INLAND EMPIRE HEALTH PLAN

Clinical Practice Guideline for the Diagnosis and Management of Migraine

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PHARMACOTHERAPEUTIC MANAGEMENT OF MIGRAINE

Migraine associated with moderate to severe disability afflicts more than 28 million persons in the United States.[1] Direct and indirect costs are estimated to be $5.6 to $17.2 billion in time lost from work and loss of productivity.[2,3] As one of the top 10 causes for outpatient physician visits in the United States, headache requires optimal therapy.[4] Compared with patients without migraine, patients with migraine have greater morbidity in general and greater costs in health care resources.[5]

Pathophysiology of Pain

Release of vasoactive substances (e.g., substance P, calcitonin-gene related peptides and neurokinin A) from trigeminal nerve fibers induces a sterile inflammatory reaction around the blood vessels at the base of the brain and in the blood vessels of the dura and pia. This "neurogenic inflammation" may be accompanied by vasodilation and is triggered by nerve impulses originating in the caudal trigeminal nucleus. Specific abortive agents for migraine such as dihydroergotamine (DHE), ergotamine, and sumatriptan can reverse this neurogenic inflammation. This effect is probably mediated by interaction with specific serotonin receptors (5-HT_{1D}).[6] Stimulation of inhibitory (5-HT_1) serotonin receptors is thought to turn off neurogenic inflammation, whereas activation of the excitatory (5-HT_2) serotonin receptors can lead to migraine. Many medications used for migraine prophylaxis work by blocking 5-HT_2 receptors.

Classification of Migraine

1. Migraine

1.1 Migraine without aura

1.2 Migraine with aura
- 1.2.1 Typical aura with migraine headache
- 1.2.2 Typical aura with non-migraine headache
- 1.2.3 Typical aura without headache
- 1.2.4 Familial hemiplegic migraine (FHM)
- 1.2.5 Sporadic hemiplegic migraine
- 1.2.6 Basilar-type migraine

1.3 Childhood periodic syndromes that are commonly precursors of migraine
- 1.3.1 Cyclical vomiting
- 1.3.2 Abdominal migraine
- 1.3.3 Benign paroxysmal vertigo of childhood

1.4 Retinal migraine

1.5 Complications of migraine
- 1.5.1 Chronic migraine
- 1.5.2 Status migrainosus
- 1.5.3 Persistent aura without infarction
- 1.5.4 Migrainous infarction
- 1.5.5 Migraine-triggered seizure

1.6 Probable migraine
- 1.6.1 Probable migraine without aura

1.6.2 Probable migraine with aura
1.6.5 Probable chronic migraine

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 2nd Edition. *Cephalalgia* 2004;24(suppl 1):1-150.

Diagnostic Criteria for Migraine Without Aura

A. At least five attacks fulfilling B to D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated).

C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

E. Not attributed to another disorder

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 2nd Edition. *Cephalalgia* 2004;24(suppl 1):1-150.

Diagnostic Criteria for Migraine with Aura

A. At least two attacks fulfilling B

B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6

C. Not attributed to another disorder

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 2nd Edition. *Cephalalgia* 2004;24(suppl 1):1-150.

Acute Therapy for Migraine

The pharmacologic treatment of migraine is divided into acute (abortive, symptomatic) treatment and preventive (prophylactic) treatment. Most patients with migraine need only abortive treatment for their headaches.[7] Table 1 lists the major antimigraine abortive agents and Table 2 summarize the recommendation for acute migraine treatment made by U.S. Headache Consortium and AAFP/ACP-ASIM Use of abortive agents should be limited when possible to two days a week, since frequent use of analgesics, ergotamine and, possibly, sumatriptan can lead to so-called “re-bound” headache and make preventive medications less effective.

