

# **Management of Chronic Headache**

*Based on a talk given by Lawrence Robbins, M.D., at the September, 2008 meeting of the AAPM*

*Key information in this talk can also be found on [www.headachedrugs.com](http://www.headachedrugs.com), under “Headache 2008-2009”*

## **Introduction**

The focus today is on outpatient management of chronic headache patients. When we assess patients who seek medical treatment for headache pain, usually they will suffer from migraine, tension, or chronic daily headache. Only about 5% of patients fall outside of that realm. Cluster headache is the third type of primary headache, but cluster headache is relatively uncommon; it is found in about 1 out of 250 men and 1 of 700 women.<sup>1</sup> In contrast, migraine is common; it occurs in 18% of women and 7% of men in the United States.

Chronic daily headache often results in a markedly decreased quality of life for patients. With triptans and other new preventives, we have all of these wonderful medications for migraine, but we don't have much that is new or effective for chronic daily headache.

## **Migraine, General**

Migraine, of course, is the more severe type of headache. There are twenty-five to twenty-eight million people in the country with migraine, making it one of the most common of illnesses. Many migraine patients can successfully take care of their headaches with over-the-counter medicines, but most are disabled to one degree or another during their headache.

I look at migraine as an inherited, chronic illness. It is characterized by moderate to severe pain, often unilateral, although it certainly may be bilateral. Migraine is usually accompanied by associated features, such as nausea, dizziness, photophobia, sonophobia or osmophobia. Exacerbation of the headache from bending or other movement is common, as is neck pain. Aura is fairly common: up to 25% of migraineurs

experience an aura, but not with every headache. It is common to have prodromal and/or postdromal fatigue and mood changes.

Migraine may begin at any age, and is surprisingly common in children and adolescents: at least 1% of 6-year-olds, and 4% by age 10. Until age 12, boys and girls suffer from migraine in equal numbers; during puberty, the familiar ratio of 3 women to 1 man is reached, and that ratio is maintained throughout the rest of life.<sup>2</sup>

In diagnosing migraine, it helps to look at consistent triggers, such as menses, weather, and undersleeping. If weather changes bring on migraine, that's always confusing; people are told (and feel) that they have a sinus headache and they take an OTC sinus medicine, which often helps. Most sinus headaches turn out to be migraines. There have been several large studies on this, and 95% of people presenting with chronic sinus headaches are found to have migraines, not sinus headaches. So we usually think, "migraine first" with pain in the sinus area.<sup>3</sup>

### **Work-up**

With a new onset headache, a more extensive work-up is needed. It is a case by case judgment, but new onset daily persistent headache necessitates a work-up. A patient in middle or later life with new onset headaches always needs a work-up. This is also true for new neurological symptoms, such as numbness, a change in mental status or visual problems. The patient with chronic daily headaches warrants an MRI more often than the patient with sporadic migraines. Children with migraine may not need an MRI. If a 12-year-old presents with two migraines per month since age 6, an MRI is not absolutely necessary. However, when the kids are followed as far as college age, often there will be an incident where they will call and complain of a severe, prolonged headache; they usually end up having a scan at some point.

Most headache patients should undergo routine hematologic exams, primarily to assess liver and kidney function. Patients are often taking OTC medicines that they don't tell us about; either they don't remember, or don't have a sense of how many OTC's they take for pain relief. It is not unusual for headache sufferers to consume 8 to 10 ibuprofen or Excedrin on a daily basis, and the liver and kidneys may be affected.

## **Triggers**

One of the primary things we can do is educate patients about triggers. Unfortunately, we can't do very much about certain triggers, but when a patient has a headache every time the weather changes, or the first day of every menstrual period, we might be able to use medicine the day or night before, so as to prevent the headache. The top triggers tend to be stress (daily hassles), menses and weather. When they occur together, that is when patients get the worst, most prolonged migraines. Of course, missing meals, under- or oversleeping, bright lights, and certain foods can contribute, but the role of foods tends to be overemphasized. People are given a forbidden-food list and told, "Avoid these foods and you won't have headaches," and then they are disappointed. Many books concentrate on diet and foods, but these are low on the list of important triggers.

