

Tales of Migraine: Migraine Overview from a Clinician's Perspective

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Learning Objectives

Upon completion of this CE program, the reader should be able to:

1. Understand the heterogeneity of migraine and migraine aura.
2. Review some concepts about the pathophysiology of migraine.
3. Understand migraine transformation and factors that transform migraine.
4. Differentiate between primary and secondary headache.
5. Review nonpharmacologic and preventive therapy in migraine.
6. Review triptans and other abortive therapy in migraine.
7. Discuss disability in migraine.

Abstract: In spite of advances in migraine and headache therapy in the last decade, migraine remains underrecognized and undertreated. This may be explained, in part, by the heterogeneity of presentation of migraine and, in part, by an unfamiliarity of the pathophysiology and chronic nature of this condition. Migraine may progress in frequency and severity and may transform into a very frequent or daily headache, particularly with comorbidities such as depression or with excessive analgesic use and analgesic “rebound.” Migraine as a primary headache disorder must be differentiated, particularly when progressive, from secondary headache because of intracranial or systemic disease. The treatment of migraine can be complex, as this involves consideration of preventive medications and nonpharmacologic therapies when headaches become frequent and disabling. Many headache-abortive therapies, particularly ergot derivatives, have been successful in the past, and remain important options for migraine, although triptan medications have revolutionized migraine abortive therapy. The proper use of these and other therapies would alleviate not only discomfort but the significant disability associated with migraine.



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Tale #1: The Emergency Room Patient

This was a 34-year-old man who had headaches since age 16, as did his father and sister. He had been successful in his estimation in keeping the headaches “under control” with various over-the-counter remedies since his youth, with the exception of “the bad ones.” The bad ones were severe, bifrontal, and, sometimes, almost explosive in onset, and his medicines never worked for these. His family doctor prescribed him a compound with the narcotic oxycodone for severe headache, which enabled him to go home and “sleep it off” and return to work the next day as a partner in a landscaping service. Unfortunately, the bad ones began to increase in frequency, and he routinely ran out of oxycodone medication. He presented to an emergency room, where he received meperidine as a parenteral narcotic. He was then referred to the headache clinic, but the encounter was brief. He interpreted suggestions for specific migraine therapy only as proscriptions against the narcotic medications that had been so “successful” in the past. He returned to his family doctor and continued oxycodone. He was permitted to return to the emergency room up to twice a month, if needed, for parenteral meperidine, at approximately \$350 per visit.¹

INTRODUCTION

Tale #1 tells of an all-too-common phenomenon of a patient with inadequate diagnosis, treatment, and overall management of a headache disorder. Ironically, a migraine disorder diagnosed early and treated appropriately yields very gratifying results. Each headache is more easily resolved, headache-specific medications are controlled in frequency and expense, and disability is prevented.

The revolution in abortive migraine therapy that began with the use of triptans in 1993 promoted new interest and understanding in the approach to headache.² In spite of these advances, the treatment of headache remains very problematic. The majority of patients with migraine do not consult a physician for treatment and those that do typically delay several years or until the headaches are disabling enough to require protracted bed rest. An even larger proportion are “lapsed consulters” who no longer follow with a physician, the majority of whom express dissatisfaction with their physician encounter. Among physicians, recognition of migraine is limited, with a correct diagnosis made in about half of migraine sufferers.³ Even when the diagnosis is correct, the severity and the disability of the headache are often not taken into account, and the headache is inadequately treated.⁴

THE SPECTRUM OF MIGRAINE

Migraine is defined as a common chronic neurologic disorder with episodic attacks. These attacks typically consist of moderate-to-severe headache, as well as autonomic symptoms (e.g., nausea, diarrhea), meningeal symptoms (causing painful head movement), and neurologic symptoms. The most common neurologic symptoms are photophobia and sonophobia, as well as a subjective blurring of vision. Neurologic symptoms of migraine aura are discussed below. Migraine is exceedingly common: it affects 6% of males and 18% of females past the age of puberty. Of migraine sufferers, 38% of men and 51% of women miss at least 6 workdays per year, and these more disabled groups account for over 90% of work loss because of migraine.⁵

Migraine is a heterogeneous disorder, and this may confound its recognition. Migraine has a variable frequency: it has a median of 1.5 attacks per month, but 20% have at least weekly attacks. Migraines can occur in “clusters” associated with physiologic stressors, such as menses, or emotional stressors. There is also great variability in duration. The typical duration of migraine is 9 to 24 hours, with 30% of attacks lasting at least 24 hours, and shorter-duration headaches occurring in younger patients. Migraine is also heterogeneous in severity, and includes headaches that are barely recognizable as painful. Studies that are limited to migraine, rather than primary headache, in general, tend to show higher frequencies of severe headache, typically near 80%.⁶ This is because of, to some extent, the International Headache Society (IHS) definition of migraine, which includes severity as a characteristic.⁷ Migraines vary in their rate of progression of symptoms and the degree of associated symptoms, such as nausea and asthenia as well as disability. Although the word migraine is derived from the old English “megrim,” meaning “half-head,” migraines are unilateral only 62% of the time. They are characteristically associated with throbbing, although this is reported in only 78% of migraine sufferers. A far more consistent complaint is aggravation by routine physical activity, at 96%.⁸ Migraine sufferers, in particular, experience a painful jolt when moving their head rapidly. This “jolt phenomenon” is attributable to meningeal irritation, and is useful in differentiating migraine from cluster headache. Moreover, while patients with cluster headache tend to be very uncomfortable staying still, those with migraine desire to stay as still (in a dark and quiet room) as possible. Nausea with or without vomiting is also extremely common in acute migraine, and complicates a patient’s attempts to take medication for it.

