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MIGRAINE PROPHYLAXIS

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Migraine is a chronic, debilitating neurological disorder with major implications on patient quality of life. As estimated in 2001, migraine affects approximately 12% of Americans.[1] Migraine occurs more frequently in women (18%) than in men (6%), and prevalence peaks around middle age, although it occurs at all ages. The cost associated with migraine and the undertreatment of migraine is significant. Direct costs include the cost of medications and health care expenses. Headache treatment accounts for approximately one third of total OTC sales in the US. The cost of prescription medications to treat migraine is estimated to be at least $2 billion.[2] The indirect cost of migraine due to lost productivity is between $5.6 and $17.2 billion.[3] Acute treatment with agents such as analgesics, anti-emetics and triptans is often necessary in migraine sufferers, but some patients require preventive treatment as well. The goals of prophylactic treatment are to reduce duration and severity of migraines, decrease frequency (successful prophylaxis is considered a 50% reduction in frequency within 3 months), improve quality of life and minimize patient disability. Migraine prevention may also decrease the rate of migraine transformation to chronic daily headache.[2] This article will focus on the current guidelines for the use of migraine prophylaxis, as well as the role of various agents in preventing migraine.

Pathophysiology

Migraine headaches have a multifactorial etiology in which genetic and environmental factors have a strong role. Migraine was initially believed to be due to a progression of vascular events, beginning with a period of vasoconstriction followed by vasodilation and inflammation. This theory has evolved into the belief that neurovascular instability is the source of migraine, where vasoconstriction is the cause of aura associated with migraine, and vasodilation is the cause of throbbing pain.

Indications for Prophylaxis

Identification of patients needing migraine prevention is imperative, as migraine is largely under treated in the US.[4] Many migraine sufferers (49%) only use over-the-counter (OTC) drugs to treat acute migraine, while even fewer (20%) use prescription medications and approximately 29% of sufferers use both. Approximately 12% of migraine sufferers utilize a daily prophylactic drug.[5] Based on the 2006 European Federation of Neurological Sciences (EFNS) Task Force guidelines, preventive treatment for migraine should be considered when there is severe impairment of quality of life, business duties, or

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school attendance; frequency of attacks is two or more per month; migraine attacks are unresponsive to acute drug treatment; and attacks are accompanied by frequent, very long, or uncomfortable auras.[6]

The 2000 US Headache Consortium Guidelines[7] offered more definitive standards for prophylaxis consideration as:

A. Recurring migraine that significantly interferes with the patient's daily routine despite acute treatment, for example:
    1. Two or more attacks a month that produce disability that lasts ≥3 days
    2. Attacks that are infrequent but pro duce profound disability
B. Failure, contraindications to, or troublesome side effects from acute medications
C. Overuse of acute medications
D. Special circumstances, such as hemiplegic or basilar migraine or attacks with a risk of permanent neurologic injury
E. Very frequent headaches (more than 2 per week) or a pattern of increasing attacks over time, with the risk of developing medication overuse
F. Patient preference

Choosing a prophylactic agent should be individualized to the patient with considerations for efficacy, contraindications, precautions, side effects, concurrent disease states, adherence and cost. Prior to initiating and along with pharmacological prevention of migraine, patients should be counseled on nonpharmacological preventative measures. These measures include maintaining regular sleep patterns, eating regular meals, exercising and avoiding known

Table 1: Evidence supporting ß-blockers for migraine prophylaxis

Study (year)	Design	Outcome	Discussion
Linde et al.[10] (2004)	Cochrane database review of 58 trials with 5,072 total participants comparing propanolol (Inderal®) to placebo or other prophylactic medications	Calculated responder ratio (comparable to relative risk) of 1.9 (95% confidence interval [CI], 1.60 to 2.35)	Many trials included had methodological limitations. Reviewers concluded that evidence on long-term effects is lacking, but propranolol seems to be as effective and safe as other drugs used for prophylaxis.
Holroyd et al.[11] (1991)	Meta-analysis of 2,403 patients receiving propanolol for migraine prevention	Propanolol resulted in a 44% average reduction of migraine activity versus 14% with placebo	Modal treatment dose of 160mg daily supported propanolol for short-term effectiveness.
Stellar et al.[12] (1987)	Comparison of timolol (Blocadren®) to placebo in 107 patients	Patients receiving 20 to 30mg/day of timolol showed significantly reduced frequency and a global response rate of 65% compared to 40% on placebo.	There was no change in severity or duration of migraines which did occur. Timolol was well tolerated.
Tfelt-Hansen et al.[13] (1984)	Compared prophylactic effect of timolol (10mg BID) and propranolol (80mg BID) to placebo in 96 chronic migraine sufferers.	The mean frequency of attacks per 28 days was 3.35 on timolol, 3.69 on propranolol and 4.83 on placebo. Mean severity of attacks (0-3) was 1.75 on timolol, 1.83 on propranolol, and 1.93 on placebo. The difference between propranolol and timolol was nonsignificant: frequency of attacks 0.34 (95% CI, 0.26 to 0.89).	Concluded that timolol and propranolol are equally effective in doses for common migraine prophylaxis.