## **Caffeine**

Caffeine, however, is a major trigger. We need to limit the patient's intake, although the limit varies. Some people can consume 800 mg. a day of caffeine and not incur rebound headaches or withdrawal. Other people get headaches from a small amount of caffeine in their diet. Caffeine is an adjunct for pain relief; it does help enhance analgesics. Small amounts often help people with their headaches. We have to watch out for the specialty coffeehouse effect: Starbucks coffee has 23 mg. of caffeine per ounce. So, in that oversized cup of Starbucks, you are going to get about 400 mg. of caffeine, which is twice the daily maximum recommended. But most home-brewed coffees have manageable doses. Coffees such as Folgers or Hills Brothers have about 150 mg. per cup, and instant coffee has half that amount. Tea, if it has caffeine, will generally have 30-60 mg per cup. Cola drinks have 40-60 mg.; Mountain Dew has a little more. The new energy drinks may have 200 mg. in 12 ounces. Watch for accumulated caffeine from these and from OTC medication; each tab of Excedrin has 65 mg. of caffeine, while Anacin has only 33 mg. I attempt to limit daily caffeine intake to 150 mg., with 200 mg. the maximum.<sup>4</sup>

## **Psychological Comorbidities**

Comorbidities guide where we go with headache patients. Psychiatric comorbidities are relatively common in headache patients, primarily due to shared genetic susceptibilities. I tell patients that migraine is an inherited medical problem just like having asthma. Similarly, in those with anxiety and depression, a genetic tendency can make the patient susceptible, as with diabetes. So, don't tell people, "it's all in their heads;" they've been told that their entire lives. If we "medicalize" these ailments, and remove some of the stigma, patients will then allow us to explore more of their psychological conditions. The psychological conditions often drive where we go with treatment.

## **Attention Deficit Disorder**

ADD is another important comorbidity. Often, in adults, the ADD goes unrecognized and untreated. ADD is common; studies have shown that about 4.7% of adults have it. When someone comes into the office, we are not looking at a just a headache, we are assessing the whole person. If we are able to concurrently manage the comorbidities, the patient will have a better quality of life. The stakes increase with age; at age 6, kids may not be doing well in school, but by age 26 they are losing their families and their jobs, and they are at a much higher risk for addiction. The risk of addiction for older adolescent boys, 18-20 year olds with ADD, is almost 75%, usually an alcohol problem. If the ADD is treated, the addiction risk decreases to 20-25%.<sup>5</sup> The stimulants prescribed for ADD often help the headaches.

Addictions are a comorbidity that complicate the treatment of a refractory patient. Ten to fifteen percent of the general population has an addiction problem. Treating pain patients in the face of addiction is complex and often requires several professionals, both medical and psychological.

## **Anxiety**

When the comorbidity is anxiety, it is usually generalized anxiety disorder. OCD is also common, and panic attacks are actually ten times more common in migraine patients than in the regular population. Separation or social anxiety tends to begin early in childhood. We often see social anxiety in high school

kids who miss days and even months of school, or are homebound. With these kids, simply prescribing meds is inadequate; we need to recruit psychotherapists in order to address the comorbid anxiety, depression, etc. Whether any adolescent should be homebound because of headaches is controversial. If an adolescent has been homebound, it helps to ease them back into school, possibly with a lighter schedule for some period of time.

### **Depression**

When the comorbidity is depression, it is usually major depression or dysthymia that we are talking about. Of course, many adults with depression are actually bipolar, or fit into the mild bipolar spectrum. Depression is often seen in headache patients, most likely due to shared inherited and environmental factors. Unipolar depression, whether it is major depression or dysthymia, is better recognized than bipolar depression. Up to 60% of adults with chronic depression fit into the bipolar spectrum. It is vital to treat both pain and depression, as they fuel one another. Patients do say, “Of course I am depressed. Wouldn’t anyone be with severe headaches?” My answer is, “Headaches do make the depression worse, but many people with chronic pain are not depressed. Depression is a separate, biological problem.”

### **Headache and the Bipolar Spectrum**

The relationship between bipolar illness and migraine has not been as well studied as depression and migraine. However, in several studies, the bipolar spectrum has been found at an increased rate in migraineurs. Recent studies confirm that at least 7% of headache patients fit onto the bipolar spectrum, whereas about 4.5% of the general population fits into the bipolar spectrum.<sup>6</sup> Studies which looked at the bipolar population found that 40 to 50% of bipolar patients have migraines, so there is a definite correspondence.

