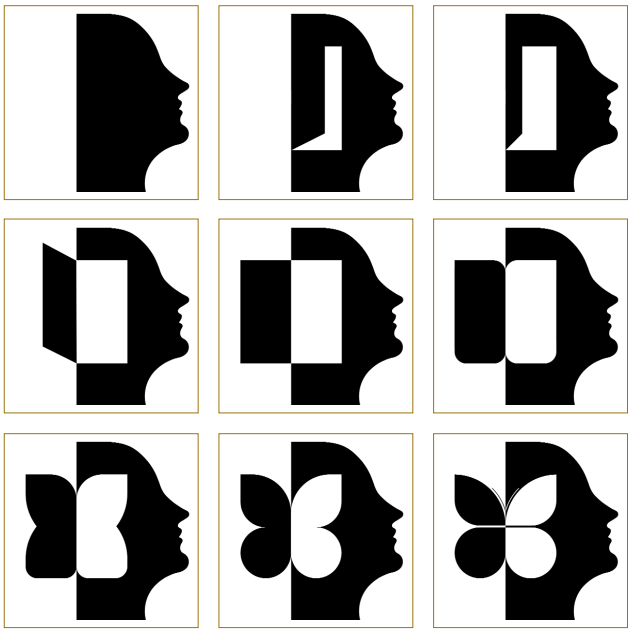
ADVANCES IN MIGRAINE PROPHYLAXIS

Current State of the Art and Future Prospects



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Needs Assessment

Many of the 28 million Americans with migraine are potential candidates for migraine prophylaxis. The decision to initiate prophylaxis is based on a variety of often complex factors involving the nature of the patient's headaches, the degree of migraine-related disability, and the presence of comorbidities. The clinician is also faced with an increasing number of medications for migraine prophylaxis; these agents often differ widely in the quality of evidence supporting their relative efficacy and tolerability. For these reasons, there is a need to update practicing physicians on the general principles of migraine prophylaxis, the available treatment options, and the issues, such as rebound headache, that may complicate therapy.

Intended Audience

This activity is intended for primary care and other physicians who treat patients with migraine headache.

Method of Participation

The information is presented in a monograph and audiotape. The reader's knowledge is tested by the CME quiz. It is anticipated to take 1 hour to complete the activity.

Educational Objectives

After listening to the audiotape and reading this monograph, participants in this activity should be better able to:

- Describe and evaluate the theory, practice, and goals of migraine prophylactic therapy
- Identify appropriate candidates for migraine prophylaxis
- Compare the characteristics of currently available prophylactic agents
- Describe promising new prophylactic agents
- Diagnose and treat migraine patients with confidence

Evaluation

An evaluation form will provide the participants with the opportunity to review the activity content and method of delivery, and to help identify future educational needs and any possible bias in the monograph.

Faculty Disclosure

David Dodick, MD:
Speaker, consultant, and/or advisory board member: GlaxoSmithKline, AstraZeneca, Merck US Human Health, Abbott, Pharmacia, and Ortho-McNeil.

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Alexander Mauskop, MD:
Research support: Allergan. Consultant: Natural Science Corporation of America. Speaker's Bureau: Allergan. Advisory Board: Allergan and Ortho-McNeil.

Professional Credit

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Finch University of Health Sciences/The Chicago Medical School and the National Headache Foundation. Finch University of Health Sciences/The Chicago Medical School is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Finch University of Health Sciences/ The Chicago Medical School certifies that this continuing medical education activity meets the requirements for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Finch University of Health Sciences/The Chicago Medical School is solely responsible for the content of this continuing medical education activity. This educational activity was planned and produced in accordance with the ACCME essentials and standards. This activity expires on July 31, 2003.

