CLINICAL GUIDELINES

Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache

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Migraine headache is a common disorder seen in primary care. It affects 18% of women and 6.5% of men in the United States, almost half of whom are undiagnosed or undertreated (1, 2). These guidelines, developed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine, with assistance from the American Headache Society, are based on two previously published papers (3, 4). The papers, titled "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management of Acute Attacks," by Matchar and colleagues (3), and "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine," by Ramadan and coworkers (4), can be found at http://www.aan.com/professionals/practice/guidelines.cfm.[1]

The target audience for this guideline is primary care physicians. The guideline applies to patients with acute migraine attacks, with or without aura, and patients with migraine who are candidates for preventive drug therapy. Although these guidelines are all based on the articles by Matchar and Ramadan and colleagues, the recommendations may differ because different thresholds of evidence were needed for making a positive recommendation. Table 1 compares the AAFP/ACP–ASIM guideline and the U.S. Headache Consortium Guideline.

Throughout the text, asterisks indicate drugs that are currently not available in the United States.

Diagnosis

Headache has many potential causes. Most headaches are caused by the primary headache disorders, which include migraine, cluster, and tension-type headaches. Secondary headaches, which are those with underlying pathologic causes, are far less common. Migraine is a chronic condition with recurrent acute attacks whose characteristics vary among patients and often among attacks within a single patient. Migraine is a syndrome with a wide variety of neurologic and non-neurologic manifestations. The International Headache Society (6) has developed diagnostic criteria for migraine with and without aura (Appendix Table 1). This classification system serves to diagnose headache syndromes, 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 have episodic tension-type headaches.

Management of Acute Attacks

Effective long-term management of patients with migraine is challenging because of the complexity of the condition. Experts suggest several goals for successful treatment of acute attacks of migraine. These include treating attacks rapidly and consistently to avoid headache recurrence, to restore the patient's ability to function, and to minimize the use of backup and rescue medications.

Clinicians need to educate people with migraine about their condition and its treatment and encourage them to participate in their own management. 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 and helps the physician to better understand and accommodate patient treatment goals. Developing an effective acute migraine management strategy can be complex, and an engaged patient is more likely to negotiate this process successfully. Encouraging patients to identify and avoid triggers (Table 2) and to be actively involved in their own management by tracking their own progress may be especially useful.

Once a diagnosis of migraine is established, patients and their health care providers should decide together how to treat acute attacks and whether the patient is a candidate for preventive medications. A wide range of acute treatments with varying efficacies is currently in use (Appendix Table 2). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy in the management of acute 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 antiemetics, barbiturate hypnotics, ergot alkaloids and derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), combination analgesics and nonopiate analgesics, opiate analgesics, triptans, and other agents found good evidence of the efficacy of only a few agents in the treatment of acute migraine (3).

Available Agents

NSAIDs

Their demonstrated efficacy and favorable tolerability make NSAIDs a first-line treatment choice for all migraine attacks, including severe attacks that have responded to NSAIDs in the past. Among the NSAIDs, the most consistent evidence exists for aspirin (8-10), ibuprofen (11, 12), naproxen sodium (13, 14), tolfenamic acid* (8, 15), and the combination agent acetaminophen plus aspirin plus caffeine for the acute treatment of migraine (16). The evidence shows that acetaminophen alone is ineffective (17).

Serotonin$_{1B/1D}$ Agonists (Triptans)

There is good evidence for the effectiveness of the oral triptans naratriptan (18, 19), rizatriptan (20-23), sumatriptan (24-31), and zolmitriptan (32-34). In addition, there is good evidence for the effectiveness of subcutaneous (35-38) and intranasal (39-41) sumatriptan,

making it an option for patients with nausea and vomiting. Adverse effects of the triptans include chest symptoms, but postmarketing data indicate that true ischemic events are rare. Triptans are contraindicated in patients with risk for heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension. Subcutaneous sumatriptan is associated with a very rapid onset of action, and oral naratriptan is associated with a slower onset of action.

Ergotamines

There is good evidence for the efficacy and safety of intranasal dihydroergotamine (DHE) as monotherapy for acute migraine attacks (42-46). Placebo-controlled studies of intravenous DHE did not clearly establish its efficacy in the acute treatment of migraine (47, 48). The evidence was inconsistent to support efficacy of ergotamine or ergotamine–caffeine, and the studies documented frequent adverse events.

Opioids

It is well recognized that opiates are good analgesics, but there is good evidence only for the efficacy of butorphanol nasal spray (49, 50). Although opioids are commonly used, surprisingly few studies of opioid use in headache pain document whether overuse and the development of dependence are as frequent as clinically perceived. Until further data are available, these drugs may be better reserved for use when other medications cannot be used, when sedation effects are not a concern, or the risk for abuse has been addressed.

