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MIGRAINE: MANAGEMENT

Chapter 47

General and Pharmacologic Approach to Migraine Management

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DOCTOR–PATIENT RELATIONSHIP

The first step in the successful management of migraine is to develop a good doctor–patient relationship that results in confidence on the part of the patient. Patients trust physicians more when the physician demonstrates an interest in the patient's symptoms and overall well-being. Patients appreciate an explanation of their illness by the physician. Good management of headache results from a partnership between doctor and patients.

HEADACHE DIARY

Patients should be encouraged to keep a headache diary, which should include the frequency, severity, duration, associated symptoms, and medications they are taking. Triggers for each attack, if identifiable, also should be recorded. During each follow-up visit, the diary should be checked and appropriate instruction given.

REALISTIC EXPECTATIONS

Physicians should encourage the patient to develop realistic expectations of the treatment of chronic migraine. It is important to explain that migraine is a recurrent disorder and that there is no total cure; the best that can be done is to keep the headaches under some control with abortive as well as preventive medications. Unrealistic expectations usually lead to therapeutic failure. It is natural for the physician to become frustrated when dealing with chronic conditions such as migraine, but it is important the physician not communicate that frustration to the patient. Expressions of encouragement and hope are important therapeutic strategies.

EDUCATION

Patient education is extremely important. The clinician may wish to provide the patient with educational materials on headache disorders, which include clinical presentations, triggers, biologic aspects, and myths about headaches.

One of the major myths is the so-called sinus headache as a common cause of recurrent headache. Any headache that is frontal or periorbital, brought on by weather changes, and relieved by analgesic plus decongestants are mistakenly diagnosed as sinus, even in the presence of a long history of episodic headache, family history, and migrainous features. This myth leads to delay in diagnosis, improper and ineffective treatment, and prolongs disability.

Good educational materials should encourage the patient to seek help, taking advantage of modern treatments available for these conditions. It is easier to treat a well-informed patient over the long term; education leads to cost-effective management of headache, avoiding unnecessary doctor visits, emergency room visits, and tests.

BIOLOGIC NATURE OF MIGRAINE WITH EMPHASIS ON TRIGGERS

Migraine is a disorder of the neurovascular system and is a special response of the human brain to both external and internal triggers. This tendency toward peculiar central nervous system response is probably genetically determined. Migraine patients have a lower threshold for triggering migraine attacks than nonmigraineurs. This threshold is influenced by various factors including female hormones, which account for hormone-related fluctuations in headache, such as in menstrual migraine. Other triggers also must be explained to the patient. Patients

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TABLE 47-1 Common Triggers for Migraine

Hormonal	Menstruation, ovulation, oral contraceptive, hormonal replacement
Dietary	Alcohol, nitrite-laden meat, monosodium glutamate, aspartame, chocolate, aged cheese, missing a meal
Psychological	Stress, poststress (weekend or vacation), anxiety, worry, depression
Physical-environmental	Glare, flashing lights, visual stimulation, fluorescent lighting, odors, weather changes, high altitude
Sleep-related	Lack of sleep, excessive sleep
Miscellaneous	Head trauma, physical exertion, fatigue
Drugs	Nitroglycerin, histamine, reserpine, hydralazine, ranitidine, estrogen

should be given a list of common triggers for migraine so that they can avoid headache episodes. Patients should be taught to look for the triggers that initiate their attacks and to record those triggers in their headache diaries. Common triggers are listed in Table 47-1. Clinicians should teach their patients behavioral modifications to avoid triggers. A simple explanation is all that is necessary in the majority of patients, which can be offered even by the busiest practitioner. The importance of regular eating and sleeping habits should be emphasized. Too much and too little sleep can induce headaches, as can missing a meal.

Patients should scrutinize their diets carefully. Special inquiry into caffeine intake and reducing it may reduce the frequency of migraine. The myths about allergy to food should be dispelled by explaining that dietary activators usually cause chemical reactions rather than an allergic response, and that the chemical reaction influences neurotransmitter functions, resulting in a migraine attack. This understanding of food triggers may circumvent the need for consultation with allergists and various expensive and extensive allergy tests with no beneficial outcome.