Table 1 Selected Agents Used in Symptomatic Treatment of Migraine

Drug	Route	Availability	Cost	Initial dose and frequency	Rebound headache potential	Remarks
Acetylsalicylic acid (ASA)	Oral	325mg, 500mg	$0.32	Maximum initial dose: 1g; can repeat every 6 hours	Yes	Maximum daily dosage: 4g
Acetaminophen (Tylenol)	Oral	325 mg, 500mg	$0.24	Maximum initial dose: 1g; can repeat every 6 hours	Yes	Maximum daily dosage: 4g
Ibuprofen (Advil, Motrin, Nuprin, etc.)	Oral	200mg, 300mg, 400mg, 600mg, 800mg	$0.20	Maximum initial dose: 800mg; can repeat every 6 hours	Unlikely	Use lowest effective dosage; avoid doses > 2.4g per day
Naproxen sodium (Aleve, Anaprox) naproxen (Naprosyn)	Oral	220mg, 275mg, 550mg	$0.62	Maximum initial dose: 825mg; can repeat 220 to 550mg in 3 to 4 hours	Unlikely	Use lowest effective dosage; avoid doses > 1.5g per day; naproxen sodium (Aleve, Anaprox) is absorbed more rapidly than naproxen (Naprosyn)
Isometheptene, dichloralphenazone, acetaminophen (Isocom, Isopap, Midrin)	Oral	—	$1.05	Maximum initial dose: 2 capsules at onset; can repeat 1 capsule every hour if needed; maximum: 5 per 12 hours, 20 per month	Yes	Limit use to no more than 2 days per week
Aspirin, butalbital, caffeine (Fiorinal)	Oral	—	$0.18	Maximum initial dose: 2 tablets at onset; can repeat 1 tablet every 4 to 6 hours if needed; maximum: 5 per day, 15 per month	Yes	Limit use to no more than 2 days per week
Acetaminophen, butalbital, caffeine (Fioricet, Esgic)	Oral	—	$0.20	Maximum initial dose: 2 tablets at onset; can repeat 1 tablet every 4 to 6 hours if needed; maximum: 5 per day, 15 per month	Yes	Limit use to no more than 2 days per week
Metoclopramide (Reglan)	Oral	10mg	$0.08	1 tablet 20 to 30 minutes before or with a simple analgesic, NSAID or ergotamine derivative	No	Caution: dystonic reaction, especially in children
Indomethacin (Indocin)	Rectal	50mg	$1.72	1 to 2 suppositories at onset	Unlikely	—
Ergotamine tartrate (Wigraine)	Rectal	—	$3.88	Maximum initial dose: 1 suppository at onset; can repeat in 1 hour; maximum: 2 per day, 12 per month	Yes	Use subnauseating dose; pretreatment with an antiemetic may be needed; limit use to no more than 2 days per week; can use perimenstrually for menstrual migraine
Ketorolac (Toradol)	Intramuscular	15mg, 30mg, 60mg	$15	Maximum initial dose: 30 to 60mg at onset; can repeat 15 to 30mg every 6 hours	Unlikely	Useful when ergotamine derivative, D.H.E. or sumatriptan is contraindicated; do not exceed 5 consecutive days of use
Dihydroergotamine (D.H.E.)	Intramuscular	1mg = 1 ample	$38	Maximum initial dose: 1mg; can repeat at 1-hour intervals to total of 3mg per day, 6 mg per week; in general, monthly use should not exceed 20mg	Unlikely	Can use for treatment of acute severe migraine headaches if no medical contraindication exists; pretreatment with an antiemetic is not necessary (unlike ergotamine)
Dihydroergotamine (Migranal)	Intranasal	4mg/mL 1 spray = 1 dose	$84.7	Transnasal 0.5mg/spray. 1 spray in each nostril; if headache returns, the dose can be repeated once, after one hour.	Unlikely	Can use for treatment of acute severe migraine headaches if no medical contraindication exists.
Meperidine (Demerol)	Intramuscular	25mg, 50mg, 75mg, 100mg	$5.53	Maximum initial dose: 150mg: can repeat 50 to 100mg every 3 to 4 hours	Yes	Use only when other standard symptomatic treatment is contraindicated or ineffective
Butorphanol (Stadol)	Transnasal	1mg = 1 spray*	$30.1	1 spray in 1 nostril; repeat in 1 hour if needed; limit use to 4 doses per day	Yes	Consider use only in patients for whom nonopioid therapy failed or who have

Drug	Route	Availability	Cost	Initial dose and frequency	Rebound headache potential	Remarks
						contraindications to nonopioid therapy; limit use to 2 days per week.
Triptans *Formulary						
Almotriptan (Axert)	Oral	6.25mg, 12.5mg	$21.49/ dose	Initial dose: 6.25mg or 12.5mg. May repeat in > 2 hours maximum: 25mg/day; no more than 2 doses/ day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours
Eletriptan (Relpax)	Oral	20mg, 40mg	$20.03/ dose	Initial dose: 20mg or 40mg. May repeat in > 2 hours maximum: 80mg/day; no more than 2 doses/ day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours
Frovatriptan (Frova)	Oral	2.5mg	$17.40/ dose	Initial dose: 2.5mg. May repeat in > 2 hours maximum: 7.5mg/day; no more than 3 doses/ day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours
Naratriptan (Amerge)	Oral	1mg, 2.5mg	$24.28/ dose	Initial dose: 1mg or 2.5mg. May repeat in > 4 hours maximum: 5mg/day;	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours
Rizatriptan* (Maxalt)	Oral	5mg 10mg	$21.73/ dose	Initial dose: 5 or 10mg. May repeat in > 2 hours maximum: 30mg/day (Quantity Limit: 18 doses/30days)	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours; screen for asymptomatic cardiac disease in patients at risk. Dosage adjustment required if taken with propranolol.
Sumatriptan (Imitrex)	Subcutaneous	6mg	$156.8	Maximum initial dose: one 6mg injection at onset; can repeat in 1 hour if needed; maximum: 12mg per day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours
Sumatriptan (Imitrex)	Oral	25mg, 50mg, 100mg	$19.58/ dose	Maximum initial dose: 100mg; can repeat every 2 hours; maximum: 300mg per day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours; screen for asymptomatic cardiac disease in patients at risk
Sumatriptan (Imitrex Nasal Spray)	Transnasal	5mg, 20mg*	$33.57	5, 10 or 20mg; maximum: 40mg daily; if headache returns, the dose can be repeated once, after 2 hours, not to exceed a total daily dosage of 40mg	Likely	Doses above 20mg do not provide greater relief than the 20mg dose; the safety of treating an average of more than 4 headaches in a 30-day period has not been established; screen for asymptomatic cardiac disease in patients at risk
Zomitriptan* (Zomig)	Oral	2.5mg 5mg	$20.27/ dose	Initial dose: 2.5mg. May repeat in > 2 hours, maximum: 5mg per dose; 10mg per day (Quantity Limit: 12 doses/30days)	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours; screen for asymptomatic cardiac disease in patients at risk
Zomitriptan (Zomig Nasal Spray)	Transnasal	5mg	$29.35/ dose	Initial dose: 5mg. May repeat in > 2 hours, maximum: 5mg per dose; 10mg per day	Likely	Limit use to no more than 2 days per week; not to be used if ergotamine derivative has been used in prior 24 hours; screen for asymptomatic cardiac disease in patients at risk

* = One spray equals one dose.

