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IN THIS ISSUE

Drugs for Migraine

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Key Points: Drugs for Migraine

Acute Treatment

- An oral nonopioid analgesic is often sufficient for treatment of mild to moderate migraine pain.
- Use of butalbital- or opioid-containing products for migraine treatment is not recommended.
- A triptan is the drug of choice for moderate to severe migraine pain in most patients without vascular disease.
- The shorter-acting oral triptans sumatriptan, almotriptan, eletriptan, rizatriptan, and zolmitriptan are similar in efficacy, speed of onset, and duration of action.
- Intranasal triptan formulations are faster-acting than oral triptans. Subcutaneous sumatriptan is the most effective triptan formulation, but it causes the most adverse effects.
- CGRP receptor antagonists and the 5-HT_{1F} receptor agonist lasmiditan appear to be less effective than triptans, but they can be used in patients with vascular disease.
- A neuromodulatory device can be tried when pharmacotherapy cannot be used.

Preventive Treatment

- Beta blockers and the antiseizure drugs topiramate and valproate are effective for preventive treatment of migraine, but they may be difficult to tolerate.
- CGRP antagonists are effective, but expensive. A CGRP monoclonal antibody can be effective when other drugs have failed.
- Pericranial onabotulinumtoxinA injections can be used in adults with severe chronic migraine.
- Nonpharmacologic options include neuromodulatory devices, behavioral therapy, and acupuncture.

DRUGS FOR ACUTE TREATMENT

An oral nonopioid analgesic is often sufficient for acute treatment of mild to moderate migraine pain without severe nausea or vomiting. A triptan is the drug of choice for treatment of moderate to severe migraine in most patients without vascular disease.[1] Treatment of pain when it is still mild to moderate in intensity improves headache response and reduces the risk of recurrence.

ANALGESICS — Aspirin and **acetaminophen**, used alone, together, or combination with caffeine, and **nonsteroidal anti-inflammatory drugs (NSAIDs)** are effective in relieving mild to moderate migraine pain.[2-4] The NSAID diclofenac is available in a powder for oral solution *(Cambia)* for treatment of migraine; it has a rapid onset of action (~15 minutes).[5]

Products that contain **butalbital** or an **opioid** are not recommended for acute treatment of migraine. There is limited evidence that butalbital is effective in relieving migraine pain. Opioids can be effective, but they can cause serious adverse effects. Regular use of butalbital- or opioid-containing analgesics can lead to medication overuse headache, tolerance, dependence, and addiction.

Pregnancy – Occasional use of acetaminophen during pregnancy is generally considered safe.[6] Use of NSAIDs during the third trimester may cause premature closure of the ductus arteriosus and persistent pulmonary hypertension in the neonate, but these effects appear to be uncommon if the drug is stopped 6-8 weeks before delivery.

TRIPTANS — The shorter-acting oral 5-$HT_{1B/1D}$ receptor agonists (triptans) **sumatriptan, almotriptan, eletriptan, rizatriptan,** and **zolmitriptan** are similar in efficacy (placebo-corrected 2-hour headache response rates of ~30-50% with maximum initial doses). The longer-acting oral triptans **naratriptan** and **frovatriptan** are generally better tolerated than shorter-acting triptans, but they have a slower onset of action and lower initial response rates. Patients

Table 1. Triptan Pharmacology

Drug	Onset of Action	Half-Life
Almotriptan	30-60 min	3-4 hrs
Eletriptan	30-60 min	~4 hrs
Frovatriptan	~2 hrs	~26 hrs
Naratriptan	1-3 hrs	~6 hrs
Rizatriptan	30-60 min	2-3 hrs
Sumatriptan – tablets nasal spray and powder subcutaneous injection	30-60 min 10-15 min ~10 min	~2-2.5 hrs
Zolmitriptan – tablets nasal spray	30-60 min 10-15 min	2-3 hrs

who do not respond to one triptan may respond to another. An oral fixed-dose combination of sumatriptan and naproxen (*Treximet*, and generics) has been more effective in relieving moderate or severe migraine than either of its components alone.[7]

Intranasal and injectable triptan formulations are faster-acting than oral tablets. Subcutaneously administered sumatriptan relieves pain faster and more effectively than oral triptan formulations, but it causes more adverse effects.[8]

Recurrence – Moderate to severe migraine recurs within 24 hours after treatment with a triptan in ~20-40% of cases. Early treatment of an attack reduces recurrence rates. Recurrences may respond to a second dose of the triptan.

