

Treatment Guidelines

from The Medical Letter®

Published by The Medical Letter, Inc. • 145 Huguenot Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 9 (Issue 102) February 2011
www.medicalletter.org

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Drugs for Migraine

Drugs for treatment of migraine are listed in Table 2 on page 9. Drugs for prevention of migraine are listed in Table 3 on page 10. 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 without nausea, disability or a need for bed rest. **Aspirin** and **acetaminophen**¹ alone have been shown to be effective for treatment of migraine. A combination of acetaminophen, aspirin and caffeine (*Excedrin Migraine*, and others) is available over the counter (OTC). *Midrin*, which contains acetaminophen, isometheptene (a sympathomimetic amine) and dichloralphenazone (a chloral hydrate compound), has also been used for mild to moderate migraine. Aspirin and acetaminophen are also marketed in combinations containing butalbital such as *Fiorinal* (aspirin, caffeine and butalbital) and *Fioricet* or *Esgic* (acetaminophen, caffeine and butalbital), but butalbital has not been shown to be effective for treatment of migraine in controlled trials and is associated with tolerance, dependence and analgesic rebound.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as **naproxen sodium** (*Anaprox*, and others) and **ibuprofen** (*Advil*, *Motrin*, and others) have been effective in relieving migraine pain.^{2,3} Naproxen has a longer half-life and may have a longer duration of action than ibuprofen. Ibuprofen 200 mg, available OTC, is FDA-approved for treatment of migraine. In one study, the combination of acetaminophen 500 mg, aspirin 500 mg and caffeine 130 mg was more effective than ibuprofen 400 mg for treatment of acute migraine and had a faster onset of action.⁴

Oral opioid combinations are effective for relief of pain, but they produce the usual opioid adverse effects

(such as nausea, drowsiness and constipation), and frequent use can lead to drug dependence.⁵ In one study, 2 tablets of tramadol 37.5 mg/acetaminophen 325 mg (*Ultracet*, and others) were more effective than placebo in patients with moderate-to-severe acute migraine pain.⁶

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

SEROTONIN (5-HT₁) RECEPTOR AGONISTS ("TRIPTANS")

Use of a triptan early in an attack, when pain is still mild to moderate in intensity, has been shown to improve outcomes compared to later use.⁷

Sumatriptan is available for subcutaneous (SC) self-injection (with or without a needle), as a nasal spray, and for oral administration. The oral tablets and SC injection (with a needle) are available generically. The injectable and nasal formulations may be useful in patients with nausea and/or vomiting and they have a more rapid onset of action than the oral tablets. Sumatriptan SC produces relief within 2 hours in about 80% of patients with moderate to severe migraine. Sumatriptan nasal spray has produced relief in about 60% of patients after 2 hours. Oral sumatriptan has been effective in about 50% to 60% of patients with acute migraine after 2 hours and in about 70% after 4 hours.⁸

A fixed-dose combination tablet containing sumatriptan 85 mg and naproxen 500 mg (*Treximet*) achieved better pain relief than either agent taken as monotherapy in patients with a moderate or severe migraine.⁹

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Table 1. Triptans: Onset of Action

	Onset of action	Elimination half-life
Almotriptan (<i>Axert</i>)	30-60 min	3-4 hrs
Eletriptan (<i>Relpax</i>)	30-60 min	3-4 hrs
Frovatriptan (<i>Frova</i>)	~2 hrs	~25 hrs
Naratriptan (<i>Amerge</i>)	1-3 hrs	~6 hrs
Rizatriptan (<i>Maxalt</i>)	30-60 min	2-3 hrs
Sumatriptan (<i>Imitrex</i>)		~2 hrs
tablets	30-60 min	
nasal spray	10-15 min	
SC injection	~10 min	
Zolmitriptan (<i>Zomig</i>)		2-3 hrs
tablets	30-60 min	
nasal spray	10-15 min	