NONPHARMACOLOGIC TREATMENT STRATEGIES

If stress is identified as a major factor, it is worthwhile to initiate a stress-management program while proceeding with pharmacologic therapy. Pharmacologic therapy alone, without addressing stress factors, may not be adequate treatment. Thus, behavioral and nonpharmacologic treatment should be administered concurrently with pharmacotherapy. For stress management, any form of relaxation exercise, including biofeedback training, is recommended. Physical exercise, relaxing to many patients, also should be encouraged. Exercise improves sleep, reduces weight, and gives the patient an overall sense of well-being. In the majority of patients, simple instructions from the physician about the broad principles of stress management are sufficient; however, in more complex cases, referral to a clinical psychologist or a behavioral therapist is beneficial.

Psychotherapy and psychiatric counseling may become necessary in patients with significant comorbidities such as depression, anxiety, poor coping abilities, and personality disorders. The practitioner usually has to make an assessment over time concerning the need for psychotherapy. The question of psychotherapy should not be introduced to the patient during the first interview because the patient may get the incorrect impression that the physician views the problem as psychological. On the other hand, if the patient suggests the approach, the clinician should follow through.

Other types of nonpharmacologic treatments may be considered, including physiotherapy, particularly with limited stretching of neck muscles. Massage, short-wave diathermy, and hot packs may be beneficial in those patients who have pericranial and neck muscle tenderness with their migraine attacks, or in those patients with tension-type headache in addition to migraine. If the interictal tension-type headache and muscle spasm can be reduced, it may secondarily reduce the migraine attacks as well.

The patient who fails to respond to conventional treatment may resort to alternative medications. The physician must warn the patient about the lack of information about many of the substances, which are often sold in health food stores. Other techniques such as acupuncture and hypnotherapy have not been evaluated in controlled scientific studies. Therefore, the physician may find it difficult to recommend those to the patient. Although individual patients may benefit from some of these alternative modalities, the rationale for use of alternative medicines varies from unknown to, at best, uncertain.

Nonpharmacologic approaches are indicated for every patient with migraine, whether or not they are candidates for pharmacotherapy. But those who have frequent disabling migraine and those with chronic migraine get best results when pharmacologic approaches are combined with nonpharmacologic approaches.

GENERAL PRINCIPLES OF PHARMACOLOGIC TREATMENT OF MIGRAINE

Treatment of migraine begins with making a diagnosis, explaining it to the patient, and developing a treatment plan that takes into account the frequency of migraine episodes, the severity, the disability they cause, general quality of life of the patient, and coincidental or comorbid conditions. Pharmacotherapy can be acute (abortive) or preventive (prophylactic). Acute treatment attempts to reverse or stop a headache's progressing once it has started.

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Preventive treatment is designed to reduce attack frequency and severity. In the majority of migraine patients, only acute (abortive) treatment of migraine attacks is required. Abortive treatment always should be optimized before prophylaxis is considered. Even in patients treated with prophylactic medication breakthrough migraine attack has to be treated with acute medications. Acute attacks of migraine vary considerably among and within subjects in terms of severity, associated symptoms, disability, and social impact. The efficacy and tolerability of medications used for migraine treatment vary a great deal and, therefore, treatment must be tailored to individual needs of the patient. The same principles hold true for prophylactic treatment.

TREATMENT OF ACUTE MIGRAINE ATTACKS

Specific antimigraine drugs such as ergotamine and triptans are only effective against migraine attacks and not useful in the treatment of episodic tension-type headaches. Accordingly, the treating physician must be aware that patients with frequent migraine attacks have interval headaches, usually tension type. This puts the patient at risk of overuse of antimigraine drugs. Headache diary and proper instructions about distinguishing migraine attacks from other headache is important. Migraine should be treated with antimigraine agents and other headaches should be treated as discussed in Chapter 84. The choice between specific and nonspecific antimigraine medications may depend on the characteristics of migraine attacks; not all attacks in the same patient may require the same drugs. Thus, mild and sometimes moderate attacks may be treated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), optionally combined with drugs that promote their absorption such as metoclopramide. Table 47-2 lists the ways of optimizing treatment of acute attacks of migraine.