Adverse Effects – Triptans can cause tingling, flushing, dizziness, drowsiness, fatigue, and a feeling of heaviness or tightness in the chest. Subcutaneous sumatriptan can cause injection-site discomfort. Intranasal triptan formulations can leave an unpleasant aftertaste. CNS symptoms such as somnolence and weakness are commonly reported following triptan therapy, but they may be part of the migraine attack, unmasked by the successful treatment of pain, rather than adverse effects of the drug. Use of triptans for ≥10 days per month can cause medication overuse headache. Sumatriptan and naratriptan are contraindicated for use in patients with severe hepatic impairment. Naratriptan is also contraindicated for use in patients with severe renal impairment.

Angina, myocardial infarction, cardiac arrhythmias, stroke, seizures, and death have occurred very rarely with use of triptans.[9] All triptans are contraindicated for use in patients with ischemic or vasospastic coronary artery disease, Wolff-Parkinson-White syndrome, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, or a history of stroke, transient ischemic attack, or hemiplegic or basilar migraine. They should be used with caution in patients with other significant risk factors for vascular disease, particularly diabetes.

Drug Interactions – Triptans should not be used within 24 hours of another triptan or an ergot because vasoconstriction could be additive. Concurrent use of monoamine oxidase (MAO) inhibitors and triptans can result in additive serotonergic effects. Use of sumatriptan, rizatriptan, or zolmitriptan within 2 weeks after an MAO-A inhibitor can result in increased triptan serum concentrations and is contraindicated. Propranolol increases serum concentrations of rizatriptan. Cimetidine increases serum concentrations of zolmitriptan. Inhibitors of CYP3A4 can increase serum concentrations of almotriptan and eletriptan; use of eletriptan is contraindicated within 72 hours after taking a strong CYP3A4 inhibitor.[10] Serotonin syndrome has been reported with concurrent use of triptans and serotonin reuptake inhibitors, but data from large observational studies suggest that the risk is low.[11]

Pregnancy and Lactation – In a population study in Norway, there was no association between triptan use during pregnancy and birth defects.[12] Levels of sumatriptan and eletriptan in breast milk are low and are not expected to cause adverse effects in most breastfed infants.[13]

CGRP RECEPTOR ANTAGONISTS — Three small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists are FDA-approved for acute treatment of migraine in adults: **rimegepant** *(Nurtec ODT)* and **ubrogepant** *(Ubrelvy)* are taken orally,[14,15] and **zavegepant** *(Zavzpret)* is available as a nasal spray.[16] In clinical trials, about 10% more patients were free of headache 2 hours post-dose with these drugs compared to placebo.[17-19]

The onset of pain relief appears to occur sooner with zavegepant than with rimegepant or ubrogepant (~15 vs ~60 minutes). The half-life of rimegepant (~11 hours) is longer than that of ubrogepant (5-7 hours) or zavegepant (~6.5 hours). No trials directly comparing these drugs with each other or with triptans are available. CGRP receptor antagonists appear to be less effective than triptans, but they can be used in patients with vascular disease and do not cause medication overuse headache.[20]

Adverse Effects – Systemic adverse effects are uncommon with use of CGRP receptor antagonists.

Nausea, somnolence, and (rarely) hypersensitivity reactions can occur. Zavegepant can cause dysgeusia, ageusia, and nasal discomfort.

Drug Interactions – Ubrogepant and rimegepant are substrates of CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Concurrent use of these drugs with strong inhibitors or inducers of CYP3A4 or with inhibitors of P-gp or BCRP should be avoided.[10]

Zavegepant is a substrate of organic anion transporting polypeptide 1B3 (OATP1B3) and sodium taurocholate cotransporting polypeptide (NTCP); its use with inhibitors or inducers of these transporters should be avoided. Intranasal decongestants can decrease zavegepant absorption; concurrent use should be avoided.

