

Headache

(and Selected Psychological Topics) 2008-2009

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(over 800 headache articles)



About Dr. Robbins

In 2008, Dr. Robbins was awarded The Clinical Pain Management Award, by the American Academy of Pain Management. It is given to only one nationally recognized physician per year.

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The Dr. Robbins Show is an interesting internet health talk show, available 24/7, on headachedrugs.com (and talkzone.com).

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INFORMATION FOR HEADACHE PATIENTS

Non-Medication Strategies for Headache Patients

With migraine and chronic daily headache sufferers, we like to emphasize avoidance of triggers. The most common triggers are, in descending order: stress, weather changes, perimenstrually, missing meals, bright lights or sunlight, undersleeping, foods, perfume, cigarette smoke, after stress is over, over sleeping, exercise, and sexual activity.

Headache patients, in general, do better with regular schedules, eating three or more meals per day and going to bed and awakening at the same time every day. Managing stress with psychotherapy, exercise, yoga, etc., often will reduce the headaches. The “headache foods” tend to be overemphasized as a headache trigger.

Sleeping is crucial; sleeping on a regular schedule, and enough, usually helps.

Exercise for 15 to 20 minutes per day (or more) is often helpful for headache patients; if patients will do the treadmill, bike, or walk on average 15 minutes per day, they will achieve 80% of the goals of exercise. Relaxation techniques such as biofeedback, deep breathing, and imaging can be helpful for daily headache patients, particularly where stress is a factor. Regarding stress, it is not so much “bad stress”, but “daily hassles” that increase headaches. When patients are faced with overwhelming daily hassles, particularly when they cannot sleep well that night, headaches can be worse the next day.

Psychotherapy is extremely useful for many headache patients with regard to stress management, coping, life issues, family of origin issues, etc. Patients can often learn relaxation techniques from books or tapes that are readily available in bookstores, so that learning relaxation techniques often does not require extended visits to a therapist. If patients are willing and able to see a therapist, working with a therapist who teaches biofeedback can be very useful. However, even though we may recommend psychotherapy, it is crucial to legitimize the headaches as a physical condition; they are not a “psychological” problem, but rather a physical one that stress may exacerbate.

Yoga may be helpful for some headache patients. The idea is to take a class once weekly, and then do the yoga stretches and breathing for 5-10 minutes per day. This may help associated neck or back pain. Physical therapy may also be helpful. Massage may be useful, particularly for the neck pain.

The following are the general food lists including the sources of caffeine that we have found useful in migraine patients:

Foods to Avoid, and Sources of Caffeine:

(Foods are often overemphasized as triggers)

You may or may not be sensitive to any of the following foods. If a particular food is going to cause a headache, the headache will usually occur within three hours of eating. Also, the response to the foods may not be consistent. On one occasion, you may have a headache caused by a particular food; however, the next time you eat that same food, it is possible that a headache may not occur.

While foods are not as common a headache trigger as stress, weather, hormones, missing meals, bright lights, and undersleeping, some patients are sensitive to the following:

- Monosodium Glutamate (MSG) – also labeled Autolyzed Yeast Extract, Hydrolyzed Vegetable Protein, or Natural Flavoring.
 - ◆ Possible sources of MSG include broths or stocks, seasonings, whey protein, soy extract, malt extract, caseinate, barley extract, textured soy protein, chicken or port or beef flavoring, smoke flavor, spices, carrageenan, meat tenderizer, seasoned salt, TV dinners, instant gravies, and some potato chips and dry-roasted nuts.
- Red Wine (White wine is not as likely to trigger a headache)
- Beer
- All alcohol can trigger a headache; beer and wine are the worst offenders
- Chocolate
- Citrus Fruits, ripe bananas.
- Ripened, aged cheeses (Colby, Roquefort, Brie, Gruyere, cheddar, blue, brick, mozzarella, Parmesan, boursalt, Romano) and processed cheese.
 - ◆ Not likely to trigger headache: cottage cheese, cream cheese, and American cheese.
- Hot dogs, pepperoni, bologna, salami, sausage, canned or cured meats (bacon, ham), aged meats, or marinated meats.
- Nuts, peanut butter, large amounts of Nutrasweet.
- Yogurt, sour cream.

Caffeine

While caffeine can help headaches, the overuse of caffeine may increase via rebound mechanisms. Some patients do not suffer rebound headaches from the ingestion of 500 mg. of caffeine per day, while others develop rebound headaches with as little as 30 mg. In general, I like to limit caffeine to 150 mg., or at most, 200 mg. per day.

The average 8 ounce cup of coffee has 75 to 125 mg. caffeine. Drip coffee is stronger than percolated, and instant is the weakest form. Depending on the size of the cup and its strength, instant coffee may contain from 40 to 150 mg., but is usually closer to 40 mg. Decaffeinated coffee contains from 2 to 5 mg. per cup. However, the caffeine levels may be much higher at restaurants and coffee houses. These calculations all depend upon the strength of the product and the brew. Specialty coffeehouses (Starbucks, Caribou, etc.) often contain twice the usual amount of caffeine per cup.

Tea usually contains 30 to 50 mg. of caffeine per cup, and soft drinks average approximately 40 mg.

Chocolate contains 1 to 15 mg. of caffeine per ounce; however, cocoa has considerably more caffeine, up to 50 mg. for an 8 ounce serving.

Caffeine is available in both food products and as tablets or capsules. Caffeine tablets such as NoDoz, Tirend, and Vivarin are available, but I do not use the higher strength products. Beware of “energy drinks.”

When patients find that caffeine significantly decreases their headaches, I will occasionally utilize the pure caffeine tablets, with a dose of 1/2 of a 100 mg. pill (50 mg. total) every 3 to 4 hours as needed. At times, it is helpful to combine the caffeine with medications that do not contain caffeine.

In whatever form that patients receive caffeine, whether in coffee, caffeine pills, or combination analgesics, it is necessary to limit the total amount of caffeine. The maximum amount of caffeine to take each day varies from person to person, depending upon their sleeping patterns, the presence of anxiety, and their sensitivity to possible rebound headaches.

Caffeine Sources

Limit caffeine to 150 mg. per day, or, at most, 200 mg. per day

Coffee: 8 ounces: average cup: 75-125 mg.

drip is stronger than percolated, which is stronger than instant

instant = 40-150 mg. per cup, usually closer to 40 mg.

decaf = 4 mg. per cup (but may be much more)

latte = 90 mg

Tea: 8 ounces: average cup: 30-50 mg.

Soft drinks: approximately 40 mg. per cup

Chocolate: 1-15 mg. per ounce

Cocoa - 50 mg. per 8 ounces

Caffeine tablets: (NoDoz, Vivarin, Tirend) = 100 mg. of caffeine

Caffeine is present in many analgesic medications, such as Excedrin Migraine (65 mg.), Anacin (32 mg.) and Vanquish (33 mg.) MigraTen has 100mg. of caffeine.

Characteristics of Migraine, Chronic Daily, and Cluster Headache

Characteristics of Migraine:

Attacks are 4 to 72 hours

Moderate or moderate-to-severe pain

History by the patient gives the diagnosis, not lab tests

Often early morning, but may be anytime

Unilateral in one half of patients

One to five migraines per month is typical\Gradual onset of pain, a peak for hours, slow decline

Pain is throbbing, pounding, pulsatile, or deep aching

Sharp “ice-pick” jabs are common

Peak ages are between 20 and 35 years

18% of women, 7% of men experience migraine in their lifetime; female/male ratio is 3:1

Family history is often positive for migraine

Associated nausea, photophobia, blurred vision, phonophobia, dizziness is common; however, these may be absent

In women, there is often a positive relationship with menses

Cold hands and feet, or motion sickness is common in migraine patients.

Criteria for Chronic Daily Headache (CDH):

1. Chronic tension headache; more than 4 hours per day, and 15 or more days per month. The chronic daily headaches usually evolve over a period of months or years.
2. Transformed migraine: more than 4 hours per day, and 15 days per month. Previous history of migraine. There is usually a slow increase in tension type headache, with a concomitant decrease in migraine features. No organic causes. Eighty percent of transformed migraine patients have been reported to overuse analgesics. The analgesic abuse may create the daily headaches in some of these patients. Most common reason for daily headache. “Chronic Migraine” is a term for frequent/daily headaches with migraine features.
3. New daily persistent headache: sudden (over 1 to 3 days) onset of chronic daily headache. No significant previous migraine history, but patients may have had episodic tension headaches in the past.
4. Posttraumatic chronic daily headache: often present with migrainous features. Very difficult to effectively treat. Does not seem to be responsive to the usual medications.
5. Headache associated with cervical spine problems, particularly arthritis: usually posterior occipital. Can be exceedingly difficult to effectively treat.
6. Chronic migraine: CDH that has migraine features (throbbing pain, one-sided, with nausea, sensitivity to light or sound, dizziness).

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Links Connecting Tension and Migraine Headache:

Both respond to similar medications: antidepressants and Triptans.

Similar serotonergic changes are found in tension and migraine headache patients.

Neck pain and muscle spasm are common to both tension and migraine.

Family history of headache is present in both migraine and tension headache patients.

Cranial muscle tenderness and cerebral blood flow changes are common to both conditions.

Mild migraine is very difficult to clinically distinguish from a severe tension headache.

The vast majority of patients with CDH also experience migraine.

Typical Characteristics of Patients with Cluster Headache:

Begin between ages 20 and 45, approximately 1 out of 250 men

Male predominance (3:1)

Same time of year, with no headache in between the cluster cycles

Primarily nocturnal attacks

During cluster cycle, alcohol triggers the headaches

Severe, excruciating, unilateral pain, usually periorbital, 45 minutes on average

Ipsilateral rhinorrhea, lacrimation, conjunctival hyperemia, sweating of the forehead, Horner's syndrome

90% of patients have episodic cluster, with breaks between cycles of months.

10% suffer from chronic cluster, with no significant breaks.

