Pharmacological Management for Prevention of Migraine Headache: Clinical Practice Guideline

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Migraine headache is a common disorder seen in primary care. It affects 18% of women and 6% of men in the United States, almost half of who are undiagnosed and/or undertreated (1,2). This guideline, developed by the American College of Physicians-American Society of Internal Medicine and the American Academy of Family Physicians (AAFP), with assistance from the American Headache Society, (AHS), is based on a paper entitled, "Evidence-based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine," by Ramadan, et al which can be found at www.aan.com/public/practiceguidelines/headache_gl.htm.[1] The target audience for this guideline is primary care physicians and it applies to migraine patients who are candidates for preventive therapy. Although this guideline is based on the above paper, our recommendations may differ based on differing thresholds of evidence needed to make a positive recommendation.

Diagnosis

Migraine is a chronic condition with recurrent episodic attacks, and its characteristics vary among patients, and often among attacks within a single patient. Migraine is a syndrome with a wide variety of neurologic and nonneurologic manifestations. The International Headache Society (IHS) has developed diagnostic criteria for migraine with and without aura. The IHS criteria (see appendix and for more detail visit their website at www.painforum.com/en/1/hcpmigihs.html) use both clinical features and laboratory tests to provide criteria of inclusion (features needed to establish a particular diagnosis) and exclusion (features that prevent assigning a particular diagnosis). This classification system serves to diagnose headache attacks, not patients. Thus, one patient could have more than one type of headache disorder. For example, it is not uncommon for migraine patients to also suffer from episodic tension-type headaches.

Management of Migraine with Preventive Therapy

[1] In an effort to educate clinicians and patients about headache's impact, diagnosis, management, and prognosis, the US Headache Consortium was founded in 1996. The Consortium was made up of seven member organizations representing primary care, emergency medicine, neurology, and headache specialists. The objective of the US Headache Consortium was to develop scientifically sound, clinically relevant practice guidelines on chronic headache and particularly migraine, in the primary care setting. Five documents on headache and migraine were produced. These documents can be found on the American Academy of Neurology website (www.aan.com).

* *not available in the US.*

Effective long-term management of patients with migraine is challenging because of the complexity of the condition. Once a diagnosis of migraine is established, patients and their health care providers should together decide how to treat acute attacks *(see acute attack treatment guideline)* and whether to use preventive medications. Generally accepted indications for migraine prevention include:

- Two or more attacks a month that produce disability that lasts three or more days.
- Contraindication to, or failure of, acute treatments.
- The use of abortive medication more than twice a week.
- The presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Other factors to consider as well are adverse events with acute therapies, patient preference, and the cost of both acute and preventive therapies.

A wide range of preventive treatments with varying efficacies is currently in use. A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have been demonstrated to be effective in the prevention of migraine headache. It also provides a clear understanding of the adverse events associated with various agents. The Headache Consortium's review of the evidence on alpha-2 agonists, anticonvulsants, antidepressants, beta-blockers, calcium channel blockers, NSAID's, serotonergic agents (ergot derivatives, methysergide and others), hormone therapy, feverfew, magnesium, and riboflavin found the there was good evidence of the efficacy of only a few agents in migraine prevention. A summary of these results follows.

Preventive Therapies

Beta-blockers

Evidence consistently showed the efficacy of propranolol in a daily dose of 80 mg to 240 mg/day and timolol in a dose of 20-30 mg/day for the prevention of migraine. One trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was superior for patients with mixed migraine and tension-type headache. There is limited evidence of a moderate effect for atenolol, metoprolol, and nadolol. Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) appear to be ineffective for the prevention of migraine. Adverse effects reported most commonly with beta-blockers were fatigue, depression, nausea, dizziness, and insomnia. These symptoms appear to be fairly well tolerated and were seldom the cause of premature withdrawal from trials.

Antidepressants

Amitriptyline has been more frequently studied that the other antidepressants, and is the only one with consistent support for efficacy in migraine prevention. The doses that were most efficacious in the clinical trails ranged from 30-150mg/day. Drowsiness, weight gain and anticholinergic symptoms were frequently reported with the tricyclic antidepressants studied, including amitriptyline. There is no evidence for the use of

nortriptyline, protriptyline, doxepin, clomipramine, or imipramine. There is limited evidence of a modest effect for fluoxetine at doses ranging from 20 mg every other day to 40 mg a day. There is no evidence for the use of fluvoxamine, paroxetine, sertraline, phenelzine, bupropion, mirtazepine, trazodone, or venlafixine.

Anticonvulsants

For the anticonvulsants, there is good evidence for the efficacy of divalproex sodium and sodium valproate. Adverse events with these therapies are not uncommon and include weight gain, hair loss, tremor, and teratogenic potential, such as neural tube defects. These agents may be especially useful in patients with prolonged or atypical migraine aura. Carbamazepine and vigabatrin* have been shown not to be effective, and there is limited evidence for moderate efficacy of gabapentin.

NSAID's

A meta-analysis of five of seven placebo-controlled trials of naproxen or naproxen sodium showed a modest effect on headache prevention. Similar trends were observed in placebo-controlled trials of flurbiprofen, indobufen*, ketoprofen, lornoxicam*, mefanamic acid, and tolfenamic acid*, but fewer studies supported efficacy of each of these agents. Placebo-controlled trials of aspirin, aspirin plus dipyridamole, fenoprofen, and indomethacin were inconclusive. In a single placebo-controlled, randomized, double-blind trial of nabumetone, no difference from placebo was found. There is no evidence for the use of ibuprofen in the prevention of migraine.

The rates of patients reporting side effects for naproxen were not significantly higher than those seen with placebo. The most commonly reported adverse events with all NSAIDs were gastrointestinal symptoms; these included nausea, vomiting, gastritis, and blood in the stool. In the trials reviewed, such symptoms were reported by 3% to 45% of participants.