TABLE 47-2 Optimizing the Treatment of Acute Attacks of Migraine

A. Use effective doses
B. Treat early in the attack when the pain is still mild
C. Avoid medications with high medication overuse potential:
   1. Caffeine, acetaminophen–aspirin combinations
   2. Butalbital/caffeine/acetaminophen/aspirin combinations with or without codeine
   3. Opioids
D. Stratify treatment
   Step care versus stratified care
E. Treat the associated symptoms, when needed
F. Utilize prior experience to select or reject drugs
G. Choose the appropriate route of delivery of the medications
H. Observe contraindications
I. Combine medications if necessary, for example:
   1. Triptan + NSAIDs
   2. NSAIDs + metoclopramide

Optimizing Treatment

Use of Effective Doses

Inadequate dosing of nonspecific medications results in poor response. Ibuprofen 800 mg or naproxen sodium 550 to 750 mg are more effective doses. The same principle applies to triptans as well; for example, 25 mg of oral sumatriptan or 5 mg of rizatriptan are not adequate doses in the majority of patients.

Early Treatment

Early treatment with adequate dose should apply to all acute migraine treatments. It is clinical common sense to treat migraine head pain before it becomes severe. The new paradigm in the treatment of acute migraine attacks is early treatment when the pain is still mild. This has been shown to be partially true in the case of triptans.

Early treatment has clinical rationale because most migraine attacks start out as mild headache and progress to moderate or severe in a few hours and therefore, it is clinically logical to treat mild. Nausea and vomiting develops as the attack progresses, making it difficult to retain orally administered agents. Physiologic rationale are twofold: (a) Early treatment with a triptan before the central sensitization and resultant allodynia develops ensures better pain-free response (1). Late treatment after allodynia develops may result in a response that is relatively less satisfactory than the robust pain-free response obtained by early treatment. Central sensitization sets the stage for recurrence of headache, and may be responsible also for inconsistent response. (b) A relative gastroparesis develops during untreated migraine attacks, resulting in poor passage of oral medication to the intestines and subsequent poor absorption (7). Early treatment before the gastroparesis sets in is, therefore, important.

Early treatment, when the pain is mild, results in early pain relief, less recurrence of headache, less need for multiple medications, less disability, and fewer side effects.

Avoid Medications With High Medication Overuse Potential

Caffeine, Acetaminophen, and Aspirin Combinations

Caffeine is a major risk factor for development of chronic daily headache in the migraine population (5). In addition, excess amounts of caffeine causes other symptoms of caffeinism such as nervousness, tremor, sleeplessness, and anxiety. Many patients with high caffeine intake

may have to resort to sleeping pills on a regular basis. Inability to relax, because of excess caffeine, is an additional factor that may perpetuate the headache.

Patients may not volunteer the information about the caffeine-containing over-the-counter medication intake, because many believe it is not significant enough to report. Therefore, during history taking, it is critical to ask the patient specifically about nonprescription over-the-counter medication use.

Butalbital, Caffeine, Acetaminophen, and Aspirin Combination With and Without Codeine

The addictive potential of butalbital, a short-acting barbiturate, is well recognized. Sudden withdrawal of these medications may result in a number of withdrawal symptoms such as restlessness, sleeplessness, diarrhea, increased sweating, tremor, and most disturbingly, generalized seizures.

Concomitant frequent use of medication, which causes medication overuse headache, results not only in increased frequency of headache and escalation of doses, but also relative ineffectiveness of preventive medication as well as specific abortive medication such as triptans. It is imperative to discontinue such agents before proper treatment is prescribed. It is also advisable not to combine such combination analgesic with triptans. The best combination, if needed, in the acute therapy is triptans and NSAIDs.