Keys to Headache Management

1. Watch headache triggers (sleep on a regular schedule and get enough sleep)
2. Treat a migraine early in the headache
3. Do not overuse pain meds/abortives; try and limit to 3 days a week
4. If appropriate, treat with preventative meds (Botox is a preventive)
5. Watch sleep and eating, exercise, do yoga or other relaxation techniques.

Exercise, Weight Loss and Supplements for General Health

Exercise

Exercise will sometimes help headaches. It certainly is crucial for weight loss.

To get 80% of the benefits of exercise, you only need to think of exercising in little chunks of time - 10 to 20 minutes. Most people are able to fit it more easily into their life when thinking this way. First thing in the morning, getting up and walking or using the treadmill or riding the bike for 10 or 15 minutes provides you with at least the minimum daily exercise. We are looking for 20 to 30 minutes on average, but 10 or 15 minutes will do. For weight loss, we need to increase it to 40 to 60 minutes daily. Having a treadmill or a bicycle at home, a headset for walking, or belonging to a health club can help.

Weight Loss (visit www.sparkpeople.com= good free site)

Permanent weight loss is difficult. It takes a huge effort, and a change in life style and behavior. It never comes about by saying "I need to watch my weight, lose a few pounds and exercise". It only really comes about via a concerted effort where exercise and weight control are a main project in your life. You need to get up that morning thinking about it and thinking how am I going to get my exercise and what am I going to eat today. Recently, a university studied over 5000 people who kept weight off long-term. Some of the keys to long-term weight loss, which all of these people seemed to find on their own, included the following:

7 Keys to Long-Term Weight Loss

1. Exercise 40-60 minutes daily (walking, biking, treadmill)
2. Graze (small meals throughout the day)
3. Portion control
4. Count calories (or points; Weight Watchers is a good program)
5. Weigh yourself often
6. Eat low-fat foods
7. Do NOT diet

Supplements for General Health

Most herbs/vitamins have not held up to scrutiny; many have turned out to be harmful. Even multivitamins are questionable, particularly in men (a recent study indicated that men who have prostate cancer may have a more severe form of the cancer if they were taking multivitamins). The following have held up to scrutiny.

Calcium

As we age, our absorption of calcium goes down. After age 45, most people, particularly post-menopausal women, should probably take calcium supplements. Calcium is found in milk, yogurt, cheeses, broccoli, tofu, some fruit juices or fortified cereals, and some other foods.

Calcium citrate has advantages over calcium carbonate. Citrocal Caplets plus D are a good form of calcium and D; they have 315 mg. of calcium plus 200 IU of D; the usual dose is one or 2 twice a day. Our system cannot absorb more than 500 mg. of calcium at one time. Consult your physician. To learn about calcium, www.nih.gov (and then search calcium) is a good site.

Vitamin D

Vitamin D is important for skin and bones, and it helps to prevent a number of cancers (and probably Multiple Sclerosis). Most people in colder climates are low in Vitamin D, as we are not in the sun enough. 1200 units per day should be taken, at least, of Vitamin D3, not D2. Almost all Vitamin D supplements (but not the D in multivitamins) are D3, which is the kind that we want. Most people need to take a Vitamin D supplement. Do not take more than 2,000 units of D without consulting your physician. If you take calcium with D, you probably still need to take an extra D supplement.

Omega-3's (Fish/Fish oil/Flaxseed)

These have held up as beneficial for the heart, moods, and possibly headaches. Eating fish is good, particularly fatty fishes (tuna/salmon/trout/mackerel), and fish oil supplements are also beneficial. On the back of the fish oil bottle, choose the brand with the most EPA and DHA. Taking 1 or 2 per day is recommended. In studies, much higher doses have been utilized. Flaxseed capsules, or flaxseed itself, is also helpful. There are other sources of Omega-3's, such as tofu (and soybeans), walnuts, and canola oil.

Aspirin

If you are at risk for heart disease, your doctor may recommend daily aspirin. Aspirin may help prevent heart attacks, strokes, and certain cancers. The dose is usually one (325 mg.) aspirin (Bayer or generic) a day. Baby aspirin (81mg) or _ aspirin (162 mg.) may be sufficient. The dose varies from person to person. Eventually we will test people's blood to determine the correct dose. In general, I recommend one (325mg) aspirin per day. Aspirin can cause stomach ulcers; if it hurts your stomach or causes heartburn, stop it. Consult your physician.

Biofeedback Training for Headache and Anxiety

Biofeedback is a technique for developing greater awareness of and voluntary control over physiological processes (like muscle tension) that are often beyond our awareness and control. Sensitive recording instruments are used to measure and "feedback" physiological information back to the client about processes like muscle tension and skin temperature in order to develop control over them.

In recent years, biofeedback techniques for treating headaches has improved significantly. In the past, the focus was often on reducing tension in the forehead and increasing blood flow. But these approaches, while still useful today, sometimes miss tension in the shoulder and neck region that is linked to headache. We know, for example, that headache patients tend to carry higher tension levels in their shoulders when under stress when compared to those without headache. They also take longer to recover to lower levels of muscle tension in these areas after stress. Accordingly, a major focus of current headache treatment is on muscle tension in the shoulder area.

Like headache patients, those suffering from high levels of anxiety use biofeedback training to gain greater awareness of how their bodies respond to stress. This is done to help the client develop a more effective and complete relaxation response. Individuals with high levels of anxiety experience more autonomic nervous system arousal and slower recovery than those with less anxiety. Biofeedback training targets these physiological processes. It is important to be trained by a good Biofeedback person; once you know how, you do it on your own (it is a limited # of sessions).

Who Conducts the Biofeedback Sessions. Joshua Levy, PhD, is a certified biofeedback therapist and a family therapist. He received his doctorate in social work from the University of Chicago. Dr. Levy has completed post-graduate training at the Chicago Center for Family Health, an affiliate of the University of Chicago, and at the University of Illinois, Department of Psychiatry. He has completed biofeedback certification with the Stens Corporation, a leading provider of advanced biofeedback training. He is the therapist on staff at the Robbins Headache Clinic, and Associate Faculty at the Chicago Center for Family Health.

To Find Out More or Schedule an Appointment. You can leave a message for **Dr. Levy at (312) 321-6047**. He would be happy to answer any questions about his work with headache or anxiety patients.

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Clinical Pearls for Treating Headache Patients

1. Legitimize the headache problem as a physical illness. Statements such as “headaches are just like asthma, diabetes or hypertension: a physical medical condition” go a long way toward establishing trust between the patient and physician. When we mention that it is a medical condition, primarily inherited, and that there is too little serotonin in the brain in people with headaches, patients respond exceedingly well to this. Once we have established this, the patients are much more amenable to addressing anxiety, depression, etc. with therapy or other means. However, if we focus on the patient’s stress, anxiety, depression, and psychological comorbidities, they are often turned off to the physician unless we do state that we are treating the headaches as a legitimate medical illness.
2. We must try and achieve a balance between medication and headache; I tell the patients that we are trying to improve the headaches 50% to 90%, while minimizing medications.
3. The initial history and physical is the best time to consider a differential list of medications, because at that point we have a good grasp of the patient’s comorbidities. If we list in the chart the other possibilities (in case our initial medications do not work), later we (or our partners) do not have to reconstruct the entire history with the patients.
4. In choosing preventives, look at comorbidities, particularly: anxiety, depression, insomnia, gastritis, GERD, IBS, constipation, hypertension, asthma, and sensitivities or allergies to other drugs. These often determine which way to proceed with medication.
5. Keep track of sensitivities and allergies to medications in a prominent place in the chart. If the patient has had severe reactions to two SSRI’s, a third is not a good choice. However, those reactions may not be readily apparent in the chart. If they are extremely fatigued on one β -blocker, a second will probably not work for the long term.
6. It helps to view chronic headache as a continuum or spectrum. The “in between” headaches may not fall neatly into the current tension or migraine categories. Whether these are severe tension or milder migraines, they often respond to the same medications.
7. Start with low doses of medication, particularly with antidepressants and other preventives. Headache patients tend to be fairly somatic, and there is no need to push medicine very quickly. One exception to this is in patients with severe “new onset daily persistent headache”; these patients may be less patient.
8. Keep a drug medication flow chart. Headache patients are constantly having medications stopped and re-started, and over ten years, a patient may have been on 50 different medications at various times. It is impossible to piece through forty progress notes trying to determine what the next best course of action is. A drug medication flow chart from the beginning helps immensely.

9. When we place patients on antidepressants, we need to make it clear that we are trying to directly help their headache by increasing serotonin. We also state that we certainly hope this helps anxiety, depression, etc. Patients are often confused as to the reason why they are given an antidepressant. It helps if we make it clear that we are not trying to treat their headache by treating depression.
10. Watch for soft bipolar signs in headache patients who have anxiety and depression. Bipolar disorder tends to be underdiagnosed, and the clinical stakes for missing it are enormous. The Bipolar spectrum fits about 4.5% of the population. Bipolar disorder, primarily mild and soft (Bipolar II or III), is seen in as many as 6% to 8% of migraineurs. While some of these patients will do well on an antidepressant, it is almost always necessary to add a mood stabilizer (Depakote, Lamictal, Atypicals, etc.). See Bipolar section.
11. Many patients are frustrated by the lack of efficacy and/or side effects of daily preventives. Tell them that only 50% (at most) of patients achieve long-term relief with preventives. This helps them to realize they are in a big boat, and that it is not their fault. Preventives do not work for everyone, and it is unfair to label people as “drug overusers”; if preventives do not help, we are just left with abortives.
12. We need to stick with preventive medications for at least four weeks (or longer); if we abandon them too soon, we may not see the beneficial effect. However, few patients are willing to wait months for positive benefits from a medication.
13. We cannot promise patients that their headaches will improve with psychotherapy (as it often does not), but coping with headaches and the stresses that headaches produce is often improved with therapy. Unfortunately, because of stigma, time and money, only a small minority of patients will actually go to a therapist. However, those that do go will usually benefit. Biofeedback is underutilized, and should be offered more often.
14. Patients with chronic daily headache may view the headache situation in black and white terms; they will come back for a return visit and state, “Well, I still have a headache everyday.” They need to accept that if we have gone from moderate to severe headaches (7 on a scale of 1-10) to mild to moderate (4 on a scale of 1-10), that the situation is improved and we should not change all the medication. If the patients keep a headache chart or calendar, this may help. Patients need to be willing to accept 50% to 90% improvement in frequency and/or severity.
15. While most patients are honest about analgesic use, some are embarrassed to tell us how much they are utilizing. Between OTC analgesics and herbal preparations, many patients are consuming larger quantities of medications than we realize.