Other Agents

Fair evidence suggests that the antiemetic metoclopramide, given intravenously, may be an appropriate choice as monotherapy for acute attacks (51-53), particularly in patients with nausea and vomiting when the sedating side effect may also be useful. Isometheptene and isometheptene combinations obtained only borderline significance in relieving headache pain (17, 54, 55). Other agents used in practice, such as intravenous corticosteroids and intranasal lidocaine, are not effective.

Choice of Treatment

Since patient responses to these therapies are not always predictable, individualized management is important. The choice of treatment should be based on, among other characteristics, the frequency and severity of attacks; the presence and degree of temporary disability; and the profile of associated symptoms, such as nausea and vomiting. The patient's history of, response to, and tolerance for specific medications must also be considered. Coexisting conditions (such as heart disease, pregnancy, and uncontrolled hypertension) may limit treatment choices.

No studies document the effectiveness of specific treatment schedules, but experts suggest that acute therapy should be limited to no more than two times per week to guard against medication-overuse headache (or drug-induced headache). Medication-overuse headache is thought to result from frequent use of acute medication and has a pattern of increasing headache frequency, often resulting in daily headaches. In patients with suspected medication overuse or patients at risk for medication overuse, preventive migraine therapy

should be considered.

Although some use the term *rebound headache* interchangeably with the term *medication-overuse headache*, rebound headache is a distinct entity. Rebound headache is associated with withdrawal of analgesics or abortive migraine medication. There is no uniform agreement about which agents can cause rebound headache, although ergotamine (not DHE); opiates; triptans; and simple and mixed analgesics containing butalbital, caffeine, or isometheptene are generally thought to do so. There is less uniform opinion about other antimigraine agents.

Another clinical consideration is the use of a self-administered rescue medication for patients with severe migraine attack that is not responding to (or failing) other treatments. A rescue medication is an agent such as an opioid or a butalbital-containing compound that the patient can use at home when other treatments have failed. Although rescue medications often do not completely eliminate pain and allow patients to return to normal activities, they permit the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department. A cooperative arrangement between provider and patient may extend to the use of rescue medication in appropriate situations.

Summary of Treatment of Acute Migraine

A body of evidence now points to effective first- and second-line agents for acute treatment of migraine. Beyond the choice of agent lies the choice of management strategy. Recently, interest and research in step care versus stratified care have increased. Step care refers to the initial use of safe, effective, and inexpensive medications as first-line agents in acute attacks of any severity. If the initial agent fails, a second-line, more expensive, migraine-specific medication is then used. The stratified care model initially stratifies migraine attacks by severity, advocating migraine-specific agents for moderate to severe attacks, regardless of previous response to or an unknown response to other agents. Which approach is more effective is still an open question (56).

Management of Migraine with Preventive Therapy

Once patients and their health care providers decide how to treat acute attacks, use of preventive medications should be considered. Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) the use of abortive medication more than twice per week; and 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. Other factors to consider are adverse events with acute therapies, patient preference, and the cost of both acute and preventive therapies. (The U.S. Headache Consortium also produced a document on behavioral and other nonpharmacologic therapies for headache prevention, which can be found at http://www.aan.com/professionals/practice/guidelines.cfm.)

A wide range of preventive treatments with varying efficacies is currently in use (Appendix Table 3). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy 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 α_2-agonists, anticonvulsants, antidepressants, β-blockers, calcium-channel blockers,

NSAIDs, serotonergic agents (ergot derivatives, methysergide, and others), hormone therapy, feverfew, magnesium, and riboflavin found that there was good evidence of the efficacy of only a few agents in migraine prevention. A summary of these results follows.

Available Agents

β-Blockers

Evidence consistently showed the efficacy of propranolol, 80 to 240 mg/d (57-63), and timolol, 20 to 30 mg/d (63-65), 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 (66). There is limited evidence of a moderate effect for atenolol (67, 68), metoprolol (69-71), and nadolol (72-74). β-Blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) seem to be ineffective for the prevention of migraine. Adverse effects reported most commonly with β-blockers were fatigue, depression, nausea, dizziness, and insomnia. These symptoms appear to be fairly well tolerated and seldom caused premature withdrawal from trials.

Antidepressants

Amitriptyline has been more frequently studied than the other antidepressants and is the only one with consistent support for efficacy in migraine prevention (75-77). The dosages that were most efficacious in the clinical trials ranged from 30 to 150 mg/d. 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 dosages ranging from 20 mg every other day to 40 mg per day (78, 79). There is no evidence from controlled trials for the use of fluvoxamine, paroxetine, sertraline, phenelzine, bupropion, mirtazapine, trazodone, or venlafaxine.