Pregnancy and Lactation – Rimegepant, ubrogepant, and zavegepant have not been adequately studied in pregnant women. Levels of rimegepant in breast milk are low; ubrogepant and zavegepant are also likely to be minimally secreted into breast milk because they are highly protein-bound.[21,22]

SELECTIVE 5-HT$_{1F}$ RECEPTOR AGONIST — Lasmiditan *(Reyvow)* selectively binds to 5-HT$_{1F}$ receptors expressed on trigeminal neurons, inhibiting pain pathways in the trigeminal system. In clinical trials, the rate of freedom from headache 2 hours post-dose was modestly higher with lasmiditan (~30%) than with placebo (15-20%).[14,17] Lasmiditan appears to be less effective than triptans, but it can be used in patients with vascular disease.[20]

Adverse Effects – Lasmiditan can cause CNS adverse effects including dizziness, paresthesia, sedation, vertigo, incoordination, cognitive changes, and confusion. Fatigue, nausea and vomiting, muscle weakness, lethargy, palpitations, increases in blood pressure, decreases in heart rate, reactions consistent with serotonin syndrome, and hypersensitivity reactions, including angioedema and rash, have also been reported. Like triptans, lasmiditan can cause medication overuse headache.

Lasmiditan can decrease wakefulness and impair driving ability. The lasmiditan labeling warns against driving or operating machinery for at least 8 hours after taking the drug. Lasmiditan is classified as a schedule V controlled substance.

Drug Interactions – Use of lasmiditan with alcohol or other CNS depressants could result in additive effects. Coadministration of lasmiditan with serotonergic drugs may increase the risk of serotonin syndrome. Lasmiditan should be used with caution in patients who are taking other heart rate-lowering drugs. Lasmiditan inhibits P-gp and BCRP; coadministration with P-gp or BCRP substrates should be avoided.[10]

Pregnancy and Lactation – No data on the use of lasmiditan in pregnant or breastfeeding women are available. Lasmiditan and its metabolites have been detected in the milk of lactating rats.

ERGOTS — A fixed-dose combination of **ergotamine tartrate**, a nonspecific serotonin agonist and vasoconstrictor, and caffeine is available in tablets and suppositories for acute treatment of moderate to severe migraine. The combination is less effective than a triptan.[23]

Dihydroergotamine can be effective in some patients whose migraine headaches do not respond to triptans.[17] It is available parenterally and as a nasal spray (*Migranal*, and generics; *Trudhesa*). In clinical trials, *Migranal* relieved migraine pain after 2 hours in ~30-60% of patients.[24] Systemic bioavailability is greater with *Trudhesa* than with *Migranal*; it requires only one spray per nostril rather than two to deliver a full dose.[25]

Adverse Effects – Dihydroergotamine is a weaker arterial vasoconstrictor than ergotamine and causes fewer serious adverse effects. Nausea and vomiting are common with ergotamine, but pretreatment with or concurrent use of an antiemetic drug such as metoclopramide can reduce GI adverse effects. Serious adverse effects, such as vascular occlusion and gangrene, are rare and are usually associated with overdosage (>6 mg in 24 hours or >10 mg per week). Hepatic impairment or fever can accelerate development of severe vasoconstriction. Ergots are contraindicated for use in patients with arterial disease or uncontrolled hypertension.

Drug Interactions – Concurrent use of ergots and strong CYP3A4 inhibitors is contraindicated.[10] The effects of ergots can also be potentiated by triptans, beta blockers, dopamine, and nicotine. *Trudhesa* is contraindicated for use with peripheral and central vasoconstrictors. Ergots and triptans should not be taken within 24 hours of each other. Rarely, reactions consistent with serotonin syndrome have been observed when 5-HT$_1$ agonists such as dihydroergotamine were coadministered with selective serotonin reuptake inhibitors.