16. Weight gain is a major issue; even though a drug may be more effective, choosing one that avoids weight gain (in those prone to it) is more likely to lead to long term success. Fatigue is another major reason for patients abandoning a preventive medication. Headache patients commonly complain of fatigue.
17. Do not confuse addiction with dependency; when treating chronic daily headache, dependency has to be accepted. Unfortunately, DSM-IV is inadequate in addressing prescription abuse.
18. What to do when nothing works: Before “giving up” on a patient with severe, refractory chronic daily headache, consider “end of the line” strategies such as: MAOI’s, daily long-acting opioids (methadone, Kadian, Oxycontin, MS-Contin, Duragesic), stimulants (dextroamphetamine, methylphenidate, phentermine), daily triptans in limited amounts, Botox injections, or combinations of approaches. In some pts. with difficult, refractory headaches, abortive medications are all that we have to offer.
19. Using a medication to establish a diagnosis may not be accurate. For instance, DHE or triptans have been effective for the pain of SAH or tumors.
20. Acceptance of the chronic illness (headache) is a helpful state of mind for patients to achieve. Acceptance is different than resignation. Acceptance helps to ease anxiety (“isn’t there a cure; these must be curable”). The road to acceptance may take years, and involve many doctors and alternatives.
21. When patients feel that they can actively help their headaches (“self-efficacy”), by medication or biofeedback or other means, it improves their sense of well-being. Whether by taking a medication, watching triggers, exercising, or doing Yoga, etc., increasing “self-efficacy” enhances outcomes.
22. It can “take a village to help a person with severe pain”. Don’t try and do it all by yourself; get other villagers involved. such as psychotherapy, massage, physical therapy, pain specialists, acupuncture, etc. Direct the patient to whichever of these other professionals is appropriate. Get other “villagers” involved.
23. Learn about and recognize personality disorders (Axis II). Many medical clinics allow a small number of personality disorders to drain much of the clinic’s energy. Get others (psychiatrists, etc.) involved and set limits
24. Pain pts. are often desperate, and search the internet for a cure, or seek alternative practitioners. We should not castigate them for doing so; they are just looking for answers.
25. When dismissing a patient from your practice(for abusive or drug-seeking behavior, or other reasons) do not abandon the patient; offer 3 other physician's names and #'s, suggest that you will transfer records and assist in any way to help obtain another physician, and give 1 to 3 months to find another provider.

26. In treating pain patients, utilizing pre-made stamps(or software with EMR) can be helpful for documenting that a discussion occurred about side effects, risk/benefits, limits, etc.. Opioid stamps for each visit include: level of pain and functioning, moods, overuse, physical exam(pupils/gait/speech).
27. Catastrophizing greatly inhibits pts. from improving; work with your patient on decreasing the level of catastrophizing and histrionics. This will improve the pain level and associated anxiety.
28. Heed red flags in your pts. on opioids; while pervasive behaviors help to determine addiction, even 1 red flag early in treatment should be seriously considered. For instance: you see a new patient, begin Tylenol#3; they call 4 days later and state 'I got the generic, the regular works better, can you call some in?'"
29. Kindling of the brain is important in depression, seizures, and headache: It is crucial to treat depression to remission, control seizures, and treat headaches. Possibly, if we treat younger pts. with frequent headaches fairly aggressively, we may prevent the progression into chronic daily headache.
30. For depression to improve, it is important to control pain and, likewise, to help pain, we must treat depression.
31. ADD in adults is common(4.7% prevalence); look for it, as ADD decreases QOL and is relatively easy to treat in adults. See section on ADD.
32. There are cultural and ethnic differences in perception and experience of pain; being aware of this can aid treatment.
33. In using opioids, you must be willing to say NO and set LIMITS.
34. What is pain: There is the official definition, but I like "pain is what the patient says it is, and it's as bad as the patient says it is".
35. Central sensitization is an important phenomenon that occurs in chronic headache, peripheral neuropathy, and probably also in IBS and fibromyalgia. Once this occurs, treatment is difficult.
36. The "level of pain" is not an accurate predictor of disability in chronic pain patients. Accurate predictors are active coping (versus passive), and catastrophizing (not good). Active coping is therapy / exercise / working / socializing, etc.

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Rebound (Withdrawal) Headache

Rebound occurs when a drug is used, or overused, and causes a headache later on, or the next day. The medicines that contain higher amounts of caffeine (such as Excedrin) are more likely to induce rebound. This is a murky area, as many patients are told that they have rebound when it is just their natural headache pattern. Some people have rebound from small amounts of caffeine, while others have no rebound from high caffeine doses.

A variety of meds may cause rebound: Nsaids (Ibuprofen, Advil, Naproxen, Aleve), Excedrin, Butalbital (Fiorinal, Esgic), Opioids (Vicodin, Codeine), and Triptans (Imitrex, Maxalt, Zomig, etc.). If a patient usually does not get a headache the 2nd day, and subsequently has a 2nd day headache after taking a drug, it may be from that medication. Or some people have 2 days / week of headache, go on a new abortive med., and within months have daily (or near daily) headaches; we then think about rebound.

We don't know the reasons (pathophysiology) behind rebound; probably brainstem pathway connections are involved. Many patients diagnosed as "rebound" have refractory (difficult to treat headaches), the daily preventives have not helped, and they are simply treating their headache with whatever works (Triptans, Excedrin, Opioids, etc.). Patients often say "the doctor diagnosed me as being in rebound; I had the same headaches for 10 years before going on that drug". We need to stop blaming the patients, just because are medications are not adequate.

The only practical management approach is to attempt to withdraw off of daily pain meds, daily triptans, and high-caffeine meds. We also need to minimize caffeine (but small amounts help headaches). A trial period of at least 4 weeks is suggested. However when I suggest this, the usual response is "OK, but what do I take in the meantime, I do have to function." We try and use a combination of preventives and to minimize the abortives for at least 4 weeks. There are various strategies for withdrawing off of daily pain meds.

The bottom line is: we do not know who gets rebound, and from which drugs. It is very individual, case by case situation. Practically, what we attempt to do, if possible, is minimize abortives.

First Line Migraine Abortive Medications

Triptans: Treat early in the migraine for better efficacy.

These may be combined with nsaids or analgesics. (see Triptan Section for side effects)

1. Sumatriptan (Imitrex): The usual oral dose is one 50 mg. or 100 mg. tablet, q 2-3 hours, 200 mg per day at most. The SQ (4 or 6 mg.) Imitrex is the most effective migraine abortive for more severe, faster onset migraines. The addition of an nsaid to a triptan may enhance efficacy, and prevent headache recurrence. Also available as a nasal spray. Over 70 million people have had Imitrex, and it has been utilized for 17 years. It is highly effective. Sumatriptan plus naproxen (in one tablet) is in development.
2. Maxalt: Very similar to Imitrex. Maxalt is very effective for migraine. The usual dose is one 10 mg. tablet, or the 10 mg. Maxalt MLT rapidly disintegrating tablets, which are placed on the tongue. These rapidly disintegrating tablets have a pleasant taste. Side effects are similar to those of Imitrex. Maxalt is very well tolerated. Certain patients tolerate one of these triptans better than another and it is worthwhile to try several in an individual patient. While some patients utilize the 5 mg. tablet, 10 mg. is well tolerated and more effective. The MLT form may be taken without water, which is an advantage.
3. Relpax is an effective and well-tolerated triptan. It is available in 20 and 40 mg. strengths, 40 mg. is the usual dose. The side effects have, in general, been found to be fairly minimal. These include possible nausea, pressure in the throat, dizziness and tiredness or weakness. Although chest pressure / pain / tightness may occur with Relpax, these symptoms have not been seen very often (only 1 to 2% of patients). In long-term studies, only 8.3% of patients discontinued the Relpax due to side effects. There have been excellent cardiac safety studies. Avoid with 3A4 inhibitors.
4. Zomig: Zomig, 2.5 mg. or 5 mg., is another very effective abortive. The usual dose is 5 mg. every three to four hours, as needed, two per day at most. Zomig ZMT, 5 mg., is a pleasant tasting dissolvable tablet. Like Maxalt MLT, it provides an alternative to the oral tablets. Zomig has the same general tolerability and efficacy profile as the others. Again, if patients do not tolerate one triptan, it is often worthwhile to try another because they may be able to tolerate another version. Zomig nasal spray is fast-acting and very effective.
5. Amerge: The usual dose is 2.5 mg. every three to four hours as needed, two or three in a day at most. Amerge is a “kinder, gentler, smoother” triptan. Amerge may take longer to work, up to two hours, but has a long half-life. With a half or one tablet of Amerge, most patients will not have more than minimal side effects. It is better tolerated than most other triptans, but somewhat less effective than Imitrex. Amerge is good for long lasting headaches or headaches of slow, rambling onset. Amerge can also be used as a preventive medication for menstrual migraine. If triptans are used as preventive medications, Amerge may be a good choice.

6. Frova is well tolerated. The long (26 hours) half-life is advantageous for those with prolonged migraines. Mean maximal blood concentrations are seen approximately 2 to 4 hours after a dose of Frova. Frova has been particularly useful for those with slower-onset moderate or moderate to severe migraines. Frova is available in 2.5 mg tablets. Frova has been effective for preventing menstrual migraines
7. Axert: Very similar to the other triptans, effective for migraine headache. The usual dose is one 12.5 mg. tablet, every 3 to 4 hours, 2 per day only. Side effects are similar to those of the other triptans; Axert is very well tolerated, "kinder and gentler." Axert is able to combine good efficacy with excellent tolerability.