The clinical spectrum of bipolar disorders is an evolving concept. The DSM has historically inherent biases against independently diagnosing bipolarity, and bipolar II is defined very conservatively in DSM-IV. For example, in DSM-IV, the important hypomanic reaction to an antidepressant is not included

in helping determine bipolarity. Some authors feel DSM-IV has an inherent bias towards diagnosing personality disorders rather than bipolar disorders. These biases lead to bipolar disorders being missed and underdiagnosed. The name, “bipolar,” is unfair and misleading; the stigma inhibits the diagnosis. We need books and materials aimed at the milder end.

It is the milder end of the bipolar spectrum that tends to be missed; look for patients with persistently agitated, angry personalities, with frequent depressions and/or, “too much energy,” with a strong bipolar or depressive family history. They may not have had a clear hypomanic or manic episode. Soft bipolar signs include: early depression (beginning as teens), severe depression, quick onset depression, bipolar reaction to certain meds (up all night, thoughts racing, etc.) agitated and angry depression, very high anxiety and mood swings, poor response to medication, and moody personality. Sleep disorders are commonly seen. Cyclical depression, “for no reason,” with high anxiety, is common for bipolar depression. The therapeutic implications for recognizing bipolarity are enormous. These patients tend to bounce from antidepressant to antidepressant, with predictably poor results. Mood stabilizers (lithium, lamotrigine, “atypicals” such as quetiapine) are much more effective.

### **Personality Disorders**

It is crucial to recognize personality disorders within your practice. Approximately 10-15% of people have strong features of a personality disorder. There are a number of personality disorders, some of which are more dangerous and difficult to deal with than others. In general, characteristics of personality disorders include: lack of insight, poor response to psychotherapy or other therapeutic interventions, difficulty with attachments and trust, a sense of entitlement, the creation of a great deal of chaos and distress in family, friends and co-workers around the person, etc.

Personality disorders have a wide range of severity, from mild to very severe. They often flip between victim, rescuer and persecutor. When they turn persecutor, they can be dangerous to the person they have their sights set on. Personality disorder patients often create chaos and drama, and comorbid substance abuse is common. The more difficult personality disorders include paranoid, antisocial, borderline and narcissistic.

In general, therapy only helps people with personality disorders over long periods of time. Seeing a therapist for 5-7 years may help to some degree. However, our goals and expectations are limited. The concept of plasticity of the brain is very important, as some people do improve naturally over time. One study of borderline personality disorder in adolescence indicated that, by age 30, 1/3 of the subjects no longer had borderline personality. Many people do not fit neatly into any of these categories, but have features of two or three personality disorder types. Failure to identify those with personality disorders leads to increased risk for the provider and the patient. The small percentage of patients with moderate-to-severe personality disorders in a typical practice are the ones who create the majority of the drama, and legal and regulatory problems for the treating physicians.<sup>7</sup>

### **Medical Comorbidities**

As far as medical comorbidities in headache patients, the GI system is a common site, particularly irritable bowel syndrome (IBS). Most of our serotonin is in our gut, and certain medicines that help IBS increase or decrease serotonin. IBS is frequently seen in migraine patients, and very often we're trying to use medicines that help the GI symptoms as well as the headache. It is much easier to help patients who have primarily diarrhea, because some of our medicines, such as the older tricyclics, slow the gut transit time. Constipation is tougher to ameliorate.

**Hypertension.** A number of the antihypertensives do help decrease migraine. Most beta blockers will help, as will the calcium channel blockers. More recently, the angiotensin receptor blockers (ARB's) have been utilized.

**Insomnia.** Sleep disorders are frequently seen in headache patients. Insomnia is common, and the available treatments are not ideal. Of course, we should institute sleep rules and behavioral treatments. For patients with comorbid insomnia and headache, sedating tricyclic antidepressants may be of benefit. Also, certain muscle relaxants, such as tizanidine or cyclobenzaprine, may help both conditions. Of course, we need better meds for insomnia to come along.

**Fibromyalgia (or Chronic Pain Syndrome.)** We do have a few drugs that are indicated for fibromyalgia. Many people with fibromyalgia do have chronic daily headaches and insomnia. These groups overlap, not only with the pain, but the psychological comorbidities as well. Fibromyalgia patients share the allodynia commonly felt by headache patients. A number of medicines are used for both headache and fibromyalgia, such as tricyclics and muscle relaxants.