National Headache Foundation

The National Headache Foundation (NHF) is a non-profit organization established in 1970 to provide services to headache sufferers, their families and the healthcare professionals who treat them. Physician membership in the NHF provides the following benefits: *Standards of Care for the Diagnosis and Treatment of Headache,* the *Therapeutic Guide for the Treatment of Headache*, copies of ***NHF Head Lines***, our award-winning bimonthly newsletter, patient education information, inclusion on the NHF physician membership list (if desired), listing in the NHF professional membership directory, opportunities to speak at public education seminars in your area, details on grants available through NHF, discounts on audio and videotapes, toll-free access to the NHF office, information via our web site, assistance in organizing local support groups, and more. Take advantage of all these great membership benefits for only $100 a year. To join as a professional member or learn more about the services we offer call 888-NHF-5552 or visit our web site at *www.headaches.org*.

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This Continuing Medical Education monograph is a companion piece to an audiotape of a roundtable discussion held January 19, 2001 in Bal Harbour, Florida.

When to Choose Migraine Prophylaxis

Migraine is a common, disabling, inherited malfunction of the pain-regulating mechanism of the brain; it afflicts as many as 28 million Americans.[1] Fortunately, the treatment of this disorder has advanced dramatically in recent years, with new drugs available for both acute treatment and prophylaxis.

The primary goal of migraine prophylaxis is to restore functionality, so the decision to initiate prophylaxis should be based in part on the degree of migraine-related functional impairment. If a patient experiences numerous incapacitating attacks per month, the clinician should consider the possibility of initiating prophylactic therapy rather than allowing the patient to rely on the frequent use of abortive medications. In general, prophylaxis should be considered if attacks occur more frequently than twice per week, if the severity or duration of attacks justifies prophylaxis, if acute medications are ineffective or contraindicated, or if there is a need to enhance the efficacy of symptomatic medications.[2]

Thus, while migraine frequency is a major factor in selecting candidates for prophylactic therapy, other factors should also be considered (Table 1). If, for example, patients lose three or more days of work or school per month because they are incapacitated by migraine, then prophylaxis is a reasonable option. The willingness and ability of the patient to comply with a daily medication regimen is an obvious factor. One of the principal criteria for choosing the option of migraine prophylaxis is simply how well acute treatment is working. Certainly, if acute medications are incompletely effective or contraindicated, then prophylactic medications should be considered. If a patient is taking a large amount of acute medications to abort frequent migraines, he or she may be at risk for analgesic rebound headaches and prophylaxis may be a preferable alternative. Migraine patients with comorbid disorders, such as depression, anxiety disorders, severe symptomatic auras, or epilepsy may also be appropriate candidates for daily prophylactic medication. Patients at risk for migrainous infarction might also be added to this list. Migrainous infarction is the result of migraine-related cerebral ischemia, which is characterized by weakness, numbness, speech difficulty, and/or visual field defects. Finally, the patient's wishes must also be taken into account. Is the patient content with acute therapies or does she want to limit her exposure to migraine attacks?

TABLE 1

CRITERIA FOR CONSIDERING MIGRAINE PROPHYLAXIS

- Headache frequency
- Degree and frequency of migraine-related disability
- Amount of prescription and OTC abortive medications used by patient
- Presence of concomitant disorders (e.g., depression)
- Willingness and ability of patient to comply with daily medication regimen
- Success or failure of nondrug prophylactic therapies

Although headache frequency is usually the primary criterion for choosing migraine prophylaxis, it should be noted that many patients have very inaccurate ideas about the frequency of their own headaches, as well as the amount of medication they use to treat their headaches. For this reason, a headache diary may be particularly useful. A diary enables patients to develop an accurate record about how many headaches they actually have, when they occur, what triggers them and what they do to relieve them. This record can subsequently be used as the basis for treatment decisions. Diaries are also useful for revealing patterns of medication intake. For example, a patient may initially report having only two headaches during the previous month, but a diary might reveal that he took 50 butalbital/caffeine/aspirin during that period. The diary reveals that what is occurring is a pattern of daily headaches aborted by medication, with two occasions of breakthrough headaches. However, the patient regards "headache days" only as days when he is incapacitated by headache, not days when headaches are aborted by butalbital. This patient is clearly a candidate for prophylaxis, both as a function of headache frequency and analgesic overuse.