Table 2. Some Drugs for Acute Treatment of Migraine

Drugs	Some Formulations	Usual Adult Dosage[1]	Cost[2]
NSAIDs[3]			
Diclofenac potassium – generic	50 mg single-dose packets	50 mg PO dissolved in 1-2 oz water once	$64.60
Cambia (Assertio)			98.60
Celecoxib – *Elyxyb* (Scilex)	120 mg/4.8 mL oral solution	120 mg PO once (max 1 dose/day)	135.00
Triptans			
Almotriptan[4] – generic	6.25, 12.5 mg tabs	6.25 or 12.5 mg PO; can be repeated after 2 hrs (max 25 mg/day)	33.40
Eletriptan – generic	20, 40 mg tabs	20 or 40 mg PO; can be repeated after 2 hrs (max 80 mg/day)	13.10
Relpax (Pfizer)			76.90
Frovatriptan – generic	2.5 mg tabs	2.5 mg PO; can be repeated after 2 hrs (max 7.5 mg/day)[5]	26.20
Frova (Endo)			129.70
Naratriptan – generic	1, 2.5 mg tabs	2.5 mg PO; can be repeated after 4 hrs (max 5 mg/day)	6.10
Rizatriptan[6] – generic	5, 10 mg tabs	5 or 10 mg PO; can be repeated after 2 hrs (max 30 mg/day)[7,8]	2.10
	5, 10 mg orally disintegrating tabs		1.90
Maxalt (Organon)	10 mg tabs		40.70
Maxalt-MLT	10 mg orally disintegrating tabs		36.60
Sumatriptan – generic	25, 50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/day)	1.40/73.50[9]
Imitrex (GSK)	6 mg/0.5 mL vials	6 mg SC; can be repeated after 1 hr (max 12 mg/day)	40.10[10]
	4, 6 mg/0.5 mL auto-injectors[11]		114.10/468.50[9]
	5, 20 mg/0.1 mL nasal spray	5, 10, or 20 mg intranasally; can be repeated after 2 hrs (max 40 mg/day)	52.90/93.50[9]
Onzetra Xsail (Avanir)	11 mg nasal powder capsules	22 mg intranasally; can be repeated after 2 hrs (max 44 mg/day)	117.50
Tosymra (Upsher-Smith)	10 mg single-use nasal spray	10 mg intranasally; can be repeated after 1 hr (max 30 mg/day)	106.30
Zembrace SymTouch (Upsher-Smith)	3 mg/0.5 mL auto-injectors	3 mg SC; can be repeated after 1 hr (max 12 mg/day)	188.40
Zolmitriptan – generic	2.5, 5 mg tabs	2.5 or 5 mg PO; can be repeated after 2 hrs (max 10 mg/day)[12]	5.70
	2.5, 5 mg orally disintegrating tabs		6.50
Zomig (Amneal)	2.5, 5 mg tabs		129.40
Nasal spray[4] – generic	5 mg/0.1 mL nasal spray	2.5 or 5 mg intranasally; can be repeated after 2 hrs (max 10 mg/day)[12]	69.40
Zomig	2.5, 5 mg/0.1 mL nasal spray		97.80
Triptan/NSAID Combination			
Sumatriptan/naproxen[4] – generic	85/500 mg tabs	85/500 mg PO; can be repeated after 2 hrs (max 170/1000 mg/day)[13]	53.30
Treximet (Curax)			140.20

1. Dosage adjustments may be needed 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. May 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.
3. Other NSAIDs such as ibuprofen and naproxen are often used off-label.
4. Also approved for use in patients 12-17 years old.
5. Should be taken with fluids.
6. Also approved for use in patients 6-17 years old.
7. 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.
8. Adults and children (≥40 kg) also taking propranolol should use a 5-mg dose (max 15 mg/day for adults and 5 mg/day for children). Concurrent use of rizatriptan and propranolol is not recommended for children weighing <40 kg.
9. Cost of generic/cost of *Imitrex*.
10. Cost of generic; not available as *Imitrex*.
11. Also available in refill cartridges for the auto-injectors, and generically as a 6-mg syringe.
12. Patients also taking cimetidine should use a 2.5-mg dose (max 5 mg/day).
13. Dosage for adolescents 12-17 years old is 10/60 mg (max 85/500 mg/day).

Pregnancy and Lactation – Ergots can reduce placental blood flow and ergotamine is secreted into breast milk. Use of ergots in pregnant or breastfeeding women is contraindicated.

ANTIEMETICS — The dopamine receptor antagonists **metoclopramide, prochlorperazine, chlorpromazine,** and **droperidol** can reduce nausea and headache pain in patients with migraine.[26] These drugs can cause extrapyramidal adverse effects and prolong the QT interval, increasing the risk of torsades de pointes.

