migraine prophylaxis. The European Federation of Neurological Societies recommends the beta-blockers metoprolol and propranolol, calcium channel blockers flunarizine and the antiepileptic drugs sodium valproate and topiramate as the first line drugs and amitriptyline, venlafaxine, naproxen and bisoprolol as drugs of second choice for migraine prophylaxis[9].

The American Headache Society and the American Academy of Neurology in the updated guidelines of 2012 recommends sodium valproate, topiramate, metoprolol, timolol, propranolol and frovatriptan as the dugs with established efficacy (based on at least 2 class 1 trials) and amitriptyline, venlafaxine, atenolol, nadolol, naratriptan and zolmitriptan as drugs that are probably effective in the prevention of migraine[10].

Of the several drug used by the medical professional the beta blockers propranolol and timolol and the antiepileptic drugs topiramate and sodium valproate (divalproex sodium) are the only four that are approved by the US Food and Drug Administration[11]. Novel antiepileptic drugs, calcium channel blockers, serotonin and noradrenaline reuptake inhibitors, glutamate blockers and drugs from several other classes are prescribed off-label by doctors[11]. The NICE guidelines recommend topiramate and propranolol as preventive therapy for migraine[12]. If both are unsuitable or ineffective NICE recommends trying a course of acupuncture 10 sessions over 5-8 weeks or gabapentin according to patient preference.

Goal for preventive treatment

The 2000 US Headache Consortium defined the goals of preventive treatment as "50% decrease in attack frequency and decrease in intensity and duration; improve responsiveness to acute therapy; improve function and decrease disability and prevent occurrence of medication overuse headache and chronic daily headache".

Indications to commence prophylactic treatment

The American Migraine Prevalance and Prevention Study recommends prophylactic treatment to be commenced when a patient has at least 6 headache days per month or at least four headache days with at least some impairment or at least three headache days with severe impairment or requiring bed rest. Preventive medication is not advised with less than four headache days per month with no impairment in functioning or one or two headache days per month regardless of severity.

Therapeutic principles when prescribing preventive treatment

Preventive treatment is usually commenced at a low dose and titrated gradually till therapeutic outcome is achieved, maximal tolerable dose is reached. An adequate trial of more than two months for each preventive medication is recommended. Medication should be re-evaluated and patient should be followed up. The patient should be involved in the care to improve compliance. The choice of medication will be influenced by comorbid problems. Contraception should be discussed with women in childbearing age and the potential risk of teratogenicity and risks to the fetus should be discussed. The drug should be chosen based on efficacy, patient's preferences, headache profile, the drugs side effects and the presence or absence of coexisting or co-morbid conditions[13]. In this review we hope to analyze the evidence for the different medications used for prevention of migraine with emphasis on the drugs available in Sri Lanka.

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Antiepileptic Drugs

The antiepileptic drugs studied most with respect to migraine prophylaxis have been sodium valproate, topiramate, gabapentin, lamotrigine and oxcarbazepine.

Topiramate

Data analyzed from 9 trials[14-22] with 1737 participants showed that topiramate reduced headache frequency by about 12 attacks per 28 days compared to placebo and that topiramate doubled the proportion of responders relative to placebo. Topiramate 50 mg compared with a placebo showed a significant increase in number of responders but no significant decrease in monthly headache frequency in two trials[14, 21]. However in a smaller study Gupta[19] showed that 50 mg topiramate reduced headache frequency and increased the responder rate. Trials[14-17,20,21,23] comparing topiramate 100 mg to placebo in 478 patients showed statistically significant superiority of topiramate. Four large trials[14,16,21,24] comparing topiramate 200 mg to placebo showed statistically superiority for topiramate with regard to responder rate but only two studies[14,21] showed a reduction in headache frequency. Two other smaller trials[18,22] on topiramate and placebo did not reveal a significant difference. When topiramate was compared with active comparators there was no significant difference in efficacy between maximal doses of topiramate and amitriptyline[25]; topiramate 100 mg and flunarizine 5 mg[26]; topiramate 50 mg and propranolol 80 mg[27]; and topiramate 200 mg, 100 mg and propranolol 80 mg, 160 mg[16]. There was a slight but significant advantage of topiramate 50 mg over sodium valproate 400 mg[28,29]. The trials comparing flunarizine and sodium valproate were underpowered.

Topiramate does not give an unexpectedly high rate of adverse events when used for migraine prophylaxis. Significant adverse effects of topiramate include paresthaesias, memory and concentration problems, glaucoma, hyperchloremic acidosis, renal stones, poor appetite and weight loss.