Non-Triptan First Line Abortives

1. Migraten: MigraTen caps are a combination of 100mg. caffeine, 65mg. isomethaptane, and 325 mg. acetaminophe. Isophtheptane is a mild vasoconstrictor. The usual dose is one capsule every 2 to 3 hours as needed. I usually limit, with some exceptions, these to 2 or 3 per day only(due to the caffeine). MigraTen is not addicting and non-sedating. Because of the caffeine, it can cause nervousness or faster heartbeat. Patients with insomnia should not use it past 3pm or so; with high blood pressure MigraTen should be used with caution, and only if the pressure is controlled. MigraTen is helpful for the smaller headaches, as well as for migraines; it fits the need for a non-addicting medication that does not cause drowsiness. If used daily, we limit it to 2 per day only.
2. Migranal Nasal Spray: Migranal Nasal Spray is dihydroergotamine (DHE). This has been available since 1945 in one form or another with remarkably few serious side effects in all of that time. The usual dose is one spray in each nostril and you can repeat it, and often do need to repeat it, in 15 or 20 minutes. That would be the maximum for the day, which is two sprays in each nostril. Migranal is relatively well tolerated. As with the triptans, tightness in muscles, a flushing feeling, or slight chest heaviness can occur. Nasal stuffiness is relatively common with Migranal. Since DHE is primarily a venoconstrictor and is only a mild arterial constrictor, Migranal may be safer in the population with risk factors for cardiac disease. Migranal may also be useful for menstrual migraines, as it has a fairly long duration of action. Not as effective as triptans. The newer spray bottle is easy to use.
3. Excedrin (Excedrin Migraine): Useful as an over-the-counter preparation with 250 mg. aspirin, 65 mg. caffeine, and 250 mg. acetaminophen. Anxiety from the caffeine or nausea from the aspirin is common. One or two tablets every 3 hours as needed are effective for many patients with mild or moderate migraines. Excedrin Tension Headache is also available, but is less effective. This contains acetaminophen plus caffeine. Rebound may occur with overuse; 4 per day (and not on a daily basis) should be the maximum.

4. Naproxen (Anaprox, Aleve): Useful in younger patients, occasionally helpful for menstrual migraine. Nonsedating, but very frequent GI upset. The usual dose is 500 mg. with food or Tums to start, then may repeat in one hour (if no severe nausea), and then in 3 or 4 hours. Three per day at most. OTC as Aleve, 220 mg., and generic is available. Adding caffeine increases efficacy. Naproxen may be used at the same time as a triptan.
5. Ibuprofen: Over-the-counter, and approved for children. Liquid Advil is available. Occasionally useful in menstrual migraine. GI side effects are common. The usual dose is 400 to 800 mg., every three hours, limiting the total dose to 2,400 mg. per day. Combining with caffeine may be helpful. The short half-life is a drawback. May be used with triptans, even at the same time.

Second Line Abortive Migraine Medications

1. Ketorolac (Toradol = trade name): The injections are much more effective than the tablets. Patients may use the injections, 60 mg. per 2 cc at home. The syringes have changed, where Toradol is now available in vials, which the patient must draw up into the syringe. These have the advantage over the pre-filled syringes in that we can use a smaller gauge and shorter needle than was previously available. The usual dose is 60 mg., which may be repeated in 1 hour if necessary. Nausea or GI pain may occur. Ketorolac is nonaddicting and does not usually cause sedation. Limit to 3 per week due to possible nephrotoxicity. Generic is available. IV Ketorolac is very effective.
2. DHE Injections: Effective as an IV or IM injection, and occasionally as a nasal spray. DHE is safe and well tolerated. Nausea, leg cramps, and burning at the injection side are common. IV DHE is very effective in the office or emergency room. One mg. IM or IV is the usual dose, but this may be titrated up or down. Migranal is the brand name of DHE Nasal Spray. If it is the first time using DHE start with $\frac{1}{3}$ or $\frac{1}{2}$ cc only. A new (inhaled) form of DHE is in development.
3. Fiorinal, Fioricet, Esgic, Phrenilin: (see section on Butalbital Compounds for ingredients of these compounds). Fiorinal contains ASA, butalbital, and caffeine; Fioricet, Phrenilin and Esgic replace the ASA with acetaminophen. Generics of these compounds do not work well. These are addicting, but very effective for many patients. Dosage is one or two tablets or capsules every 3 hours, with a limit of 30 or 40 pills per month at most. Fiorinal #3 or Fioricet with codeine adds 30 mg. of codeine, and is more effective than plain Fiorinal or Fioricet. Esgic Plus adds additional acetaminophen to Esgic. Phrenilin contains no aspirin or caffeine, and is very useful at night, or in those with GI upset. Short-lasting tiredness, spaciness, or euphoria are common.

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4. Narcotics: Fiorinal with codeine, Vicoprofen, Vicodin, oxycodone, meperidine, etc. PO or IM, these are often the best of the 'last resort' approaches. IM, they are usually combined with an antiemetic. While addiction is a potential problem, the difference between dependency and addiction is crucial to understand. Ultram (Tramadol = generic) is milder, with relatively few side effects. Vicoprofen combines 7.5 mg. of hydrocodone with 200 mg. ibuprofen; generic is available and it is more effective than the other hydrocodone preparations because of the addition of ibuprofen, and generally is well tolerated. Actiq (Fentanyl oral) has been used in several small studies, but is not indicated for this use. Fentora (Fentanyl tablets) is similar to Actiq; it also is not indicated for headache.
5. Corticosteroids: Cortisone is often the most effective therapy for severe, prolonged migraine. Dexamethasone (Decadron) or Prednisone are the usual oral forms, and are dosed at 4 mg. of Decadron or 20 mg. of Prednisone, 1/2 or 1 every 8 to 12 hours, as needed. Smaller doses may also be effective. Three tablets a month is the usual maximum. These are very helpful for menstrual migraine. The small doses limit side effects, but nausea, anxiety, fatigue and insomnia are seen. IV or IM steroids are very effective as well. Patients need to be informed of, and accept, the possible adverse events.
6. Ergots: Vasoconstrictors, with many side effects, but usually effective. Use, at most, 2 days out of 7. Nausea and anxiety are common with ergotamine compounds. Cafergot adds caffeine to the ergotamine. Only compounded Cafergot PB is available. Suppositories are more effective than tablets. Rebound headaches are common with overuse of ergots. Use with caution after age 40, particularly with cardiac risk factors. Ergomar SL tabs are back on the market. Ergomar is an excellent brand, pure ergot with no caffeine. The Ergomar dose is 1/2 or 1 tab once or twice a day PRN.
7. Miscellaneous Approaches: Muscle relaxants (Soma, Valium) or tranquilizers (Klonopin, Xanax) are occasionally useful, primarily to aid in sleeping. IV Depacon (sodium valproate) is safe and can be effective. The newer "atypical antipsychotics", such as Zyprexa or Seroquel, may be occasionally useful on a prn basis. In the ER, IV Compazine or Reglan may be useful. Certain preventative medications (Depakote, Topamax, amitriptyline) may be useful on an "as-needed" basis, utilizing low doses every 4 to 6 hours PRN.

Antiemetic Medication

1. Promethazine (Phenergan): Mild but effective for most patients. Very sedating. Low incidence of extrapyramidal side effects. Available as tablets, suppositories and oral lozenges (formulated by compounding pharmacists). Used for children and adults.
2. Prochlorperazine (Compazine): Very effective but high incidence of extrapyramidal side effects. Anxiety, sedation and agitation are common. Given intravenously, it may stop the migraine pain as well as the nausea. Tablets, long-acting spansules, and suppositories are available.

3. Metoclopramide (Reglan): Mild, but well tolerated, commonly used prior to IV DHE. Fatigue or anxiety occur but are not usually severe. Five to 10 mg. are given PO, IM or IV. Pregnancy Category B (relatively safe).
4. Trimethobenzamide (Tigan): Well tolerated, useful in children and adults. Tablets, suppositories or oral lozenges may be used (lozenges formulated by compounding pharmacists).
5. Zofran: (Ondansetron = generic is available) 4 or 8 mg. PO, very effective with few side effects. Not sedating. Zofran is extremely useful for patients who need to keep functioning and not be sedated with an antiemetic. Most patients who use Zofran also utilize another less expensive antiemetic for other times. Available as oral tablets or as Zofran ODT, orally disintegrating tablets. Pregnancy Category B (relatively safe).

Information that Patients Need to Know Prior to Starting Prevention Medication

1. The realistic goals of the medications are to decrease the tension headache severity by 40% to 70%, not to completely eliminate the headaches. It is always wonderful when the headaches are 90% to 100% improved, but the idea is to minimize medication. Most patients need to be willing to settle for moderate improvement. Chronic Daily Headache is the toughest to prevent.
2. Patients must be willing to change medication, if necessary. They need to know that what is effective for someone else may not work for them. Trial and error may be needed to find the best preventive approach for that person.
3. The preventive medications may take weeks to become effective. The doses often need to be adjusted, and thus patience will be necessary with these medications. The physician needs to be available for phone consultations pertaining to the headaches and medicine.
4. Most preventive medications are utilized in medicine for another purpose. It is best if patients are informed, for instance, that Elavil is also used for depression, usually in much higher doses. Patients should be told why we are utilizing Evavil, and that it is not because they are depressed.
5. Side effects are possible with any medication, and the patient has to be prepared to endure mild side effects in order to achieve results. We cannot simply stop medication and switch to another because of very mild side effects. Most patients are willing to put up with mild, annoying side effects.
6. In the long run, preventive medications are only effective for approximately 50% of patients.
7. Preventive medications are individualized toward the patient's needs. We use a particular preventive depending upon the person's comorbidities, GI system, medication sensitivities, etc.