Anticonvulsants

For the anticonvulsants, there is good evidence for the efficacy of divalproex sodium (80-82) and sodium valproate (83, 84). 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 to be ineffective, and there is limited evidence for moderate efficacy of gabapentin (85).

NSAIDs

A meta-analysis (4) of five of seven placebo-controlled trials of naproxen or naproxen sodium showed a modest effect on headache prevention (62, 86-92). Similar trends were observed in single placebo-controlled trials of flurbiprofen, indobufen*, ketoprofen, lornoxicam*, and mefenamic acid and in two trials of tolfenamic acid*. Placebo-controlled trials of aspirin, aspirin plus dipyridamole, fenoprofen, and indomethacin were inconclusive. There is no

evidence for the use of ibuprofen or nabumetone in the prevention of migraine.

Side effect rates for naproxen were not significantly higher than those seen with placebo. The most commonly reported adverse events with all NSAIDs were gastrointestinal symptoms, including nausea, vomiting, gastritis, and blood in the stool. In the trials reviewed, such symptoms were reported by 3% to 45% of participants (86).

Serotonergic Agents

Of these agents, time-released DHE* had the strongest support, with consistently positive findings in four placebo-controlled trials (93-96). Evidence is insufficient for the efficacy of ergotamine or ergotamine plus caffeine plus butalbital plus belladonna alkaloids 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 (97-100), a semisynthetic ergot alkaloid. However, there are reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted administration. The manufacturer suggests that methysergide therapy be discontinued for 3 to 4 weeks after each 6-month course of treatment. Other adverse events most commonly reported included gastrointestinal symptoms 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 (101-104) and pizotifen (87, 99, 105-110) have consistent evidence that supports their efficacy in the prevention of migraine. Published data on adverse events associated with lisuride are limited, and pizotifen is often associated with weight gain and drowsiness.

Calcium-Channel Blockers

The evidence for nifedipine, nimodipine, cyclandelate*, and verapamil is poor quality and difficult to interpret, suggesting only a modest effect (see reference 4 for study references). 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.

Flunarizine*, 10 mg/d, has proven efficacy in the prevention of migraine and is commonly used in countries where it is available (111-115). Adverse events reported with flunarizine include sedation, weight gain, and abdominal pain. Depression and extrapyramidal symptoms can be observed, particularly in elderly persons.

α_2-Agonists

There is good evidence for the lack of efficacy of the α_2-agonist clonidine in the prevention of migraine (116-120). Limited evidence shows moderate efficacy of guanfacine (121).

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 the existing trials had small sample sizes, had self-referred or special patient samples, or had other methodologic flaws (see reference 4 for more details and references).

Summary of Preventive Therapy

To alleviate the suffering of many patients with migraine, clinicians need to be aware of the commonly accepted indications for preventive therapy and initiate effective therapy in those patients. Although many agents are available for the preventive treatment of migraine, only a few have proven efficacy. Once an agent has been chosen, clinicians should 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. Because a clinical benefit may take as long as 2 to 3 months to manifest, each treatment should be given an adequate trial. Once preventive treatment is under way, interfering medications, such as overused acute medications such as ergotamine, should be avoided. After a period of stability, clinicians should consider tapering or discontinuing treatment. Patient and clinician need to engage in an ongoing dialogue in which patient expectations and goals for therapy are taken into account when agents are chosen, titrated, or discontinued.

Recommendations

Recommendation 1: For most migraine sufferers, nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy.

To date, the most consistent evidence exists for aspirin, ibuprofen, naproxen sodium, tolfenamic acid*, and the combination agent acetaminophen plus aspirin plus caffeine. There is no evidence for the use of acetaminophen alone.

Recommendation 2: In patients whose migraine attack has not responded to NSAIDs, use migraine-specific agents (triptans, DHE).

There is good evidence for the following triptans: oral naratriptan, rizatriptan, and zolmitriptan; oral and subcutaneous sumatriptan; and DHE nasal spray. Few data in the literature demonstrate which triptans are more effective. Oral opiate combinations and butorphanol may be considered in acute migraine when sedation side effects are not a concern and the risk for abuse has been addressed.

Recommendation 3: Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea and vomiting with an antiemetic.

Evidence is limited, but in some patients, concomitant treatment with an antiemetic and an oral migraine medication may be appropriate. Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.

Recommendation 4: Migraine sufferers should be evaluated for use of preventive therapy.

Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or

failure of, acute treatments; 3) use of abortive medication more than twice per week; or 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Recommendation 5: Recommended first-line agents for the prevention of migraine headache are propranolol (80 to 240 mg/d), timolol (20 to 30 mg/d), amitriptyline (30 to 150 mg/d), divalproex sodium (500 to 1500 mg/d), and sodium valproate (800 to 1500 mg/d).