Cost = Average Wholesale Price (AWP) or Maximum Allowable Cost (MAC) per day 1/2007

Adapted from Capobianco DJ, Cheshire WP, Campbell JK. An overview of the diagnosis and pharmacologic treatment of migraine. *Mayo Clin Proc* 1996;71:1062-3.

Table 2. Summary of U.S. Headache Consortium Recommendations Compared with AAFP/ACP-ASIM Recommendation on Acute Migraine Treatment.

U.S. Headache Consortium Recommendations	
Use migraine-specific agents in patients with severe migraine and in patients whose migraines respond poorly to NSAIDs or combination analgesics such as aspirin+acetaminophen+caffeine.	Oral acetaminophen+aspirin+caffeine Oral aspirin IN Butorphanol SC, IM, IV, IN DHE IV DHE + antiemetic Oral ibuprofen Oral naproxen sodium Oral naratriptan IV prochlorperazine Oral rizatriptan SC, IN, oral sumatriptan Oral zolmitriptan
AAFP/ACP-ASIM Recommendations	
Use NSAIDs as first-line therapy	Aspirin Ibuprofen Naproxen Acetaminophen+aspirin+caffeine
If fails, use migraine-specific agents.	DHE nasal spray Oral naratriptan SC, oral sumatriptan Oral rizatriptan Oral zolmitriptan

Adapted from U.S. Headache Consortium: Matchar DB, Young WB, Rosenberg JH, Pietrzak MP, Silberstein SD, Lipton RB, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. 2000. Accessed at www.aan.com/professionals/practice/guidelines.cfm.
Ramadan NM, Silbertsein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2000. Accessed at www.aan.com/professionals/practice/guidelines.cfm.
AAFP/ACP-ASIM Recommendations: Snow V, Weiss K, Wall EM, Mottur-Pilson C. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med.* 2002;137:840-849

Simple analgesics such as aspirin and acetaminophen or nonsteroidal anti-inflammatory drugs may be effective for mild to moderate attacks that are not associated with severe nausea or vomiting. Note that acetaminophen alone is not recommended for migraine according to the Consortium.
Even if the patient is not vomiting, however, oral agents may be ineffective for severe migraine attacks because of decreased gastric motility. Effervescent analgesic preparations are more rapidly absorbed and may be more effective.[8,9] Concurrent use of metoclopramide (Reglan) at 10 mg can improve gastric motility and increase the efficacy of oral agents.[10]

Migraine attacks that peak in one hour or less and attacks associated with severe nausea and vomiting may not respond to oral agents. Rectal, nasal or intramuscular/subcutaneous routes should be used to treat these attacks.

Table 3compares dihydroergotamine and sumatriptan in the treatment of severe migraine attacks. These agents can treat the entire migraine complex, including the associated nausea, vomiting. Photophobia and phonophobia. They are also effective in the treatment of prolonged attacks, although ideally they should be taken at an early stage.

Table 3 Comparison of Sumatriptan (Imitrex) and Dihydroergotamine (D.H.E.) for Severe Migraine Attacks

Feature	*Sumatriptan*	*Dihydroergotamine*
Efficacy in relief of pain	++++	++++
Efficacy in relief of nausea, vomiting and photophobia	++	—
Efficacy in relief of aura symptoms	—	+++
Efficacy in relief of status migrainous (disabling headaches lasting ≥ 72 hours)	++	++++
Recurrence of pain	Common (40 percent)	Uncommon
Precautions	Ischemic heart disease or coronary vasospasm Uncontrolled hypertension Concurrent use of ergotamine, dihydroergotamine, methysergide or combination drug (Midrin), in prior 24 hours Hemiplegic or basilar migraine Pregnancy Previous hypersensitivity	Peripheral vascular disease Coronary artery disease Uncontrolled hypertension Impaired hepatic or renal function Pregnancy Previous hypersensitivity
Rebound headache with frequent or daily use	Rare	Not reported

++++ = Strong association
— = no association

Sumatriptan should not be taken until after the aura of a migraine abates and the actual pain has begun. Efficacy ranging from 54 to 80 percent has been demonstrated in clinical trials of oral and injectable sumatriptan formulations.[11, 12] Because of short half-life of both subcutaneous and oral sumatriptan, up to 40 percent of the headaches that originally respond to the drug recur.[13,14] In many patients, a second dose of sumatriptan can provide relief of recurrent headache. A second dose should not be administered, however, if the patient does not initially respond to the first dose.

Dihydroergotamine is less likely to be associated with headache recurrence[15,16] and has not been associated with the development of rebound headache.