First Line Preventive Medications for Migraine

Patients with more than 3 migraines per month, that are not well controlled, may be candidates for preventatives. Those with CDH may be more likely to need preventatives. We choose a preventative based upon headaches and comorbidities (anxiety, depression, GI, etc.) The patient must accept the possibility of side effects. Preventives may take 3 to 6 weeks to work (at least 40% improvement). Start on low doses.

1. Topamax (topiramate): Topamax is FDA approved as a migraine preventive. This anti-seizure medication has been utilized for migraine, CDH, and cluster headache. It does not irritate the liver. Sedation and cognitive side effects (such as confusion or memory problems) may limit use. Topamax often decreases appetite, which leads to weight loss; this is unusual among headache preventatives. The starting dose is 25 mg. once or twice daily; this may be pushed to 100 mg. once or twice per day. 100 mg. daily is the usual dose. Acute glaucoma has been a rare side effect. GI upset may occur. Tingling sensations are common. With increasing doses, Potassium (fruits) may offset this. The risk of forming kidney stones is increased by the use of Topamax. Bicarbonate levels should be monitored, as Topamax may cause a dose-related metabolic acidosis. Usually well-tolerated in lower doses. May be effective for some milder bipolar patients. (mood stabilizer).
2. Valproate (Depakote): This seizure medication is a long time staple, popular for migraine prevention. Usually well tolerated in the lower doses utilized for headaches. Liver functions need to be monitored in the beginning of treatment. Side effects include lethargy, GI upset, depression, memory difficulties, weight gain and alopecia. Dosage ranges from 250 to 1500 mg. per day, in divided doses. The average dose is 500 to 1000 mg. per day. Levels need to be checked for toxicity on the higher doses. Depakote is also one of the primary "mood stabilizers" for bipolar. Available in 125, 250 and 500 mg. tablets. Depakote ER, 500 mg., is an excellent long-acting tablet that may be dosed at once daily. 250 ER is also available. Should not be used during pregnancy. As with most preventives, Depakote may not become effective prior to 4 or 6 weeks. Along with Topamax, it is FDA approved for migraine prevention.
3. Beta Blockers: Effective. Long-acting (LA) Inderal capsules may be dosed once per day. Occasionally effective for daily headaches. Sedation, diarrhea, lower GI upset and weight gain are common. Very useful in combination with amitriptyline. Dosage begins with LA 60 mg., and is usually kept between 60 and 160 mg. per day. Other β -blockers also are effective, such as metoprololER (Toprol XL) and atenolol. Some of these are easier to work with than propranolol because they are scored tablets, and metoprolol and atenolol have less respiratory effects. Lower doses are sometimes effective (20 BID of propranolol). Depression may occur. Useful for those with concurrent HTN, tachycardia, panic, anxiety, and MVP.
4. Amitriptyline (Elavil): Effective, inexpensive and also useful for daily headaches and insomnia. Use in low doses, at night. Sedation, weight gain, dry mouth and constipation are common. Starting dose is 10 mg., working up to 25 or 50 mg.;

can be pushed up to 150 mg., or decreased to 5 mg. Other tricyclic antidepressants such as doxepin and protriptyline can be effective for migraine. Nortriptyline is similar to amitriptyline, with somewhat fewer side effects. These are also used for daily tension-type headaches. Protriptyline is one of the only older antidepressants that does not cause weight gain. However, anticholinergic side effects are increased with protriptyline. While the SSRI's are utilized, they are more effective for anxiety and depression than for migraine. Tricyclics are more effective for pain than are the SSRI's.

5. Naproxen (Naprosyn, Naprelan, Anaprox, Aleve), and other nsaid: Useful in younger patients, once a day dosing. Sometimes helpful for daily headaches. Particularly useful for menstrual migraine. Nonsedating, but frequent GI upset. Effective as an abortive, and may be combined with other first line preventive medications. The usual dose is 500 or 550 mg. once a day, but this may be pushed to twice a day. OTC as Aleve. Other anti-inflammatories can be utilized for prevention of migraine. As with all anti-inflammatories, GI side effects increase as people age, and so we use these much more in the younger population.
6. Verapamil: Reasonably effective for migraine, once a day dosing with the slow release (ER) tablets. Usually nonsedating, and weight gain is uncommon. Occasionally helpful for daily headaches. May be combined with other first line medications, particularly amitriptyline or naproxen. Constipation is common. Starting dose is 1/2 of a 240 mg. ER tablet, increasing quickly to one 240 mg. tablet per day. May be pushed to 240 mg. twice a day, or decreased to 120 mg. or 180 mg. per day. Verelan is a useful brand name. (100, 200, 300mg). An EKG should be performed for those on verapamil.
7. Natural: See "Natural Herbs / Supplements" section. Petadolex (safer form of the herb, butterbur) has been the most effective "natural" preventive, and has held up well in multicenter trials. Many patients prefer to start with the natural preventives.

Second Line Migraine Preventive Therapy (Start with low doses)

1. Botulinum Toxin Injections: Botulinum Toxin A (Botox) has been extensively studied in migraineurs. Approximately 50 to 60% of patients have significant relief after Botox injections; low doses, primarily frontal and temporal, are usually used (50 to 100 units total per patient, in 8 to 12 injections). While expensive, Botox is relatively safe and only takes a few minutes to inject. One set of injections can decrease the headaches for 1 to 3 months. The role of botulinum toxin will become more clear in the next 5 years. Posterior (occipital), or upper cervical injections are just starting to be investigated, and appear to have some utility. Botulinum toxin may be safer than many of the medications that are utilized.

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2. Neurontin (gabapentin): An anti-seizure medication that has been demonstrated to be useful in migraine and tension headache prophylaxis. Doses are available in 100 mg., 300 mg., 400 mg., 600 mg. and 800 mg. sizes. The usual dose for headache prevention is 600 to 2400 mg. per day. In a large study on migraine, doses ranged around 2,300 mg. per day. Sedation and dizziness may be a problem; however, Neurontin does not appear to cause end-organ damage, and weight gain is relatively minimal. Neurontin can be used as an adjunct to other first line preventive medications. Some patients do well with very low doses (200 or 300 mg. per day). The generic, gabapentin, is now widely in use. A newer drug, Lyrica (pregabalin), has a similar mechanism of action to gabapentin. Lyrica is an anti-seizure drug, useful also for preventing pain. Side effects are similar to those of gabapentin. Lyrica is not "indicated" for headaches, but early results are promising. The dose varies from 25mg BID to 75mg TID. Start with low doses.
3. Polypharmacy: Two first line medications are used together. The combination of two preventives is more effective than one drug alone. Depakote is often combined with an antidepressant. Amitriptyline may be combined with propranolol, particularly if the tachycardia of the amitriptyline needs to be offset by a β -blocker. This combination is commonly used for "mixed" headaches(migraine plus chronic daily headaches). The NSAIDs may be combined with most of the other first line preventive medications. Thus, naproxen is often given with amitriptyline, propranolol or verapamil. Naproxen is employed simultaneously as preventive and abortive medication. Polypharmacy is commonly employed when significant comorbidities (i.e., anxiety, depression, HTN,etc.) are present.
4. Tizanidine and cyclobenzaprine: A safe, non-addicting muscle relaxant, tizanidine is useful for migraine and CDH. The usual dose is one or two 4 mg. tablets qhs; the 4 mg. tablets are double-scored, so that patients may begin with 1/4 or 1/2 tablet. Sedation and dry mouth are common. Tizanidine may be used on a prn basis for milder headaches, or for neck or back pain. A 2 mg. tablet is also available. Cyclobenzaprine (10mg) is helpful for sleeping, and helps some with migraine and CDH. 1/2 tablet may be used. Sedation is common.
5. Ace inhibitors and ARB's: There have been a number of studies on this category of blood pressure meds; ARB's are preferred due to the minimal side effects. Examples include Cozaar, Benicar, and Atacand. For the pt. with HTN and migraine, these may be useful. SE's include dizziness, among others. They are usually well tolerated, with no sedation/weight gain.
6. Effexor XR(venlafaxine extended release): Effexor XR has been an excellent antidepressant; primarily an SSRI at lower doses, and at 100 to 150mg. norepinephrine is also increased. The antidepressants with dual mechanisms(serotonin and norepinephrine) are more effective for pain and headache. Doses vary from 75mg to 225mg, and Effexor XR is particularly useful for anxiety/depression. The newer duloxetine(Cymbalta) also has a dual mechanism of action, and has been useful for pain.

Preventive Medication: When to Proceed Quickly with Two Preventives at One Time

1. With most patients, we utilize one prevention medication at a time, in low doses, slowly raising the dose as needed. Most of the patients appreciate the approach, and are perfectly willing to wait for the medication to work.
2. At times, patients may become extremely frustrated with the headaches, and they desire quick results. When these patients suffer from moderate or severe CDH, with bothersome migraines, it is justified to push ahead at a faster rate with a preventive approach. For instance, amitriptyline and verapamil, or amitriptyline and propranolol may be initiated at the same time. Alternatively, doses may be increased very quickly. The initial amount of preventive medication utilized for a patient depends upon the severity of the headaches and the frustration level of the patient.
3. Patients with new onset of severe headaches, which are usually daily headaches plus migraine, are often extremely upset and frustrated with the pain. In this situation, pushing preventive medication at a faster pace is justified. Of course, patients need to be willing to put up with certain side effects

Third Line Migraine Prevention (For Refractory Patients)

1. Long-acting opioids (methadone, Oxycontin, Kadian, MS-Contin, Avinza, Duragesic): In a very small select group of severe headache patients, particularly with severe, chronic daily headaches and migraines, long-acting opioids have some demonstrated utility. Methadone may work because of its antagonism on NMDA. Methadone is relatively well-tolerated, but sedation and constipation are limiting factors. Doses need to be kept low, from 5 mg. to 20 mg. per day. Morphine is available in multiple forms. Kadian is usually dosed at 20 mg. once or twice daily; it is remarkably smooth and long-acting. Kadian is a terrific formulation. Avinza is a good once-daily morphine. Oxycontin is a long-acting oxycodone without the acetaminophen or aspirin. Oxycontin can also be useful, but may be more prone to abuse, and only lasts 5 to 8 hours in most patients. A generic is now available. The Duragesic patch lasts 72 hours. Generic is out, but not recommended. A new low dose (12mcg) is available. Opioids may be combined (in low doses) with stimulants. Stimulants may help the pain, and also offset fatigue. Patients must accept the risks of these medications.
2. Repetitive IV DHE Therapy: Helpful for patients with frequent migraine, severe daily headache, and status migraine. Weeks of headache improvement are often seen. IV DHE is useful in patients withdrawing from analgesics. The protocol can be done in the office or hospital. In the office, the first dose, 1/3 mg. is given, and if it is well tolerated, the subsequent doses are 1/2 or 1 mg. Oral Reglan is usually given prior to the DHE. Three or four doses are given in the office, and up to nine in the hospital. Side effects include nausea, heat flashes, muscle contraction headache, leg cramps, diarrhea, and GI pain.

