A Nonprofit Publication

Vol. 2 (Issue 25) September 2004

Treatment Guidelines from The Medical Letter®

Published by The Medical Letter, Inc.
1000 Main Street
New Rochelle, N.Y. 10801
www.medicalletter.org

Drugs for Migraine

Drugs for treatment of migraine attacks are listed in the table on page 64. All of the oral drugs are most effective if taken early in an attack when the pain is mild (H Christoph-Diener et al, Neurology 2004; 63:520). Drugs for prevention of migraine are listed in the table on page 65. Treatment of migraine in the emergency room, which may involve use of intravenous drugs, is not included here.

ANALGESICS — Treatment with a nonopioid analgesic may be sufficient for mild or moderate episodes of migraine (RG Wenzel et al, Pharmacotherapy 2003; 23:494). **Aspirin** can be effective; it is widely used for treatment of migraine both alone and in combinations such as *Fiorinal,* which contains caffeine and butalbital. **Acetaminophen** has also been shown to be effective for treatment of migraine (RB Lipton et al, Arch Intern Med 2000; 160:3486). It is marketed for this indication in combinations such as *Fioricet* or *Esgic,* which also contain caffeine and butalbital, and *Midrin,* which contains isometheptene (a sympathomimetic amine) and dichloralphenazone (a chloral hydrate compound). A combination of acetaminophen with aspirin and caffeine (*Excedrin Migraine*, and others) is FDA-approved and available for over-the-counter use in migraine.

Ibuprofen 200 mg (*Advil*, *Motrin*, *Advil Migraine, Motrin Migraine Pain*, and others) is FDA-approved for OTC treatment of migraine attacks. Other nonsteroidal anti-inflammatory drugs (NSAIDs) such as **naproxen sodium** *(Anaprox,* and others) also have been effective in relieving the pain of some migraine attacks. The COX-2 selective NSAID **rofecoxib** *(Vioxx)* has been approved by the FDA for acute treatment of migraine, and produces relief after 2 hours in about 50% of patients (S Silberstein et al, Neurology 2004; 62:1552).

Oral opioid combinations and injected opioids are effective for relief of pain, but they produce the usual opioid adverse effects, and frequent use can lead to drug dependence (Treatment Guidelines 2004; 2:47). **Butorphanol nasal spray**, an opioid agonist-antagonist, has been rapidly effective for relief of moderate to severe migraine, but drug dependence and abuse have been reported (L Robbins, Headache 2002; 42:386).

Decreased gastric motility during an acute migraine attack may interfere with absorption of oral analgesics. **Metoclopramide** *(Reglan,* and others) taken promptly at the onset of symptoms can enhance absorption by increasing gastric motility and may prevent the nausea associated with many migraine attacks.

ERGOT ALKALOIDS — Ergotamine tartrate, a non-specific serotonin agonist and a vasoconstrictor, has been used for many years for treatment of moderate to severe migraine headache. It is available alone in sublingual tablets and combined with caffeine in oral

Some Drugs for Treatment of Migraine Attack

Drug	Usual dosage	Cost[1]
ERGOT ALKALOIDS		
Dihydroergotamine mesylate – average generic	1 mg IM or SC; can be repeated	$34.56
D.H.E. 45 (Xcel)	at 1 hr intervals (max 3 mg/24 hrs, 6 mg/wk)	43.78
Migranal Nasal Spray (Xcel)	1 spray (0.5 mg) into each nostril, repeated 15 min later (2 mg/dose; max 3 mg/24 hrs)	31.77
Ergotamine tartrate – *Ergomar* (Harvest)	2-mg sublingual tab, can be repeated q30min PRN (max 3 tabs/24 hrs, 5 tabs/wk)	8.28
Ergotamine 1 mg/caffeine 100mg – *Cafergot* (Novartis)	2 tabs PO, then 1 q30min x 4 PRN (max 6 tabs/attack)	2.50
Ergotamine 2 mg/caffeine 100mg – *Cafergot* (Novartis)	1 rectal suppository; can be repeated once 1 hr later	6.96
5-HT$_1$ RECEPTOR AGONISTS ("TRIPTANS")		
Almotriptan – *Axert* (Ortho-McNeil)	12.5 mg PO; can be repeated once after 2 hrs	17.40
Eletriptan – *Relpax* (Pfizer)	20 or 40 mg PO; can be repeated after 2 hrs (max 80 mg/d)	16.21
Frovatriptan – *Frova* (Vernalis)	2.5 mg PO; can be repeated after 2 hrs (max 7.5 mg/d)	16.29
Naratriptan – *Amerge* (GlaxoSmithKline)	2.5 mg PO; can be repeated once after 4 hrs	20.37
Rizatriptan[2] – *Maxalt*, *Maxalt-MLT*[3] (Merck)	5 or 10 mg PO; can be repeated after 2 hrs (max 30 mg/d)	17.76
Sumatriptan – *Imitrex* (GlaxoSmithKline)	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)	17.52
	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs	25.47
	6 mg SC; can be repeated once after 1 hr	60.68
Zolmitriptan – *Zomig*, *Zomig ZMT*[3] (AstraZeneca)	2.5 or 5 mg PO; can be repeated after 2 hrs (max 10 mg/d)	16.39
	5 mg intranasally; can be repeated once after 2 hrs	24.45