Menstrual migraine presents a special category of candidates for prophylaxis. Since many of these patients can predict when headaches are likely to occur, they often take prophylactic measures on their own, with varying degrees of success. Some clinicans employ cyclic prophylaxis in these patients, prescribing either abortive or prophylactic medications for a specific, limited number of days per month to prevent perimenstrual migraine attacks.[3,4]

In summary, when considering whether to initiate migraine prophylaxis, it is important to employ an individualized, rather than a "cookbook" approach, based on a variety of factors.

Addressing Patient Expectations

Once the decision to initiate prophylaxis has been made, patients must be educated about the nature and goals of prophylactic therapy. Patient expectations should be addressed. They need to understand that complete freedom from headaches is not a generally attainable goal with currently available prophylactic agents. A review of published studies showed that none of the most popular prophylactic medications demonstrated an efficacy over placebo ≥ 50%. The authors note that this may not be satisfactory for patients with four or more migraine attacks per month.[5] For this reason, patients should be provided with multiple levels of defense, including adequate abortive medications to treat breakthrough headaches and, in appropriate patients, rescue medications as a third line of defense. One of the primary goals of providing patients with rescue medications to use at home is to keep them out of hospital emergency departments. Emergency-department treatment of headache is not cost-effective; in many states it costs $400-$600 simply to sign in to an emergency department, even before a treating physician is seen. Hospital emergency rooms are also bright, busy, and noisy places — environments that tend to exacerbate migraine symptoms.

Patients also need to understand that all of the current prophylactic agents are associated with side effects, but that many of these effects diminish over time (the nausea associated with valproate is a common example). Many of the medications employed for migraine prophylaxis are associated with weight gain and patients should be counseled to deal with this possibility. Amitriptyline, nortriptyline, cyproheptadine, and valproate are particular offenders in this regard. Weight gain, however, does not appear to be associated with Depakote ER, a new extended-release formulation of valproate approved for migraine prophylaxis.

Patients also need to be counseled that some prophylactic medications may take weeks or even months before they are fully effective. Some patients may need additional abortive medications to ease the transition from abortive to prophylactic therapy.

Many patients have the mistaken idea that prophylaxis will last indefinitely, perhaps even for the rest of their lives. They need to understand that the goal of prophylaxis is to stabilize the migraine mechanism; once the patient responds and the patient is headache-free for several months to a year, the drug may be withdrawn. In many cases, patients will remain headache-free for an extended period, a phenomenon that suggests that prophylaxis may favorably alter the natural history of migraine.[6] Other patients who have been withdrawn from prophylaxis may need to have prophylaxis reinstated at some point in the future.

Analgesic Rebound Headaches

One of the most important discoveries in headache management in recent years is analgesic dependency. This phenomenon occurs when the daily use of analgesics renders the headache mechanism dependent upon a continuous supply of analgesic medications. The rebound cycle typically begins with the patient's habit of taking an analgesic at the first sign that a headache is imminent. The patient is soon consuming immediate-relief medications on a daily basis. Eventually, falling analgesic blood levels trigger a rebound headache, which leads in turn to the ingestions of more analgesics. The patient assumes that her headaches are under control, but she has actually established a pattern of chronic, refractory, daily headache. The result is a pharmacologically maintained headache. Rebound headaches can occur with both acute and rescue medications, including triptans, opioids, benzodiazepines, ergotamine, aspirin, acetaminophen, other NSAIDs, and dietary caffeine.[7-9] Drugs most likely to cause rebound are combination drugs, such as butalbital/aspirin/caffeine.