The IV DHE is usually well tolerated and effective. After the DHE, patients are continued on prevention medication. Occasionally, Migranal (DHE) nasal spray, used daily for several weeks, is also effective. DHE has a long track record of a good safety profile.

3. Stimulants: (Dextroamphetamine, Methylphenidate, Phentermine, Adderall, Vyvanse): Occasionally useful as a “last resort” therapy. These also offset fatigue. They are relatively safe. Phentermine is also a possibility and can be used as an adjunct to other medications. Phentermine is activating and can cause insomnia. However, it can also help decrease appetite, which is its primary use, and decreases sedation in patients with chronic fatigue. Dexedrine and Ritalin (or Concerta) may be used in combination with long-acting opioids. Adderall is also a useful, longer-acting compound. Adderall XR is a good, once-daily form. Addiction is always a risk with the use of stimulants. Fatigue is a common problem for headache patients, and stimulants may help. Adderall (generic is available) is the most commonly used formulation; the Adderall XR is an excellent longer-lasting preparation. Vyvanse is fairly new and may be useful.
4. Phenelzine (Nardil): This MAO inhibitor (MAOI) is a powerful migraine and daily headache preventive medication. Phenelzine is very helpful for depression, anxiety and panic attacks. The risk of a hypertensive crisis is small, but is a major drawback to the MAOIs. Dietary restrictions render MAOIs difficult for the patient. Side effects include insomnia and weight gain, both of which are often major problems. Dry mouth, fatigue, constipation and cognitive effects may also occur. Patients need to be aware of the symptoms of hypertensive reactions. The usual dose is 45 mg. each night (3 of the 15 mg. tablets). This is adjusted up or down, and the range varies from one to five tablets per day. One other major drawback is that certain triptans cannot be used with MAOIs. The use of MAOI’s has declined due to the newer medications.
5. Frequent Triptans: In some patients with chronic daily headache and frequent migraines, or “chronic migraine”, the only medication that is useful is a low dose triptan. Long-term side effects are unknown at this time, and this needs to be understood by the patient. Rebound headache needs to be excluded in these patients. Cost and insurance issues often limit the use of frequent triptans.

“Natural” Headache Herbs/Supplements

Feverfew, Petadolex, and magnesium oxide, have all held up in double-blind studies as migraine preventatives. Petadolex has been the most effective.

1. **Petadolex:** Commonly used in Europe, this herb has been successful in several well-designed blinded studies. The usual dose is 2 per day. Earlier concerns about carcinogenesis with this family of herbs have decreased with Petadolex. It is prudent to stop it every 3 months or so. Available at 1-888-301-1084. Petadolex is a very effective preventive. Patients occasionally experience GI upset or a bad taste. Usually well tolerated.
2. **Magnesium Oxide:** It has been shown that magnesium levels are low in the brain of migraine patients. 400 or 500 mg. per day is used as a preventive; mild GI side effects may limit use. 250 mg. tablets are found in most pharmacies. Only mildly effective.
3. **Feverfew:** Feverfew has been demonstrated to be mildly effective in some patients for prevention of migraine headache. Feverfew can cause a mild increased tendency toward bleeding, and should be discontinued 2 weeks prior to surgery. Feverfew should not be used during pregnancy. Patients occasionally will be allergic to feverfew. The problem with many herbal supplements is quality control, and certain farms consistently have better quality than others. The parthenolide content (the active ingredient) varies widely from farm to farm. The usual dose is 2 capsules each morning. Eclectic Institute (a blue and white bottle, widely available in health food stores and Whole Foods) freeze dries their herbs, and the product is highly consistent and reliable.
4. **Long Chain Fatty Acids (Omega-3 fatty acids):** These may play a role in headache prevention, as well as (possibly) useful for anxiety, HTN, arthritis, high lipids, depression and heart disease. We usually recommend fish oil or Flaxseed oil, 1000 mg., 2 or 4 per day (in studies on depression, 8 per day have been utilized). Fish oil capsules may be more effective than Flaxseed oil. Oily, fatty fishes (Salmon, Tuna) contain more than other fishes. Look for the brands with the highest amounts (EPA / DHA) listed on the back.
5. **Coenzyme Q-10:** COQ-10 is relatively safe, and has started to be investigated as a headache preventive. Doses for headache are not known. COQ-10 may have some positive effects on the heart as well. We usually recommend 150 to 300 mg. daily.

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Treatment of Menstrual Migraine

Menstrual headaches are often severe, prolonged and debilitating. The abortive therapy follows the general abortive therapy for migraine. (See abortive therapy section.) In addition to the usual abortives, cortisone (Prednisone, Dexamethasone) is effective for many women; they are utilized in very limited amounts. We use 10 or 20mg Prednisone or 2 to 4mg dexamethasone every 8 to 12 hours, 3 tabs/month only. The severe intensity of menstrual migraines often dictates stronger abortive measures. Triptans are particularly useful. Many women with severe menstrual migraines require combinations of triptans, low dose cortisone, analgesics, and antiemetics.

Preventive Treatment: The timing of preventive therapy is difficult for most women; either their menstrual periods are irregular, or the headaches occur at different times. However, in some women the following may be helpful:

1. NSAIDs (Naproxen, etc.): Effective for many women and usually well tolerated. These are started 1 day prior to the expected onset of the headache. Many NSAIDs have been utilized, including naproxen, ibuprofen, flurbiprofen, meclufenamate sodium, etc. GI upset is common.
2. Triptans: Frova is a long-acting, smooth, well-tolerated triptan. Its utility in menstrual migraine has been established. One method of dosing it is 2.5 mg. once or twice a day for three to five days around the time that the menstrual migraine would occur. While not as well studied, the other triptans may also be helpful as menstrual migraine preventives. They are started the day prior to headache onset.
3. Hormonal approaches: Estrogen has been used, but is questionably effective. Occasionally, the birth control pill, even on a cyclic basis, will reduce headaches. If used continuously (no break), it may provide some relief. The birth control pill, however, can also increase migraines. As with other preventives, hormonal approaches often are disappointing, or they may initially provide relief, with declining efficacy over months. The most commonly utilized hormonal approach is the continuous b.c.p., with a menstrual period every 4 months.

First Line Tension Headache Abortive Medications

1. Acetaminophen, Aspirin: These are the staple of OTC pain relief; acetaminophen is less effective for headache, but better tolerated. These need to be limited, so as to avoid the rebound situation.
2. Ibuprofen (Motrin, Advil, Nuprin): Helpful for migraine and tension headache. Useful in children, and a liquid form is available. GI upset is relatively common, but ibuprofen is more effective for headache than acetaminophen. Adding caffeine can increase efficacy.
3. Caffeine: Caffeine beverages or tablets (100 mg.) are helpful for migraine and tension headache, either alone or as an adjunct to analgesics. Caffeine added to other abortives enhances their effectiveness and decreases drowsiness.

For example, Midrin plus caffeine is an effective combination. Caffeine must be limited so as to avoid “rebound” headaches. The usual limit should be 150 or 200 mg., at most, in one day. See section on “caffeine sources”.

4. Caffeine-aspirin combinations: Excedrin Migraine has 65 mg. caffeine, 250 mg. of aspirin, and 250 mg. of acetaminophen; this is a very effective OTC preparation, but overuse leads to rebound headaches. Anacin contains much less caffeine (32 mg.), but more aspirin. Excedrin Tension Headache is a very useful combination of acetaminophen and caffeine. Norgescic Forte is a very useful combination of aspirin, caffeine, and orphenadrine (a non-addicting muscle relaxant; generic is available).
5. Naproxen (Anaprox, Aleve (OTC), Naprelan): Useful in younger patients, nonsedating, but very frequent GI upset. The usual dose is one 500 mg. tablet with food, which may be repeated up to a maximum of three per day. If used on a daily basis, two per day should be the limit. Adding caffeine can increase efficacy. Naprelan is an excellent long-acting form of naproxen, available in 375 mg. and 500 mg. One Aleve = 220 mg. Also available as generic naproxen OTC (220 mg.). Other nsoids (Diclofenac, Arthrotec, etc.) may be useful.
6. Migraten: MigraTen caps are a combination of 100mg. caffeine, 65mg. isomethaptane, and 325 mg. acetaminophen. Isophtheptane is a mild vasoconstrictor. The usual dose is one capsule every 2 to 3 hours as needed. I usually limit, with some exceptions, these to 2 or 3 per day only (due to the caffeine). MigraTen is not addictive and non-sedating. Because of the caffeine, it can cause nervousness or faster heartbeat. Patients with insomnia should not use it past 3pm or so; with high blood pressure MigraTen should be used with caution, and only if the pressure is controlled. MigraTen is helpful for the smaller headaches, as well as for migraines; it fits the need for a non-addicting medication that does not cause drowsiness. If used daily, we limit it to 2 per day only.
7. Tramadol (Ultram): 50 mg. tablets, 1 or 2 every four hours, relatively few side effects but sedation, nausea, and dizziness may occur. Addiction uncommon but is occasionally seen. Need to limit to 4 per day, 10 per week. Generally well tolerated. Ultram is an “opioid-like” medication that is milder than codeine or hydrocodone. Overuse may lead to seizures. There is now a long-acting Ultram ER (100, 200 mg.); usual dose is 100 or 200 mg. per day.
8. Ultracet (37.5 mg. Tramadol, 325 mg. Acetaminophen): A milder, somewhat effective analgesic. Need to limit to 4 per day, 10 per week. *See Tramadol above* Generic is available.