**Fatigue.** If you ask large groups of headache or migraine patients what their biggest problem is other than headache pain, it tends to be excessive daytime sleepiness. Fatigue is such a prevalent problem that we don't want to add medicines that fatigue people even more. There are no algorithms for headache patients; everyone is different. Suppose a woman comes in, 45 years old and 25 pounds overweight, and she is always tired. We don't want to prescribe amitriptyline or valproate, medicines that are going to make her more tired, and gain more weight. Some medicines do not exacerbate fatigue, such as protriptyline (Vivactil) or ARB's. Occasionally, we will use small doses of stimulants.

### **Outside of medicine**

It does take a village to treat a severe pain patient. We want to seek treatments outside of the pharmacy. We need to promote active coping. We must have other modalities involved. Pharmacotherapy may be important, but certainly we want to try everything else, whether it's physical therapy, yoga, biofeedback, etc.

Psychotherapy is often important. If it were up to me, the whole country would see a psychotherapist. However, whether it is because of money or time, most people don't go. Cognitive-behavioral therapy is the usual approach, but with personality disorders, we take more of a dialectical tack. It is important to identify the best therapists in your area, as the skill levels of psychotherapists vary widely.

**Acceptance.** Acceptance of the pain as an illness is a very important concept. There are actually scales that measure acceptance. The road to acceptance of a chronic illness can be littered with many wrong turns along the way, looking for sudden cures. But at the end, when people accept that they have a chronic illness, when they know they don't have to simply give up and suffer, when they know the situation is bad but there is quite a bit that they can do, they can accept that the pain is chronic and needs to be managed, and there is



no cure. This relieves a lot of the inner angst, where patients feel that there must be a cure. So we do promote acceptance. Acceptance does not mean resignation; people need to realize that much can be done about the headaches.

**Biofeedback.** Biofeedback is a very useful tool. I think that the providers who have been trained in the last 5 or 10 years often do a better job with biofeedback. The home-based therapies with relaxation techniques, where patients are taught by just giving them a booklet and tapes, can help, but a good biofeedback therapist is much more effective. When it is done well, biofeedback promotes an internal locus of control, which helps to promote self-efficacy. Exercise and yoga can have similar effects. We want people to feel that they can effect a positive outcome in their illness by doing something other than taking a pill.

**Resilience.** Resilience is an interesting concept. Resilience involves the early life experiences, plus genetics. Resilience can be viewed in individuals, couples or families. In looking at resilience in individuals, the serotonin transporter gene is crucial. There are two arms on the gene, which can be either short or long. If a person has two long arms on the serotonin transporter gene, it turns out that he is going to be a lot more resilient. His childhood may be unhappy, but when the person has two long arms on the gene, he usually turns out very well. If the patient has an abusive childhood, and he has two short arms on the serotonin transporter gene, it is almost a certainty that he is going to have major problems in life, possibly borderline personality disorder, or some other major psychiatric problem. So resilience is very important in view of who can cope despite severe headaches, and who ends up disabled.

**Disability and Catastrophizing.** One might think that the pain level is the major predictor of disability. It has been shown, in well-done studies, that other factors are probably more important. Catastrophizing is one of these factors, i.e., a patient who seems to think his headache is always a 14 on a scale of 1 to 10. Part of my job is to turn down the volume and limit the drama. We can talk to people about catastrophizing, and work on the fear that underlies it. Catastrophizing by proxy also happens, where a parent thinks his child has the worst headaches on the planet and even says, "Have you ever seen such bad headaches in a kid before?" Studies of disability have shown that some of this is the result of fear of pain.

Some people have more fear and anticipation of pain than others; as with catastrophizing, fear of pain can be worked on through therapy.

**Neck and Occipital Pain.** Physical therapy can be very helpful when there is associated pain in the neck and shoulders. At least half of headache patients have neck pain, particularly with their migraines. I often advocate physical therapy; chiropractic treatment can also be very helpful. It depends, of course, on the individual practitioner; there are better medical doctors than others and there are better physical therapists than others. It is worthwhile to establish a relationship with the best chiropractor in your area, one who is good with headaches and neck pain. Occipital pain may be derived from the cervical region, and doing blocks or injections may help. Always think about treating the whole person; if they have fibromyalgia or other pains, the treatment should include those conditions.