Although no longer considered the treatment of choice for severe migraine attacks (except in pregnant patients), narcotic analgesics should not be withheld in a patient in genuine distress if non-narcotic agents have failed and the patient does not have a history of substance abuse. The risk of addiction is low[17,18] if the frequency of narcotic use is appropriately limited (e.g., up to four times a month).

A stepwise approach to selecting pharmacotherapy for abortive treatment is helpful. Table 4 provides an outline for the use of abortive agents based on the severity of pain and associated symptoms.

Table 4 Prioritizing Abortive Therapy in Migraine Management

Stage or setting	Recommended therapy
Early and mild headache (zero to 2 hours)	Quiet, dark room; combination drug (Midrin) or NSAID for headache; metoclopramide (Reglan) or hydroxyzine (Atarax) for nausea.
Moderate to severe headache or headache unresponsive to combination drug (Midrin) or NSAID (zero to 4 hours)	No vomiting: oral antiemetic agent and ergotamine suppository (or indomethacin [Indocin] suppository if previous migraine attacks have not responded to ergotamine) Vomiting: antiemetic suppository plus ergotamine suppository or sumatriptan (Imitrex) by subcutaneous injection if previous migraine attacks have not responded to ergotamine
Moderate to severe headache unresponsive to ergotamine or sumatriptan (2 to 6 hours)	No vomiting: oral combination analgesic (e.g., Fiorinal) or codeine Vomiting: Transnasal butorphanol or chlorpromazine suppository
Severe migraine headache unresponsive to outpatient therapy—emergency department treatment (6 to 72 hours)	Intravenous metoclopramide or prochlorperazine (Compazine) plus dihydroergotamine (D.H.E.); intramuscular ketorolac (Toradol); intravenous dexamethasone; parenteral opiate
Persistent severe migraine headache unresponsive to outpatient and emergency care (> 48 hours)	Admit to hospital for repetitive dihydroergotamine protocol; parenteral antiemetics; intravenous hydrocortisone or methylprednisolone; intravenous lidocaine (100mg followed by 2 mg per minute) with cardiac monitoring
Headache with persistent neurologic deficits	Exclude ischemic, structural, inflammatory or metabolic brain disease
"First or worst" severe migraine headache	Withhold potent narcotics until more serious conditions are excluded by clinical evaluation and CT scan; laboratory procedures if patient is seriously ill and febrile, or if meningeal signs are present

NSAID -= nonsteroidal anti-inflammatory drug CT = computed tomography

Management of Rebound Headache

Frequent use of abortive headache medications can cause rebound headache or perpetuate chronic daily headache.[19,20] Table 5 describes the clinical characteristics of rebound headache. Discontinuation of analgesics, ergotamine, sedatives and decongestants, and institution of appropriate preventive therapy are successful in most cases. Withdrawal of over-the-counter medications can usually be accomplished on an outpatient basis. However, when analgesics are combined with a barbiturate or codeine, or when an ergotamine preparation is overused, withdrawal is more severe, and the patient may require hospitalization for detoxification. Table 6 summarizes a study showing that continued use of analgesics decreases the success rate in treatment of chronic daily headache.[20] Before withdrawal, patients should be given the following information:

1. After cessation of abortive agents, headache may worsen within 24 to 48 hours, and severe headache may last 72 hours or longer;
2. Measures will be taken to minimize the severity of the rebound headache;
3. Hospitalization is an option if the rebound headache is prolonged, severe or associated with nausea or vomiting;
4. It may take eight to twelve weeks for patients to regain normal responsiveness to appropriate therapy (the analgesic wash-out period), and a positive response to preventive agents may also be delayed.[21]

Table 5

Clinical Characteristics of Rebound Headache
Headaches are daily or nearly daily, often occurring early in the morning (2 a.m. to 5 a.m.).
Headaches occur in a patient with migraine headache who uses abortive medications frequently, in excessive quantities (more than 15 to 20 days per month).
Headache varies in type, severity and location.
The slightest amount of physical or mental effort may precipitate the headache.
Symptoms accompanying the headache include nausea and other gastrointestinal symptoms, asthenia, anxiety, irritability, depression, memory problems and difficulty in concentration.
Patient has a drug-dependent pattern of headaches.
Evidence exists of tolerance over time, with patients needing progressively larger doses of medication.
Withdrawal symptoms are observed when patient is taken off pain medications abruptly.
Spontaneous improvement of headache occurs on final discontinuation of medications.
Concomitant preventive medications are relatively ineffective, while the patient is using excessive amounts of abortive medications.

Information from Mathew NT. Transformed migraine, analgesic rebound, and other chronic daily headaches. *Neurol Clin* 1997;15(1):167-86.

Table 6 Effect of Continued Analgesic Use in 100 Patients with Chronic Daily Headache

Treatment group	Mean improvement (%)
Amitriptyline (Elavil) plus no analgesics	72
Placebo plus no analgesics	43
Amitriptyline plus as-needed analgesics	30
Placebo plus as-needed analgesics	18

Adapted from Kudrow L. Paradoxical effects of frequent Analgesic use. *Adv Neurol* 1982;33:339.

Outpatient management of rebound headache is summarized in Table 7.[21-24] Preventive therapy is usually begun when the withdrawal process is initiated. It may be useful, however, to begin preventive therapy two to three weeks before the withdrawal process or one week after the withdrawal process, since patients may stop the preventive agent if withdrawal symptoms are misinterpreted as "side effects" caused by this agent.