1. Cost of one dose at the lowest dosage, according to the most recent data (June 30, 2004) from retail pharmacies nationwide available from NDCHealth, a healthcare information services company.
2. Patients taking propranolol should only use the 5-mg tablet or wafer (max 15 mg/24 hrs).
3. Orally disintegrating tablet.

tablets and suppositories. **Dihydroergotamine mesylate,** which can be injected subcutaneously, intramuscularly or intravenously, or sprayed intranasally, is also effective in treating migraine attacks. It is a weaker arterial vasoconstrictor than ergotamine. Dihydroergotamine nasal spray relieves migraine after two hours in about 50% of patients and after four hours in up to 70%, with a 15% incidence of headache recurrence within 24 hours.

Adverse Effects – Nausea and vomiting are fairly common with ergotamine, but can be prevented by pretreatment with or concurrent use of an antiemetic such as prochlorperazine *(Compazine,* and others). Serious adverse effects, such as vascular (including coronary) occlusion and gangrene, are rare and usually associated with overdosage (more than 6 mg in 24 hours or 10 mg per week). Liver disease or fever can accelerate development of ergotism. Long-term continuous use of ergotamine has been associated with retroperitoneal, pleural and pericardial fibrosis and fibrotic thickening of the cardiac valves. Dihydroergotamine causes fewer adverse effects than ergotamine; it can cause diarrhea and muscle cramps.

Drug Interactions – The effects of ergotamine may be potentiated by triptans, beta-adrenergic blockers, dopamine, or CYP3A4 inhibitors. Ergots and triptans should not be taken within 24 hours of each other. Use of ergotamine is contraindicated with potent CYP3A4 inhibitors such as erythromycin, ritonavir *(Norvir)* or itraconazole *(Sporanox)* (Medical Letter 2003; 45:46). Dihydroergotamine has drug interactions similar to those of ergotamine.

5-HT$_1$ RECEPTOR AGONISTS ("TRIPTANS") — Sumatriptan was the first triptan marketed in the US and is available for subcutaneous self-injection, as a nasal spray, and for oral administration. A selective serotonin-receptor agonist with a short duration of action, it is more effective than ergotamine for treatment of acute migraine attacks. The injection and nasal spray formulations often begin to produce relief in 10 to 15 minutes, compared to 30 minutes to two hours with the tablets. The nasal spray has been effective and well tolerated in children (K Ahonen et al, Neurology 2004; 62:883). A subcutaneous injection of sumatriptan produces relief within two hours in 70% to 80% of patients with moderate to severe migraine. Sumatriptan nasal spray has produced a response in about 60% of patients after two hours. Oral sumatriptan has been effective in about 50% to 60% of patients with acute migraine after two hours and in about 70% after four hours (SD Silberstein, Lancet 2004; 363:381).

Almotriptan may cause a lower incidence of chest pain and **rizatriptan** may have a slightly more rapid onset of action than oral sumatriptan (G Nappi et al, Drug Saf 2003; 26:93; P Tfelt-Hansen and RE Ryan Jr, Neurology 2000; 55 suppl 2:S19). **Zolmitriptan**, like sumatriptan, is available as a nasal spray as well as orally; how it compares in efficacy with sumatriptan nasal spray remains to be established, but fewer patients complain about its taste (Medical Letter 2004; 46:7). **Naratriptan** and **frovatriptan**, which have