**Dental, Massage, Acupuncture.** Dental consultations may help when people are clenching their jaws, and certainly if they are bruxing. Massage can benefit a wide range of patients, as can acupuncture. It's been difficult to prove in studies that acupuncture is more effective than sham treatment. After examining over 500 randomized controlled trials of acupuncture for various conditions, nothing definite can be concluded as far as efficacy.<sup>8</sup> I think, with many pain studies, the outcome of the study can be predicted from how robust the placebo response is. Unfortunately, with acupuncture studies, when the sham acupuncture is performed along with the real acupuncture, there is going to be a robust placebo response. It has been difficult to prove efficacy over placebo. But, there are patients who do very well with acupuncture. Acupuncturists are another one of the "villagers" whom we recruit to help take care of pain patients.

### **Medications: Abortives**

Most people with migraines do not need preventive medicines, particularly when they don't have comorbidities, or not enough headaches. There is no good algorithm that applies to headache treatment. How many headaches a month are too many? With two headaches a month that are severe and prolonged and are not relieved by drugs, we might use preventive medicine. For another person with five headaches a

month, who can take an Excedrin or a triptan and obtain relief, we may choose to not use preventive medicine, because all of the medicines have their possible side effects.

There are many choices among the triptans. Injections of sumatriptan are probably the most effective. A newer tablet, Treximet, combines sumatriptan (Imitrex) with naproxen. It is reasonably effective at keeping the headache from returning. All of the triptans do work; unfortunately, they are all expensive, and have annoying side effects. The triptan nasal sprays, particularly Zomig, can be very effective, bypassing the GI tract. Side effects of tingling and pressure may initially occur with the triptans, followed by the headache lifting away. Since 1992, we have had over 85 million people treated with the triptans. I think safety has been well established. We have become more comfortable using triptans in higher risk populations. I am not saying that we want to use them in someone at high risk for cardiovascular problems, but we will use them more than we did 10 or 15 years ago. If one triptan is ineffective, I usually will use one or two more before giving up on the class.

Outside of the triptans, most patients have tried over-the-counter products. Aspirin and metoclopramide together sometimes help. MigraTen is an interesting product; it was available in the 1980's as Migralam. For those intermediate headaches, it is pretty good, and MigraTen is not addicting. I advise patients to avoid other caffeine on the day they take MigraTen. We do want to limit the caffeine, and there is a considerable amount, 100 mg., in MigraTen. It doesn't contain aspirin, so it is better than Excedrin, and it has a vasoconstrictor. It is a good product that fits the bill for many headaches, but, as with any caffeine-containing med, MigraTen should be limited to one or two per day.

DHE is probably underutilized. Migranal nasal spray is safe, but is not always effective. The DHE injections work better. Since 1945, when DHE was introduced, there have been relatively few bad side effects reported. It is primarily a venoconstrictor, so it is actually safer than other ergotamines, which are arterial constrictors.<sup>9</sup>

The antiemetics, such as ondansetron, can work wonders. Ondansetron lets people go on with their day without sedating them. We use the others also, such as metoclopramide or prochlorperazine. The goal is to keep people out of the ER, and the antiemetics can help in this regard.

I do use opioids and butalbital in some patients. We limit their use; they often lead to more problems, but 9 out of 10 patients do not overuse them. It's the one patient out of 10 who can create a lot of problems, of course. Butalbital is controversial, and is not used in Europe. It does lead to more rebound headaches than analgesics, and rebound is always a concern. Opioids and butalbital medicines are a major source of the transformation of episodic headache into daily pain.

Occasionally we will use injectable opioids, or fentanyl oral suckers. In my experience, the problem with fentanyl oral (Actiq), which is now out in generic form, has been that many people will abuse the fentanyl. The quicker-onset medicines do tend to be overused, and there are more withdrawal symptoms. Actiq does work quickly, and there have been a couple of small headache studies involving Actiq. Again, to keep people out of the emergency room, we will occasionally use parenteral opioids. The antiemetics can also keep people out of the emergency room. As a last resort, when sedation is needed, we will occasionally use some meds off-label, such as quetiapine (Seroquel), or benzodiazepines.