Medications with proven efficacy but limited published data on adverse events or frequent or severe adverse events include flunarizine*, lisuride*, pizotifen*, time-released DHE*, and methysergide.

Recommendation 6: Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan. Therapy should be reevaluated on a regular basis.

There is strong consensus about the need for educating people with migraine. The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms, such as medication-overuse headache. Encouraging patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example, may be especially useful. Diaries should measure attack frequency, severity, and duration; resulting disability; response to type of treatment; and adverse effects of medication. Patient input can provide the best guide to treatment selection.

[1] In an effort to educate clinicians and patients about headache's impact, diagnosis, management, and prognosis, the U.S. 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 U.S. Headache Consortium was to develop scientifically sound, clinically relevant practice guidelines on chronic headache, 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 Web site (http://www.aan.com).

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP–ASIM clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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References

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41:646-57. [PMID: 11554952] **| PubMed |**

2. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. Headache. 2001;41:638-45. [PMID: 11554951] **| PubMed |**

3. Matchar DB, Young WB, Rosenberg JH, Pietrzak MP, Silberstein SD, Lipton RB, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. 2000. Accessed at http://www.aan.com/professionals/practice/guidelines.cfm.

4. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2000. Accessed at http://www.aan.com/professionals/practice/guidelines.cfm.

5. McCrory DC, Matchar DB, Gray RN, Rosenberg JH, Silberstein SD. Evidence-based guidelines for migraine headache: overview of program description and methodology. 2000. Accessed at http://www.aan.com/professionals/practice/guidelines.cfm.

6. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia. 1988;8 Suppl 7:1-96. [PMID: 3048700] **| PubMed |**

7. Silberstein SD, Lipton RB, Goadsby PJ. Classification and diagnosis of headache. In: Silberstein SD, Lipton RB, Goadsby PJ, eds. Headache in Clinical Practice. Oxford, UK: Isis Medical Media; 1998:11-8.

8. Hakkarainen H, Vapaatalo H, Gothoni G, Parantainen J. Tolfenamic acid is as effective as ergotamine during migraine attacks. Lancet. 1979;2:326-8. [PMID: 89390] **| PubMed |**

9. Boureau F, Joubert JM, Lasserre V, Prum B, Delecoeuillerie G. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. Cephalalgia. 1994;14:156-61. [PMID: 8062355] **| PubMed |**

10. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. Cephalalgia. 1984;4:107-11. [PMID: 6375873] **| PubMed |**

11. Havanka-Kanniainen H. Treatment of acute migraine attack: ibuprofen and placebo compared. Headache. 1989;29:507-9. [PMID: 2676908] **| PubMed |**

12. Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. Cephalalgia. 1992;12:169-71; discussion 128. [PMID: 1623513] **| PubMed |**

13. Sargent JD, Baumel B, Peters K, Diamond S, Saper JR, Eisner LS, et al. Aborting a migraine attack: naproxen sodium v ergotamine plus caffeine. Headache. 1988;28:263-6. [PMID: 3139584] **| PubMed |**

14. Johnson ES, Ratcliffe DM, Wilkinson M. Naproxen sodium in the treatment of migraine. Cephalalgia. 1985;5:5-10. [PMID: 3886154] **| PubMed |**

15. Tokola RA, Kangasniemi P, Neuvonen PJ, Tokola O. Tolfenamic acid, metoclopramide, caffeine and their combinations in the treatment of migraine attacks. Cephalalgia. 1984;4:253-63. [PMID: 6394143] **| PubMed |**

16. Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. Arch Neurol. 1998;55:210-7. [PMID: 9482363] **| PubMed |**

17. Diamond S. Treatment of migraine with isometheptene, acetaminophen, and dichloralphenazone combination: a double-blind, crossover trial. Headache. 1976;15:282-7. [PMID: 1107267] **| PubMed |**

18. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. Naratriptan S2WA3001 Study Group. Headache. 1997;37:640-5. [PMID: 9439085] **| PubMed |**

19. Mathew NT, Asgharnejad M, Peykamian M, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, crossover study. The Naratriptan S2WA3003 Study Group. Neurology. 1997;49:1485-90. [PMID: 9409334] **| PubMed |**

20. Cutler NR, Claghorn J, Sramek JJ, Block G, Panebianco D, Cheng H, et al. Pilot study of MK-462 in migraine. Cephalalgia. 1996;16:113-6. [PMID: 8665577] **| PubMed |**

21. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Dutch/US Rizatriptan Study Group. Arch Neurol. 1996;53:1132-7. [PMID: 8912486] **| PubMed |**