Some Drugs for Prevention of Migraine

Drug	Usual dosage	Cost[1]
BETA-BLOCKERS		
Propranolol – average generic	80 to 240 mg divided bid, tid or qid	$28.20
Inderal (Wyeth-Ayerst)		50.40
Sustained-release – average generic	160 to 240 mg once/d	46.80
Inderal LA (Wyeth-Ayerst)		72.00
Timolol – average generic	10 to 15 mg bid	18.00
Blocadren (Merck)		38.40
ANTIEPILEPTIC DRUGS		
Divalproex sodium –		
Depakote (Abbott)	250 to 500 mg bid	70.20
Depakote ER (Abbott)	500 to 1000 mg once/d	62.40
Topiramate – *Topamax* (Ortho-McNeil)	50 mg bid	199.20
TRICYCLIC ANTIDEPRESSANTS		
Amitriptyline[2] – average generic	30 to 150 mg once/d	12.60
CALCIUM-CHANNEL BLOCKERS		
Verapamil[2] – average generic	80 mg tid or qid	25.20
Calan (Searle)		68.40
Sustained-release – average generic	240 mg once/d	32.10
Calan SR		63.60

1. Cost for 30 days' treatment with the lowest daily dosage, according to the most recent data (June 30, 2004) from retail pharmcies nationwide, available from NDCHealth, a healthcare information services company.
2. Not approved by the FDA for this indication.

longer half-lives, appear to have slower onsets of action and lower initial response rates. The rate of recurrence in patients with moderate or severe migraine within 24 hours after treatment with a triptan is generally 20% to 40%; it is slightly lower with naratriptan and frovatriptan. Recurrences usually respond to a second dose of the triptan.

Adverse Effects – A burning sensation at the injection site is common with subcutaneous sumatriptan. Tingling, flushing, dizziness, drowsiness, fatigue, and a feeling of heaviness, tightness or pressure in the chest may occur with all triptans, but most commonly with injectable sumatriptan. Angina, myocardial infarction, cardiac arrhythmia, stroke and death have occurred rarely with these drugs. They are contraindicated in patients with coronary or other arterial disease or uncontrolled hypertension.

Drug Interactions – A triptan should not be used within 24 hours after another triptan or an ergotamine-containing drug because vasoconstriction could be additive. Rizatriptan, sumatriptan and zolmitriptan are contraindicated in patients taking an MAO-A inhibitor or within two weeks of stopping one. Propranolol increases serum concentrations of rizatriptan and zolmitriptan *(The Medical Letter Adverse Drug Interactions Program)*. Inhibitors of CYP3A4, including verapamil, increase serum concentrations and may increase the toxicity of eletriptan.

MEDICATION OVERUSE HEADACHE — Overuse (more than two or three days a week) of analgesics, ergots (except dihydroergotamine) or triptans can cause a daily dull headache. Triptan overuse can also cause a migraine-like daily headache or an increase in migraine headache frequency (V Limmroth et al, Neurology 2002; 59:1011).

PREVENTION — Patients with frequent or severe disabling migraine headaches and those who cannot take vasoconstrictors or are refractory to acute treatment may benefit from prevention. Menstrual or other predictable migraine attacks may sometimes be prevented by a brief course of an NSAID, ergotamine or low doses of a triptan, taken for several days before and during the first few days of menstruation (SD Silberstein et al, Neurology 2004; 63:261).

For continuous prophylaxis, **beta-adrenergic blocking agents** are commonly used. Propranolol and timolol are the only beta-blockers approved by the FDA for this indication. Metoprolol *(Lopressor,* and others), nadolol *(Corgard,* and others) and atenolol *(Tenormin,* and others) also have been effective in preventing migraine (V Limmroth and MC Michel, Br J Clin Pharmacol 2001; 52:237). All beta-blockers can cause fatigue, exercise intolerance, depression and orthostatic hypotension, and in the short term they may aggravate heart failure. All are relatively contraindicated in patients with asthma.