When nothing works for refractory headaches, particularly prolonged menstrual migraines, we do use corticosteroids, but in limited amounts. It is important to minimize the cortisone dose. We use dexamethesone, 4 mg., ½ or 1 every 12 hours, or Prednisone, 20 mg., ½ or 1 every 12 hours. I would usually limit these to three or four tabs a month, at most.

### **Chronic Daily Headache Meds**

Each person is different, of course, when it comes to preventives. The comorbidities guide where we go. Patient preferences are important, also; patients have to be willing to put up with possible side effects. We tend to use more preventives in people with chronic daily headache than in semi-monthly migraines.

Chronic daily headache is basically defined as headaches at least 15 days per month. About 3% of people, in almost every country that has been assessed, have chronic daily headache. Chronic daily headache greatly decreases one's quality of life. It is a major problem, it is difficult to treat, and most analgesic overuse stems from chronic daily headache. The severity of the daily headache is important. Some people will say, "My daily headaches don't bother me, they're mild; it's the severe migraines that are

important.” Other people say, “It’s these daily headaches that are the problem, the migraines are easily taken care of.” We aim our preventive meds at the predominant, more severe type of headache.

With chronic daily headache, we need to limit the drugs prescribed as abortives. If patients are taking OTC medications, and need to take more than two a day, we must consider daily preventive medicine. We might consider Norgesic forte, which is orphenadrine, aspirin and caffeine, or MigraTen. Neither of these is addicting. The problem is that all abortives for daily headaches have their own side effects. There is a longer-acting form of tramadol, but tramadol is a mild opioid agonist, and is somewhat addicting itself. Whatever is used abortively for CDH should be strictly limited to two per day, on average.

### **Abortives and Rebound Headache**

The abortives for chronic migraine are basically the same as for episodic migraine. We don’t want to use triptans every day, except in unusual circumstances. Rebound headache is always a consideration, and is remarkably complex; it involves a complicated pathophysiology at the brainstem level. The major question with rebound are which drugs, and how much of the drugs, will trigger it. It appears that the butalbital and opioid meds, and the high caffeine drugs such as Excedrin, may be more likely to cause rebound. Rebound does tend to be somewhat overdiagnosed. The situation with nsaids and rebound is interesting. It appears that in patients with 10 days or less of headache per month, certain nsaids may trigger rebound. However, for those with CDH, nsaids are less likely to cause rebound.

### **Preventives: Long-term Results**

The goal with preventives is to help reduce the headache by 25 to 75%. If patients think their headaches are going to be completely cured, they may come back and say, “The medicines are not working because I still have some migraines.” They may be 50% better, which is often as good as we can achieve. Headache diaries can help, but we also need to convey realistic goals to the patient. In my experience, only 50% of people do well on long-term preventives. I’ve done two long term studies, looking at usage over a year’s time, with a total of nearly 800 patients on preventives. Only 46% found any preventive they could

tolerate and that worked for at least nine months.<sup>10</sup> The other group discontinued preventives for various reasons. We have a ways to go; we need much better preventives.

### **Natural Remedies**

Natural remedies can be useful. Petadolex is an improved form of the herb butterbur, where the molecule that we worry about in butterbur is limited. Petadolex is effective, and holds up well in RCT's. It is popular in a number of countries; for instance, in Germany, Petadolex is the number one preventive. I find it is more effective than feverfew, etc. In my years of experience with Petadolex, very few side effects have been reported. Occasionally there is an upset stomach or a bad taste in the mouth. Most people in the US order Petadolex directly from the company (1-888-301-1084). We also use feverfew, magnesium, vitamin B-2, omega-3's, and others. I think the Petadolex and magnesium are the most consistent. Feverfew lags behind as far as efficacy, but it is fairly safe. I have not found vitamin B-2 to be very helpful in the long term.

### **Tricyclics**

As the prescription drugs go, the tricyclics are important. With amitriptyline and nortriptyline, we do see weight gain, dry mouth and constipation, but we use small to medium doses for most patients. I will start a patient at 5 mg., half of a 10 mg. tablet of amitriptyline; it is very cheap. The cost of medicine has increased but the generic tricyclics are very inexpensive. Some people remain on 10 mg. or 20 mg. a day of amitriptyline for years, and do very well. Amitriptyline is metabolized into nortriptyline, so by using capsules of nortriptyline we see fewer side effects. Protriptyline is the only tricyclic that does not cause weight gain, but it does have increased anticholinergic side effects. With protriptyline, we will have dry mouth and constipation, but it can help chronic daily headache with minimal sedation and without the weight gain, which can be crucial.