triggers such as specific food items (i.e. foods containing nitrites and MSG), stress, bright lights and strong odors. It is important for patients to maintain a headache diary to allow prophylactic measures, pharmacological and nonpharmacological, to be assessed for efficacy and appropriateness.

Pharmacologic Options for Prophylaxis

β-blockers

Current clinical evidence suggests the use of the β-blockers in migraine prophylaxis is appropriate. Both propanolol (Inderal®) and timolol (Blocadren®) are identified as first-line agents by the 2002 American Academy of Family Physicians and American College of Physicians-American Society of Internal Medicine guidelines.[8] Migraine prophylaxis does not appear to be a class effect however. Of the β-blockers, only timolol and propanolol are identified as first line agents for migraine prophylaxis (**Table 1**). There is limited evidence supporting the use of atenolol (Tenormin®), the long-acting preparation of metoprolol (Toprol XL®), and nadolol (Corgard®).[8] Silberstein et al. has proven several β-blockers to be ineffective in the prevention of migraine, including acebutolol (Sectral®) and pindolol (Visken®).[9] Common side effects of β-blockers include drowsiness, fatigue, bradycardia and decreased exercise tolerance. In patients with comorbid chronic heart failure, asthma, Raynaud's disease and insulin-dependent diabetes, alternative first-line agents may be appropriate.

Tricyclic antidepressants

Amitriptyline (Elavil®) is the only antidepressant with consistent evidence supporting its use as a prophylactic agent. Couch et al.[14] studied 162 persons with migraines compared amitriptyline therapy (50 to 100 mg daily) with placebo over 4 weeks. Results showed an odds ratio (OR) of 2.4 (95% CI, 1.1 to 5.4) for the number of patients reporting a 50% improvement in migraine index. Ziegler et al.[15] compared amitriptyline with propranolol, suggesting that propranolol is more effective in patients with a single migraine type, whereas amitriptyline is more beneficial for patients with mixed migraine and tension features. Amitriptyline significantly reduced severity, frequency, and duration whereas propanolol only reduced severity in this study. Amitriptyline is also useful in patients with comorbid insomnia or, when used at higher dosages, depression.

Divalproex sodium or valproic acid

The anticonvulsants divalproex sodium (Depakote®) and valproic acid are well supported by evidence for use in migraine prevention. For a migraine frequency reduction of 50% or more, authors of a Cochrane Review of anticonvulsants for migraine prophylaxis calculated a number needed to treat (NNT) of 3.1 (95% CI, 1.9 to 8.9) for valproic acid and 4.8 (95% CI, 3.5 to 7.4) for divalproex sodium.[16] The Cochrane Review also showed that anticonvulsants as a class have a low number needed to harm (NNH).[16]

Topiramate

Several clinical trials, both open-label and controlled, indicate that topiramate (Topamax®) is effective in migraine prophylaxis, and it is now considered a first-line agent (**Table 2**). In two concurrent randomized, double-blind, placebo-controlled trials, 937 participants were randomized to receive topiramate 50, 100, or 200 mg per day or placebo for 26 weeks. In both trials, more patients had at least a 50% reduction in monthly migraine frequency with topiramate 50 to 200 mg per day (36 to 52%, respectively) than with placebo (23%). The NNT for a dosage of 100 mg topiramate per day is 3.5 (95% CI, 2.8 to 4.9).[16] Adverse events include weight loss, parasthesias and cognitive dysfunction, which can be reduced with slow dose titration. Comparative studies with other prophylactic agents have yet to be conducted.