Almotriptan (*Axert*), **eletriptan** (*Relpax*), **rizatriptan** (*Maxalt*) and **zolmitriptan** (*Zomig*) are similar in efficacy to sumatriptan.^{10,11} **Zolmitriptan**, like sumatriptan, is available as a nasal spray as well as orally; compared to sumatriptan, fewer patients complain about its taste.¹² **Naratriptan** (*Amerge*, and others) and **frovatriptan** (*Frova*) have longer half-lives and appear to have a slower onset of action and lower initial response rate than other triptans.¹³

In patients with moderate or severe migraine, the rate of recurrence within 24 hours after treatment with a triptan is generally 20% to 40%; it may be slightly lower with naratriptan and frovatriptan. Recurrences usually respond to a second dose of the triptan.

Adverse Effects – 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. Also a burning sensation at the injection site is common with subcutaneous sumatriptan. CNS symptoms such as somnolence and asthenia following triptan therapy may be part of the migraine attack, unmasked by the successful treatment of pain, rather than adverse effects of the drugs.¹⁴ Angina, myocardial infarction, cardiac arrhythmia, stroke and death have occurred rarely with triptans. They are contraindicated in patients with coronary, cerebrovascular or other arterial disease, or uncontrolled hypertension. They should be used with caution in patients with other risk factors for vascular disease.

Drug Interactions – A triptan should generally not be used within 24 hours after another triptan or an ergotamine-containing drug because vasoconstriction could be additive. Rizatriptan, sumatriptan and zolmitriptan are not recommended in patients taking an MAO inhibitor or within two weeks of stopping one. Propranolol (*Inderal*, and others) increases serum concentrations of

eletriptan, rizatriptan and zolmitriptan; the dose of rizatriptan should be reduced if taken with propranolol. Inhibitors of CYP3A4, including verapamil (*Calan*, and others), can increase eletriptan serum concentrations; eletriptan should not be used within 72 hours of a strong CYP3A4 inhibitor such as clarithromycin (*Biaxin*, and others).¹⁵ Triptans are frequently taken together with SSRIs or SNRIs; serotonin syndrome has been reported only rarely with concurrent use.^{16,17}

ERGOT ALKALOIDS

Ergotamine tartrate, a non-specific serotonin agonist and vasoconstrictor, has been used for many years for treatment of moderate to severe migraine headache. It is available alone in sublingual tablets and in combination with caffeine in oral tablets and suppositories. Comparative studies have shown that oral ergotamine plus caffeine is less effective than a triptan for treatment of acute migraine.¹⁸

Dihydroergotamine mesylate, which can be injected subcutaneously, intramuscularly or intravenously, or sprayed intranasally, is also effective in treating acute migraine. It is a weaker arterial vasoconstrictor than ergotamine. Dihydroergotamine nasal spray relieves migraine after 2 hours in about 50% of patients with a 15% incidence of headache recurrence within 24 hours. According to Medical Letter consultants, it can be effective in some patients who do not respond to triptans.

Adverse Effects – Dihydroergotamine causes fewer adverse effects than ergotamine. 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 overdose (>6 mg in 24 hours or 10 mg per week). Liver disease or fever can accelerate development of severe vasoconstriction. In one retrospective case-control study in >17,000 patients, overuse of ergotamine (≥90 daily doses/yr), particularly in patients taking cardiovascular drugs, increased the risk of ischemic events, while overuse of a triptan did not.¹⁹

Drug Interactions – The effects of ergot alkaloids may be potentiated by triptans, beta-blockers, dopamine, nicotine or CYP3A4 inhibitors. Ergot alkaloids and triptans should not be taken within 24 hours of each other. Use of ergot alkaloids is contraindicated with strong CYP3A4 inhibitors such as clarithromycin or itraconazole (*Sporanox*, and others).¹⁵