## **Anticonvulsants**

The primary anticonvulsants have been topiramate and sodium valproate (Topamax and Depakote.) These are indicated for migraine. With topiramate, we often see memory problems and spaciness, and occasionally depression as well. As the dose is increased, tingling will occur, due to carbonic anhydrase effects. Headache patients often quit the preventives due to annoying side effects, so it is crucial to keep the dosage to a minimum. We try to start low and build up the dose. With topiramate, I will slowly increase towards 50 mg., and then towards 100 mg. if needed, but many people do well on 25 or 50 mg. The average dose has been 100 mg. Sodium valproate (Depakote) will cause more weight gain; topiramate may cause weight loss. The anorexic effects of topiramate do wane over a number of months, unfortunately. However, with sodium valproate, we see the weight gain often contributing to discontinuation. Of course, we do not want a patient to become pregnant while on sodium valproate. We will start with 250 mg. of sodium valproate and move up the dosage very slowly. Many other anticonvulsants have been used with less solid evidence. Oxcarbazepine (Trileptal) has failed in several headache studies, though it has been positive in some bipolar studies. Sometimes it does help moods, and if a patient is at the mild end of the bipolar spectrum, has daily headaches and cannot tolerate the other drugs, oxcarbazepine may be useful. Zonisamide (Zonegran) has been used; it's a once-a -day, longer-acting, relatively safe anticonvulsant. Fatigue is the primary side effect. Zonisamide is usually started at 25mg. at night, and slowly titrated up to 100 mg.

## **Antihypertensives and Muscle Relaxants**

The antihypertension meds are useful as preventives: beta blockers and calcium channel blockers are the ones most commonly prescribed. There have been studies on the angiotensin renin blockers (ARBs). We encounter fewer side effects with ARBs. Remember, tiredness and weight gain are major problems in migraineurs, and beta blockers exacerbate fatigue and weight gain. So I often use one of the ARBs: Atacand is the main ARB that's been studied, but others have been utilized. Muscle relaxants certainly can help the associated neck pain and may aid sleeping. Tizanidine is non-addicting and is fairly safe, but we

use it mostly at night due to the sedation. Cyclobenzaprine now has a longer-acting version called Amrix but the generic cyclobenzaprine is inexpensive, and the tablets can be cut in half. Sedation is often a problem with these muscle relaxants.

### **Refractory Headache: Botulinum Toxin Type A**

Botulinum toxin type A (Botox) has been an interesting compound. It's been daunting to prove that it works better than placebo, as the placebo response has been high in several of the Botox studies. In one major study, the placebo response was only about 21%, but in others, it has been higher. Placebo response in migraine preventive studies, across all trials, averages about 20-23%, although, for some reason, it is lower in North America than in Europe.<sup>11</sup> The placebo response also differs among countries in Europe. Placebo response is about 5% lower in North America, on average, than in Europe. In the Botox studies, the placebo response has led to failure in achieving the primary endpoint, which is unfortunate. Many patients do find that it works. They use considerably less medicine in the two to three months post-Botox, and they can feel the effects wearing off at two and a half months. We now have had many years of Botox use, and one could make the case that it is probably safer than most of the other drugs that we use, with fewer side effects. The mechanism for why it works could be due to calcitonin-gene related peptide (CGRP) antagonism. Results of a large, multicenter RCT from 2007-08 on Botox for chronic migraine are positive and fulfill the primary endpoints. This study could lead to an FDA indication.<sup>12</sup>

### **Long-acting Opioids for Refractory Headache**

What to do when nothing works? For refractory patients, long-acting opioids are a possibility. In my new study, I assessed patients using long-acting opioids over a period of six years.<sup>13</sup> We looked at comorbidities, and predictors of overuse. The people who tend to overuse are those who also overused short-acting opioids. If they overused hydrocodone, they tended to overuse the long-acting Kadian, Oxycontin and methadone. I didn't find many cases of pseudoaddiction. I found true addiction; for people who overuse the short-acting opioids, I am reluctant to prescribe the long-acting ones. We also assessed



bipolar, ADD, depression and anxiety, and personality disorders. The other predictor for overuse is the presence of a personality disorder. If people have more than a mild personality disorder, it does not usually work out well with the opioids. However, for the right person, these drugs can be lifesavers, improving quality of life and functioning. When nothing else works, taking morphine once a day, or twice a day in a low dose, can be effective. Not every doctor should prescribe the opioids; there needs to be careful patient selection and good psychiatric screening, and solid documentation with each visit. In many patients, opioids will lead to much better functioning, and they may not develop tolerance to the drug. Older patients, whose brains cannot do the “neuronal gymnastics” needed to become tolerant, may do well on the same low dose for many years. For a small group of refractory patients, the long-acting opioids may be worthwhile.