Prophylaxis should be initiated with a first-line agent, taking into consideration potential side effects, special indications the patient may have, cost, as well as efficacy based on current evidence. Table 3 summarizes the drug classes currently considered as first-line migraine prevention options.

Second-line agents for migraine prevention

Gabapentin (Neurontin®) has demonstrated efficacy at dosages of 1,200 to 2,400 mg per day in two clinical trials. At a dosage of 2,400 mg per day, the NNT to reduce headache frequency by 50% or more was 3.3 (95% CI, 2.1 to 8.4).[16,21] Further evaluation for the use of gabapentin is warranted. The most common adverse events associated with gabapentin are dizziness and somnolence.

Table 2: Evidence supporting topiramate for migraine prophylaxis

Study (year)	Design	Outcome	Discussion
Silberstein et al.[17] (2004)	Randomized, double-blind, placebo-controlled trial; 487 patients	Reduction in migraine frequency of 36% (50mg/day dose), 54% (100mg/day), and 52% (200mg/day) compared to 22% reduction on placebo.	No additional benefit was seen in topiramate 200mg/day over 100mg/day.
Brandes et al.[18] (2004)	Randomized, double-blind, placebo-controlled trial; 483 patients	Reduction in mean monthly migraine frequency, migraine days and rescue medication use significant in both 100mg/day and 200 mg/day groups versus placebo.	Participants reported improvement in migraine frequency within the first month of treatment, and effect continued for duration of treatment.
Peres et al.[19] (2006)	Open label study of 64 patients receiving topiramate 25-500mg (median dose of 100mg)	$\geq$50% reduction in migraine frequency achieved in 66% of patients, with 28% having a complete response (frequency reduction > 95%)	Topiramate was well-tolerated; only 6 patients dropped out of study due to adverse events. Target dose appeared to be 100mg.
Silvestrini et al.[20] (2003)	Randomized, double-blind, placebo-controlled trial of 28 patients with chronic migraine with analgesic overuse received 50mg or placebo	Significant reduction in frequency with topiramate use (mean number of days with headache 8.1 in topiramate group vs 20.6 in placebo, $P < 0.0007$).	Topiramate reduced migraine frequency in patients with chronic migraine associated with analgesic overuse.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used daily or intermittently for migraine prophylaxis. When migraine triggers are predictable, such as during menstruation, intermittent therapy may be used. Migraines can be prevented during menstruation when NSAIDs are used beginning several days prior to start of menstruation and continuing for the first few days of menses.[22] Naproxen sodium (Naprosyn®) is the most commonly used NSAID for migraine prophylaxis and the dose is 1,100 mg daily. Adverse effects include dyspepsia, peptic ulceration and GI bleeding, but tend to be infrequent with short-term therapy, increasing with extended treatment. NSAIDs can be especially helpful in patients with concurrent osteoarthritis or dysmenorrhea.

Schrader et al.[23] found the angiotensin-converting enzyme inhibitor lisinopril (Zestril®) to be effective in the prevention of migraine. In a randomized, double-blind, crossover trial with 55 patients, lisinopril 20 mg per day for 12 weeks reduced the mean number of days with headache and the mean number of days with migraine compared with placebo. Thirty percent of patients receiving lisinopril experienced a 50% or greater reduction in the number of days with migraine. Lisinopril was well tolerated, although it was associated with a higher incidence of cough than placebo.

The angiotensin receptor blocker candesartan (Atacand®) was evaluated in a prospective, randomized, double-blind, crossover study with 60 patients.[24] As with lisinopril, candesartan 16 mg per day reduced the mean number of days with headache and with migraine compared with placebo. Candesartan also appeared to significantly decrease headache severity, level of disability, and days of sick leave due to headache. The rate of response to candesartan, based on a 50% or more reduction in the number of days with migraine, was 40.4%, compared with 3.5% for placebo ($P < .001$). Adverse effects with candesartan were similar to those with placebo.