22. Gijsman H, Kramer MS, Sargent J, Tuchman M, Matzura-Wolfe D, Polis A, et al. Double-blind, placebo-controlled, dose-finding study of rizatriptan (MK-462) in the acute treatment of migraine. Cephalalgia. 1997;17:647-51. [PMID: 9350384] **| PubMed |**

23. Teall J, Tuchman M, Cutler N, Gross M, Willoughby E, Smith B, et al. Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study. Rizatriptan 022 Study Group. Headache. 1998;38:281-7. [PMID: 9595867] **| PubMed |**

24. Cutler N, Mushet GR, Davis R, Clements B, Whitcher L. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. Neurology. 1995;45:S5-9. [PMID: 7644082] **| PubMed |**

25. Myllylä VV, Havanka H, Herrala L, Kangasniemi P, Rautakorpi I, Turkka J, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. Headache. 1998;38:201-7. [PMID: 9563211] **| PubMed |**

26. Nappi G, Sicuteri F, Byrne M, Roncolato M, Zerbini O. Oral sumatriptan compared with placebo in the acute treatment of migraine. J Neurol. 1994;241:138-44. [PMID: 8164015] **| PubMed |**

27. Sumatriptan—an oral dose-defining study. The Oral Sumatriptan Dose-Defining Study Group. Eur Neurol. 1991;31:300-5. [PMID: 1653137] **| PubMed |**

28. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. The Oral Sumatriptan International Multiple-Dose Study Group. Eur Neurol. 1991;31:306-13. [PMID: 1653138] **| PubMed |**

29. Pfaffenrath V, Cunin G, Sjonell G, Prendergast S. Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine: defining the optimum doses of oral sumatriptan. Headache. 1998;38:184-90. [PMID: 9563208] **| PubMed |**

30. Pini LA, Sternieri E, Fabbri L, Zerbini O, Bamfi F. High efficacy and low frequency of headache recurrence after oral sumatriptan. The Oral Sumatriptan Italian Study Group. J Int Med Res. 1995;23:96-105. [PMID: 7601299] **| PubMed |**

31. Sargent J, Kirchner JR, Davis R, Kirkhart B. Oral sumatriptan is effective and well tolerated for the acute treatment of migraine: results of a multicenter study. Neurology. 1995;45:S10-4. [PMID: 7644079] **| PubMed |**

32. Rapoport AM, Ramadan NM, Adelman JU, Mathew NT, Elkind AH, Kudrow DB, et al. Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. The 017 Clinical Trial Study Group. Neurology. 1997;49:1210-8. [PMID: 9371896] **| PubMed |**

33. Solomon GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. The 042 Clinical Trial Study Group. Neurology. 1997;49:1219-25. [PMID: 9371897] **| PubMed |**

34. Visser WH, Klein KB, Cox RC, Jones D, Ferrari MD. 311C90, a new central and peripherally acting 5-HT1D receptor agonist in the acute oral treatment of migraine: a double-blind, placebo-controlled, dose-range finding study. Neurology. 1996;46:522-6. [PMID: 8614525] **| PubMed |**

35. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA. 1991;265:2831-5. [PMID: 1851894] **| PubMed |**

36. Mathew NT, Dexter J, Couch J, Flamenbaum W, Goldstein J, Rapoport A, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. Arch Neurol. 1992;49:1271-6. [PMID: 1333181] **| PubMed |**

37. Russell MB, Holm-Thomsen OE, Rishøj Nielsen M, Cleal A, Pilgrim AJ, Olesen J. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. Cephalalgia. 1994;14:291-6. [PMID: 7954759] **| PubMed |**

38. Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group. N Engl J Med. 1991;325:316-21. [PMID: 1647495] **| PubMed |**

39. A placebo-controlled study of intranasal sumatriptan for the acute treatment of migraine. The Finnish Sumatriptan Group and the Cardiovascular Clinical Research Group. Eur Neurol. 1991;31:332-8. [PMID: 1653141] **| PubMed |**

40. Salonen R, Ashford E, Dahlöf C, Dawson R, Gilhus NE, Lüben V, et al. Intranasal sumatriptan for the acute treatment of migraine. International Intranasal Sumatriptan Study Group. J Neurol. 1994;241:463-9. [PMID: 7964913] **| PubMed |**

41. Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine. Results of two clinical studies. Neurology. 1997;49:1225-30. [PMID: 9371898] **| PubMed |**

42. Efficacy, safety, and tolerability of dihydroergotamine nasal spray as monotherapy in the treatment of acute migraine. Dihydroergotamine Nasal Spray Multicenter Investigators. Headache. 1995;35:177-84. [PMID: 7775172] **| PubMed |**

43. Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. Dihydroergotamine Working Group. Arch Neurol. 1996;53:1285-91. [PMID: 8970458] **| PubMed |**

44. Rohr J, Dufresne JJ. Dihydroergotamine nasal spray for the treatment of migraine attacks: a comparative double-blind crossover study with placebo. Cephalalgia. 1985;5(Suppl 3):142-3.