#### **Frequent Triptans: Sumatriptan, Rizatriptan, etc.**

There are many patients taking daily, or near-daily, triptans. Some are experiencing rebound headaches from the triptans, but they say, “If I don’t take my triptan, I have a severe headache and need to take 6 to 10 Excedrin!” I do think that we need more studies of people who have taken frequent triptans. I published one study of 100 patients, where we did cardiac echocardiograms and ECGs. In this particular study, no long-term adverse effects were found. The patients averaged near-daily triptans for almost 4 years.<sup>14</sup> I don’t advocate such frequent use, but many people do lapse into it. The physician must make sure that the headaches are not rebounds.

#### **Refractory Patients: Stimulants**

I do think there is a case for using stimulants in selected patients. They may help with fatigue, concentration and moods. In the right person, they are remarkably useful. For some people, stimulants improve the quality of life, and can help the headaches. There have been some validating studies, and I believe that stimulants are underutilized.

### **Refractory Patients: MAO Inhibitors**

We tended to use MAO inhibitors frequently in the '80s, but do so much less now. The right patient, who is refractory, sometimes with a difficult depression, may respond to MAOI's. Of course, drug interactions and dietary restrictions limit use.

### **Refractory Patients: Occipital Stimulators**

In refractory patients, the use of an occipital stimulator is controversial. I think it can help for a period of time, depending on the skill of the neurosurgeon. It is difficult to anchor the leads, and migration away from the occipital nerve often occurs. The pain implants and stimulators are coming along, but there are probably better treatments under development, such as magnetic stimulation.

### **Patent Foramen Ovale and Migraines**

The jury is still out on the issue of PFO's (the hole in the heart that may contribute to headache). One recent trial did not reach its primary endpoint, but the endpoint chosen was a very difficult one.<sup>15</sup> Several trials are still in progress, seeking to assess whether closure of a PFO will decrease migraines.

### **Conclusion**

Treating headache patients involves assessing the headache frequency and severity, and also the comorbidities. The psychiatric and medical comorbidities help guide us where to go. It "takes a village" to help a severe headache or pain patient; get the other villagers involved. These may include psychotherapists, physical therapists, chiropractors, etc. We want to achieve a balance between headaches and medication, and try to minimize drug usage.

Most patients do well with the usual ministrations, but for the refractory patient we need to do more. It may be a regimen that includes botulinum toxin injections, or opioids. When used appropriately, some of these "out of the box" therapies are the key to restoring a patient's quality of life.

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## Authors

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## Questions on the lecture, “Management of Chronic Headache.” Answer each as True or False.

1. The pain of migraine is usually accompanied by one or more of the following: nausea, dizziness, photophobia, sonophobia, osmophobia.
2. Triptans (sumatriptan, rizatriptan) are the first line drugs of choice for migraine.
3. The bipolar spectrum occurs in less than 2% of migraineurs.
4. Opioids should not be used in headache patients.
5. Migraine occurs in 4% of children at age ten.
6. Approximately 83% of headache patients find a headache preventive that works well in the long term.
7. The drugs most frequently associated with rebound headaches are: butalbital, opioids, and high-caffeine drugs such as Excedrin.
8. Biofeedback is not an effective therapy for headache patients.
9. “Sinus headaches” turn out to be migraine headaches about 5% of the time.

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**Answers on the lecture, “Management of Chronic Headache.”**

1. True
2. True
3. False; the bipolar spectrum is found in approximately 7% of headache patients
4. False; the opioids may be useful in certain refractory headache patients with proper screening and supervision
5. True
6. False; less than half of headache patients find a tolerable daily preventive that is effective long-term
7. True
8. False; biofeedback is a safe and effective alternative therapy for headache patients
9. False; sinus headaches are usually migraines