Table 2. Some Drugs for Treatment of Migraine

Drug	Formulations	Usual dosage
Serotonin (5-HT_{1B/1D}) Receptor Agonists ("Triptans")		
Almotriptan – <i>Axert</i> (Ortho-McNeil)	6.25, 12.5 mg tabs	6.25-12.5 mg PO; can be repeated once after 2 hrs (max 25 mg/d)
Eletriptan – <i>Relpax</i> (Pfizer)	20, 40 mg tabs	20 or 40 mg PO; can be repeated after 2 hrs (max 80 mg/d)
Frovatriptan – <i>Frova</i> (Endo)	2.5 mg tabs	2.5 mg PO; can be repeated after 2 hrs (max 7.5 mg/d)
Naratriptan – <i>Amerge</i> (GSK)	1, 2.5 mg tabs	2.5 mg PO; can be repeated once after 4 hrs (max 5 mg/d)
Rizatriptan – <i>Maxalt, Maxalt-MLT</i> (Merck)	5, 10 mg tabs; 5, 10 mg orally disintegrating tabs	5 or 10 mg PO; can be repeated after 2 hrs (max 30 mg/d) ¹
Sumatriptan – generic	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)
	4, 6 mg/0.5 mL injectable kit	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)
<i>Imitrex</i> (GSK)	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)
	5, 20 mg/0.1 mL nasal spray	5, 10 or 20 mg intranasally; can be repeated once after 2 hrs (max 40 mg/d)
	4, 6 mg/0.5 mL cartridges; 6 mg/0.5 mL vials	6 mg SC; can be repeated once after 1 hr (max 12 mg/d)
<i>Sumavel DosePro</i> (Zogenix)	6 mg/0.5 mL SC (needle-free)	6 mg SC single dose (max 2 doses in 24 hrs at least 1 hr apart)
Zolmitriptan – <i>Zomig, Zomig-ZMT</i> (AstraZeneca)	2.5, 5 mg tabs; 2.5, 5 mg orally disintegrating tabs	2.5 or 5 mg PO; can be repeated after 2 hrs (max 10 mg/d)
	5 mg/0.1 mL nasal spray	5 mg intranasally; can be repeated once after 2 hrs
Triptan Combination Product		
Sumatriptan/naproxen – <i>Treximet</i> (GSK)	85 mg/500 mg tabs	85 mg/500 mg PO; can be repeated once after 2 hrs (max 170 mg/1000 mg/d)
Ergot Alkaloids		
Dihydroergotamine mesylate – generic	1 mg/mL ampules	1 mg IM or SC; can be repeated at 1 hr intervals (max 3 mg/24 hrs, 6 mg/wk)
<i>D.H.E. 45</i> (Valeant)		
<i>Migranal Nasal Spray</i> (Valeant)	4 mg/mL nasal spray	1 spray (0.5 mg) into each nostril, repeated 15 min later (2 mg/dose; max 3 mg/24 hrs)
Ergotamine tartrate – <i>Ergomar</i> (Rosedale)	2 mg sublingual tabs	2 mg sublingually; can be repeated q 30 min PRN (max 6 mg/24 hrs, 10 mg/wk)
Ergotamine/caffeine – <i>Cafergot</i> (Novartis)	1 mg/100 mg tabs	2 tabs PO, then 1 q 30 min x 4 PRN (max 6 tabs/attack)
	2 mg/100 mg rectal suppositories	1 rectal suppository; can be repeated once 1 hr later

1. Patients also taking propranolol should only use a 5-mg dose (max 15 mg/d).

PREVENTION

Patients with frequent or severe disabling migraine headaches and those who cannot take vasoconstrictors or are refractory to acute treatment should receive prophylactic treatment. Menstrual or other predictable migraine attacks may sometimes be prevented by a brief course of an NSAID or triptan, particularly naratriptan or frovatriptan, taken for several days before and during the first few days of menstruation.^{20,21}

For continuous prophylaxis, **beta-blockers** are commonly used. Propranolol and timolol are the only beta-

blockers approved by the FDA for this indication, but metoprolol (*Lopressor*, and others), nadolol (*Corgard*, and others) and atenolol (*Tenormin*, and others) also have been effective in preventing migraine.²² All beta-blockers can cause fatigue, exercise intolerance and orthostatic hypotension, and should not be used in patients with decompensated heart failure. All are relatively contraindicated in patients with asthma. Patients with migraine often have comorbid depression which may be aggravated by beta-blockers.

