Treatment of Migraine

An oral nonopioid analgesic may be sufficient for treatment of mild to moderate migraine without severe nausea or vomiting. A triptan is the drug of choice for treatment of moderate to severe migraine. Use of a triptan early in an attack when pain is still mild to moderate in intensity improves headache response and reduces recurrence rates.

**ANALGESICS –** Aspirin and acetaminophen, used alone or together in combination with caffeine (Excedrin Migraine, and others), and nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen sodium (Aleve, and others) and ibuprofen (Advil, Motrin, and generics) are effective in relieving mild to moderate migraine pain. The NSAID diclofenac is FDA-approved as a powder for oral solution (Cambia) for treatment of migraine; it has a rapid onset of action (about 15 minutes). Some patients may respond better to one NSAID than to another.

Products that combine butalbital and caffeine with aspirin (Fiorinal, and others) or acetaminophen (Fioricet, and others) are used for treatment of migraine despite evidence that butalbital is not effective in relieving migraine pain. Their frequent use can lead to tolerance, addiction, and medication overuse headache. Oral combinations of aspirin or acetaminophen with an opioid can be effective for relief of migraine pain, but they cause the usual opioid adverse effects (e.g., nausea, drowsiness, and constipation), and regular use can lead to dependence and addiction.

**Pregnancy –** Occasional use of acetaminophen for treatment of mild to moderate migraine during pregnancy is generally considered safe.

**TRIPTANS –** The short-acting oral serotonin (5-HT<sub>1B/1D</sub>) receptor agonists (triptans) sumatriptan (Imitrex, and others), almotriptan (Axert, and generics), eletriptan (Relpax), rizatriptan (Maxalt, and generics), and zolmitriptan (Zomig, and generics) are similar in efficacy and speed of onset. Intranasal triptan formulations have a faster onset of action than oral triptans. Subcutaneous sumatriptan is the fastest-acting and most effective triptan formulation. Patients who do not respond to one triptan may respond to another. Use of opioids and butalbital for migraine treatment is discouraged.

An oral fixed-dose combination of sumatriptan and naproxen (Trexima) is more effective in relieving moderate or severe migraine pain than either of its components alone.

Intranasal triptan formulations have a more rapid onset of action than oral tablets, but their efficacy is partially dependent on GI absorption of the portion of the dose that is swallowed. Use of sumatriptan nasal powder (Ozema Xsail) results in a faster rise in sumatriptan levels than oral sumatriptan tablets.
risk factors for vascular disease, particularly diabetes.

used with caution in patients with other signi-
migraine with brainstem aura. Triptans should be
uncontrolled hypertension, or a history of stroke,
peripheral vascular disease, ischemic bowel disease,
artery disease, Wolff-Parkinson-White syndrome,
in patients with ischemic or vasospastic coronary

intranasally with the powder.10

suggesting that a larger portion of the dose is absorbed
than use of a similar dose of sumatriptan nasal spray,
plasma concentrations and higher peak concentrations
may respond to a second dose of the triptan.

migraine, the rate of recurrence within 24 hours after
treatment with a triptan is generally 20-40%. Early treat-
men of an attack reduces recurrence rates. Recurrences
and zolmitriptan can have an unpleasant taste.

Subcutaneously administered sumatriptan relieves
pain faster (in about 10 minutes) and more effectively
than other triptan formulations, but it causes more
adverse effects.

Recurrence – In patients with moderate to severe
migraine, the rate of recurrence within 24 hours after
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ment of an attack reduces recurrence rates. Recurrences
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Adverse Effects – Tingling, flushing, dizziness, drowsi-
ness, fatigue, and a feeling of heaviness, tightness,
or pressure in the chest can occur with all triptans,
but most commonly with SC sumatriptan. A burning
sensation at the injection site is also common with SC
sumatriptan. Intranasal formulations of sumatriptan
and zolmitriptan can have an unpleasant taste.

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. Sumatriptan
is contraindicated for use in patients with severe
hepatic impairment. Naratriptan is contraindicated in
patients with severe renal or hepatic impairment.