Tale #2: A Very Sick Headache

A 24-year-old woman presented to the headache clinic on an urgent basis because of severe headache that began when she was in Cancun, Mexico 10 days previously. The headache became progressively severe since then and was accompanied by nausea, vomiting, and “loss of vision.” Because she appeared acutely ill, she was sent for a head CT scan and she was admitted to the inpatient Neurology service. This scan was negative, so plans were made for an immediate lumbar puncture. But these plans were miscommunicated. Instead, she was given intravenous dihydroergotamine and hydration, and within 12 hours her headache was entirely resolved. She was in the hospital less than 24 hours and was discharged on a tricyclic medication (doxepin), with discontinuation of birth control pills. On follow-up, the patient reported that she was nearly headache-free for 6 weeks, and she related a previously missing piece of history, that she suffered from menstrual migraine. This is a case of “status migrainosus,” so defined as a (severe) migraine that does not resolve within 72 hours.⁹

A traditional dichotomy of migraine is that of “migraine with aura” and “migraine without aura,” formally “common migraine” and “classic migraine,” respectively. Both are defined by the IHS.⁷ About 64% of migraine sufferers have migraine without aura, 18% have migraine with aura, and 13% have both types of migraine.¹⁰ The most common aura, by far, is that of “positive” visual symptoms, that is, an addition or replacement to a visual field, followed by a scotoma with absence of vision. The characteristic visual aura is a semicircular “fortification spectrum,” a shimmering zigzag that migrates to the peripheral visual field over 4 to 15 minutes.

The sufferer may also experience paresthesias, typically progressing from the hand to the arm and affecting the face. Isolated facial paresthesias, especially affecting the angle of the jaw, can

also occur. Left hemispheric aura can be accompanied by a degree of receptive or expressive aphasia. Motor deficit occurs in only 6% of migraine aura,¹¹ tends to last longer, and is otherwise suspicious for structural lesion.

Tale #3: Did He Have a Stroke?

The patient was a 12-year-old boy who was being seen in the pediatric clinic for follow-up after chemotherapy for Hodgkin's disease. He had a history of headaches since age 7. As the nurse was flushing his central catheter, he had a sudden onset of complete blindness. Ten minutes later, he had left hemiparesis, and was combative and confused. Twenty minutes after this, the left hemiparesis was resolved; he then had right hemiparesis and was completely aphasic. He was given an emergent head computed tomography (CT) and electroencephalogram (EEG) at that time – both negative. The real surprise came 1 hour after the onset of his symptoms. His neurologic exam was completely normal, he was comfortable and headache-free. This is an example of migraine aura with associated paresis, aphasia, and acute confusional state. It represents an extreme case of migraine aura.¹²

THE THEORY OF MIGRAINE

The concept that migraine is associated with the cerebral and extracerebral vasculature dates at least back to the mid-19th century, and it was eloquently formulated by Wolff in 1937 following studies with the potent vasoconstrictor ergotamine.¹³ In 1944, Leao described the phenomenon of an electrical “spreading depression” in animals.¹⁴ This discovery remained relatively dormant as a biological curiosity until the 1980s when, beginning with positron emission tomography (PET) studies by Oleson, it was suggested to occur in humans during migraine.¹⁵ Other PET studies and studies with functional Magnetic Resonance Imaging (MRI) have supported the role of spreading depression in migraine.¹⁶ According to this theory, migraine is initiated by a brief excitation, then depression of neuronal activity, mediated by calcium channel instability and release of excitatory transmitters, particularly glutamate. This depression begins in the occipital cortex and spreads anteriorly through contiguous neurons at a rate of 3 mm/min. It has been further and convincingly postulated that this cortical spreading depression can occur in migraine without aura, and that it is associated with the pain of migraine attributed directly to perivascular and dural trigeminal nerve stimulation.¹⁷ Thus has evolved a *neurogenic* theory of migraine.

In 1995, Weiler obtained a PET scan on a patient who suffered a migraine attack but was headache-free at the time of the scan following treatment with sumatriptan. This PET scan demonstrated hypermetabolism in the region of the basal nucleus of Meynert, as well as the rostral pons and midbrain in the area of the reticular activating system.¹⁸ This suggests that these areas are associated with the cause of migraine and anatomically may represent a migraine generator. Migraine, then, may consist of an aberration in neuronal transmission between these brain stem nuclei and the cortex, such that the nuclei are inappropriately sensitive to descending trigeminal input and, conversely, the brainstem nuclei may decrease the cortical threshold for spreading depression. It is not uncommon for (particularly older) migraineurs to experience migraine aura without significant headache, a so-called “migraine accompaniment.”¹⁹ Moreover, the majority of patients with migraine experience no aura, and many patients who have frequent migraines experience a daily and even constant non-migrainous headache.