Meta-analysis (2012) of above studies showed that topiramate in a 50 or 100 mg/day dose is effective in reducing headache frequency and was reasonably well tolerated in adult patients with migraine[30].

Sodium valproate

Two cross-over trials[31,32] with a total of 63 patients showed that sodium valproate had a significant reduction in headache frequency compared to placebo. In one trial[32] responder rate with sodium valproate was significantly superior to placebo. The number needed to treat was 3. In these trials the doses ranged from 150 mg/day to an individualized target dose of maximum 1200 mg/day. A parallel group trial[33] compared different doses of sodium valproate by measuring serum sodium valproate concentrations. The study showed that lower (21-50μg/ml) serum levels gave a slightly but significantly lower headache frequency compared to higher (>50 μg/ml) serum levels and recommended a daily dose of 500-600 mg as effective.

When sodium valproate was compared with flunarizine there was no significant difference between the two in the proportion of responders, but data was insufficient to calculate significance in headache frequency[34]. Two smaller studies compared topiramate 50 mg with sodium valproate 400 mg[28,29] and found no significant difference in efficacy between the two drugs. However the pooled results of these two studies indicate a significant difference in favour of topiramate. There was no significant difference in Migraine Disability Assessment (MIDAS) scores between sodium valproate and topiramate[28]. The main adverse effects were asthenia/fatigue, dizziness/vertigo, nausea, tremor and weight gain.

A recently published Cochrane review on 10 trials on sodium valproate concluded that valproate is effective in reducing headache frequency and is reasonably well tolerated in adult patients with episodic migraine[35].

Gabapentin

Pooled data from 5 trials of gabapentin suggest that it is not efficacious for the prophylaxis of episodic migraine in adults[36]. Doses of 900 mg to 2400 mg were used in these trials.

Other antiepileptic drugs

A recent Cochrane review did not show robust conclusions regarding the efficacy of other antiepileptic drugs (acetazolamide, carisbamate, clonazepam, lamotrigine, oxcarbazepine and vigabatrin) in the prophylaxis of episodic migraine in adults.

Beta-blockers

Beta-blockers are one of the commonly prescribed groups of drugs used in migraine prophylaxis. Of the beta-blockers propranolol, metoprolol and timolol are considered effective (Level A) based on the evidence from at least 2 high quality randomized controlled trials[10]. Atenolol is a Level B drug according to the 2012 AAN and AHS guidelines[10].

Propranolol

Propranolol is the commonest drug used in migraine prophylaxis. The Cochrane study group reviewed 26 trials, which compared propranolol with a placebo and

concluded that the proportion of responders was higher with propranolol than with placebo, and the responder ratios tended to be higher in trials with higher doses of propranolol[37]. However a trial with the lowest dose (80mg) of propranolol had the most positive result[38]. Meta-analysis of 10 trials by the Cochrane group suggested that propranolol 160 mg might be slightly more effective than 120 mg[37]. The authors conclude that propranolol is superior to placebo showing clear short-term effects. The meta-analysis of propranolol versus other beta-blockers (nadolol, metoprolol), calcium antagonist (9 trials with flunarizine, 1 each with a combination of propranolol and flunarizine, nimodipine and nifedipine) and other drugs (including amitriptyline and naproxen) did not show statistically significant difference between propranolol and the comparator. Evidence on long-term effects of propranolol is limited[37].

Propranolol was found to be as effective as topiramate[27] and another study showed similar efficacy between topiramate 100 and 200 mg / day and propranolol 160 mg /day[16].

Metoprolol

The more recent large trials showed statistically significant effects of metoprolol resulting in it being classified as a Class I drug in the 2012 AAN guidelines. A recent trial showed that metoprolol 200mg / day was superior to aspirin 300 mg/ day[39] while another trial showed that metoprolol had similar efficacy compared with nebivolol in migraine prevention[40].

Calcium channel blockers

Flunarizine was efficacious in migraine prophylaxis when compared with a placebo but when compared with the beta-blockers propranolol[41], and metoprolol[42] there was no difference between the beta-blockers and flunarizine. Recommended flunarizine dose is 5-10 mg per day.

Studies on nimodipine and nifedipine as prophylaxis for migraine were equivocal and general consensus is that nimodipine and nifedipine are ineffective as prophylaxis.

Trials on verapamil were not rigorous randomized control trials and thus the evidence for use in migraine is not strong. Studies are insufficient to recommend diltiazem.

Common side effects of the group include dizziness, depression, vasomotor changes, tremor, gastrointestinal side effects, peripheral oedema and hypotension. Patients may complain of an initial increase in headache, which improves, with a few weeks of treatment. Sedation, weight gain, dry mouth, dizziness, hypotension, occasional extrapyramidal reactions, exacerbation of depression and abdominal pain are the common adverse effects associated with flunarizine.