45. Tulunay FC, Karan O, Aydin N, Culcuoglu A, Guvener A. Dihydroergotamine nasal spray during migraine attacks. A double-blind crossover study with placebo. Cephalalgia. 1987;7:131-3. [PMID: 3301001] **| PubMed |**

46. Ziegler D, Ford R, Kriegler J, Gallagher RM, Peroutka S, Hammerstad J, et al. Dihydroergotamine nasal spray for the acute treatment of migraine. Neurology. 1994;44:447-53. [PMID: 8145914] **| PubMed |**

47. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. Headache. 1986;26:168-71. [PMID: 3519528] **| PubMed |**

48. Klapper J, Stanton J. The emergency treatment of acute migraine headache; a comparison of intravenous dihydroergotamine, dexamethasone, and placebo. Cephalalgia. 1991;11(Suppl 11):159-60.

49. Hoffert MJ, Couch JR, Diamond S, Elkind AH, Goldstein J, Kohlerman NJ 3rd, et al. Transnasal butorphanol in the treatment of acute migraine. Headache. 1995;35:65-9. [PMID: 7737863] **| PubMed |**

50. Goldstein J, Gawel MJ, Winner P, et al. Comparison of butorphanol nasal spray and fiorinal with codeine in the treatment of migraine. Headache. 1998; 38:516-22.

51. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. Ann Emerg Med. 1995;26:541-6. [PMID: 7486359] **| PubMed |**

52. Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of metoclopramide in the treatment of migraine headache. Ann Emerg Med. 1993;22:191-5. [PMID: 8427430] **| PubMed |**

53. Tek DS, McClellan DS, Olshaker JS, Allen CL, Arthur DC. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. Ann Emerg Med. 1990;19:1083-7. [PMID: 2221512] **| PubMed |**

54. Diamond S, Medina JL. Isometheptene—a non-ergot drug in the treatment of migraine. Headache. 1975;15:211-3. [PMID: 1100566] **| PubMed |**

55. Ryan RE. A study of midrin in the symptomatic relief of migraine headache. Headache. 1974;14:33-42. [PMID: 4599014] **| PubMed |**

56. Matchar DB, McCrory DC, Gray RN. Toward evidence-based management of migraine [Editorial]. JAMA. 2000;284:2640-1. [PMID: 11086374] **| PubMed |**

57. Borgesen SE, Nielsen JL, Moller CE. Prophylactic treatment of migraine with propranolol. A clinical trial. Acta Neurol Scand. 1974;50:651-6. [PMID: 4611129] **| PubMed |**

58. Forssman B, Henriksson KG, Johannsson V, Lindvall L, Lundin H. Propranolol for migraine prophylaxis. Headache. 1976;16:238-45. [PMID: 977330] **| PubMed |**

59. Johnson RH, Hornabrook RW, Lambie DG. Comparison of mefenamic acid and propranolol with placebo in migraine prophylaxis. Acta Neurol Scand. 1986;73:490-2. [PMID: 3524092] **| PubMed |**

60. Mikkelsen B, Pedersen KK, Christiansen LV. Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo. Acta Neurol Scand. 1986;73:423-7. [PMID: 3727918] **| PubMed |**

61. Pradalier A, Serratrice G, Collard M, Hirsch E, Feve J, Masson M, et al. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia. 1989;9:247-53. [PMID: 2692838] **| PubMed |**

62. Sargent J, Solbach P, Damasio H, Baumel B, Corbett J, Eisner L, et al. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. Headache. 1985;25:320-4. [PMID: 3902723] **| PubMed |**

63. Tfelt-Hansen P, Standnes B, Kangasneimi P, Hakkarainen H, Olesen J. Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand. 1984;69:1-8. [PMID: 6367336] **| PubMed |**

64. Briggs RS, Millac PA. Timolol in migraine prophylaxis. Headache. 1979;19:379-81. [PMID: 511540] **| PubMed |**

65. Stellar S, Ahrens SP, Meibohm AR, Reines SA. Migraine prevention with timolol. A double-blind crossover study. JAMA. 1984;252:2576-80. [PMID: 6387197] **| PubMed |**

66. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache. 1981;21:105-9. [PMID: 7021472] **| PubMed |**

67. Forssman B, Lindblad CJ, Zbornikova V. Atenolol for migraine prophylaxis. Headache. 1983;23:188-90. [PMID: 6350226] **| PubMed |**

68. Johannsson V, Nilsson LR, Widelius T, Jäverfalk T, Hellman P, Akesson JA, et al. Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. Headache. 1987;27:372-4. [PMID: 3308768] **| PubMed |**

69. Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Kristensen TN, et al. Prophylactic treatment of classical and non-classical migraine with metoprolol—a comparison with placebo. Cephalalgia. 1983;3:207-12. [PMID: 6640652] **| PubMed |**

70. Kangasniemi P, Andersen AR, Andersson PG, Gilhus NE, Hedman C, Hultgren M, et al. Classic migraine: effective prophylaxis with metoprolol. Cephalalgia. 1987;7:231-8. [PMID: 3322569] **| PubMed |**

71. Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. Headache. 1988;28:15-23. [PMID: 3277926] **| PubMed |**

72. Freitag FG, Diamond S. Nadolol and placebo comparison study in the prophylactic treatment of migraine. J Am Osteopath Assoc. 1984;84:343-7. [PMID: 6150909] **| PubMed |**

73. Ryan RE Sr, Ryan RE Jr, Sudilovsky A. Nadolol: its use in the prophylactic treatment of migraine. Headache. 1983;23:26-31. [PMID: 6131052] **| PubMed |**

74. Sudilovsky A, Stern MA, Mayer JH. Naldolol: the benefits of an adequate trial duration in the prophylaxis of migraine. Headache. 1986;26:325.

75. Couch JR, Hassanein RS. Migraine and depression: effect of amitriptyline prophylaxis.

Trans Am Neurol Assoc. 1976;101:234-7. | PubMed |

76. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol. 1979;36:695-9. | PubMed |

77. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry. 1973;36:684-90. [PMID: 4731336] | PubMed |

78. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache. 1992;32:101-4. [PMID: 1551787] | PubMed |

79. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia. 1998;18:283-6. [PMID: 9673809] | PubMed |

80. Klapper JA. An open-label cross-over comparison of divalproex sodium and propranolol HCl in the prevention of migraine headaches. Headache Quarterly. 1994;5:50-3.

81. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia. 1997;17:103-8. [PMID: 9137847] | PubMed |

82. Mathew NT, Saper JR, Silberstein SD, Rankin L, Markley HG, Solomon S, et al. Migraine prophylaxis with divalproex. Arch Neurol. 1995;52:281-6. [PMID: 7872882] | PubMed |

83. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia. 1992;12:81-4. [PMID: 1576648] | PubMed |

84. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology. 1994;44:647-51. [PMID: 8164818] | PubMed |

85. Mathew N, Saper J, Magnus-Miller L. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis [Abstract]. San Diego, CA: 17th Annual Meeting of the American Pain Society; 5–8 November 1998. Abstract no. 645.

86. Drug Treatments for the Prevention of Migraine Headache. Technical Review 2.3. February 1999. Prepared for the Agency for Healthcare Policy and Research (contract no. 290-94-2025). Available from the National Technical Information Service (NTIS Accession No. 127953.

87. Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache. 1990;30:710-5. [PMID: 2074163] | PubMed |

88. Lindegaard KF, Ovrelid L, Sjaastad O. Naproxen in the prevention of migraine attacks.

A double-blind placebo-controlled cross-over study. Headache. 1980;20:96-8. [PMID: 6989789] **| PubMed |**

89. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. Headache. 1990;30:705-9. [PMID: 2074162] **| PubMed |**

90. Szekely B, Merryman S, Croft H, Post G. Prophylactic effects of naproxen sodium on perimenstrual headache: a double-blind, placebo-controlled study. Cephalalgia. 1989;9(Suppl 10):452-3.

91. Welch KM, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. Neurology. 1985;35:1304-10. [PMID: 4022376] **| PubMed |**

92. Ziegler DK, Ellis DJ. Naproxen in prophylaxis of migraine. Arch Neurol. 1985;42:582-4. [PMID: 4004602] **| PubMed |**

93. Autret A, De Chasteigner C. DHE methane sulfonate with programmed liberation: preliminary results of a controlled study in common migraine. Cephalalgia. 1987;7(Suppl 6):451-2.

94. Martucci N, Manna V, Mattesi P, Troiani G, Manzoni GC, Lanfranchi M, et al. Ergot derivatives in the prophylaxis of migraine: a multicentric study with a timed-release dihydroergotamine formulation. Cephalalgia. 1983;3 Suppl 1:151-5. [PMID: 6352046] **| PubMed |**

95. Neuman M, Demarez JP, Harmey JL, Le Bastard B, Cauquil J. Prevention of migraine attacks through the use of dihydroergotamine. Int J Clin Pharmacol Res. 1986;6:11-3. [PMID: 3514491] **| PubMed |**

96. Bousser MG, Chick J, Fuseau E, Soisson T, Thevenet R. Combined low-dose acetylsalicylic acid and dihydroergotamine in migraine prophylaxis. A double-blind, placebo-controlled crossover study. Cephalalgia. 1988;8:187-92. [PMID: 3197098] **| PubMed |**

97. Lance JW, Fine RD, Curran DA. An evaluation of methysergide in the prevention of migraine and other vascular headaches. Med J Aust. 1963;(Jun):814-8.