MIGRAINE TRANSFORMATION

The co-occurrence of migraine and tension-type headache with increasing migraine frequency is often seen in the setting of “migraine transformation” described by Mathew.²⁰ With migraine transformation, a patient with previously stable migraines occurring once or twice monthly begins to experience migraines once a week or even more frequently. As this happens, headaches of a milder severity and typical of tension-type headaches occur with increasing frequency. In time, a “transformed migraine” ensues where the patient experiences chronic daily headache, even constant headache, with frequent and disabling migraines. Such a transformation typically occurs in 1 or both of 2 common settings. The first is with an emotional disturbance, as particularly occurs with a major depressive episode or anxiety disorder, or perhaps only protracted anxiety. Depression itself is a particularly common comorbidity with migraine, as well as primary headache in general.²¹

The second setting is with the overly frequent use of headache analgesic medications, particularly narcotic medications.²² This latter scenario is especially problematic, as with increasing severity and frequency of the patient’s headaches he becomes more prone to taking the analgesic medication itself. A vicious cycle ensues, wherein withdrawal from analgesic medication begins to induce additional headaches. These added headaches are often worse than the original headache treated or, in any case, progressively worse. This phenomenon is known as “analgesic rebound,” and is described especially, but not only, in the frequent use of narcotic analgesics. Analgesic rebound is also experienced with frequent use of over-the-counter medications, particularly those containing caffeine.

Both mechanisms are commonly involved, since the coincidence of depression and analgesic overuse is seen in 80% each in transformed migraine. In addition, transformation can be accelerated or brought on by factors associated with secondary headache, including head or neck trauma, sinusitis, and meningitis.²⁰ An important feature of transformed migraine is an increasingly refractive nature, that is, resistance to benefit from typically prescribed abortive or preventive medications. This refractoriness often generates suspicion by the caregiver (sometimes justified) of drug seeking behavior and suspicion by the patient that the lack of efficacy of medications implies that the cause of their headache has not been adequately explored. The headaches will remain refractory to medications unless the “transforming factor(s),” especially depression or analgesic rebound (or both) are resolved. Withdrawal of the offending analgesics is both mandatory and extremely difficult, even when the patient appears to have motivation for this.²⁰ Medications I have tried include clonidine (for opiate withdrawal); dopamine agonists, such as prochlorperazine or metoclopramide; short-term steroids; and, more recently, short-term scheduled naratriptan. These and other therapies specifically for analgesic rebound or “medication-induced” headache have been reviewed by Zed, although no rigorously conducted clinical trials for these have been performed.²³

Tale #4: Perpetual Headache

This is a 26-year-old woman who is a primary school teacher and who had been recently married. She had stable migraines for many years, treated with atenolol and occasional butalbital compound. With her change in lifestyle after marriage, she began to experience increasing frequency in her headaches, which she had attributed to “stress.” Within a month of that she

began to increase her request for butalbital tablets from 30 and then to 60 a month. This situation continued to accelerate until she took 60 tablets of butalbital, which she used up within 2 weeks. She secretly began to contact a previously visited physician for extra butalbital at that time, and the physician, in turn, contacted her current physician at the headache clinic. The physician then confronted the patient with this behavior and the need to withdraw butalbital. In spite of the excessive use of this medication, or rather because of it, her headaches were described as constant and “worse than they’ve ever been.” After butalbital was withdrawn, she was treated with some adjustments in her preventive therapy, the judicious use of triptans, and counseling for an anxiety disorder. As a result, her headaches returned to their previously stable state. It is important to note that these adjustments required 4, time-intensive months, and was very frustrating for both the patient and the physician.²⁴ This is a characteristic example of transformed migraine, specifically with butalbital rebound and subsequent dependence.

SECONDARY HEADACHE: SCREENING AND EVALUATION

It is customary for migraine sufferers to attribute their headaches to abnormalities in the sinuses, neck, eyes, or brain. Without any evaluation or testing whatsoever most of these patients can be assured correctly that such is not the case – that they have “primary headache” – that the headaches are spontaneous. But herein lies the problem. About 1% of patients *will* have a significant structural cause for their headache, that is, a secondary headache; this may be overlooked unless appropriate imaging or other testing is not obtained.²⁵ A larger percentage will have both a tendency to migraine headache and a more proximate structural cause. It is, thus, important to judiciously screen patients who present with a first-time headache, or headaches that are changing in character or frequency. This particularly applies to patients over the age of 40, in whom migraine is less likely to be new in onset.²⁶