MEDICATION OVERUSE HEADACHE — Overuse of drugs for acute treatment of migraine, especially butalbital and opioids but also triptans, lasmiditan, NSAIDs, and ergots, can lead to increased frequency and severity of headache with poor response to acute and preventive treatment. Treatment of medication overuse headache involves withdrawing the overused drug(s); abrupt withdrawal may require hospitalization and bridge therapy with other drugs. Preventive treatment for migraine should be considered, and

Table 2. Some Drugs for Acute Treatment of Migraine (continued)

Drugs	Some Formulations	Usual Adult Dosage[1]	Cost[2]
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
Rimegepant – *Nurtec ODT* (Biohaven/Pfizer)	75 mg orally disintegrating tabs	75 mg PO (max 75 mg/day)	$118.90
Ubrogepant – *Ubrelvy* (Abbvie)	50, 100 mg tabs	50 or 100 mg PO; can be repeated after 2 hrs (max 200 mg/day)	98.40
Zavegepant – *Zavzpret* (Pfizer)	10 mg single-use nasal spray	10 mg intranasally (max 10 mg/day)	N.A.
5-HT$_{1F}$ Receptor Agonist			
Lasmiditan[14] – *Reyvow* (Lilly)	50, 100 mg tabs	50, 100, or 200 mg PO (max 1 dose/day)	92.60
Ergots			
Dihydroergotamine mesylate – generic	1 mg/mL ampules	1 mg IM or SC; can be repeated at 1 hr intervals (max 3 mg/day, 6 mg/wk)	104.10
Nasal spray – *Migranal* (Bausch)	4 mg/mL nasal spray	1 spray (0.5 mg) into each nostril, repeated 15 min later (2 mg/dose; max 3 mg/day, 4 mg/wk)	477.90
generic			277.60
Trudhesa (Impel)	4 mg/mL nasal spray	1 spray (0.725 mg) into each nostril (1.45 mg/dose); can be repeated after 1 hr; max 2.9 mg/day, 4.35 mg/wk	223.10[15]
Ergotamine tartrate – *Ergomar* (TerSera)	2 mg sublingual tabs	2 mg sublingually; can be repeated at 30 min intervals (max 6 mg/day, 10 mg/wk)	71.20
Ergotamine/caffeine – generic	1/100 mg tabs	2 tabs PO at attack onset, then 1 tab q30 min prn (max 6 tabs/attack)	11.10
Migergot (Cosette)	2/100 mg rectal suppository	1 suppository at attack onset, repeat in 1 hr if needed (max 2 suppositories/attack)	186.70

N.A. = cost not yet available
14. Classified as a schedule V controlled substance.
15. Only available through specialty pharmacies.

some expert clinicians suggest limiting future acute migraine treatment to 2 days per week.[27] CGRP receptor antagonists have not been associated with development of medication overuse headache.

DRUGS FOR PREVENTIVE TREATMENT

Indications for preventive treatment of migraine include frequent or severe attacks, a contraindication to or toxicity with acute treatments, and patient preference.[1] Menstrual migraine can sometimes be prevented by taking an NSAID or a triptan (particularly frovatriptan) for several days before and after the onset of menstruation.[28]

BETA BLOCKERS — Propranolol and **timolol** are FDA-approved for preventive treatment of migraine, but **metoprolol, atenolol, bisoprolol,** and **nadolol** are also effective.

Adverse Effects – Beta blockers can worsen asthma symptoms and depression, and cause fatigue, exercise intolerance, sleep disorders, and orthostatic hypotension. They should not be used in patients with decompensated heart failure.

ANTISEIZURE DRUGS — Valproate and **topiramate** are FDA-approved for migraine prevention. About 50% of patients achieve a ≥50% reduction in headache frequency with use of either drug.[29] In double-blind trials, topiramate was at least as effective as propranolol for migraine prevention.[30] Topiramate has reduced migraine frequency and symptoms in adults with ≥15 headache days/month for ≥3 months and in those with medication overuse headache.[31]

Adverse Effects – Valproate can cause nausea, fatigue, tremor, weight gain, and hair loss. Acute hepatic failure, pancreatitis, and hyperammonemia (in patients with urea cycle disorders) occur rarely. Polycystic ovary syndrome, hyperinsulinemia, lipid abnormalities, hirsutism, and menstrual disturbances have also been reported.

Topiramate commonly causes paresthesias; fatigue, language and cognitive impairment, taste perversion, weight loss, and nephrolithiasis can also occur. Topiramate can rarely cause narrow-angle glaucoma, oligohidrosis, and metabolic acidosis.