Opioids

Opioids such as codeine, hydrocodone, oxycodone (OxyContin), if taken frequently, may also result in escalation of headache frequency and result in eventual excessive use and habituation. Presence of opioids in the system may reduce the effectiveness of preventive and specific antimigraine drugs.

Indications for opioids in acute treatment are very limited; the best indications are in a patient with ischemic heart disease and migraine and migraine in pregnancy, where triptans are contraindicated. In a small percentage of patients who are true nonresponders to specific medications, opioids may be considered as rescue. A major disadvantage of injectable opioids like morphine or meperidine is their sedating effect, which prolongs the disability of migraine attacks.

Opioids have no place in the routine management of migraine attacks. A recent report indicates that daily scheduled opioids have not only a low percentage of efficacy, but also high prevalence of misuse (6). Agents like butorphanol nasal spray should be avoided because of its high addictive potential with frequent use.

Stratify Treatment

Step Care

The mainstream approach to acute treatment of migraine in many countries might be termed *step care across attacks*. Patients are started at the bottom of the therapeutic pyramid, such as simple analgesic and if the treatments fail, the therapy is escalated to combination analgesics or opioids and eventually to triptans.

The fundamental assumption of step care is that all patients have the same treatment needs. This is a useful cost-effective methodology if the patient responds favorably to first-line therapy. The disadvantages of step-wise care are that successful treatment may be delayed, resources may be wasted on follow-up visits and failed prescriptions, patients and physicians may become discouraged, and patients may lapse from care (3).

Stratified Care

Stratified care, on the other hand, stratifies attacks and patients according to their therapeutic need. Heterogeneity of migraine demands a stratified approach. Those with severe, disabling episodes are assigned specific medications that have proven efficacy such as triptans. Patients with mild or low disability, whose therapeutic needs are less, may be treated with simple analgesics or NSAIDs, optionally combined with drugs that promote their absorption such as metoclopramide. Patients and physicians should be flexible in using medications according to need. Patients and their attacks must be stratified. Patient education is essential. Not every attack requires high-end therapy; some flexibility in the treatment approach is necessary. Because of the high cost of specific medications like triptans and poor accessibility because of managed care restrictions, the following approach is recommended by the French Agence Nationale D'accedilation et D'evaluation en Sante October 2002 (ANAES). It is a reasonable guideline, which in essence is a step-care written attack.

ANAES Guidelines

Therapeutic Strategy for Patients Already Treated With Nonspecific Medications

During the first consultation evaluate the efficacy and tolerability of current nonspecific therapy by ascertaining the following:

- Is the headache significantly relieved within two hours of taking the medication?
- Is the patient taking this medicine only once?
- Does the treatment allow this patient to return quickly to normal social, family, and professional activities?
- Is the treatment well tolerated?

If the answer is *yes* to all four questions, no change in the treatment is indicated. If the answer is *no* to one or more out of four questions, prescribe both an NSAID and a triptan.

- Instruct the patient to treat first with the NSAID.
- Use a triptan if relief is not achieved in 2 hours with the NSAID.

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- If the NSAID is not efficacious or well tolerated, then treat with triptan alone.

The French recommendations take into account the heterogeneity of migraine and combine both nonspecific treatment (NSAIDs) and specific agents (triptans).

When patients are uncertain if a headache will develop into a migraine attack, they may choose to stage their treatment, first using nonspecific medications. Using a specific antimigraine drug is best when there is an aura, when an impending migraine attacks is recognized based on experience as potentially severe, or when the attack is already severe. When a short-lasting aura of 30 minutes or less is expected, ergotamine or triptans that are known to penetrate the central nervous system may be used, although the effective use of sumatriptan during the aura phase remains to be established.

Associated Symptoms

The associated symptoms of a migraine, such as nausea and vomiting, may be as disabling as headache. Gastric stasis may delay absorption of oral medications. Starting treatment with antiemetic and prokinetic drugs such as metoclopramide may ameliorate the gastrointestinal manifestations of migraine and improve gastric motility with consequent rapid and more complete absorption. Most triptans ameliorate nausea and vomiting and, uniquely to the antimigraine drugs, relieve photophobia. Early treatment with a triptan may help to reduce nausea and vomiting more effectively.