Angina, myocardial infarction, cardiac arrhythmia,
stroke, seizure, and death have occurred rarely with
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Drug Interactions – The labels of all triptans state that
a triptan should not be taken within 24 hours of another
triptan or an ergot because vasoconstriction could be
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should not be used within 2 weeks of each other.
Propranolol increases serum concentrations of
eletriptan, frovatriptan, rizatriptan, and zolmitriptan.
Inhibitors of CYP3A4 can increase serum
concentrations of almotriptan and eletriptan.12 Cases of
serotonin syndrome have been reported with concurrent
use of triptans and selective serotonin reuptake
inhibitors (SSRIs) or serotonin-norepinephrine reuptake
inhibitors (SNRIs), but data from large observational
databases suggest that the risk is low.13,14

Pregnancy and Lactation – Based on available
evidence, use of sumatriptan, or possibly rizatriptan,
eletriptan, or zolmitriptan during pregnancy does not
appear to be associated with an increased risk of
birth defects.15,16 Levels of sumatriptan and eletriptan
in breast milk are low and these drugs would not be
expected to cause adverse effects in most breastfed
infants17; avoiding breastfeeding for 8-12 hours after
taking a short-acting triptan would reduce the infant’s
risk of exposure to the drug.

ERGOTS – A fixed-dose combination of ergotamine
tartrate, a nonspecific serotonin agonist and vaso-
constrictor, and caffeine is available as tablets (Cafergot)
and suppositories (Migergot) for treatment of moderate
to severe migraine. The combination is less effective
than a triptan for acute treatment of migraine.18

Dihydroergotamine, which can be administered
subcutaneously, intramuscularly, intravenously (D.H.E.,
and generics), or intranasally (Migranal), is effective for
acute treatment of migraine. Dihydroergotamine nasal
spray relieves migraine after 2 hours in about 50% of
patients, with a 15% incidence of recurrence within 24
hours. It can be effective in some patients who do not
respond to triptans.

Adverse Effects – Dihydroergotamine is a weaker
arterial vasoconstrictor than ergotamine and causes
fewer serious adverse effects. Nausea and vomiting
are fairly common with ergotamine, but pretreatment
with or concurrent use of an antiemetic such as
metoclopramide (Reglan, and generics) can reduce
GI effects. Serious adverse effects, such as vascular
(including coronary) occlusion and gangrene, are rare
and are usually associated with overdosage (>6 mg
in 24 hours or >10 mg per week). Hepatic impairment

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<table>
<thead>
<tr>
<th>Table 1. Triptans</th>
<th>Onset of action</th>
<th>Elimination half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan</td>
<td>30-60 min</td>
<td>3-4 hrs</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>30-60 min</td>
<td>~4 hrs</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>~2 hrs</td>
<td>~25 hrs</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>1-3 hrs</td>
<td>~6 hrs</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>30-60 min</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>Sumatriptan pills</td>
<td>30-60 min</td>
<td>~2 hrs</td>
</tr>
<tr>
<td>Sumatriptan nasal</td>
<td>10-15 min</td>
<td>~10 min</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>30-60 min</td>
<td>2-3 hrs</td>
</tr>
</tbody>
</table>