Pregnancy – Use of topiramate or (especially) valproate during pregnancy has been associated with congenital malformations.[32,33]

ANTIDEPRESSANTS — Amitriptyline is the only **tricyclic antidepressant** that has been shown to be effective (off-label) for preventive treatment of migraine,[34] but it often causes sedation, dry mouth, and weight gain. Other tricyclics such as nortriptyline, which may have fewer adverse effects, are frequently used as alternatives.

Table 3. Some Drugs for Preventive Treatment of Migraine

Drugs	Some Formulations	Usual Adult Dosage[1]	Cost[2]
Beta Blockers			
Metoprolol[3] – generic	25, 50, 100 mg tabs	50-100 mg PO bid	$3.20
Lopressor (Validus)	50, 100 mg tabs		151.20
extended-release – generic	25, 50, 100, 200 mg ER tabs	100-200 mg PO once/day	13.80
Toprol-XL (AstraZeneca)			39.40
Propranolol – generic	10, 20, 40, 60, 80 mg tabs	40-160 mg PO divided bid	21.00
extended-release – generic	60, 80, 120, 160 mg ER caps	60-160 mg PO once/day	27.90
Timolol – generic	5, 10, 20 mg tabs	20 mg PO once/day or 10-15 mg bid	75.40
Antiseizure Drugs			
Valproate[4] – generic	125, 250, 500 mg delayed-release tabs;	250-500 mg PO bid	13.00
Depakote (Abbvie)	125 mg sprinkle caps		219.80
extended-release – generic	250, 500 mg ER tabs	500-1000 mg PO once/day	27.70
Depakote ER			185.50
Topiramate[5] – generic	25, 50, 100, 200 mg tabs;	50 mg PO bid[6]	11.70
Topamax (Janssen)	15, 25 mg sprinkle caps		784.70
Oral Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists			
Rimegepant[7] – *Nurtec ODT* (Biohaven/Pfizer)	75 mg orally disintegrating tabs	75 mg PO every other day	1784.00
Atogepant – *Qulipta* (Abbvie)	10, 30, 60 mg tabs	10, 30, or 60 mg PO once/day	1040.60
CGRP Antibodies[8]			
Eptinezumab – *Vyepti* (Lundbeck)	100 mg/mL single-dose vials	100 or 300 mg IV q3 months[9]	1650.20[10]
Erenumab – *Aimovig* (Amgen/Novartis)	70, 140 mg/mL single-dose auto-injectors	70 or 140 mg SC once/month[11]	737.90
Fremanezumab – *Ajovy* (Teva)	225 mg/1.5 mL single-use syringes and auto-injectors	225 mg SC once/month or 675 mg q3 months	698.30
Galcanezumab – *Emgality* (Lilly)	120 mg/1 mL single-use pens, syringes[12]	240 mg SC once, then 120 mg once/month	679.20
Tricyclic Antidepressants[3]			
Amitriptyline – generic	10, 25, 50, 75, 100, 150 mg tabs	25-150 mg PO once/day	7.60
Nortriptyline – generic	10, 25, 50, 75 mg caps	25-150 mg PO once/day	12.70
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)[3]			
Venlafaxine – generic	25, 37.5, 50, 75, 100 mg tabs	25-50 mg PO tid	33.50
extended-release – generic	37.5, 75, 150 mg ER caps, tabs; 225 mg ER caps	75-150 mg PO once/day	42.50
Effexor XR (Pfizer)	37.5, 75, 150 mg ER caps		547.50
Duloxetine[3] – generic	20, 30, 40, 60 mg delayed-release caps	60 mg PO once/day	17.60
Cymbalta (Lilly)	20, 30, 60 mg delayed-release caps		280.50
Botulinum Toxin Type A			
OnabotulinumtoxinA – *Botox* (Allergan)[13]	100, 200 unit vials	155 units IM q12 weeks[14]	1268.00[15]