In the 2012 guidelines both verapamil and nimodipine were downgraded because of confounding data on these drugs.

Antidepressants

Of the antidepressants amitriptyline and venlafaxine are the only drugs recommended in the 2012 AHS/AAN guideline and the EFNS guidelines and they are recommended as second line drugs.

Amitriptyline is efficacious in migraine prophylaxis and there is no significant difference between amitriptyline and topiramate. Venlafaxine is probably effective in migraine prophylaxis and evidence with regards to fluoxetine is conflicting. One study showed fluoxetine to be better than placebo[43] however overall the other studies on fluoxetine have been negative or equivocal.

Amitriptyline

Amitriptyline is a tri-cyclic antidepressant which up until recently was recommended as having proven benefit in migraine prophylaxis. In the 2012 AAN/ AHS guidelines it is classified as a Level B medication for migraine prophylaxis.

There was no significant difference between amitriptyline and propranolol[44]. Some studies showed that amitriptyline was more efficacious than propranolol in patients with mixed migraine and tension type headache while propranolol was significantly better in patients with migraine alone[45]. Amitriptyline was found to have similar efficacy to venlafaxine[46] and topiramate[47,48].

Amitriptyline is a tertiary amine and is usually started at a dose of 10 mg at bedtime. The dose ranges from 10 to 300mg a day. Tricyclic antidepressants are sedating and thus should be started with a low dose at bedtime. Common side effects encountered when using tricyclic antidepressants include orthostatic hypotension, dry mouth, a metallic taste, epigastric distress, constipation, dizziness, mental confusion, tachycardia, palpitation, blurred vision, urinary retention and weight gain. Tremors, confusion and delirium are particularly common in the elderly.

Venlafaxine

Venlafaxine is a 5HT-norepinephrine reuptake inhibitor with some evidence of efficacy in migraine prophylaxis. Significant reduction in headache days was reported in a study at a dose of 150 mg / day while a dose of 75 mg /day was ineffective[49]. Another study reported

venlafaxine and amitriptyline to have similar efficacy in reducing headache frequency[46] at doses of 150 mg and 75 mg respectively but the latter group had more side effects. Adverse effects included nausea with VLF and hypersomnia, poor concentration with AMT.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers

The 2012 AHS/AAN guidelines have recommended lisinopril and candesartan as level C drugs in the prevention of episodic migraine, as the trials are not robust. These were not recommended in the 2000 guidelines as there were no studies but in the past decade there have been three studies published, one each for candesartan, lisinopril and telmisartan. Lisinopril[50] and candesartan[51] were possibly effective while telmisartan[52] was ineffective.

Triptans

Frovatriptan, zolmitriptan and naratriptan are efficacious in the short-term prevention of menstrual migraine. The triptan is started 2-3 days before the menstrual period or expected onset of menstrual migraine and continued for 5-6 days and stopped. This prevents migraine occurring at menses only.

Two class 1 trials established the efficacy of frovatriptan[53,54] in preventing menstrual migraine. A dose of 2.5 mg twice daily after a loading dose of 10 mg was used in the studies. In another Class 1 study the number of migraine days and perimenstrual migraines were reduced in patients receiving oral naratriptan 1 mg twice daily for 5 days commencing 2 days before menses onset[55]. Zolmitriptan 2.5 mg twice daily or three times daily significantly decreased the frequency of mens-trually related migraine, however there was no advantage in the three times daily dosing over the twice daily dosing[56].

Onabotulinumtoxin A

Onabotulinumtoxin A is currently being used as prophylaxis for chronic migraine, defined as 15 or more headache days per month, with 4 or more headache hours per day[57]. Cost remains a potential barrier to its use. The clinical effect of onabotulinumtoxin A may be delayed or transient after the first set of injections and a second set of injections is warranted before concluding that the therapy is unhelpful. Repeat injections, initially every 3 months, are usually required to maintain benefit.

Conclusion

When selecting an appropriate drug for prevention of migraine one should consider the frequency, severity and disability due to migraine. One should also consider the level of evidence for efficacy, adverse effect profile and patient comorbidities. Treatment failures can be due to various reasons including unrealistic expectations of the patient, poor drug compliance and overuse of acute medication in the treatment of migraine.

Based on current evidence the AAN/AHS guidelines and the EFNS guidelines recommend topiramate, sodium valproate, propranolol and metoprolol as first line drugs and atenolol, venlafaxine and amitriptyline as the second line drugs. The EFNS guidelines recommend flunarizine as a first line drug in addition to the ones mentioned in the AAN/AHS guidelines.

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