Table 7 Empiric Outpatient management of Rebound Headache

Withdrawal from:	*Possible treatment regimens**
Simple analgesics	Combination drug (Midrin), 1 orally three times daily for 1 week Cyproheptadine (Periactin), 4mg three times daily
Butalbital-containing agents (Fiorinal, Fioricet, Esgic, etc.), < 8 pills (400mg butalbital per day); consider drug detoxification program for > 8 pills per day	One or more of the agents above *plus* Clonazepam (Klonopin), 0.5 to 1.0mg daily for 1 week, then taper *or* Phenobarbital, 30mg three times daily for 1 week *plus* Promethazine (Phenergan), 25 to 50mg three times daily or as needed for 1 to 2 weeks
Ergotamine (Cafergot, Wigraine, etc.), not exceeding 0.5 to 1.0mg daily; consider inpatient management for use > 1.0mg per day	Naproxen (Aleve, Anaprox, Naprosyn), 500 to 1,000mg daily for 1 to 3 weeks Methylergonovine (Methergine),0.2 to 0.4mg three times daily *plus* Promethazine, 25 to 50mg three times daily or as needed for 1 to 2 weeks
Codeine-containing analgesics	Clonidine (Catapres), 0.1 to 0.2mg three times daily for 1 to 2 weeks, then taper Naproxen, 500 to 1,000mg daily for 1 to 3 weeks Promethazine, 25 to 30mg three times daily or as needed for 1 to 2 weeks

* - These regimens are suggestions only and have not been subjected to rigorous comparative study in patients with rebound headaches.

Beta blockers can mask early withdrawal symptoms from butalbital-containing agents (Fiorinal, Fioricet, Esgic, etc.) and benzodiazepines. Serious withdrawal symptoms such as delirium and seizures can appear without warning. Therefore, it is advisable to wait five to seven days before starting beta-blocker therapy in patients who are withdrawing from butalbital or similar agents. It is common for patients with headache to underestimate their use of analgesics. Quantitative drug screens may be helpful.

Preventive Therapy

Avoidance of known migraine triggers is a key first step in preventing migraine recurrence. Some patients, however, require the addition of preventive (prophylactic) medication. In most cases, preventive medication must be taken daily by the patient with migraine for months or years. However, therapy can be given episodically for migraines triggered by

exercise or other activity. In addition, migraines provoked by time-related events such as menstruation can be managed effectively with preventive therapy before and after the event. Table 8[22] provides a checklist for physicians and patients considering preventive therapy. Patients who are on preventive therapy usually also require abortive treatment for migraines.[23]

Table 8 Checklist For Preventive Migraine Therapy

Do migraine attacks occur more than twice a month?
Does patient have one attack a month with sufficient severity or disability (from pain or associated symptoms) to warrant the cost and inconvenience of daily medication?
If patient is a young woman of childbearing age, is effective contraception used?
If headaches are not frequent or disabling, does patient have a medical condition that is a relative indication for a preventive agent (e.g., hypertension and beta blocker use)?
Is patient in good general health without serious obstructive lung disease, heart disease, liver disease, renal impairment or other condition that would contraindicate use of preventive agents?
Would a 30 to 60 percent reduction in headache frequency or severity provide meaningful improvement in patient's quality of life?
Is patient likely to be compliant with directions and precautions? Is he or she willing to return for periodic clinical evaluation?
Does patient understand and accept the limitations and risks of preventive medications?

Adapted from Tfelt-Hansen P. Prophylactic pharmacotherapy of migraine. Some practical guidelines. *Neurol Clin* 1997;15:153-65.

Beta-adrenergic blockers, antidepressants, anticonvulsants, calcium channel blockers, nonsteroidal anti-inflammatory agents (NSAIDs) and serotonin antagonists are the major classes of drugs used for preventive migraine therapy. Table 9 lists the major therapeutic options for prevention of migraine headache.