ER = extended-release
1. Dosage adjustments may be needed for renal or hepatic impairment or for drug interactions.
2. Approximate WAC for 30 days' treatment at the lowest usual adult 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. May 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.
3. Not FDA-approved for preventive treatment of migraine.
4. Oral formulations marketed as divalproex sodium (*Depakote*, and others) and valproic acid. Only divalproex sodium is FDA-approved for prevention of migraine. *Depakote Sprinkle Capsules* are not FDA-approved for prevention of migraine.
5. Extended-release formulations of topiramate (*Trokendi XR*; *Qudexy XR*, and generic) are not FDA-approved for migraine prevention.
6. Dosage should be titrated to 100 mg/day over 4 weeks: week 1: 25 mg in the evening; week 2: 25 mg morning and evening; week 3: 25 mg morning and 50 mg evening; week 4: 50 mg morning and evening.
7. Not FDA-approved for preventive treatment of chronic migraine.
8. Eptinezumab, fremanezumab, and galcanezumab target CGRP. Erenumab targets the CGRP receptor.
9. Some patients may require a 300-mg dose.
10. Cost for one dose.
11. Some patients may benefit from a dosage of 140 mg once/month administered as 2 consecutive 70-mg SC injections.
12. Also available in cartons of three 100 mg/mL syringes for treatment of episodic cluster headache.
13. *Botox* is FDA-approved for prevention of headaches in adults with chronic migraine (≥15 days/month with headaches lasting ≥4 hours). *Botox Cosmetic* is not FDA-approved for migraine prevention.
14. Total dosage of 155 units is divided over 7 specific head/neck muscle areas (detailed information provided in package insert).
15. Cost of one 200-unit vial.

The **serotonin-norepinephrine reuptake inhibitors (SNRIs)** venlafaxine and duloxetine may also be effective in preventing migraine.[35,36] Adverse effects include nausea, vomiting, sweating, tachycardia, urinary retention, and blood pressure elevations.

CGRP ANTAGONISTS — The long-acting CGRP monoclonal antibodies **erenumab** *(Aimovig)*, **fremanezumab** *(Ajovy)*, **galcanezumab** *(Emgality)*, and **eptinezumab** *(Vyepti)* and the oral CGRP receptor antagonists **atogepant** *(Qulipta)* and **rimegepant**

Table 4. Neuromodulatory Devices for Treatment of Migraine

Device	Description	Age	Rx/OTC	Use for Acute Treatment	Use for Preventive Treatment
Cefaly (Cefaly Tech)	Trigeminal stimulator; worn on the forehead	≥18 years	OTC	60 min PRN[1,2]	20 min once/day[3]
Gammacore (electroCore)	Handheld vagal stimulator; applied to the neck	≥12 years	Rx	Two consecutive 2-min uses PRN[4]	Two consecutive 2-min uses bid[5]
Nerivio (Theranica)	Remote neuromodulator; worn on the upper arm	≥12 years	Rx	45 min PRN[6]	45 min q2 days[7]
Relivion (Neurolief)	Occipital and trigeminal stimulator; worn around the head	≥18 years	Rx	20-60 min PRN[8,9]	Not FDA-cleared
Savi Dual (eNeura)	Transcranial magnetic stimulator; applied to back of head	≥12 years	Rx	Up to 4 pulses (<1 min) PRN[10]	Up to 4 pulses (<1 min) bid[11]

Rx = available by prescription; OTC = available over the counter

1. DE Chou et al. Cephalalgia 2019; 39:3.
2. DE Kuruvilla et al. Sci Rep 2022; 12:5110.
3. J Schoenen et al. Neurology 2013; 80:697.
4. C Tassorelli et al. Neurology 2018; 91:e364.
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(Nurtec ODT) have reduced the number of migraine days by about 1-2 per month compared to placebo in double-blind trials in patients with episodic or chronic migraine.[37-41] CGRP monoclonal antibodies may be effective when other therapies have failed.[42-45] No head-to-head comparisons of these drugs are available. Erenumab has been shown (off-label) to be effective for prevention of menstrual migraine.[46]

Adverse Effects – Injection-site reactions and constipation are the most common adverse effects of CGRP antibodies. Hypersensitivity reactions have been reported.[47] Erenumab has been associated with hypertension and hair loss.[48,49]

Systemic adverse effects are uncommon with use of oral CGRP receptor antagonists. Nausea and somnolence can occur. Hypersensitivity reactions have been reported with use of rimegepant.

Pregnancy – No adequate data are available on use of CGRP antagonists in pregnant women. Fetal exposure to CGRP antibodies could occur for months after stopping them.