One can consider the broad category of secondary headache as composed of three subcategories: intracranial disease, extracranial disease, and systemic disease. Intracranial diseases especially include tumor, and this is often a primary concern of the patient.³ Other causes may include abscess (acute setting) or pseudotumor cerebri (chronic setting). Intracerebral vascular disease may also cause headache, particularly with aneurysm (unruptured or ruptured), arteriovenous malformation, carotid artery dissection, vertebral artery stroke, cerebral vasculitis, and cerebral venous thrombosis. Infectious causes include meningitis, not necessarily acute but occasionally chronic, owing to fungal or viral causes. With these conditions, headache will occasionally occur in isolation, but will more often be seen in the context of neurologic deficits or other symptoms suggesting intracranial mass lesions.²⁷ Such symptoms include change of vision (with papilledema), worsening of headache with supine state, abnormalities of gait, and cranial nerve abnormalities – particularly diplopia. Cognitive or behavioral changes often accompany progressive intracranial causes of headache.

Extracranial causes include sinus disease, cervical spine arthritis, otolaryngologic infection or neoplasm, glaucoma, and temporal arteritis. The involvement of extracranial disease can often be determined by local tenderness as well as the acuity and rapid progression of symptoms. Finally, systemic diseases including sleep apnea, thyroid disease, anemia, or chronic illness might be considered. Patients may have headaches because of complications from their medications, particularly estrogen-containing medications.²⁸

Tale #5: The Deadly Migraine

This was 37-year-old man with a previous history of occasional headaches of moderate severity. He presented to an emergency room with a sudden onset of severe generalized headache. His vital signs and exam were otherwise normal and his headache improved significantly after subcutaneous administration of the anti-migraine agent sumatriptan. He was scheduled to see a neurologist for follow-up, and he was discharged. Before the neurology appointment, however, and within 2 weeks, he presented again to the emergency room. On the second presentation he had somnolence as well as severe headache. His emergent head CT and angiogram disclosed a left anterior communicating aneurysmal subarachnoid hemorrhage. He barely survived this hemorrhage with emergency aneurysm surgery, complicated by severe cerebral vasospasm. His recovery was limited then by persistent global aphasia and right hemiparesis. He was placed in a nursing home.

The most notorious secondary headache is the “sentinel” headache of subarachnoid hemorrhage.²⁷ This is a very sudden (“thunderclap”) headache produced by a leak from a saccular aneurysm. The notoriety derives from a person presenting to the emergency room with the “worst headache of my life,” with either a history of no headaches or only mild or occasional migraine headaches. The patient is treated with migraine remedies or parenteral narcotics and often improves. The patient is then discharged from the emergency room, only to present days or weeks later in a moribund state from a recurrence of subarachnoid hemorrhage, often with a devastating outcome. This scenario is not common, but is infamous, and doubly unfortunate because of the high mortality of subarachnoid hemorrhage itself, as well as the very common complaint of the migraine sufferer: “This is the worst headache of my life.” Indeed, such a scenario would suggest obtaining a head CT scan on every patient that presents with migraine; this simply isn’t practical or necessary.²⁷

I believe the best approach to new-onset headache with these considerations is to consider evidence of the “Peril signs” below in screening a patient:

1. **Progression**, particularly if unexplained and subacute. Most patients with primary headache of any severity will recall a previous headache of similar character and severity.
2. **Personality** or behavioral change. This especially applies to episodes of confusion or stroke/seizure-like states. These episodes are especially worrisome when the patient describes these changes. And, they are especially worrisome when those who are accompanying the patient describe these changes.
3. **Papilledema** or other deficits on neurologic exam. It is important to do a satisfactory neurologic exam on a new-onset headache. This exam should include a careful examination of the fundus for evidence of papilledema.

I believe that the perils of secondary headache can be prevented most of the time by an attentive history and examination, whether this is done in the outpatient clinic or in the emergency room. For patients who have episodic headache with no “Peril Signs,” a trial of therapies is certainly warranted, and brain imaging and other evaluations are unnecessary. For patients with frequent, chronic, progressive headache the situation is more complicated. Again, if “Peril Signs” are not

present, then an individualized approach can be undertaken. If there are “Peril Signs,” further tests including imaging are warranted.

If an intracranial lesion is strongly suspected, MRI is probably superior to CT scanning. In an acute setting, such as an emergency room, however, a CT scan followed by a consideration of lumbar puncture is strongly recommended.²⁷ Other laboratories may include blood count, sedimentation rate (particularly in the elderly), blood sugar, thyroid tests, and, in endemic areas, lyme titer. In the more chronic setting, evaluations for chronic headache may also well include psychologic evaluation and sleep study. Unfortunately, none of these tests is specific for primary headache. They merely “rule out” disorders and, thus, have sensitivities and specificities that are dependent on the examiner’s suspicion prior to testing, or “pre-test probability,” in Bayes’ terminology.²⁹