98. Pedersen E, Moller CE. Methysergide in migraine prophylaxis. Clin Pharmacol Ther. 1966;7:520-6. [PMID: 5328472] **| PubMed |**

99. Ryan RE. Double-blind crossover comparison of bc-105, methysergide and placebo in the prophylaxis of migraine headache. Headache. 1968;8:118-26. [PMID: 4892617] **| PubMed |**

100. Shekelle RB, Ostfeld AM. Methysergide in the migraine syndrome. Clin Pharmacol Ther. 1964;5:201-4.

101. Herrmann WM, Kristof M, Sastre M, Sastre M. Preventive treatment of migraine headache with a new isoergolenyl derivative. J Int Med Res. 1978;6:476-82. [PMID: 363486] **| PubMed |**

102. Sances G, Martignioni E, Rosettino G, et al. Lisuride in menstrual migraine prophylaxis. Cephalalgia. 1989;9(Suppl 10):444-55.

103. Somerville BW, Herrmann WM. Migraine prophylaxis with Lisuride hydrogen maleate—a double blind study of Lisuride versus placebo. Headache. 1978;18:75-9. [PMID: 348647] **| PubMed |**

104. Zuddas A. Usefulness of lisuride on menstrual migraine in a double-blind trial. Cephalalgia. 1985;5(Suppl 3):514-5.

105. Arthur GP, Hornabrook RW. The treatment of migraine with BC 105 (pizotifen): a double blind trial. N Z Med J. 1971;73:5-9. [PMID: 4925988] **| PubMed |**

106. Carroll JD, Maclay WP. Pizotifen (BC 105) in migraine prophylaxis. Curr Med Res Opin. 1975;3:68-71. [PMID: 1095308] **| PubMed |**

107. Krakowski AJ, Engisch R. A new agent for chemotherapy of migraine headaches: a controlled study. Psychosomatics. 1973;14:302-8. [PMID: 4604015] **| PubMed |**

108. Lawrence ER, Hossain M, Littlestone W. Sanomigran for migraine prophylaxis, controlled multicenter trial in general practice. Headache. 1977;17:109-12. [PMID: 330465] **| PubMed |**

109. Osterman PO. A comparison between placebo, pizotifen and 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2.3.5.6-tetrahydroindol (Divascan) in migraine prophylaxis. Acta Neurol Scand. 1977;56:17-28. [PMID: 327746] **| PubMed |**

110. Ryan RE. BC-105 a new preparation for the interval treatment of migraine—a double blind evaluation compared with a placebo. Headache. 1971;11:6-18. [PMID: 5554982] **| PubMed |**

111. al Deeb SM, Biary N, Bahou Y, al Jaberi M, Khoja W. Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population). Headache. 1992;32:461-2. [PMID: 1446992] **| PubMed |**

112. Diamond S, Freitag FG. A double-blind trial of flunarizine in migraine prophylaxis. Headache Quarterly. 1993;4:169-72.

113. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. Headache. 1981;21:235-9. [PMID: 7031016] **| PubMed |**

114. Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial

of flunarizine in common migraine. Cephalalgia. 1986;6:7-14. [PMID: 3516409] **| PubMed |**

115. Frenken CW, Nuijten ST. Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. Clin Neurol Neurosurg. 1984;86:17-20. [PMID: 6325065] **| PubMed |**

116. Adam EI, Gore SM, Price WH. Double-blind trial of clonidine in the treatment of migraine in general practice. J Coll Gen Pract. 1978;28:587-90.

117. Das SM, Ahuja GK, Narainaswamy AS. Clonidine in prophylaxis of migraine. Acta Neurol Scand. 1979;60:214-7. [PMID: 393047] **| PubMed |**

118. Mondrup K, Moller CE. Prophylactic treatment of migraine with clonidine. A controlled clinical trial. Acta Neurol Scand. 1977;56:405-12. [PMID: 339659] **| PubMed |**

119. Ryan RE Sr, Diamond S, Ryan RE Jr. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache. 1975;15:202-10. [PMID: 1100565] **| PubMed |**

120. Shafar J, Tallett ER, Knowlson PA. Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet. 1972;1:403-7. [PMID: 4110641] **| PubMed |**

121. Elkind AH, Webster C, Herbertson RK. Efficacy of guafacine in a double-blind parallel study for migraine prophylaxis. Cephalalgia. 1989;9(Suppl 10):369-70.