The presence, or even the risk, of rebound headache has important implications for therapy. If a patient is taking a large amount of acute medications to abort frequent migraines, he or she may be at risk for rebound headaches and prophylaxis may be a desirable alternative. On the other hand, if a physician attempts to implement prophylactic therapy while the patient is experiencing analgesic rebound headaches, he or she is unlikely to benefit unless the offending medications are withdrawn. Sudden withdrawal of the medications is likely to result in a severe, disabling headache, so the patient must be gradually weaned over a period of several days to a week. Patients dependent on daily ergotamine may need to be hospitalized during drug withdrawal and given sedatives, intravenous fluids and possibly a narcotic analgesic. Patients consuming large amounts of butalbital need to be withdrawn slowly or placed on phenobarbital for a short period to prevent withdrawal seizures. Table 2 outlines a possible strategy for implementing migraine prophylaxis in patients with rebound headaches.

TABLE 2

STRATEGY FOR IMPLEMENTING MIGRAINE PROPHYLAXIS IN PATIENTS WITH REBOUND HEADACHES

1. Initiate prophylactic agent and increase dose to therapeutic levels over a period of 4 to 6 weeks.

2. After therapeutic blood levels are reached, patients are instructed to stop analgesics for a one-week period. (Patients should be educated about what to expect and should make plans for sick leave, child care, etc.)

3. During analgesic holiday, patients should be provided with medical support for acute headaches: SC sumatriptan, DHE 45, and chlorpromazine (for sedation and prevention of nausea).

Pharmacological Options for Migraine Prophylaxis

There is a wide variety of agents available for migraine prophylaxis, although only four have received FDA approval: propranolol (Inderal®), timolol (Blocadren®), methysergide (Sansert®), and divalproex sodium (Depakote®). These drugs, and amitriptyline, have the strongest evidence for efficacy in migraine prophylaxis.[10] Table 3 lists these medications along with others that have evidence of efficacy in migraine prophylaxis. This list is not exhaustive; the faculty of the current program employ several additional drugs, including imipramine, protriptyline, nefazodone, trazodone, venlafaxine, topiramate, gabapentin, and magnesium.

Any one of the listed agents may be effective in a given patient; selection should be based on the patient profile, comorbidities, the drug's side effect profile, drug cost, and the physician's comfort level with the agent. For example, beta blockers should not be used in patients with asthma, diabetes, depression, cardiac conduction defects, or low blood pressure. Divalproex sodium may be the agent of choice in patients with cardiac disease or seizures, because it has no cardiac adverse effects and is a broad-spectrum antiepilepsy drug. Tricyclic antidepressants may be particularly useful in migraine patients with concomitant depression. Patients who don't want to take, or can't comply with, a daily medication may be candidates for botulinum toxin.

Some prophylactic medications may take weeks or even months before they are fully effective.

TABLE 3

ORAL PROPHYLACTIC MEDICATIONS FOR MIGRAINE

DRUG	DAILY ORAL DOSAGE RANGE (mg)	MAJOR SIDE EFFECTS
BETA BLOCKERS		
Propranolol*	40 - 240	Fatigue, depression, weight gain, edema, dizziness, memory disturbances, hallucinations, GI complaints, decreased excercise tolerance, bradycardia, impotence
Nadolol	40 - 160	
Atenolol	50 - 100	
Timolol*	20 - 60	
Metoprolol	50 - 200	
CALCIUM CHANNEL BLOCKER		
Verapamil	120 - 480	Constipation, hypotension, dizziness
H_2 BLOCKER/ SEROTONIN ANTAGONIST		
Cyproheptadine	8 - 16	Weight gain, sedation, urinary retention
SEROTONIN ANTAGONIST/PARTIAL AGONIST		
Methysergide*	4 - 8	Fibrotic changes, edema, hallucinations, vasoconstriction, cramping
ANTIDEPRESSANTS		
Tricyclics		
Amitripyline	10 - 200	Dry mouth, dry eyes, constipation, weight gain, fatigue, urinary retention
Nortriptyline	10 - 150	
Selective Serotonin-Reuptake Inhibitors		
Fluoxetine	20 - 80	GI complaints, tremor, dizziness, insomnia, male sexual dysfunction
Sertraline	50 - 150	
MAO Inhibitor		
Phenelzine	30 - 90	Dietary precautions, hypotension, nausea, weight gain, edema, hepatotoxicity
Isocarboxid	30 - 40	
ANTICONVULSANT		
Divalproex sodium*	250 - 2000	GI disturbances, sedation, tremor, hepatotoxicity, transient hair loss, weight gain, asthenia (Depakote ER is not associated with weight gain or hair loss.)
Depakote ER*	1000	
NONSYSTEMIC PROPHYLACTIC MEDICATIONS		
Botulinum toxin type A	50 - 200 U injected into the glabellar, temporal, frontal and/or suboccipital regions of the head and neck	Injection-site discomfort, muscle weakness, diffuse skin rash