MIGRAINE THERAPY: NONPHARMACOLOGIC, ALTERNATIVE

Although nonpharmacologic therapy may be a secondary consideration in many patients with episodic migraine, it becomes a much more important and even primary consideration for those with frequent primary headaches. This particularly applies to changes in lifestyle with a goal of reducing headache triggers, such as alcohol, nicotine, and caffeine.³⁰ In general, patients with frequent headaches should avoid sleep deprivation and limit intake of caffeine, nicotine, and alcohol as well as avoid illicit drugs. Keeping a headache diary is particularly effective for frequent migraine sufferers, as it may reveal recurrent headache patterns that provide insight into previously unrecognized environmental or lifestyle triggers for headaches. Unfortunately, effecting lifestyle changes is often very difficult for the patient with frequent headaches. This is particularly true with respect to caffeine and cigarette use, and is compounded by the patient’s tendency to minimize such use. A common sight in our headache clinic is that of a patient complaining bitterly about frequent headaches as he sits next to a 20-oz. bottle of caffeinated soda. When this is pointed out he will often still claim, “I don’t drink that much caffeine.”

Many nonpharmacologic therapies have become popular in recent years, and many of these can be very helpful.³¹ These include biofeedback and relaxation therapy,³² massage or manipulation, trigger point injection of the cervical paraspinal areas or shoulder girdle, acupuncture, and many herbal or “alternative” remedies. Of the latter, feverfew³³ and riboflavin³⁴ have shown some favorable results in clinical trials and are popular with many of my patients. My policy regarding these alternative therapies is not to object to them, but instruct patients to minimize their use somewhat, and be aware that there may be unforeseen interactions between the remedies and prescribed medications.

ABORTIVE THERAPY FOR MIGRAINE: NONTRIPTAN

It is common lore that triptans have revolutionized the abortive treatment of migraine, but this is not quite the case. The majority of migraine patients still treat their severe headaches with non-triptan therapies, particularly with non-steroidal medications and Schedule III narcotics.³⁵

Among these agents, compounds containing 50 mg of butalbital are perhaps most commonly prescribed. Other commonly used oral narcotics include codeine, hydrocodone, oxycodone, and butorphanol. Nasal butorphanol can be very useful as a rapidly acting alternative to migraine-specific therapy, although its potential for abuse is also high and previously underappreciated.³⁶

Compounds containing the mild vasoconstrictive agent isometheptene and over-the-counter medications, particularly those combining aspirin, acetaminophen, and caffeine have become very popular. These compounds are reasonably effective for headache and, to the extent they are not effective, they are, at least, familiar and well tolerated. Their limitation derives from their more limited efficacy in severe headaches prompting frequent doses and the effects of intoxication from excessive dosing of the medications. Thus, disability persists in spite of subjective improvement on the patient's part, and the patient may compound his original migraine with headache resulting from analgesic rebound.¹ This problem is often magnified in the case of potent narcotic preparations, particularly when used by patients with dependency issues.³⁶

Ergotamine and dihydroergotamine (DHE) deserve special consideration here. Ergotamine itself is remarkably effective for headache and is a very potent serotonin receptor agonist.³⁷ Its use has been limited by its significant side-effect profile, and these side-effects, particularly nausea, are dose limiting. A partial solution to this toxicity is to administer ergotamine as a sublingual or rectal formulation. DHE remains a very important alternative, since it is more potent than oral ergotamine with intravenous or intramuscular administration, and has a marked decrease in side effects compared with ergotamine. It has been prescribed, particularly in the pre-triptan era, subcutaneously for severe migraines. It is now available as a nasal preparation (Migranal[®]), and in this form is a long-acting and excellent alternative to triptan therapy.³⁸ By the parenteral route, DHE is first-line therapy for status migrainosus.³⁹ This and other parenteral therapies for severe headache and status migrainosus are listed in Table 1.

Table 1. Parenteral Therapy for Severe Migraine and Status Migrainosus

Medication and Dosage

Comment

Sumatriptan

6 mg SC

First-line therapy. Contraindicated for coronary or vascular disease or within 24 hours of other triptans or DHE. Maximum dose is 12 mg/day.

Dihydroergotamine (DHE, DHE-45)

1 mg IV

First-line therapy. Contraindications similar to sumatriptan. Premedication with antiemetic medication is recommended. May repeat hourly to a maximum dose of 3 mg in 24 hours.

Steroid

Methylprednisolone 100 mg IV - 500 mg IV

Dexamethasone 2 mg IV - 10 mg IV

Effect typically delayed by 12 hours. Agitation common. Use with caution in diabetes or peptic ulcer disease.

Nonsteroid

Ketorolac 60 mg IM (30 mg IV)

Use ½ dose in renally impaired or less than 60 kg. May repeat every 6 hours to a maximum 180 mg IM (90 mg IV). Do not give for more than 5 days. Contraindicated for bleeding or ulcer risk.

Dopamine Antagonist

Prochlorperazine or

Chlorperazine 5 mg IM/IV - 40 mg IM/IV

Haloperidol 0.5 mg - 5 mg

Droperidol 2.5 mg IM/IV - 10 mg IM/IV

Can be used as adjunctives for associated nausea or primarily for severe headache. Contraindicated for hypotension, cardiac compromise, and parkinsonism. Caution: orthostatic hypotension.