Tricyclic antidepressants can prevent migraine in some patients and may be given concurrently with

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Table 3. Some Drugs for Prevention of Migraine

Drug	Formulations	Usual dosage
Beta-Blockers		
Metoprolol ¹ – generic	25, 50, 100 mg tabs	50-100 mg bid
<i>Lopressor</i> (Novartis)	50, 100 mg tabs	
Extended-release – generic	25, 50, 100, 200 mg tabs	100-200 mg once/d
<i>Toprol-XL</i> (AstraZeneca)		
Propranolol – generic	10, 20, 40, 60, 80 mg tabs	160-240 mg/d divided bid, tid or qid
<i>Inderal</i> (Pfizer)		
Extended-release – generic	60, 80, 120, 160 mg caps	160-240 mg once/d
<i>Inderal LA</i> (Pfizer)		
Timolol – generic	5, 10, 20 mg tabs	10-15 mg bid or 20 mg once/d
Tricyclic Antidepressants¹		
Amitriptyline – generic	10, 25, 50, 75, 100, 150 mg tabs	30-150 mg once/d
Nortriptyline – generic	10, 25, 50, 75 mg caps	30-150 mg once/d
Calcium Channel Blockers¹		
Verapamil – generic	40, 80, 120 mg tabs	80 mg tid or qid
<i>Calan</i> (Pfizer)		
Extended-release – generic	120, 180, 240 mg tabs; 120, 180, 240 mg caps	240 mg once/d
<i>Calan SR</i> (Pfizer)	120, 180, 240 mg caplets	
Antiepileptic Drugs		
Valproate ² – generic	125, 250, 500 mg tabs; 125 mg sprinkle caps	250-500 mg bid
<i>Depakote</i> (Abbott)		
<i>Depakote ER</i>	250, 500 mg tabs	500-1000 mg once/d
Topiramate – generic	25, 50, 100, 200 mg tabs; 15, 25 mg caps	50 mg bid
<i>Topamax</i> (Ortho-McNeil)		
Angiotensin-Converting Enzyme (ACE) Inhibitors¹		
Lisinopril – generic	5, 10, 20 mg tabs	5-40 mg once/d
<i>Prinivil</i> (Merck)		
<i>Zestril</i> (AstraZeneca)	2.5, 5, 10, 20, 30, 40 mg tabs	
Angiotensin Receptor Blockers (ARB)¹		
Candesartan cilexetil – <i>Atacand</i> (AstraZeneca)	4, 8, 16, 32 mg tabs	8-32 mg once/d
Botulinum Toxin Type A		
Onabotulinumtoxin A – <i>Botox</i> (Allergan)	50, 100, 200 unit vial	155 units IM every 12 weeks ³

1. Not FDA-approved for this indication.

2. Marketed as divalproex sodium (*Depakote*) and valproic acid (*Depakene*, and others). Only divalproex sodium is FDA-approved for prevention of migraine.

3. FDA-approved for prophylaxis of headaches in adult patients with chronic migraine. Total dosage of 155 units is divided over 7 specific head/neck muscle areas (detailed information provided in package insert).

other prophylactic agents, but often cause sedation, dry mouth and weight gain. Amitriptyline is the only tricyclic shown to be effective in clinical trials.²³ Nortriptyline and protriptyline (*Vivactil*, and others), which may have fewer adverse effects than amitriptyline are also frequently used.

There is some evidence that newer antidepressants such as the SNRI venlafaxine (*Effexor*, and others) may be effective in preventing migraine.²⁴

Calcium channel blockers are also used for prevention of migraine, but evidence for their effectiveness is weak. Verapamil was somewhat more effective than placebo in some small studies.²² It is an inhibitor of CYP3A4 and may interact with other drugs used to treat migraine including ergotamine and eletriptan. Calcium channel blockers should not be used with beta-blockers because of the potential for heart block.