* Approved by the FDA for migraine prophylaxis. Source: package inserts for each drug

On the Horizon: A new Prophylactic Option

Botulinum Toxin Type A (BOTOX®) is currently indicated for the treatment of strabismus, blepharospasm, and cervical dystonia. There have been several promising recent studies of botulinum toxin in the treatment of tension-type headaches[11-16] and the prophylaxis of migraine.[17,18] In addition to early reports of efficacy in migraine prophylaxis, there are several attributes of the agent that patients find attractive. First, the efficacy and tolerability of traditional agents is limited and patients frequently seek better alternatives. Most traditional therapies are only modestly effective as preventive agents; a 50% reduction in headaches for 50% of patients is the general criterion for efficacy. The side effects of traditional agents are also difficult for many patients to tolerate; weight gain, sedation, and constipation may be considered "nuisance" side effects, but they're not trivial for patients who live with them every day. Furthermore, many patients don't like the idea of taking systemic medications over a long time period; a medication that appears to act nonsystemically is very appealing. In fact, the mechanism of action of botulinum toxin is unknown and currently under investigation. The program faculty speculated that its action is primarily peripheral. Botulinum toxin relaxes muscles, which blocks a pain feedback mechanism from the affected muscle to the brain.

Patients should be educated to have reasonable expectations from their prophylactic medications.

The efficacy of botulinum toxin type A was assessed in a double-blind, vehicle-controlled study of 123 subjects with a history of two to eight moderate-to-severe migraine attacks per month, with or without aura.[17] Subjects were randomized to receive either vehicle or total doses of botulinum toxin type A, 25 U or 75 U, injected into multiple sites of pericranial muscles at the same visit. During a one-month baseline period and for three months following injection, subjects kept daily diaries in which they recorded migraine frequency, migraine severity, and the occurrence of migraine-related symptoms.

The results showed that patients receiving botulinum toxin type A had significantly fewer migraine attacks per month, a reduced maximum severity of migraine, a reduced number of days using acute medications, and a reduced incidence of migraine-related vomiting. Both the 25-U and 75-U treatment groups were significantly better than the vehicle group on global assessments by the subjects. The treatment was well tolerated; only the 75-U group had a significantly higher rate of adverse events than the group receiving vehicle.

Botulinum toxin type A was further investigated in an open-label study of 106 patients at four sites.[18] These patients, who were predominantly female, either sought treatment with botulinum toxin for hyperfunctional facial lines or other dystonias with concomitant headache disorders, or were candidates for treatment with botulinum toxin specifically for headaches. Botulinum toxin was injected into the glabellar, temporal, frontal, and/or suboccipital regions of the head and neck. Main outcome measures were determined by reduction in headache severity and duration of response. The degrees of response were classified as (1) complete (no symptoms), (2) partial ≥ 50% reduction in headache frequency or severity, and (3) no response. Duration of response was measured in months for the prophylactic group. Among the 77 patients in this study who were diagnosed with true migraine and were treated prophylactically, 51% reported a complete response, with a mean response duration of 4.1 months; and 38% reported a partial response, with a mean response duration of 2.7 months. Overall improvement was independent of baseline headache characteristics. Of the 10 patients with true migraine who were treated acutely, seven reported a complete response, with improvement one to two hours after treatment. No adverse effects were reported. The authors conclude that, based on this study, botulinum toxin may be safe and effective for both acute and prophylactic treatment of migraine and that further research is needed to explore the therapeutic potential of the neuroinhibitory effects of this agent.