Table 9 Pharmacotherapeutic Alternatives in Migraine Prophylaxis

Drug	*Dosage*	*Cost (generic)**	*Special considerations*
Beta blockers			
Atenolol (Tenormin)	50 to 150mg per day	50mg tablet: $0.03 (0.03 to 0.09)	Efficacy and safety of beta blockers are well established by several double-blind studies. Maximal benefit may be delayed for two to three months. Begin with low dosage and increase dosage slowly. Underdosing of beta blockers in general is major cause of therapeutic failure.
Metoprolol (Lopressor)	50 to 300mg per day	100mg tablet: $0.07 (0.03 to 0.21)	
Nadolol (Corgard)	20 to 240mg per day	40mg tablet: $0.44 (0.22 to 2.64) 80mg tablet: $0.54 (max. 1.62)	Nadolol and propranolol are most widely used agents. Failure to respond to one beta blocker does not preclude successful use of another beta blocker in the same patient.
Propranolol (Inderal)†	40 to 320mg per day‡	40mg tablet: $0.01(0.01 to 0.08) 80mg tablet: $0.28 (max. 1.12)	When propranolol is used with rizatriptan, a lower dose of rizatriptan should be given.
Timolol (Blocadren)†	20 to 60mg per day	20mg tablet: $0.30 (0.30 to 0.60)	
Note: The drugs above are most commonly used in migraine prophylaxis. They do not reduce aura. Agents with intrinsic sympathomimetic activity, such as acebutolol (Sectral) and pindolol (Visken), should be avoided. Beta blockers should not be used in patients with coexistent asthma, cardiac insufficiency, or Raynaud's disease. May exacerbate depression.			
Tricyclic antidepressants			
Amitriptyline (Elavil)	10 to 300mg per day	10mg tablet: $0.02 (0.02 to 0.60) 50mg tablet: $0.02 (0.09 to 0.12) 150mg tablet: $1.38 (0.14 to 0.27)	Effective for migraine with tension-type headache or depression; combined use with beta blocker can reduce tension-type headaches but not migraines; efficacy of tricyclic agents other than amitriptyline for treatment of migraine is not well established.
Doxepin (Sinequan)	10 to 200mg per day	10mg capsule: $0.03 (0.03 to 0.60) 50mg capsule: $0.06 (max. 0.24) 100mg capsule: $0.09 (max. 0.18)	
Imipramine (Tofranil)	10 to 200mg per day	10mg tablet: $0.15 (0.15 to 3.00) 50mg tablet: $0.03 (max. 0.12)	
Nortriptyline (Aventyl, Pamelor)	10 to 150mg per day	10mg capsule: $0.09 (1.35) 50mg capsule: $0.14 (max. 0.42)	
Note: The drugs above are particularly useful in patients with depression or insomnia. They offer a central analgesic effect.			
Calcium channel blockers			
Diltiazem (Cardizem)	90 to 360mg per day	90mg IR tablet: $0.15 (0.15 to 0.60)	Well tolerated by most patients. Efficacy of calcium channel blockers is uncertain but may be useful for patients with migraine with prolonged aura. Start with low dosage and increase gradually.
Verapamil (Calan, Isoptin)	120 to 720mg per day‡	120mg IR tablet: $0.07 (0.07 to 0.42)	
Note: verapamil is used most often. Calcium channel blockers are a good first choice in patients with neurologic symptoms; they are an alternative to beta blockers in patients with asthma or chronic obstructive pulmonary disease. Avoid use of dihydropyridine group of calcium channel blockers (e.g., Nifedipine), as these agents can cause chronic headache. Nimodipine is too expensive and inconvenient (four times daily dosing) for extended use as a preventive medication.			

Drug	*Dosage*	*Cost (generic)**	*Special considerations*
Anticonvulsants			
Divalproex sodium (Depakote)† or valproic acid (Depakene)	250 to 1,500mg per day; begin with 125 to 250mg twice daily and increase dosage gradually by 125 to 250mg weekly; average dosage: 250 to 500mg three times daily	Divalproex, 250mg capsule: $1.71 Valproic acid, 250mg capsule: $0.27 250mg teaspoonful: $0.15	Particularly effective in patients with severe migraine, as opposed to tension-type headache. Recommended for patients with prolonged or atypical migraine aura. Common dose-related side effects: gastrointestinal, tremor, weight gain
Note: These drugs may be particularly useful in patients with anxiety, bipolar disorder or seizure disorder. Effective contraception in women of child-bearing age is essential. Consider folic acid supplementation.			
Selective serotonin reuptake inhibitors			
Fluoxetine (Prozac)	10 to 80mg per day	10mg capsule: $0.58 20mg capsule: $0.25 20mg teaspoonful: $0.98	
NOTE: Specific anti-migraine activity is not yet defined but appears useful, particularly in patients who do not tolerate tricyclic antidepressants.			
Serotonin antagonists			
Cyproheptadine (Periactin)	4 to 16mg per day; daily maximum: Children aged 2 to 6: 12mg per day Children aged 7 – 14: 16mg per day	4mg tablet: $0.02 (0.02 to 0.08) 5mL: $0.125	Commonly used to treat childhood migraine but no controlled studies confirm efficacy; weight gain can be a major side effect.
NOTE: The above is probably the drug of choice for treatment of migraine in pediatric patients. Total daily dosage is calculated on the basis of weight or size: 0.25mg per kg or 8mg per meter.			
Methysergide (Sansert)†	2 to 8mg per day; maximum: 14mg per day	2mg tablet: $2.11 (2.11 – 8.44)	FDA approved for severe migraine unresponsive to other agents. Consider stopping therapy for three to four weeks after each six-month treatment course; discontinue use if no response after three weeks of therapy.
NOTE: the above is a semisynthetic ergot derivative and serotonin antagonist. It is a drug of last resort in patients with frequent or severe uncontrollable migraines. It is very effective but difficult to tolerate and can cause serious adverse reactions. Use is contraindicated in pregnant women. Not recommended for use in children.			
Monoamine oxidase inhibitors			
Phenelzine (Nardil)	30 to 90mg per day	15mg tablet: $0.47 (0.94 – 2.82)	Can help 80 percent of patients refractory to other preventive agents but risk of life-threatening food and drug reactions and side effects limits use to the most desperate and compliant patients; not recommended for use by physicians inexperienced with MAOI agents.
NOTE: Patients must avoid tyramine-rich foods and sympathomimetic agents, and should be closely monitored. Like methysergide, phenelzine is used for refractory headaches.			