OTHER PREVENTIVE DRUGS – Pericranial intramuscular injections of **onabotulinumtoxinA** *(Botox)* are FDA-approved for preventive treatment of chronic migraine in adults with ≥15 days per month of headaches lasting ≥4 hours.[50] Botulinum toxin is not recommended or FDA-approved for prevention of episodic migraine.

NSAIDs, such as naproxen and ibuprofen, have been used to prevent episodic migraine.[51] The antihypertensive drugs **lisinopril, candesartan,** and **verapamil** have reduced migraine frequency in small studies.[52-54]

NONPHARMACOLOGIC ACUTE AND PREVENTIVE TREATMENT

DEVICES – Five neuromodulatory devices are FDA-cleared for acute treatment of migraine; four of these are also FDA-cleared for preventive treatment. Some can be used in adolescents as well as adults (see Table 4). These devices have decreased migraine frequency and/or severity compared to sham treatment or historical controls in clinical trials. No trials comparing them to each other or to pharmacologic treatments are available, and experience with their use in clinical practice is limited.[1]

OTHER INTERVENTIONS – **Behavioral interventions**, such as cognitive behavioral therapy and biofeedback, and **acupuncture** have been found to be effective for preventive treatment of migraine, but study quality is mixed.[53-57] ■

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Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

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Principal Faculty for this Activity:

Mark Abramowicz, M.D., President has disclosed no relevant financial relationships
Jean-Marie Pflomm, Pharm.D., Editor in Chief has disclosed no relevant financial relationships
Brinda M. Shah, Pharm.D., Consulting Editor has disclosed no relevant financial relationships.

In addition to the Principal Faculty above, the following have also contributed to this activity:
Michael Viscusi, Pharm.D., Associate Editor has disclosed no relevant financial relationships.

LEARNING OBJECTIVES FOR THIS ACTIVITY:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in *The Medical Letter* with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:

1. Explain the current approach to the management of migraine.
2. Discuss the pharmacologic options available for acute and preventive treatment 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 individual presentation of a patient with migraine.

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Note: The participant should read the post-activity questions prior to beginning the activity. After careful review of the text, tables, and cited references, the participant should take time to reflect on how the newly acquired knowledge will be applied to clinical practice, affect patient care, and improve outcomes.

Issue 1678 Post-Activity Questions

(Correspond to questions #111-120 in Comprehensive Activity #88, available July 2023)

1. The drug of choice for acute treatment of moderate to severe migraine in most patients without vascular disease is:
   a. an NSAID
   b. acetaminophen
   c. aspirin
   d. a triptan

2. Which of the following drugs is not recommended for acute treatment of migraine pain?
   a. diclofenac
   b. butalbital
   c. acetaminophen
   d. aspirin

3. Compared to other oral triptans, naratriptan and frovatriptan:
   a. are better tolerated
   b. have lower initial response rates
   c. have a slower onset of action
   d. all of the above

4. About how many cases of moderate to severe migraine treated with a triptan recur within 24 hours?
   a. 20-40%
   b. 30-50%
   c. 40-60%
   d. 50-70%

5. CGRP receptor antagonists:
   a. are less effective than triptans for acute treatment of migraine
   b. do not cause medication overuse headache
   c. can be used in patients with vascular disease
   d. all of the above

6. In clinical trials, the rate of freedom from headache pain 2 hours post-dose was greater with lasmiditan than with placebo by about:
   a. 10-15%
   b. 20-25%
   c. 30-35%
   d. 40-45%

7. Which of the following drug classes has been associated with development of medication overuse headache?
   a. triptans
   b. ergots
   c. NSAIDs
   d. all of the above

8. Which of the following drugs has been shown to be effective for preventive treatment of migraine?
   a. propranolol
   b. topiramate
   c. valproate
   d. all of the above

9. In clinical trials, compared to placebo, use of CGRP antagonists for preventive treatment of migraine has reduced migraine frequency by about:
   a. 1-2 days per month
   b. 2-4 days per month
   c. 6-8 days per month
   d. 8-10 days per month

10. OnabotulinumtoxinA is approved by the FDA for:
    a. preventive treatment of chronic migraine
    b. preventive treatment of episodic migraine
    c. acute treatment of episodic migraine
    d. all of the above

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Successful completion of the post-test is required to earn AAPA Category 1 CME credit. Successful completion is defined as a cumulative score of at least 70 percent correct.

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