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### Table 2. Some Drugs for Treatment of Migraine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost $</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triptans</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan – generic Axert (Janssen)</td>
<td>6.25, 12.5 mg tabs</td>
<td>6.25 or 12.5 mg PO; can be repeated after 2 hrs (max 25 mg/d)</td>
<td>33.00</td>
</tr>
<tr>
<td>Eletriptan – Relpax (Pfizer)</td>
<td>20, 40 mg tabs</td>
<td>20 or 40 mg PO; can be repeated after 2 hrs (max 80 mg/d)</td>
<td>53.60</td>
</tr>
<tr>
<td>Frovatriptan – generic Frova (Endo)</td>
<td>2.5 mg tabs</td>
<td>2.5 mg PO; can be repeated after 2 hrs (max 7.5 mg/d)</td>
<td>73.60</td>
</tr>
<tr>
<td>Naratriptan – generic Amerge (GSK)</td>
<td>1, 2.5 mg tabs</td>
<td>2.5 mg PO; can be repeated after 4 hrs (max 5 mg/d)</td>
<td>11.00</td>
</tr>
<tr>
<td>Rizatriptan – generic Maxalt (Merck)</td>
<td>5.10 mg tabs, 5.10 mg orally disintegrating tabs</td>
<td>5 or 10 mg PO; can be repeated after 2 hrs (max 30 mg/d)</td>
<td>52.00</td>
</tr>
<tr>
<td>Zolmitriptan – generic Zomig (Impax)</td>
<td>2.5, 5 mg tabs</td>
<td>2.5 or 5 mg PO; can be repeated after 2 hrs (max 10 mg/d)</td>
<td>26.20</td>
</tr>
<tr>
<td>Sumatriptan – generic Imitrex (GSK)</td>
<td>25, 50, 100 mg tabs</td>
<td>50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/d)</td>
<td>81.00</td>
</tr>
<tr>
<td>Sumatriptan/naproxen – Treximet (Pernix)</td>
<td>10/60, 85/500 mg tabs</td>
<td>85/500 mg PO; can be repeated after 2 hrs (max 170/1000 mg/d)</td>
<td>84.00</td>
</tr>
<tr>
<td>Ergots</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine mesylate – generic D.H.E. 45 (Valeant)</td>
<td>1 mg/mL ampules</td>
<td>1 mg IM or SC; can be repeated at 1 hr intervals (max 3 mg/d, 6 mg/wk)</td>
<td>124.80</td>
</tr>
<tr>
<td>Dihydroergotamine mesylate – generic Migranal nasal spray (Valeant)</td>
<td>4 mg/mL nasal spray</td>
<td>1 spray (0.5 mg) into each nostril, repeated 15 min later (2 mg/dose; max 3 mg/d)</td>
<td>421.40</td>
</tr>
<tr>
<td>Ergotamine/caffeine – generic Cafergot (Sandoz)</td>
<td>1/100 mg tabs</td>
<td>2 tabs PO at attack onset, then 1 tab q30 min PRN (max 6 tabs/attack)</td>
<td>11.10</td>
</tr>
<tr>
<td>Ergotamine/caffeine – generic Migergot (Horizon)</td>
<td>2/100 mg rectal suppository</td>
<td>1 supp at attack onset, repeat in 1 hr if needed (max 2 supp/attack)</td>
<td>63.90</td>
</tr>
</tbody>
</table>

1. Dosage may need to be adjusted for renal or hepatic impairment or for drug interactions.
2. Approximate WAC for one dose at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly, January 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.
3. Also approved for use in patients 12-17 years old.
4. Also approved for use in patients 6-17 years old.
5. Dose for pediatric patients is 5 mg (<40 kg) or 10 mg (≥40 kg). In pediatric patients, the efficacy and safety of redosing within 24 hours have not been established.
6. Adults and children (<40 kg) also taking propranolol should only use a 5-mg dose (max 15 mg/d for adults and 5 mg/d for children). Combined use not recommended for children weighing <40 kg.
7. Generic also available as a 6-mg syringe.
8. Patients also taking cimetidine should only use a 2.5-mg dose (max 5 mg/d).
9. Dosage for adolescents 12-17 years old is 10/60 mg (max 85/500 mg/d).

or fever can accelerate development of severe vasoconstriction. Ergots are contraindicated in patients with arterial disease or uncontrolled hypertension.

**Drug Interactions** – The effects of ergots can be potentiated by triptans, beta blockers, dopamine, nicotine, or CYP3A4 inhibitors. Use of ergots is contraindicated with strong CYP3A4 inhibitors such as clarithromycin (Biaxin, and generics) or itraconazole (Sporanox, and generics). Ergots and triptans should not be taken within 24 hours of each other.