The antiepileptic drugs valproate (*Depakote*, and others) and topiramate (*Topamax*, and others) have been effective in decreasing migraine frequency and are approved by the FDA for migraine prophylaxis. About 50% of patients achieve a $\geq 50\%$ reduction in headache frequency with these drugs.²⁵⁻²⁷ Other antiepileptic drugs such as gabapentin (*Neurontin*, and others) have also been used for this indication with varying degrees of success.^{26,28} In randomized, placebo-controlled studies, topiramate and valproate have shown efficacy similar to that of propranolol for migraine prevention.²⁹ Topiramate has also reduced the number of migraines per month in patients with chronic migraine (≥ 15 headaches/month for ≥ 3 months).^{30,31}

Adverse effects of valproate include nausea, fatigue, tremor, weight gain and hair loss. Acute hepatic failure, pancreatitis and hyperammonemia (in patients

with urea cycle disorders) occur rarely. Other effects include polycystic ovary syndrome, hyperinsulinemia, lipid abnormalities, hirsutism and menstrual disturbances. **Topiramate** commonly causes paresthesias; fatigue, language and cognitive impairment, taste perversion and weight loss can also occur.³² Topiramate can rarely cause angle-closure glaucoma, oligohydrosis, nephrolithiasis and symptomatic metabolic acidosis. An analysis of data from clinical trials found that patients taking antiepileptic drugs, including valproate and topiramate, were more likely to report suicidal ideation or behavior than those taking a placebo (0.43% vs. 0.24%).³³

In small double-blind trials, the **angiotensin-converting enzyme (ACE) inhibitor** lisinopril (*Prinivil*, and others) and the **angiotensin receptor blocker (ARB)** candesartan cilexetil (*Atacand*) have reduced migraine frequency.^{34,35}

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly naproxen sodium 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.

The **dietary supplements** petasites (butterbur) 100-150 mg per day, riboflavin 400 mg per day, magnesium citrate 600 mg per day, coenzyme Q10 300 mg per day, and feverfew 18.75 mg per day have been reported to be effective in preventing migraine in small randomized placebo-controlled trials.³⁶⁻⁴⁰

The FDA has recently approved pericranial injections of **onabotulinumtoxinA** (*Botox*) for prophylaxis of headaches in adult patients with chronic migraine (≥ 15 headache days/month for ≥ 3 months).⁴¹

PREGNANCY

Acetaminophen and/or opioids are commonly used for treatment of migraine during pregnancy. NSAIDs should not be used in the 3rd trimester because they can cause premature closure of the ductus arteriosus. The triptans are classified as category C (risk cannot be ruled out) for use in pregnancy, but sumatriptan, which has been used the longest, does not appear to be associated with an increased risk of birth defects.^{42,43} All ergot alkaloids are contraindicated in pregnancy. Preventive therapy is generally not recommended in pregnancy.

DRUGS OF CHOICE

A nonopioid analgesic may be effective for **treatment** of mild to moderate migraine. A triptan is the drug of choice for treatment of moderate to severe migraine

headache. Short-acting oral triptans are similar in their efficacy and speed of onset; naratriptan and frovatriptan have a slower onset and longer duration of action. The nasal spray forms of sumatriptan and zolmitriptan have a faster onset of action than oral triptans and may be helpful in patients with vomiting. Sumatriptan SC is the fastest acting and most effective triptan formulation. Some patients may respond to one triptan and not to another. Oral ergot preparations are not as effective as triptans and may cause more adverse effects.

For **prevention** of migraine attacks, beta-blockers, tricyclic antidepressants and verapamil are commonly used. The antiepileptics valproate and topiramate are increasingly being used, but there is no evidence that they are more effective than older therapies, and they may cause more disturbing adverse effects. Short courses of an NSAID or a triptan may help prevent menstrual migraines.

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from The Medical Letter

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Founded in 1959 by

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