IR = Immediate release; FDA = U.S. Food and Drug Administration; MAOI = monoamine oxidase inhibitors
* = Estimated cost to the based on average wholesale prices in Red book. 1998
† = Approved by the U. S. Food and Drug Administration for treatment of migraine.
‡ = Exceeds manufacturer's recommended dosage.
Adapted from Kumar KL, Mathew NT, Silberstein SD. Migraine: finding the road to relief. *Patient Care* 1995;29(14):90-115.

Patients should be instructed to keep a headache calendar before and after initiating preventive therapy, recording headache frequency, duration and severity. This calendar will aid the physician in assessing the efficacy of a preventive regimen.

Prescribing inadequate doses of preventive medications for brief periods (one to two weeks) is a major cause of therapeutic failure. In general, it is best to begin with a low dosage and titrate gradually upward until the agent is given at full therapeutic dosage for two to three months. If the patient's migraine attacks are well controlled at relatively low dosages, additional increases in dosage should be delayed until it becomes apparent that higher dosages are necessary.

The correct dosage for preventive agents must be determined individually, and each drug should be tried for at least two months.

The selection of a preventive medication is based on the relative indications, contraindications, and side effect profile of the drug[24] (Table 10). The drugs of first choice for migraine prevention are the beta blockers. Propranolol (Inderal), metoprolol (Lopressor), timolol (Blocadren), nadolol (Corgard) and atenolol (Tenormin) have established efficacy in preventing migraine, primarily reducing headache frequency.[25] Although beta blockers will not reduce headache aura, they can be used in patients with and without aura.[26]

Table 10 Consideration of Drug Selection In Migraine Prevention

Agent	***Relative indications***	***Relative contraindications***
Beta blockers	Hypertension Angina Certain tachyarrhythmias Hypertrophic subaortic stenosis Thyrotoxicosis Essential tremor Pheochromocytoma	Sinus bradycardia Greater than first-degree heart block Congestive heart failure Asthma Wolff-Parkinson-White syndrome
Amitriptyline (Elavil)	Depression Anxiety Insomnia Tension-type headaches Chronic pain	Cardiac conduction defect Urinary retention Glaucoma (angle-closure) Acute recovery phase of myocardial infarction Prior hypersensitivity Epilepsy (uncontrolled with antiepileptic therapy) Occupations and activities requiring full alertness and concentration
Naproxen sodium (Aleve, Anaprox) Naproxen (Naprosyn)	Arthritis Other somatic pain Dysmenorrhea	Previous hypersensitivity to aspirin or other NSAIDs Active peptic ulcer disease or GI bleeding Renal impairment or high risk for renal impairment (elderly, diabetes, hypertension, atherosclerosis, diuretic use) Cirrhosis Alcoholism Coagulopathy or anticoagulation
Verapamil (Calan, Isoptin)	Angina at rest Chronic stable angina Certain arrhythmias Hypertension	Severe left ventricle dysfunction Hypotension Sick sinus syndrome Second- or third-degree atrioventricular block Atrial flutter / fibrillation with an accessory bypass tract (e.g., Wolff-Parkinson-White syndrome) Known hypersensitivity
Divalproex sodium (Depakote)	Epilepsy Mania or hypomania due to bipolar disorder Trigeminal neuralgia Cluster headache	Known hypersensitivity Pregnancy Young children (hepatotoxicity) Liver disease
Cyproheptadine (Periactin)	Children with migraines	Hypersensitivity MAOIs Angle-closure glaucoma Stenosing peptic ulcer Symptomatic prostatic hypertrophy Bladder neck obstruction Elderly, debilitated patients

Agent	*Relative indications*	*Relative contraindications*
Methysergide (Sansert)	Cluster headache	Pregnancy Peripheral vascular disease Severe arteriosclerosis Severe hypertension Coronary artery disease Valvular heart disease Phlebitis or cellulitis of the lower limbs Pulmonary disease Collagen diseases or fibrotic processes Impaired liver or renal function Serious infections
Phenelzine (Nardil)	Depression, especially atypical or "neurotic" depression Panic disorder	Known hypersensitivity Pheochromocytoma Congestive heart failure History of liver disease Use of sympathomimetic agents (e.g., asthma) Noncompliance (avoid use in patients unwilling or unable to adhere to food and drug restrictions)

NSAIDs = nonsteroidal anti-inflammatory drugs; GI = gastrointestinal; MAOI = monoamine oxidase inhibitors

NSAIDs may be reasonably safe for young healthy patients with migraine. Daily dosing with NSAIDs during the week before and through one week after menses is particularly effective in women with menstrual migraine.[27-29] NSAIDs pose a higher risk in older patients or patients with peptic ulcer disease, hepatic cirrhosis or impaired renal function.

Amitriptyline (Elavil) is the only antidepressant to have established efficacy in migraine prophylaxis, although others are sometimes used (e.g., nortriptyline, fluoxetine). Amitriptyline is effective in reducing the severity, frequency, and duration of migraine.[25,30] The antimigraine effect can often be achieved with lower dosages than are required to achieve an antidepressant effect. In many patients, migraines can be prevented effectively at a dosage of 50 mg per day; some patients require dosages between 150 and 175 mg.

Calcium channel blockers such as verapamil (Calan, Isoptin) or diltiazem (Cardizem) are usually used for migraine prevention only after trials of the more effective trials of beta blockers or amitriptyline.