Narcotic

Morphine 2.5 mg IM/IV - 15 mg IM/IV

Meperidine 50 mg IM - 150 mg IM

Hydromorphone 1 mg IM/IV/SC - 1.5 mg IM/IV/SC

Respiratory depression, hypotension, and pruritus require monitoring.

Tale #6: The Lapsed Consulter

This is a 27-year-old woman diagnosed with migraine in 1992. She was treated with several abortive and preventive medications for her headaches over several difficult visits. The therapy failed dismally either because the medication was inadequate or fraught with unacceptable side effects or both. She “no-showed” her last scheduled visit, then wrote her physician a sardonic letter regarding her success with a naturopathic practitioner. Nine months later, she reappeared at the physician’s clinic with acute severe headache – with prostration and vomiting. She was referred to the nearest hospital emergency room for acute therapy and admission. The plan was to institute intravenous hydration and narcotic analgesia. But the emergency room physician had another idea, as it was now 1993. Why not try the new subcutaneous anti-migraine medication sumatriptan? With the clinic physician’s grudging approval she received this – and her severe headache of 3 days rapidly disappeared. She literally danced out of that ER and came to that physician’s clinic the next morning with a box of candy. I was that clinic physician, and this was my introduction to the “triptan revolution.”

MIGRAINE ABORTIVE THERAPY: TRIPTANS

Since 1993, the abortive treatment of severe migraine has been profoundly changed by the introduction of triptans, beginning with sumatriptan administered as a subcutaneous formulation. Triptans are selective presynaptic serotonin (5HT) receptor agonists that generally work in 3 important sites. The first is at the 5HT-1D receptor. This results in the inhibition of dural extravasation of pain-producing neuropeptides, particularly substance-P and calcitonin gene-related peptide. The second site is at the 5HT-1B receptor, resulting in cerebral vasoconstriction.³⁹ Triptans also result in general vasoconstriction and coronary vasoconstriction, although to a much lesser extent than ergotamine and other serotonin agonists.⁴⁰ Finally, there are central actions of triptans, particularly in those that are more lipophilic than sumatriptan. These result in stimulation of 5HT-1D receptors in the trigeminal nucleus caudalis, inhibiting pain projections to the reticular activating system.³⁹

Currently available triptans and their formulations are listed below. Eletriptan and almotriptan have not yet been released but have completed phase III efficacy trials.^{41,42} In general, sumatriptan is less lipophilic, and its oral form has less bioavailability than the “second generation” oral triptans zolmitriptan and rizatriptan.⁴³ Both zolmitriptan and rizatriptan have been shown to be at least as efficacious as oral sumatriptan in producing headache relief at 2 hours.^{44,45} Sumatriptan is available in multiple forms, so that if its oral formulation proves ineffective one can then take a nasal or subcutaneous preparation within the same day. The use of more than one type of triptan in a 24-hour period is not recommended. Naratriptan occupies a relatively special niche in that it is somewhat less efficacious and more slowly acting than the other triptans, but it is extremely well tolerated.⁴⁶

Side effects, in general, of triptans are relatively mild, but can be significant in some patients. These include chest pain and “heaviness,” suggestive of myocardial ischemia in about 2% of patients. However, between 1991 and 1997, only 19 cardiac-related deaths occurred in patients within 24 hours after being given sumatriptan tablets or injections, out of more than 100 million administrations.⁴⁰ Nevertheless, triptans are contraindicated in patients who might have coronary problems, particularly in patients over the age of 40 and/or with hypertension, family history of cardiac disease, or other risk factors of coronary artery disease. Triptans are also

contraindicated in patients with cerebrovascular disease because of the relatively intense vasoconstriction they produce. Two non-stroke conditions for which triptan use is contraindicated because of cerebral vasoconstriction are vertebrobasilar migraine and familial hemiplegic migraine.⁴⁷ Table 2 contains a list of present and soon-to-be available triptans with some pertinent pharmacokinetic properties.⁴⁸

Table 2. Triptans

<u>Drug</u> <u>Bioavailability (%)</u>	<u>Tmax (hr)</u>	<u>T ½ (hr)</u>	<u>Oral</u>
Sumatriptan (Imitrex, Glaxo) SC, 6 mg Nasal, 20 mg PO, 50 mg	2.5	2.5	15
Zolmitriptan (Zomig, Astra-Zeneca) PO, 2.5 mg and 5 mg	2	2.5 - 3	40 - 48
Rizatriptan (Maxalt, Maxalt-MLT, Merck) PO, 10 mg	1.3	2	45
Naratriptan (Amerge, Glaxo) PO, 2.5 mg	1.5 - 3	5 - 6.3	63, men 74, women
Eletriptan (Relpax, Pfizer) PO, 40 mg and 80 mg	1 - 2	3.6 - 5.5	50
Almotriptan (Axert, Pharmacia) PO, 12.5 mg	1.4 - 3.8	3.2 - 3.7	80

MIGRAINE THERAPY: PREVENTIVES

In general, when severe headache frequency is greater than twice a month or, more properly, when a patient is disabled more than 3 or 4 days of the month from headaches, preventive medication becomes an important consideration.⁴⁹ Preventives are also an important consideration in patients that have headaches of a magnitude to disable them for several days or otherwise make them very ill.