The antiepileptic drugs **valproate** and **topiramate** have been effective in decreasing migraine frequency; 30% to 50% of patients achieved a 50% reduction in headache frequency with these drugs (FG Freitag et al, Neurology 2002; 58:1652; JL Brandes et al, JAMA 2004; 291:965). Common adverse effects of valproate include nausea, fatigue, tremor and hair loss. Acute hepatic failure, pancreatitis and hyperammonemia (in patients with urea cycle disorders) occur rarely. Weight gain is common in patients taking valproate, and has

been associated with polycystic ovary syndrome, hyperinsulinemia, lipid abnormalities, hirsutism and menstrual disturbances. Topiramate commonly causes paresthesia; other adverse effects include fatigue, language and cognitive impairment and weight loss, which some patients may prefer to the weight gain associated with valproate. Topiramate, which is a carbonic anhydrase inhibitor, can rarely cause angle-closure glaucoma, oligohydrosis and symptomatic metabolic acidosis (JA Racoosin and JF Knudsen, JAMA 2004; 291:2074). Other antiepileptic drugs such as gabapentin *(Neurontin)* have also been tried for this indication with varying degrees of success (E Chronicle and W Mulleners, Cochrane Database Syst Rev 2004; (3):CD003226; Medical Letter 2004; 46:29).

Tricyclic antidepressants can prevent migraine in some patients and may be given concurrently with other prophylactic agents, but often cause sedation and weight gain. Amitriptyline has been shown to be effective (DK Ziegler et al, Arch Neurol 1993; 50:825). Nortriptyline (*Aventyl*, and others) is also frequently used for this purpose.

Calcium-channel blockers also have been tried for prevention of migraine. Verapamil in particular has been somewhat effective (GD Solomon, Headache 1989; 29:425).

ACE inhibitors and ARBs – In small double-blind studies, the angiotensin-converting enzyme (ACE) inhibitor lisinopril *(Prinivil, Zestril)* and the angiotensin receptor blocker (ARB) candesartan cilexetil *(Atacand)* have reduced migraine frequency (H Schrader et al, BMJ 2001; 322:19; E Tronvik et al, JAMA 2003; 289:65).

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly naproxen sodium *(Anaprox,* and others) and flurbiprofen *(Ansaid,* and others), have been used for short-term prevention of migraine, as in menstrual migraine, as well as for aborting acute attacks.

Riboflavin – A randomized, placebo-controlled trial in 55 patients with migraine found the B vitamin riboflavin 400 mg once daily effective (≥50% decrease in number of attacks) in 59% of patients, compared to 15% of those taking a placebo (J Schoenen et al, Neurology 1998; 50:466).

Botulinum toxin – Pericranial injections of botulinum toxin type A *(Botox)* have been reported to be effective for prophylactic treatment of migraine (AV Krymchantowski et al, CNS Drugs 2002; 16:611; RK Cady and CP Schreiber, Neurology 2004; 62 suppl 5:A357).

PREGNANCY — Ergot alkaloids are contraindicated in pregnancy. None of the triptans are FDA-approved for pregnant women, but sumatriptan, which has been used the longest, does not appear to be associated with an increased risk of birth defects (JP Gladstone et al, Postgrad Med 2004; 115:39). Preventive therapy is generally not recommended in pregnancy.

DRUGS OF CHOICE — A non-opioid analgesic may be effective for **treatment** of mild to moderate migraine. A triptan or dihydroergotamine is the drug of choice for treatment of moderate to severe migraine headache. Oral ergot preparations cost less than the triptans, but are not as effective. Some patients may respond to one triptan and not to another. Short-acting oral triptans are similar in their efficacy and speed of onset; naratriptan and frovatriptan have a slower onset and longer duration. The nasal spray forms of sumatriptan and zolmitriptan have a faster onset of action than all the oral triptans and probably deserve wider use. Sumatriptan SC is expensive, but it is the fastest acting and most effective triptan.

For **prevention** of migraine attacks, the antiepileptics valproate and topiramate are increasingly being used, but beta-blockers cost much less and appear to be comparable in efficacy; comparative trials are lacking.

Subscription Services

Mailing Address
The Medical Letter, Inc.
1000 Main Street
New Rochelle, NY 10801-7537

Customer Service
Call: 800-211-2769 or 914-235-0500
M-F 8am-6pm Eastern Time
Fax: 914-632-1733
Email: custserv@medicalletter.org

Web Site
www.medicalletter.org

Back Issues
Back issues are $10 each.

Subscriptions
1 year - $89; 2 years - $151;
3 years - $214. $4.50 per year for students, interns, residents and fellows in the US and Canada.
Major credit cards accepted.

Bulk Subscriptions
Special reduced rates for bulk subscriptions. Contact Customer Service at 800-211-2769. Special Classroom rates are available.

Site license inquires to:
info@medicalletter.org
or call 800-211-2769 x315

Permissions
To reprint any portion of this issue, e-mail your request to:
permissions@medicalletter.org.