Prior Experience

Prior experience with efficacy or adverse drug effects is of considerable importance. For example, a previously ineffective drug may not have been used in the optimal dose or by the best route of administration, and therefore may merit a new trial. Taking medication too late in the attack and inadequate dose are the common reasons for poor response. Physicians must inquire about these points and may instruct the patient to try the medication properly before they are given up. Experience also can dictate whether patients choose to stage their treatment or not.

Adverse drug effects—for example, nausea accompanying ergotamine use—may be caused by high dosage. Adverse events such as "triptan sensations" (chest pressure, throat pressure, whole body tingling) must be explained to the patient. An informed patient will panic less with such symptoms, avoid going to emergency rooms, and may continue to use the agent, especially when reassured that in the majority, repeated use reduce the adverse events. Patients should be asked about side effects during follow-up and, when appropriate, the dose adjusted to minimize them.

Appropriate Route of Administration

The appropriate route of drug administration may depend on the characteristics of the attack, or the circumstances under which treatment must be taken. If vomiting prohibits oral administration of a drug, then subcutaneous injection, suppository, or intranasal preparations may be used. In attacks where speed of relief is important, the parenteral route of administration is preferable.

In general, patients prefer oral medications. However, rapidity onset of action is important to many and, therefore, it is logical to use a rapidly acting oral agent rather than a drug with a delayed onset of action. Customarily, having received appropriate advice from their physician, patients are able to treat themselves. For severe and prolonged migraine attacks, medical attendance may be essential.

Contraindications

A prior history of risk factors (personal or familial), ischemic heart disease, cerebrovascular disease, uncontrolled hypertension, and pregnancy contraindicate ergotamine and triptan use. Although cautionary labeling may vary, some practitioners consider it prudent to regard all the 5-$HT_{1B/1D}$ agonists as sharing the same risk profile in vascular diseases. Enteric ulcers and bleeding disorders contraindicate the use of aspirin and NSAIDs (see Chapters 49 and 58).

COMBINATION THERAPY FOR ACUTE ATTACKS

Efficacy of a triptan may be enhanced and recurrence reduced by combining it with NSAIDs or cyclooxygenase-2 inhibitors (2,4). Similarly, combinations of aspirin or NSAIDs with metoclopramide is worthwhile.

PROPHYLACTIC TREATMENT

When to Use?

To use preventive pharmacotherapy for migraine attacks is a decision that must not be made without considerable forethought by physician and patient. Migraine is an episodic disorder of an otherwise healthy population, and drug use can be accompanied by adverse effects. Issues of compliance and expense must also be considered. Prophylactic therapy should be considered only under one or more of the following circumstances:

1. Incidence of attacks is more than two or three per month.
2. Attacks are severe and impair normal activity.
3. Patient is psychologically unable to cope with attacks.

4. Optimal abortive therapies have failed or produced serious side effects.

Migraine prophylaxis should not be used in patients planning pregnancy. Some form of birth control, preferably not steroidal, should be instituted before prophylactic treatment in women of childbearing potential. Monotherapy should be the rule in providing prophylaxis whenever possible. No rigorous clinical trials have yielded convincing evidence of the addictive effects of a second or third preventive drug. Such a therapeutic strategy also increases side effects, and potential interactions among the common preventive drugs are not understood. Nevertheless, it has become common practice to combine prophylactic agents in many countries. Presence of comorbidities, such as depression, anxiety, or bipolar illness, may determine the combinations used. For example, in a patient with frequent migraine with significant depression, one may combine an antidepressant along with a primary antimigraine prophylaxis such as β-blocker or topiramate.

During prophylactic treatment, patients should keep a simplified headache activity diary (Fig. 47-1) to help document the effect of treatment. Each medication should be given for an adequate time to judge its effectiveness, ideally 2 to 3 months. This often introduces a compliance problem, however. After the initial visit, patients should be followed up at 2- to 3- month intervals or sooner depending on the severity and frequency of the migraine attacks or on the potential for adverse drug effects, for example, methysergide.