Second Line Tension Headache Abortive Medications

1. Butalbital compounds: Effective but habit forming. Fiorinal, Esgic, Esgic Plus, Fioricet, and Phrenilin are the primary butalbital compounds. Generic butalbital preparations do not work as well as brand names. Sedation or euphoria is common. Strict limits need to be set for daily and monthly use. If used daily, one or two is the usual limit. These should not be used daily unless preventive medications, and milder abortives, have failed.

See “Butalbital (Fiorinal) Compounds” for ingredients of butalbital compounds.

2. Opioids: Codeine, hydrocodone, and propoxyphene are a last resort, and should be limited per month, and generally should not be used on a daily basis. These need to be discontinued if patients use them to alleviate stress, depression, fatigue or anxiety. Vicoprofen (generic available) combines 200 mg. Ibuprofen with 7.5 mg. hydrocodone, and is generally more effective than Vicodin. Rebound and addiction are always a primary concern.
3. Sedatives: Most are benzodiazepines, such as diazepam (Valium) and clonazepam (Klonopin). Sedation is common. Because they are habit forming, these need to be monitored with a monthly limit. They are a last resort, not a first choice. Addiction is always the major drawback. Also helpful for insomnia and anxiety.
4. Triptans: While triptans are generally utilized for migraine and cluster headaches, the triptans can be useful for tension headaches as well, particularly the more severe tension headaches. There are some patients who only do well with a triptan with any of their headaches. In migraine patients, triptans often work for their “lesser” headaches. We usually limit to 2 or 3 days per week.
5. Muscle Relaxants: These are occasionally useful on a “prn” basis; the non-addicting ones are preferred. These include orphenadrine (Norflex), tizanidine (Zanaflex), cyclobenzaprine (Flexeril), and Skelaxin. These may be combined with caffeine or nsaid. Sedation may be a problem. Zanaflex, $\frac{1}{4}$, $\frac{1}{2}$ or 1 of the 4 mg. tablets, is particularly useful. Skelaxin is mild but nonsedating. Norgestic Forte combines aspirin, caffeine, and orphenadrine; the usual dose is $\frac{1}{2}$ or 1 every 4 hours prn, 2 in a day at most. Generic is available for all of these, except Skelaxin.

Butalbital (Fiorinal) Compounds (Generic generally not as effective)

Drug	Dose	Comment
Fiorinal Butalbital 50 mg. Aspirin 325 mg. Caffeine 40 mg.	1 or 2 every 3 hours PRN; 6 a day maximum	Habit forming; the aspirin may cause nausea. The most effective of the butalbital class.
Fioricet or Esgic Butalbital 50 mg. Acetaminophen 325 mg. Caffeine 40 mg. Esgic Plus has 500 mg. of acetaminophen	1 or 2 every 3 hours PRN; 6 a day maximum	Less nausea than with Fiorinal, but less effective, because acetaminophen not as effective as aspirin
Phrenilin Butalbital 50 mg. Acetaminophen 325 mg. Phrenilin Forte has 650 mg. of acetaminophen	1 or 2 every 3 hours PRN; 6 a day maximum	Less effective than the other butalbital; good for use at night (no caffeine), less nausea.
Fiorinal with codeine (30 mg.) Fioricet with codeine (30 mg.)	1 every 3 hours PRN; 4 a day maximum	The codeine helps but increases the side effects (nausea).

First Line Chronic Daily Headache (CDH) Prevention Medication

1. Valproate (Depakote): See “First Line Preventative Medications for Migraine”
2. Amitriptyline (Elavil): See “First Line Preventative Medications for Migraine”
3. Topamax: See “First Line Preventive Medications for Migraine”.
4. SSRI’s, Cymbalta, and Effexor: Fewer side effects than amitriptyline, but not as effective. More effective for anxiety and depression than for headache. Nausea, anxiety, sexual dysfunction, fatigue, and insomnia are common. Weight gain is relatively common. Helpful for migraine in some patients. Begin with low doses. Effexor XR may be more effective, see “Second Line Migraine Preventives”. Cymbalta is a very effective antidepressant, and may help pain. All of the SSRI’s have been somewhat useful for preventing chronic daily headache, and to a lesser extent for migraine. The dose for headache is usually lower than that for depression. Considering tolerability, these are often the best choice for chronic daily headache. Any of these may also exacerbate headaches. See antidepressant section.

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5. Protriptyline (Vivactil): Effective and nonsedating. Weight gain does not occur. Dry mouth, constipation, dizziness are common. Used in the morning, as insomnia may occur. May be used in the morning with a sedating tricyclic at night. Usual dose is 5 to 15 mg. per day (lower than for depression). The only tricyclic that tends not to cause weight gain. Increases norepi, not serotonin.
6. Nortriptyline (Pamelor): A metabolite of amitriptyline. Better tolerated than amitriptyline, but less effective. Side effects are similar to amitriptyline, but less severe. Useful in children, adolescents and the elderly. Occasionally helpful in migraine. Usual dose is 25 to 75 mg. per day; some patients do well on one 10 mg. daily.
7. Doxepin (Sinequan): Very similar to amitriptyline. Begin with very low doses (10 mg. each night), as many patients cannot tolerate more than this amount. Usual dose is 25 to 75 mg. per day. Same side effects as amitriptyline, but generally better tolerated.
8. NSAID's: Not as effective as antidepressants for chronic daily headache, but without the cognitive side effects. GI side effects are common, however. Hepatic and renal blood tests need to be monitored. NSAID's are used more frequently in younger patients. Ibuprofen is available over the counter, but is short-acting. Naproxen (Naprosyn, Naprelan, Aleve, Anaprox) is more effective than ibuprofen. Flurbiprofen (Ansaid), diclofenac sodium (Voltaren), and ketoprofen (Orudis, Oruvail) are also utilized. As always, attempt to use the minimum effective dose. See previous NSAID sections.
9. Gabapentin (Neurontin): See "Second Line Preventative Medications for Migraine" The newer Lyrica (pregabalin) may also be effective.
10. Tizanidine (Zanaflex) and cyclobenzaprine: See "Second Line Migraine Preventative Therapy." These are muscle relaxants.

Second Line CDH Prevention Medication

1. β -blockers: Occasionally useful for daily headache and very effective for migraine. See "First Line Preventative Medications for Migraine"
2. Botulinum Toxin injections (Botox): These are not as useful for CDH as for migraine. Studies in CDH patients have resulted in mixed results. However, in certain patients these do decrease the daily headaches. See "Second Line Migraine Prevention".
3. Calcium channel antagonists (Verapamil): Occasionally effective for daily headache as well as migraine and cluster. Verapamil is the most widely used calcium blocker. See "First Line Preventive Medications for Migraine"

Third Line CDH Prevention Therapy

1. Polypharmacy: Combinations of two of the first or second line preventives are often very effective. Tricyclics or SSRI's may be combined with NSAIDs or β -blockers; NSAIDs may also be combined with β -blockers or verapamil. Valproate (Depakote) may be combined with tricyclics, β -blockers, or verapamil. Topamax may be combined with certain meds. The various preventive medications possess different mechanisms of action. Tizanidine or other muscle relaxants may usually be combined with other medications.
2. Long-acting Opioids: See "Third Line Migraine Prevention".
3. Tranquilizers: More useful in patients with severe anxiety disorders. Occasionally effective for daily headache, but habit forming. Benzodiazepines are the primary sedatives used for daily headache. Doses need to be minimized and patients must be carefully monitored. Alprazolam (Xanax), Clonazepam (Klonopin), and diazepam (Valium) are the usual benzodiazepines that are used.
4. Stimulants: Helpful for some patients as an "end of the line therapy". See "Third Line Migraine Prevention". These may offset the fatigue so commonly seen in headache patients.
5. MAO inhibitors (phenelzine): Phenelzine (Nardil) is a powerful antidepressant for migraine and daily headache. See "Third Line Migraine Prevention". There are significant risks and side effects.
6. Daily Triptans: See "Third Line Migraine Prevention".

INTRODUCTION TO CLUSTER HEADACHE

Cluster headache is among the most severe pains known to mankind. It is characterized by excruciating, debilitating pain lasting from 15 to 180 minutes, and occasionally longer. The pain is usually located around or through one eye, or on the temple. The series of cluster headaches usually lasts several weeks to several months, once or twice per year. Clusters may occur every other year, or even less frequently. Several of the following are usually present: lacrimation, nasal congestion, rhinorrhea, conjunctival injection, ptosis, miosis of the pupil, or forehead and facial sweating. Nausea, bradycardia, and general perspiration also occur in many patients. Attacks usually recur on the same side of the head. Cluster headaches tend to occur more in spring and fall. There is usually no family history of cluster headache, but occasionally there is such a family history.

Specific Characteristics of Cluster Headaches

Males are afflicted more than females, by a 4:1 ratio. The onset of the clusters is usually between age 20 and 45, but there are many cases of clusters in teenagers, and occasionally clusters begin in the 50s or 60s, and rarely in the 70s. Approximately one out of 250 men has cluster headaches. Women tend to have an older age of onset for their clusters than men. Occasionally a brief aura may occur.

The pain of the cluster attack is extreme and starts very quickly, usually without an aura or a warning. Within minute, it becomes very severe. Although the pain is usually located about the eye or temple, it may be more intense in the neck or facial areas. Although usually unilateral, the pain does change sides in 10% to 15% of patients, either during a cluster cycle, or the next cycle may see pain on the opposite side. The pain itself is excruciating, described in various manners as sharp, stabbing, "like my eye is being pulled out". and occasionally, throbbing.