Some of the faculty of this program have successfully used botulinum toxin type A in their practices for several years, with a success rate of approximately 70% when treating patients outside of controlled trials. The placebo effect can be a major contributor to this high success rate, although many patients have remained responsive after repeated injections.

General Principles of Migraine Prophylaxis

Under the auspices of the American Academy of Neurology, the US Headache Consortium has recently published guidelines for the management of headache in the primary care setting, including a consensus on principles of care for the prevention of migraine.[10] The information in this section is based on the Consortium's recommendations.

Therapy for migraine prophylaxis should be initiated with the lowest effective dose of the selected agent, with the dose being increased slowly until benefits are observed in the absence of adverse events or until limited by adverse events. Each treatment should be given an adequate trial, since two to three months may be required for a clinical benefit to become apparent. During this period, patients should be counseled to avoid overusing acute medications; these may interfere with the effectiveness of the prophylactic medication.

As with any daily medication, the degree of patient compliance can have an important impact on patient outcomes. Long-acting formulations may improve compliance. Patients should understand the rationale for their particular therapy, know how to use it, and know what adverse events may occur. As noted above, patients also should be educated to have reasonable expectations from their prophylactic medications and understand that it may take several months to achieve their full benefit.

The Consortium was particularly enthusiastic about the usefulness of headache diaries. They should be designed to be user-friendly and to record information about attack frequency, severity, duration, degree of disability, response to treatment, and adverse effects of medications.

The clinician should also take into account the presence of comorbid disorders. Stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders are more common in migraineurs than in the general population. Comorbid disorders present both an opportunity (some drugs may treat both disorders) and a limitation (some drugs may treat one disorder while exacerbating the other). Finally, several of the prophylactic medications may have teratogenic effects. In women who are pregnant or may become pregnant, a medication should be selected with the lowest risk of harm to the fetus.

TABLE 4

BOTULINUM TOXIN FOR HEADACHE: CLINICAL SUMMARY

Note: botulinum toxin is not yet approved for use in headache. The following information does not necessarily represent the views of the National Headache Foundation.

POTENTIAL INDICATIONS:

- Frequent and/or disabling migraines
- Chronic tension headaches
- Rebound headaches
- Headaches with associated jaw or neck and shoulder muscle spasm

INJECTION TECHNIQUE:*

Dilution: 100 units in 4 mL of preservative-free normal saline (avoid agitation and bubbling while diluting by slow infusion of saline). Absence of vacuum indicates a defective vial.

Syringes and needles: 30-gauge, 1-inch needle and a tuberculine syringe.

Selection of injection sites: Depending on the distribution of typical headache pain and, on palpation, presence of tenderness or muscle spasm, the following sites are usually selected: four to six into frontalis muscle, five into glabellar/procerus, one to three into one or both temporalis, one or two into each masseter, one into one or both splenius capiti, occipitalis, semispinalis, one to three into trapezii, paraspinal cervical and, less often, into sternocleidomastoid, levator scapulae, rhomboids and supraspinatus.

Dose: The average dose is 100 units, although some patients (those with extensive areas of associated muscle spasm) may need up to 200 units. Other patients, with pain strictly limited to frontal or one temporal area without associated tenderness or spasm elsewhere, may need only 50 units.

POTENTIAL SIDE EFFECTS AND COMPLICATIONS:

Side effects and complications are rare and none is permanent.

Ptosis – usually can be avoided by injecting at least 1 cm above the eyebrow, although procerus and glabellar muscles medially can be safely injected closer to the eyebrow.

Neck weakness – difficulty holding up the head can occur from injecting as little as 50 units into paraspinal cervical, splenius and semispinalis muscles.