Serotonergic agents

Of these agents, Time-Released dihydroergotamine* (TR-DHE) had the strongest support, with consistently positive findings in four placebo-controlled trials. Evidence is insufficient for the efficacy of ergotamine or ergotamine plus caffeine plus butalbital plus belladonna alkaloids (Cafergot compound®) or methylergonovine for migraine prevention. Limited information was reported on adverse events associated with these agents. The most commonly reported events for all the ergot alkaloids were gastrointestinal symptoms.

There is strong evidence for the efficacy of methysergide, a semi-synthetic ergot alkaloid. However there are reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted administration. The manufacturer suggests that methysergide be discontinued for 3 to 4 weeks after each 6-month course of treatment. Other adverse events most commonly reported included gastrointestinal complaints, and leg symptoms (restlessness or pain).

Other serotonergic agents that have been evaluated for the prevention of migraine include pizotifen*, lisuride*, oxitriptan*, iprazochrome*, and tropisetron*. Only lisuride and

pizotifen have consistent evidence that supports their efficacy in the prevention of migraine. There is limited published data on adverse events associated with lisuride and it is common for pizotifen to be associated with weight gain and drowsiness.

Calcium channel blockers

The evidence for nifedipine, nimodipine, cyclandelate*, and verapamil are of poor quality and difficult to interpret suggesting only a modest effect. There is no evidence for the use of diltiazem in the prevention of migraine. Symptoms reported with these agents included dizziness, edema, flushing, and constipation.

Although flunarizine* is not available in the United States, it has proven efficacy in the prevention of migraine in a dose of 10 mg a day and is commonly used where it is available. Adverse events reported with flunarizine include sedation, weight gain, and abdominal pain. Depression and extrapyramidal symptoms can be observed, particularly in the elderly.

Alpha-2 agonists

There is good evidence for the lack of efficacy of the alpha-2 agonist clonidine in the prevention of migraine. There is limited evidence showing moderate efficacy of guanfacine in the prevention of migraine.

Hormone therapy, feverfew, magnesium, and riboflavin

There is fair evidence for modest efficacy of these agents in certain circumstances, but more trials need to be done. Most of these trials were small in number, had self-referred or special patient populations, or had other methodological flaws.

Additional Management Issues

Once an agent has been chosen, initiate therapy with a low dose and titrate the dose slowly up until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. A clinical benefit may take as long as two to three months to manifest itself, thus give each treatment an adequate trial. Once preventive treatment is underway, avoid interfering medications such as overuse of acute medications like ergotamine. Therapy should be re-evaluated on a regular basis. After a period of stability, consider tapering or discontinuing treatment.

In addition, clinicians need to educate migraine sufferers about their condition and its treatment, and encourage them to participate in their own management. Developing an effective migraine prevention strategy can be complex and an engaged patient is more likely to negotiate this process successfully. Patient input also permits the physician to better understand and accommodate patient treatment goals.

Summary

In order to alleviate the suffering of many migraine patients, clinicians need to be aware of the commonly accepted indications for preventive therapy, and initiate effective

** not available in the US.*

therapy in those patients. Although there are many agents available for the preventive treatment of migraine, only a few have proven efficacy. Patient and clinician need to engage in an ongoing dialogue in which patient expectations and goals for therapy are taken into account when choosing, titrating, or discontinuing agents.

Recommendations

Recommendation 1: Migraine sufferers should be evaluated for use of preventive therapy.

Generally accepted indications for migraine prevention include: 1. two or more attacks a month that produce disability that lasts three or more days, 2. contraindication to, or failure of, acute treatments, 3. use of abortive medication more than twice a week, or 4. the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Recommendation 2: Recommended first-line agents, currently available in the United States, for the prevention of migraine headache are: propranolol (80-240 mg/day), timolol (20-30 mg/day), amitriptyline (30-150 mg/day), divalproex sodium (500-1500 mg/day), and sodium valproate (800-1500 mg/day).

The medications with proven efficacy but frequent or severe adverse events or limited published data on adverse events include: methysergide, lisuride*, pizotifen*, TR-DHE*.

Recommendation 3: Educate migraine sufferers about preventive therapy and engage them in the formulation of a management plan. Therapy should be re-evaluated on a regular basis

The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms. Patient input can provide the best guide to treatment selection. Encouraging patients to be actively involved in their own management by tracking their own progress through daily flow sheets, etc. may be especially useful. Diaries should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.

Appendix 1: IHS Criteria for Migraine *(if papers published together, this can come out)*

Migraine without aura

A. At least five attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated).
C. Headache with at least two of the following characteristics:
    Unilateral location
    Pulsating quality
    Moderate or severe intensity (inhibits or prohibits daily activities)
    Aggravation by walking stairs or similar routine physical activity

** not available in the US.*

D. During headache at least one of the following:
   Nausea and/or vomiting
   Photophobia and phonophobia
E. At least one of the following:
   1. History and physical and neurologic examination do not suggest one of the disorders causing secondary headaches (appendix 1).
   2. History and/or physical and/or neurologic examinations do suggest such disorders, but it is ruled out by appropriate investigations.
   3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Migraine with aura
A. At least two attacks fulfilling B
B. At least three of the following four characteristics:
   1. One or more fully reversible aura symptoms indicate focal cerebral cortical and/or brain stem dysfunction.
   2. At least one aura symptom develops gradually over more than 4 minutes or two or more symptoms occur in succession.
   3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
   4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura.)
C. At least one of the following:
   1. History and physical and neurologic examinations do not suggest one of the disorders in appendix 1.
   2. History and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations.
   3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

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