**Pregnancy and Lactation** – Ergots can reduce placental blood flow and are contraindicated for use during pregnancy. Ergotamine is excreted in human breast milk; women who take an ergot should avoid breastfeeding.
Prevention of Migraine

Patients with frequent or severe migraine headaches and those who cannot take vasoconstrictors or are refractory to acute treatment should receive preventive treatment.22,23 Menstrual migraine attacks may sometimes be prevented by a brief course of an NSAID or triptan, particularly frovatriptan or naratriptan, taken for several days before and after the onset of menstruation.24,25 Preventive therapy is generally not recommended during pregnancy.

BETA BLOCKERS — Beta blockers are commonly used for prevention of migraine. Propranolol (Inderal LA, and others) and timolol are the only beta blockers approved by the FDA for this indication, but metoprolol (Lopressor, and others), nadolol (Corgard, and generics), and atenolol (Tenormin, and generics) are also effective in preventing migraine.23 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.

Pregnancy — Intrauterine growth retardation, small placentas, and congenital abnormalities have been reported with use of propranolol during pregnancy. Atenolol has been associated with the birth of small for gestational age infants and, at high doses, with embryofetal resorptions in animals.

ANTIEPILEPTIC DRUGS — Valproate (Depakote, and others) and topiramate (Topamax, and generics) are similarly effective in decreasing migraine frequency and are FDA-approved for migraine prevention. About 50% of patients achieve a ≥50% reduction in headache frequency with these drugs.26 In randomized, double-blind trials, topiramate was at least as effective as propranolol for migraine prevention.27,28 Topiramate has reduced the number of migraine headache days per month and improved associated symptoms in patients with chronic migraine (≥15 headache days/month for ≥3 months) and medication overuse headache.29,30 In a trial in pediatric patients, however, topiramate was no better than placebo in preventing migraine.31

Adverse Effects — 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 adverse effects include polycystic ovary syndrome, hyperinsulinemia, lipid abnormalities, hirsutism, and menstrual disturbances. Topiramate commonly causes paresthesias; fatigue, language and cognitive impairment, taste perversion, weight loss, and nephrolithiasis can also occur. Topiramate can rarely cause secondary narrow-angle glaucoma, oligohydrosis, and symptomatic metabolic acidosis.

Pregnancy — Use of topiramate or valproate during pregnancy has been associated with congenital malformations;32,33 neither drug should be used for migraine prevention in pregnant women.

ANTIDEPRESSANTS — Amitriptyline is the only tricyclic antidepressant shown to be effective for migraine prevention in clinical trials,34 but it often causes sedation, dry mouth, and weight gain. Other tricyclics such as nortriptyline, which may have fewer adverse effects than amitriptyline, are frequently used for migraine prevention in adults. In a trial in pediatric patients, amitriptyline was no better than placebo in preventing migraine.31

The SNRIs venlafaxine (Effexor, and others) and duloxetine (Cymbalta, and generics) may also be effective in preventing migraine.22,35,36 They can cause nausea, vomiting, sweating, tachycardia, urinary retention, and increased blood pressure.

Pregnancy — Tricyclic antidepressant use during pregnancy has been associated with jitteriness and seizures in newborns. Fetal malformations are uncommon with SNRIs, but increased risks of neonatal behavioral syndrome and perinatal complications have been reported with use of SNRIs during pregnancy.37

TRANSCRANIAL MAGNETIC STIMULATION — The FDA has approved the use of a transcranial magnetic stimulation device (SpringTMS – eNeura) for self-treatment of migraine with aura. In one trial, the pain-free response rate 2 hours after treatment of the first migraine attack was significantly higher with use of transcranial magnetic stimulation at the onset of aura than with sham stimulation (39% vs 22%).19
The combination of simvastatin (Zocor, and others) and vitamin D was effective for migraine prevention in one small, randomized, placebo-controlled trial.42

The dietary supplement petasites (butterbur; Petadolex) 100-150 mg daily reduced migraine attack frequency by 36-60% in two randomized, placebo-controlled trials in about 300 patients,38 but it has been associated with hepatic toxicity.43 Melatonin, riboflavin, magnesium citrate, coenzyme Q10, and feverfew have also been effective in preventing migraine in small, randomized, placebo-controlled trials.38,43,44