Bruising – rare with the use of a 30-gauge needle.

Headache – can occur from needling, especially in anxious patients during the first treatment.

Neck pain – some patients develop worsening of their neck muscle spasms following injections, both acutely, probably due to needling effect and sometimes for longer periods (1-2 weeks), possibly due to an insufficient dose of botulinum toxin.

Vaso-vagal response – can occur as with any other needling.

* The technique described above is recommended by Chairman, Dr. Mauskop, and does not represent the only possible technique. Before using botulinum toxin, the clinician should become familiarized with injection techniques, injection sites, and the potential adverse effects of botulinum toxin.

The question of when primary care physicians should refer a patient to a specialist is especially important in the field of headache. When headache patients are inappropriately managed for long periods, they often spiral into a chronic pain syndrome, the treatment of which requires intensive management, a specialized environment, and considerable resources. While the majority of headache patients can be adequately managed in primary care, difficult or refractory patients should be referred to specialized headache centers.

Conclusions

For many years, migraine prophylaxis had been plagued by the absence of a scientific underpinning, but today the mechanisms of headache and headache medications have become increasingly well understood. Today, the practicing physician generally has both the knowledge and the resources for effective prophylactic therapy in the vast majority of patients.

Nevertheless, there remain significant gaps in our knowledge. The US Headache Consortium has identified several specific areas in migraine prevention where more research is needed.[10] Many potentially useful drugs are still in need of randomized, controlled trials to confirm their efficacy and tolerability. Effective combination therapies for migraine prophylaxis need to be identified and studied in controlled trials. Furthermore, the ideal duration of preventive therapy has yet to be specified, as well as predictors of remission or response to treatment. Finally, there is a need to develop stepped care or other treatment strategies for particular types of migraine headache or particular subgroups of migraine patients.[10]

REFERENCES 1. Lipton RB, Stewart WF, Simon D. Medical consultation for migraine: results from the American Migraine Study. *Headache.* 1999:87-96. 2. Mathew NT. Abortive vs. prophylactic treatment of migraine: a reappraisal. *Headache.* 1990;30:238-239. 3. Raskin NH. *Headache.* 2nd ed. New York: Churchill Livingston, 1988. 4. The American Council for Headache Education. *Migraine: The Complete Guide.* New York: Dell Publishing, 1994. 5. Ramadan NM, Schultz LL, Gilkey SJ. Migraine prophylactic drugs: proof of efficacy, utilization, and cost. *Cephalalgia.* 1997;17:73-80. 6. Raskin NH. Acute and prophylactic treatment of migraine. *Neurology.* 1993;43(Suppl 3):S39-S42. 7. Kaube H, May A, Diener HC, et al. Sumatriptan misuse in daily chronic headache. *Brit Med J.* 1994;308:1573-1574. 8. Limmroth V, Kazaraw S, Fritsche G, et al. Headache after frequent use of new serotonin agonists zolmitriptan and naratriptan. *Lancet.* 1999;353:378. 9. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. *Headache.* 1987;27:102-106. 10. Ramadan NM, Silberstein SD, Freitag FG, and the US Headache Consortium. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2001;www.aan.com. 11. Wheeler AH. Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. *Headache.* 1998;38(6):468-471. 12. Schulte-Mattler WJ, Weiser T, Zierz S. Treatment of tension-type headache with botulinum toxin: a pilot study. *Eur J Med Res.* 1999;4(5):183-186. 13. Rollnik JD, Tanneberger O, Schubert M, et al. Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. *Headache.* 2000;40(4):300-305. 14. Zwart JA, Bovim G, Sand T, et al. Tension headache: botulinum toxin paralysis of temporal muscles. *Headache.* 1994;34(8):458-462. 15. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. *Headache.* 2000;40(3):231-236. 16. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of tension-type headache. *Curr Rev Pain.* 2000;4(1):31-35. 17. Silberstein S, Mathew NT, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. *Headache.* 2000; 40(6): 445-450. 18. Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. *Otolaryngol Head Neck Surg.* 2000;123(6):669-676.