There is limited evidence for the use of calcium channel blockers in migraine prophylaxis. Evidence does not support the use of diltiazem (Cardizem®) in migraine prevention, and there is only weak evidence in support of nifedipine

Table 3: Overview of First-line Agents for Migraine Prophylaxis

Drug Class	Dosages	Side effects	Special indications	ARP Cost
β-Blockers	Propranolol: 40 to 320 mg (80-240 mg)	Fatigue, Bradycardia, Dizziness, Depression, Impotence, Broncho-spasm, Nausea	Concurrent hypertension, angina, post-MI, tremor, anxiety or panic attacks (specifically propranolol)	$13-39
	Timolol: 20 to 30 mg			$32
	Nadolol: 40 to 240 mg			$11-34
	Metoprolol: 50 to 300 mg (200 mg)			$14
	Atenolol: 50 to 200 mg (100 mg)			$16
TCAs	Amitriptyline: 10 to 300 mg (30-150 mg)	Anticholinergic effects (dry mouth, constipation, blurred vision), sedation, postural hypotension, agitation, tremor, seizures, sexual dysfunction, weight gain	Tension-type headaches, concurrent depression, insomnia, and chronic pain	$11
	Doxepin: 10 to 200 mg (50-150 mg)			$8-16
	Imipramine: 10 to 200 mg (50-150 mg)			$17-51
	Nortriptyline: 10 to 150 mg (50-150 mg)			$10-26
	Protriptyline: 15 to 40 mg			$52-168
Divalproex/ Valproic acid	Divalproex: 250 to 500 mg twice per day	Nausea, vomiting, tremor, weight gain, hair loss, drowsiness, ataxia, hepatotoxicity	Concurrent seizure, or bi-polar disorders	$78-124
	Depakote ER: 500 to 1,000 mg per day			$69-140
	Valproic acid: 250 to 500 mg twice per day			$14-28
Topiramate	50 mg twice per day (titrate from 25 mg)	Paresthesia, fatigue, nausea, weight loss	Concurrent seizure disorder	$211-302

ARP: approximate retail price for typical dosage range

(Procardia®) or verapamil (Calan®). Of three small trials comparing verapamil 240 or 320 mg per day with placebo, two reported positive findings, with a moderate calculated summary effect size of 0.78 (95% CI, 0.09 to 1.50).[25,26] Two trials had high dropout rates due to adverse events.[27] Calcium channel blockers typically have a slower onset than β-blockers and may have an initial increase in headache frequency. These agents may be an option for patients who are unable to tolerate β-blockers.[28]

Miscellaneous Treatment Options

Oral magnesium (9 mg/kg per day divided three times daily with food) reduced the number of days with migraine in children.[29] Another double-blind randomized study demonstrated a 42% reduction in attack frequency in 81 adult patients taking 600 mg magnesium oxide daily.[30] An open-label study revealed efficacy of high-dose riboflavin (400 mg per day), significantly reducing headache frequency and use of abortive medications. There was no significant change in total headache hours or headache intensity however.[31]

Hormonal prophylaxis may be indicated in women suffering from menstrual migraine. Percutaneous estradiol at a dose of 1.5 mg four times daily for 3 days prior to menses and continued for a total of 6 days has demonstrated efficacy in two double-blind studies.[32,33] Hormonal prophylaxis can have variable effects on menstrual migraine. Patients should be monitored for development of aura or

worsening of headaches. Estrogen therapy should not be used in patients with a history of migraine with aura, thromboembolism, or other contraindications to estrogen therapy. The migraine rescue medication frovatriptan (Frova®) has shown benefit when used prophylactically in women with menstrual migraine. In women who are able to predict migraine occurrence based on their menstrual cycle, use of frovatriptan 2.5 mg twice daily for 6 days perimenstrually reduces the frequency of menstrually associated migraine.[34]

Recent attention has turned to the use of multiple treatments with low doses of botulinum toxin type A (Botox®) for migraine prophylaxis. In uncontrolled studies, botulinum toxin type A decreased migraine frequency. In Binder et al.[35] complete response was seen in 51% (95% confidence interval, 39% to 62%) of patients with a mean response duration of 4.1 months, and a partial response in 38% of patients with a mean response duration of 2.7 months. As of yet, botulinum toxin type A has not been proven more effective than placebo, though future trials will assess higher doses, different injection sites, and other migraine populations.[36]

Conclusion

Providers can decrease both indirect and direct healthcare costs as well as improve patient quality of life with the proper recognition of patients in need of migraine prevention. There are established guidelines for the identification of patients that would benefit from migraine prophylaxis. Propanolol (Inderal®), timolol, amitriptyline (Elavil®), divalproex (Depakote®), valproic acid and topiramate (Topamax®) are first-line options. Choice of prophylactic agent should take efficacy, contraindications, precautions, side effects, concurrent disease states, compliance issues and cost into consideration and should be individualized to the patient.

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