The calcium channel blocker verapamil (Calan, and others) was somewhat more effective than placebo in some small studies.41

The angiotensin-converting enzyme (ACE) inhibitor lisinopril (Prinivil, and others) and the angiotensin receptor blocker (ARB) candesartan (Atacand, and generics) have reduced migraine frequency by about 30-35% in small, double-blind trials.39 In a randomized, placebo-controlled, crossover trial, candesartan was noninferior to propranolol for prevention of migraine.40

Other preventive treatments — NSAIDs, such as naproxen and ibuprofen, have been used for prevention of migraine and for aborting acute attacks.38

The comparison chart of drugs for migraine prevention (online only) is provided as a reference for dosage and cost information.4
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The expected outcome of the CME program is to increase the participant’s ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in The Medical Letter.

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Upon completion of this program, the participant will be able to:
1. Explain the current approach to the management of migraine.
2. Discuss the pharmacologic options available for treatment and prevention of migraine and compare them based on their efficacy, dosage and administration, potential adverse effects, and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient with migraine.

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Have any questions? Call us at 800-211-2769 or 914-235-0500 or e-mail us at: custserv@medicalletter.org

Questions start on next page
Drugs for Migraine

1. Which of the following would be a reasonable choice for initial treatment of a mild migraine attack without nausea or vomiting in a 28-year-old nonpregnant woman?
   a. acetaminophen
   b. butalbital/acetaminophen/caffeine
   c. oxycodeone/acetaminophen
   d. ergotamine

2. Orally administered short-acting triptans have an onset of action of about:
   a. 5-10 minutes
   b. 15-30 minutes
   c. 30-60 minutes
   d. 60-90 minutes

3. Which of the following triptan formulations has the fastest onset of action?
   a. almotriptan tablets
   b. naratriptan tablets
   c. zolmitriptan nasal spray
   d. frovatriptan tablets

4. Compared to oral sumatriptan, the subcutaneous formulations:
   a. relieve pain faster
   b. are more effective in relieving pain
   c. cause more adverse effects
   d. all of the above

5. A 35-year-old woman with severe episodic migraine attacks with nausea and vomiting asks about switching from sumatriptan oral tablets to the nasal spray formulation. You should tell her that:
   a. intranasal sumatriptan generally starts relieving pain in about 10-15 minutes
   b. intranasal sumatriptan can have an unpleasant taste
   c. sumatriptan nasal spray is partially absorbed in the GI tract, and absorption of the drug could be reduced in patients with vomiting
   d. all of the above

6. Which of the following statements is true?
   a. The combination of ergotamine and caffeine is safer and more effective than a triptan for acute treatment of migraine
   b. Patients who do not respond to a triptan alone should take both a triptan and an ergot
   c. Dihydromegartamine may be effective in some patients who do not respond to a triptan
   d. all of the above

7. The drug of choice for treatment of moderate to severe migraine is:
   a. aspirin
   b. a triptan
   c. an ergot
   d. onabotulinumtoxinA

8. For migraine prevention, beta blockers should be used with caution or not be used at all in patients who have:
   a. asthma
   b. depression
   c. decompensated heart failure
   d. all of the above

9. About what percentage of patients achieve a >50% reduction in migraine headache frequency when taking topiramate or valproate for migraine prevention?
   a. 20%
   b. 50%
   c. 75%
   d. 90%

10. A 31-year-old woman with a history of frequent severe migraine attacks has been taking topiramate for 3 years for migraine prevention. She tells you that she is planning to become pregnant in the near future. You should:
    a. increase her dose of topiramate because serum concentrations of the drug decrease significantly during pregnancy
    b. switch her to valproate because it is safer for use during pregnancy
    c. switch her to dihydromegartamine nasal spray taken once weekly during pregnancy
    d. discontinue topiramate because it can cause congenital malformations

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