Eight correct answers are required for successful completion

1. How many Americans suffer from migraine?

- ☐ A. 15 million
- ☐ B. 28 million
- ☐ C. 40-45 million

2. Which of the following are criteria for considering migraine prophylaxis?

- ☐ A. If the patient uses abortive medications very frequently
- ☐ B. If migraine attacks occur more frequently than twice per week
- ☐ C. If the patient is at risk for rebound headaches
- ☐ D. All of the above
- ☐ E. A. and B. above

3. The decision to initiate migraine prophylaxis should be based in part on the degree of migraine-related functional impairment.

- ☐ A. True ☐ B. False

4. Which of the following medications for migraine prophylaxis is (are) associated with weight gain?

- ☐ A. Valproate
- ☐ B. Cyproheptadine
- ☐ C. Nortriptyline
- ☐ D. Amitriptyline
- ☐ E. All of the above
- ☐ F. A. and D. above

5. Rebound headaches have not been asociated with triptan use.

- ☐ A. True ☐ B. False

6. Which of the following drugs have received FDA approval for migraine prophylaxis?

- ☐ A. Propranolol
- ☐ B. Timolol
- ☐ C. Methysergide
- ☐ D. Divalproex sodium
- ☐ E. Amitriptyline
- ☐ F. All of the above
- ☐ G. A., B., C., and D. above

7. Which of the following are good candidates for migraine prophylaxis with beta blockers?

- ☐ A. Patients with low blood pressure
- ☐ B. Patients with cardiac conduction defects
- ☐ C. Patients with diabetes
- ☐ D. Patients with asthma
- ☐ E. All of the above
- ☐ F. None of the above

8. Divalproex sodium might be a good choice for migraine prophylaxis in patients with cardiac disease.

- ☐ A. True ☐ B. False

9. Botulinum toxin might be a good choice for migraine prophylaxis in patients who cannot comply with a daily medication regimen.

- ☐ A. True ☐ B. False

10. In an open-label study of botulinum toxin, the mean duration of response among patients with a complete response to the agent was:

- ☐ A. 2.7 months
- ☐ B. 3.8 months
- ☐ C. 4.1 months

11. Which of the following is considered to be an adequate trial of a migraine prophylactic drug?

- ☐ A. Two to three weeks
- ☐ B. Two to three months
- ☐ C. Six months

12. Many potentially useful drugs for migraine prophylaxis do not have adequate proof of efficacy from randomized, controlled trials.

- ☐ A. True ☐ B. False

Post-Test Answers

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Activity Evaluation

To earn one (1) hour of Category 1 CME credit after reading this monograph and listening to the audiotape, please send the completed post-test answers, activity evaluation, and personal information questionnaire to Finch University of Health Sciences/The Chicago Medical School in the enclosed envelope.

Separate this form along perforation, fold, and mail in the enclosed envelope.

Post-Test Answers

Circle the appropriate letter for each question.

1. A B C 2. A B C D E 3. A B
4. A B C D E F 5. A B 6. A B C D E F G
7. A B C D E F 8. A B 9. A B 10. A B C
11. A B C 12. A B

Activity Evaluation

Strongly Agree Strongly Disagree

1 2 3 4 5

1. This activity helped to increase my knowledge base.

1 2 3 4 5

2. This activity gave me new information that will influence how I practice.

1 2 3 4 5

3. The technical quality of the activity was good.

1 2 3 4 5

4. The activity met its objectives.

1 2 3 4 5

5. I would recommend this activity to my peers.

1 2 3 4 5

6. There was no significant commercial bias in the activity.

1 2 3 4 5

Comments _____

Personal Information

Name/degree (please print) _____

Address

City State Zip

Telephone

Social Security number

Medical Education (ME) number

I have read the monograph, listened to the audiotape, and completed the post-test and activity evaluation.

Signature

Date