The major group of migraine-preventive therapies includes beta-blockers and tricyclic medications.⁵⁰ Of the beta-blockers, propranolol has been the most commonly used, but by no means the only effective agent in this class. Even relatively hydrophilic agents (with lower brain penetration), such as atenolol and metoprolol, which generally have fewer side effects, can be very effective here.⁵¹ Among tricyclics, amitriptyline is probably the most commonly used tricyclic for migraine prevention. Again, this is by no means the only effective agent in this class. Medications with fewer side effects, such as nortriptyline, imipramine, and doxepin can also be very effective.⁵² It is the anticholinergic side effects of these tricyclic medications that

are frequently dose-limiting, and these can often be tolerated well if the medication is introduced slowly. Patients with more severe headache disorders or intolerance to higher doses of one preventive can sometimes be treated with a combination of a low-dose beta-blocker and tricyclics, as these two agents can be synergistic.⁵² Valproic acid is a more recent and FDA-approved preventive therapy for migraines. It is a very effective therapy,⁵³ although has a significant side effect profile at higher doses, including weight gain, tremor, alopecia, and rare hepatotoxicity. Calcium channel blockers, particularly verapamil, can be excellent headache preventive agents in many patients, being very well tolerated although less effective than beta-blockers on the balance.⁵⁴

Other agents that have been used as second-line headache preventive therapy include fluoxetine and other selective serotonin reuptake inhibitors (SSRIs); anticonvulsants, such as gabapentin and topiramate; serotonin receptor type 2 (5HT-2) antagonists cyproheptadine and methysergide; and the monoamine oxidase inhibitor (MAOI) phenelzine. SSRIs have less headache preventive effect than tricyclic antidepressants, but may be very useful in migraine transformation caused by depression, and are very well tolerated. Methysergide and phenelzine occupy a special category in preventive therapy. They are effective and frequently used in larger headache centers, but have relatively fearsome potential toxicities, so that their use must be closely monitored.⁵⁰ Methysergide has been associated with pleural or peritoneal fibrosis with chronic use. Phenelzine and other MAOIs can precipitate a hypertensive crisis with exposure to tyramine or a serotonin receptor agonist. Very long-acting narcotics, particularly methadone, can be helpful for refractive chronic daily headache, although their use must be balanced by concerns of rebound and cognitive impairment.³⁶ In addition, the use of methadone often gives a certain stigma to the patient, so use of this must be balanced with the degree of the disability caused by the headache itself. Table 3 (below) lists some migraine preventive medications with their dosages, side effects, and contraindications.

Table 3. Some Preventive Medications in Migraine

Medications and Usual Dosage

Beta Blockers

Propranolol 60 mg/day - 240 mg/day TID or sustained release
Timolol 10 mg/day - 40 mg/day QD or BID
Nadolol 20 mg/day - 80 mg/day QD or BID
Metoprolol 50 mg/day - 100 mg/day BID or sustained release
Atenolol 25 mg/day - 100 mg/day QD
Bisoprolol 5 mg/day - 20 mg/day QD

Tricyclic Antidepressants (TCAs)

Amitriptyline 25 mg - 300 mg qHS
Nortriptyline 25 mg - 200 mg qHS
Imipramine 25 mg - 300 mg qHS
Doxepin 25 mg - 200 mg qHS
Desipramine 25 mg - 200 mg qHS

Calcium Channel Blockers

Verapamil 80 mg BID to TID or 120 mg/day - 240 mg/day sustained release
Diltiazem 120 mg/day - 180 mg/day TID or sustained release
Flunarizine 10 mg/day (investigational in U.S.)

Anticonvulsants

Divalproex 250 mg - 750 mg BID to TID
Gabapentin 300 mg - 1200 mg BID to TID
Topiramate 25 mg - 150 mg BID

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine 20 mg - 60 mg QD
Paroxetine 20 mg - 40 mg QD
Sertraline 50 mg - 150 mg QD
Venlafaxine 37.5 mg - 75 mg QD or BID

Important Side Effects or Contraindications

Bradycardia is dose limiting. May aggravate asthma or depression. May induce Raynaud's phenomenon or elevation of cholesterol. Orthostatic hypotension and lassitude are common dose-dependent side effects. Decreases symptoms of hypoglycemia in treated diabetics. Rebound tachycardia and angina with abrupt withdrawal.

Anticholinergic side effects, including tachycardia, dry mouth, urinary retention, sun sensitivity (sunburn), and aggravation of glaucoma. May cause confusion, especially in elderly. Weight gain is common, especially with Doxepin. Dysphoria is dose limiting, but less of a problem if doses are escalated slowly. Seizures reported, especially at higher doses.

Constipation is common. Occasional edema. Orthostatic hypotension is seen with higher doses. High doses are associated with heart block.