Divalproex sodium (Depakote) is the most recent drug to receive FDA approval for migraine prophylaxis. Efficacy in preventing migraine headache may be obtained with divalproex sodium serum concentrations less than the usual therapeutic range for seizure prophylaxis of 50 to 100 μg per ml. Patients who have a partial response may benefit from an increase in dosage; however, if no response occurs at low dosages, there seems to be little benefit from dosage escalation.[31]

Selective serotonin reuptake inhibitors (SSRIs) have not been endorsed by the International Headache Society as treatment for migraine, but some headache experts use these agents. In the absence of significant depression, they are less effective than tricyclics for the treatment of headaches in clinical practice.[38] SSRIs should not be considered as first- or second-choice medications for migraine prophylaxis because evidence of antimigraine efficacy is insufficient.[39,40]

Methysergide can cause fibrotic syndromes and peripheral vascular complications that relegate its use to a "last resort" for patients with severe migraines uncontrolled by other preventive therapies.

Monoamine oxidase inhibitors (MAOIs) such as phenelzine (Nardil) are used for treatment in refractory patients.[38] Insomnia and orthostatic hypotension are common problems. Life-threatening reactions can occur with MAOIs if patients ingest foods high in tyramine or certain drugs such as SSRIs, sympathomimetics, buspirone, bupropion, meperidine, etc. MAOIs should only be prescribed by clinicians familiar with their pharmacokinetics, contraindications, precautions and adverse effects.

Unless the situation is desperate or urgent, simpler agents should be tried before using potentially harmful agents such as methysergide and phenelzine.

Table 11 summarize the recommendations on preventive migraine treatment made by U.S. Headache Consortium and AAFP/ACP-ASIM.

Tablet 11. Summary of U.S. Headache Consortium Recommendations Compared with AAFP/ACP-ASIM Recommendation on Preventive Migraine Treatment.

U.S. Headache Consortium Recommendations	
Recommended agents found to have medium to high efficacy and mild or infrequent side effects:	Amitriptyline Divalproex sodium Propranolol Timolol
Recommended agents found to have medium to high efficacy but with side effect concerns:	Methysergide Time-release DHE
Recommended agents based on consensus and clinical experience:	Cyprohetadine Buproprion Diltiazem Doxepin Fluvoxamine Ibuprofen Imipramine Mirtazepine Nortriptyline Paroxetine Protriptyline
AAFP/ACP-ASIM Recommendations	
Recommended first line agents	Propranolol (80-240mg/d) Timolol (20-30mg/d) Amitriptyline (30-150mg/d) Divalproex sodium (500-1500mg/d) Sodium valproate (800-1500mg/d)
Other medications proven efficacy but limited published data on adverse events, or frequent or severe adverse events:	Time-release DHE Methysergide

Adapted from U.S. Headache Consortium: Matchar DB, Young WB, Rosenberg JH, Pietrzak MP, Silberstein SD, Lipton RB, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. 2000. Accessed at www.aan.com/professionals/practice/guidelines.cfm.
Ramadan NM, Silbertsein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2000. Accessed at www.aan.com/professionals/practice/guidelines.cfm.
AAFP/ACP-ASIM Recommendations: Snow V, Weiss K, Wall EM, Mottur-Pilson C. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med*. 2002;137:840-849

Discontinuation of Preventive Agents

Migraine attack frequency and severity vary considerably over time. Use of preventive agents is often begun when attack frequency is greatest. Improvement following initiation of preventive therapy may be due to normal variations in headache frequency, nonspecific effects of treatment or a specific pharmacologic effect. If attack frequency and severity have been reduced to such a level that preventive medication is not indicated (i.e., two or less attacks per month without significant clinical disability), preventive medications can be gradually withdrawn.[7]

Refractory Migraine Headaches

A small minority of patients will not respond to standard preventive therapy. Some patients may respond to specific antimigraine abortive agents such as sumatriptan and dihydroergotamine but not to any of the usual preventive agents. A small percentage of patients with migraine may only respond to narcotic agents, but this response is unusual and should be a “red flag” to the physician. Physicians may wish to refer such patients to a headache specialist for confirmation of diagnosis and psychologic assessment. Major causes of refractory headaches are listed in Table 10.[19,21,42]

Table 10. Refractory Headache – Causative and Contributory Factors

Diagnostic error
Comorbid medical disease that precludes use of antimigraine drugs or aggravates migraine
Drug-related
Rebound headache caused by daily or near-daily use of abortive migraine medications (most common factor in patients referred to tertiary headache clinics)
Patients noncompliance
Concurrent medications (e.g., nitrates)
Substance abuse
DSM-IV disorders
Axis I disorder (e.g., depression, anxiety disorder)
Axis II disorder (especially borderline personality disorder)
Somatization disorder
Dysfunctional and abusive relationships
Child abuse
Spousal abuse
Sexual harassment or assault at work or home
Disability- or compensation-related (e.g., some cases of migraine following minor trauma)

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, D.C.: American Psychiatric Assoc., 1995

Failure with three or more successive prophylactic drugs is unusual and such a patient may benefit from consultation with a specialist experienced in the evaluation and treatment of refractory headache patients. Refractoriness may occur in the absence of any medical or psychiatric disorder. However, a contributing psychopathology is often concomitant, and an early assessment can be useful.[43]

Clinical Indications for Referral[44]

- Diagnosis is unclear
- Unsatisfactory response to treatment

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