Treatment for How Long?

The frequency of migraine attacks varies over time, and there is often uncertainty when benefit occurs whether it is from the drug or whether the disorder has gone into natural remission. This should be suspected whenever major life situations change that in themselves promote resolution of the attack frequency. Even with successful prophylactic treatment, gradual withdrawal after 6 to 12 months is an important goal to achieve. However, this goal is often not achievable in chronic migraine patients who may have to continue prophylaxis for long periods of time.

Choice of Drug

Contraindications for common migraine preventive drugs include asthma and bradycardia for β-blockers; peptic ulcer for NSAIDs; morbid obesity for pizotifen, tricyclic antidepressants, and valproic acid; and depression for flunarizine.

Side effects, even relatively minor, often limit the daily use of drugs in migraine. Patients should be warned to expect them and informed in advance about the nature of the most common ones. The importance of involving patients in decisions about their own therapy is never more in evidence than when deciding to take the available preventive medications.

In questioning about previous experiences with prophylactic treatment, the physician should check whether optimal doses were used and for how long. In addition, many patients may have tried prophylactic treatment without success because of overuse of symptomatic medications. Under these circumstances, the drug should not be judged ineffective. Unresponsive patients have multiple preventive drug experiences, often making such judgments impossible.

Dose

The bioavailability of preventive migraine drugs varies; propranolol, for example, can vary by up to 10-fold (see Chapter 54). Accordingly, there is no standard dose to be recommended for any migraine preventive medication. Customarily, drug levels are not measured in blood or urine, so the approach of relating levels to effect has never been pursued rigorously. However, it is generally advised to obtain valproic acid levels and liver function tests periodically when the patient is on valproate. This is more for safety reasons than for therapeutic efficacy. Treatment should be initiated with low doses that, depending on efficacy and side effects, are increased gradually at 2- to 4-week intervals.

POSSIBLE DRUG INTERACTIONS

Although not confirmed, methysergide combined with ergot preparations or a triptan could increase the risk of vasoconstrictive complications. Sumatriptan used for acute treatment of patients receiving selective serotonin reuptake inhibitors for prevention has in a few cases produced a serotonin syndrome that involves excessive agitation, movement disorders, and pyrexia. Clinicians must check drug information sources for drug interactions before prescribing.

PREGNANCY

Few data are available on the risks of most antimigraine drugs during pregnancy. For the treatment of migraine attacks, acetaminophen with or without metoclopramide can be used. Hospital admission and intravenous fluids may be required for severe intractable migraine that may be judged life threatening. Migraine prevention may be considered for similar reasons. Propranolol in low doses can be used. Agents like valproate are absolutely

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FIGURE 47-1. Suggested simple headache diary used to monitor headache activity during prophylactic treatment of migraine.

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contraindicated (for detailed guidelines, see Chapter 35). The decision to provide migraine preventive drugs should be taken together with a high-risk obstetric specialist.

REFERENCES

1. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann Neurol*. 2004;55(1):19–26.
2. Krymchantowski AV, Bigal ME. Rizatriptan verses rizatriptan plus rofecoxib verses rizatriptan plus tolfenamic acid in the acute treatment of migraine. *Headache*. 2004;44:465–466.
3. Lipton RB, Stewart WF. Clinical application of zolmitriptan. *Cephalalgia*. 1997;17(Suppl 18):53–59.
4. Mathew NT. Time course of symptom relief with various antimigraine therapies. *Cephalalgia*. 2003;23:698–699.
5. Scher Al, Lipton RB, Stewart W. Risk factors for chronic daily headache. *Curr Pain Headache Rep*. 2002;6:486–491.
6. Saper JS, Lake AE, Hamel RL, et al. Daily scheduled opioids for intractable head pain: long term observations of a treatment program. *Neurology*. 2004;62:1687–1694.
7. Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol*. 1975;2:57–63.