Weight gain is common with divalproex; also seen with gabapentin. Topiramate induces mild anorexia and weight loss. Dysphoria and sedation are common and dose limiting. Cognitive problems and memory loss, especially with topiramate. Rare but fatal hepatitis with divalproex requires monitoring of liver function tests. Psychosis is reported with topiramate.

Effectiveness for primary migraine prophylaxis is unclear; may paradoxically worsen headache. Agitation and dysphoria are occasional and diminished libido is common except with

Bupropion 50 mg - 150 mg QD, BID, or sustained release

bupropion.

Serotonin 5-HT₂ Receptor Antagonists

Methysergide 2 mg BID to TID

Cyproheptadine 4 mg - 8 mg BID to TID

Pizotifen 0.5 mg - 2 mg qHS

Sedation, weight gain, and agitation are common. Pleural and peritoneal fibrosis with prolonged methysergide requires 4-week drug holiday every 6 months or less. Anticholinergic side effects with cyproheptadine and pizotifen. Methysergide is contraindicated in coronary or vascular disease and with ergot or triptan medications.

Monoamine Oxidase Inhibitor

Phenelzine 30 mg BID or TID

Hypertensive crisis with tyramine-containing foods, including cheese, beer, and yogurt. Weight gain, sedation, and agitation are common. Contraindicated with sympathomimetics, SSRIs, TCAs, and triptans.

Opioid Agonist

Methadone 10 mg/day - 60 mg/day QD or BID

Cognitive problems and constipation are common. May aggravate depression. Narcotic dependence and stigma of chronic methadone use are issues.

Tale #7: Only Two Headaches a Month

This is a 32-year-old woman who had headaches since age 13. These were primarily migraines that occurred around her menstrual period, also with an occasional migraine at her midcycle. She was, otherwise, entirely headache-free. Unfortunately, the headaches that did occur at these times were particularly severe, especially in recent years when they would last up to 3 to 4 days, and were associated with intractable nausea and vomiting. In the last 6 months prior to her first office visit, she began to experience dysmenorrhea and was treated with estrogen supplements. This resulted in an increase in the severity of her headaches. In the 2 months preceding the first visit, she had been to the ER 4 times for parenteral narcotics to treat her headaches and had missed 9 days of work. Because of the disability that resulted from these severe headaches and in spite of occurring only twice a month, she was discharged from her work as a sales consultant 2 weeks prior to the clinic visit. She had never received preventive therapy for headache. She was given oral sumatriptan in the past and found this to be ineffective. At the headache clinic, she was prescribed a sustained-release preparation of metoprolol at 100 mg per day as well as rizatriptan for abortive therapy, and her headaches responded very well. As of her last follow-up, however, she was not yet back in the work force.

MIGRAINE DISABILITY

The direct costs associated with migraine are quite staggering at approximately \$1 billion per year. What is less appreciated is the indirect cost resulting from disability associated with migraine, which is estimated at \$13 billion per year.⁵⁵ To increase this appreciation, the American Council for Headache Education has devised a MIgraine Disability ASsessment (MIDAS) questionnaire.⁵⁶ It assesses migraine, not so much in terms of its severity or frequency, but as the actual disability headache in terms of loss of time from work or school or loss of productivity because of the headaches. Scores from the questionnaire are given in terms of days of productivity lost in a 3-month period, and the consideration of appropriate therapy for the patient can be based on the degree of his disability, or MIDAS score. Patients with moderate to severe disability, suffering at least 11 days of lost productivity in 3 months, are important candidates for preventive therapy as well as adequate abortive therapy for migraine. Of note, 43% of 3569 patients who presented to primary caregivers complaining of headache were in a category of least moderately severe disability according to a recent survey.⁵⁷

Tale #8: Sweet Success

This was a 20-year-old young woman at the Student Health Center of our University who had migraines over the preceding 3 years that were controlled with an isometheptene compound. She came to the headache clinic in the late fall because of headaches that were increasing in severity and frequency, associated with recent birth control pill use and the stresses of her college life. The stated reason for her referral was that she was overusing the sumatriptan, which was prescribed at the Student Health Center. Laboratory studies obtained there included normal thyroid function and hematocrit; she did not receive brain imaging. She was given a prescription for nadolol at 20 mg twice a day, but this resulted in unacceptable orthostatic side effects, and so was cut to 20 mg a day. Her birth control pills were held for 3 months. At follow-up, 2 months later, she was absolutely headache free. She expressed amazement at this, particularly as it occurred during final exams.

CONCLUSION

The practice of headache is, at times, trying and very gratifying. One may be guilty of many pitfalls in the diagnosis and treatment of migraine, including inadequate abortive therapy, inappropriate counseling on the side effects of medication, and inattention to comorbid conditions with headache, especially depression. The “tales” above are examples of the countless learning experiences that have made my own practice more effective and satisfying. The case history of tale #8 is remarkable precisely because it is so common, and demonstrates efficacy of the application of a few simple principles in headache therapy, some experience, and compassionate attention to the disability associated with a patient’s headache.

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