The length of attacks does vary, but 45 minutes is the average. Cluster patients usually experience one or two headaches per day, but this may increase to as many as seven per 24 hours, or decrease to as little as one or two per week. They usually occur around the same time each day, with the time period 9 p.m. to 10 a.m. being most frequent. Approximately half of the patients awaken from sleep with the headaches.

Cluster cycles, except in the chronic variety, usually last 3 to 8 weeks, and then stop until the next bout of the clusters. The clusters occasionally last as little as several days, or as long as 5 months, at which time we begin to think that they may have converted to the chronic cluster type. Ten percent of cluster patients have chronic clusters, where there is no break of at least 6 months between attacks. One or two bouts of the clusters per year is average for most patients. They may increase in frequency, with only several months in between bouts, or several years may elapse between attacks. When periodic clusters begin at older ages, the chance of conversion to chronic cluster becomes greater. The natural history of clusters is not known, but the tendency is for the cluster series to stop at a certain age. Many patients "lose" their clusters in the late 30s or 40s particularly if they have had them for many years.

During the cluster series, over half of the patients are very sensitive to alcohol, and most patients will have an attack triggered by ingestion of alcohol. The other "headache" foods are less important, but avoiding MSG, aged cheeses and meats, and chocolate is prudent during the cluster series. MSG, in particular, seems to trigger a more severe cluster in some patients. Cluster patients may have their clusters after stress is over, and occasionally excessive cold, heat, or bright light have been associated with the precipitation of a cluster. However, most cluster patients have very little control over the clusters, except with medication.

The typical episodic cluster series builds over 1 to 2 weeks and peaks for 1 to 3 weeks, then decreases. In the 10% of cluster patients with chronic clusters, periods of peaks and valleys with the headaches also occur, but the extended break without any clusters is not present. Chronic clusters are not usually consistent throughout the year, but tend to increase in certain seasons. In managing the clusters, we keep in mind the fact that clusters build and then peak, and I often treat them with somewhat less medication, particularly corticosteroids, in the beginning of a cluster period. The natural history of cluster is unknown; however, it appears as if the more years people have had them, the more likely they are to abate.

Nonmedication Treatment of Cluster Headache

Other than medication, very little is available for sufferers of cluster headache. The pain is too severe for relaxation methods, and some patients state that biofeedback or relaxation may actually precipitate or increase a cluster. However, learning simple deep breathing techniques or relaxation methods does aid some patients in helping to curb the anticipation of the cluster attacks. Much anxiety is generated during the day when the patient knows that nighttime brings intense, excruciating pain.

Ice to the area of pain may help, although sometimes heat will be more effective. Some patients let the shower run hot water on their cervical area, or they use a shower water massage apparatus to allow the hot water to run over their cervical or frontal area. Pressing over the temporal area with moderate pressure is occasionally helpful. Cluster patients usually feel better when moving about during an attack. They tend to be active (such as pacing) as opposed to the quiet sought by migraineurs.

First Line Abortive Medications for Cluster Headache

1. Oxygen: Very effective, with no side effects. May be combined with other abortives. Oxygen is worth trying for all patients willing to rent a tank; the usual dose is 8 liters/min., for 10 to 20 minutes as needed, with a mask, used sitting up and leaning slightly forward. 60% success rate. The rate may be pushed to 13 Liters per minute.
2. Sumatriptan (Imitrex) injection: The most effective cluster headache abortive medication. The injections often work within minutes, and cluster patients often prefer this route of administration. However, patients may at times require two or three injections in a day. Chest heaviness or pressure, tingling or hot sensation, nausea, fatigue, etc. may occur. Many cluster patients do well with 3 mg. sq of the injections; for 1/2 doses (3 mg.), the individual vials are ordered, with insulin syringes. The STATdose is 4 or 6mg; 4mg. usually is effective.

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3. Sumatriptan (Imitrex) nasal spray, or Zomig nasal spray: The 20 mg. nasal spray is convenient and easy to use. While not as effective or as fast acting as the injection, many patients do prefer this route. Side effects tend to be minimal, but an unpleasant taste in the mouth is common. Cluster patients often require two or three nasal sprays in a day. Many patients utilize nasal spray at times, and the injections at other times. Occasionally, the tablets of triptans are preferred by cluster patients. Zomig NS is effective for some cluster patients. It is stronger than Imitrex nasal spray.
4. Oral Triptans: Most tablets (including dissolving tabs) have been used for clusters; these are more helpful for longer clusters, or clusters that are more moderate in intensity. See section on Migraine Abortive Medications. Many patients prefer these to injections, despite the longer onset of action.

Quick Reference Guide: First Line Cluster Preventive Medication

1. Cortisone: Very effective for cluster headache; is used primarily for episodic clusters. It is given for 1 or 2 weeks during the peak of the cluster series. Prednisone, Decadron, or injectable forms may be utilized. When used for short periods of time, side effects are minimal. A typical regimen is prednisone (20 mg.) or Decadron (4 mg.) once a day for 3 days, then one-half tablet per day for 10 days, then stop. Additional cortisone may be given later in the cycle, when the clusters increase. Higher doses may be needed, particularly when the cluster cycle is peaking in intensity. Due to adverse events, it is very important to minimize the cortisone.
2. Verapamil (Verelan PM, Verapamil ER): A well tolerated calcium channel blocker; effective in episodic and chronic cluster. One 240 mg. ER tablet is taken once or twice per day. This is often initiated at the onset of the headaches, in conjunction with cortisone. Verapamil is then continued after the cortisone is stopped. Constipation is common. Because of its efficacy and minimal side effects, verapamil is a mainstay of cluster prevention. An EKG should be performed.
3. Lithium: Helpful for chronic cluster and, to a lesser degree, episodic cluster. Small doses, one to three of the 300 mg. tablets per day, are used for cluster headache. May be combined with verapamil and/or cortisone. Lithium is usually well tolerated in low doses; drowsiness, mood swings, nausea, tremor, and diarrhea may occur. Blood tests need to be done.
4. Indomethacin: This nsaid is helpful for some cluster patients; GI side effects may limit use.

INTRODUCTION: Headache in Children and Adolescents

The following gives a practical guideline to headache therapy in children and adolescents. Many drugs that are helpful for headache have not received a specific FDA indication for this use, and often these have not been specifically approved for children. The risks, side effects, and problems associated with medications need to be fully explained to the family, as explained in the PDR or a similar reference. Only if the family understands the risks and side effects of a medication, and accepts these potential problems, is a medication given to the child.

Introduction

Headache is a common complaint among children and adolescents. The generally stated incidence of migraine at age 6 is 1%, and at age 10 is 4%. These figures may be low. Headache is a major health problem in adolescents. Migraine is a problem in children as young as ages 2 or 3. Gathering accurate data in this age group is exceedingly difficult, as parents usually attribute headaches and nausea to "the flu." Migraine in children and adolescents, and chronic daily headache (CDH) in adolescents, is a major problem, with much lost school time caused by migraine or daily headache. Depression and/or anxiety is common with adolescents with severe, frequent headaches, and in many cases the depression is exacerbated by the headaches. Approaching headaches in children and adolescents with counseling, and biofeedback-relaxation is often crucial. With adolescents who are missing a lot of school, getting a good psychotherapist involved is invaluable.

As with adults, the vast majority of the time we are dealing with either migraine or tension headache (if this occurs 15 or more days per month, we would term it chronic daily headache, or CDH). Organic etiologies need to be excluded, of course, and an MRI scan of the brain is necessary once in the life of most of the younger patients with frequent, severe headaches. Predictors of organic pathology in children include confusion or other mental status changes, no family history of migraine, and sleep-related headaches. Other predictors include severe vomiting, abnormal neurologic exam, and headache of less than 6 months' duration. Organic pathology, the pediatric neurologic history, and the pediatric neurologic physical exam are beyond the scope of this booklet.

All of the usual migraine trigger factors, such as diet, should be discussed with the patient and family. Sleep and icepacks are usually helpful. Relaxation / biofeedback should be given to younger patients with frequent headaches. Most children cannot learn to apply biofeedback before the age of 9, but some 7 or 8 year olds can learn simple breathing and imaging techniques that may help their headaches. Children usually want to hear three things from the physician: (1) the cause of the headache, (2) treatment, and (3) reassurance that it is not serious. Individual counseling for the adolescent is often helpful. The incidence of hard-driving, perfectionistic behavior, and depression is increased in adolescents with severe headache. Children and adolescents may be in too many activities and feel extremely stressed. These issues need to be addressed. Children missing substantial blocks of time in school need to be assessed for depression, school phobia, and secondary gains. Counseling is indispensable.

We have two types of medication therapy: abortive and preventive. The decision as to how much medication to use depends upon the frequency and severity of the headaches and how much they bother the child or adolescent. Some children are simply not bothered by their daily headaches and tend to ignore them. Others may be incapacitated and miss an entire year of school. As with adult headache patients, in children and adolescents, abortive medication is used in the overwhelming majority of cases, without daily preventive medication. However, with frequent migraines that are more than mild, or moderate to severe daily headaches, daily preventive medication may be necessary. It is always reasonable to try biofeedback as the first step, with simple abortive medications, and attempt to avoid daily preventive medication.

When I do use preventive medication with children and adolescents, I always attempt to stop the preventive medication periodically, and to minimize medication. As with adults, the idea is to see if we may return to simply using abortive medication. However, if an adolescent has had headaches for a number of years, we are not so quick to jump off of a successful preventive. We always consider “natural” preventatives, particularly “Petadolex”, with adolescents. (See “Natural” Section, under Migraines)

Abortive Tension Headache Medications in Children (less than 11 years old)

1. Acetaminophen: Well tolerated, safe, not as effective as ibuprofen or aspirin. Chewable tablets and liquid are available. The usual dose is 5 to 10 mg/kg per dose. Because of safety, acetaminophen is the usual primary abortive medication to utilize in children. The addition of caffeine may enhance the effectiveness.
2. Ibuprofen: More effective than acetaminophen, but with occasional GI upset. Liquid Advil is available, which helps in younger children. Caffeine may enhance the effectiveness. The usual dose is 100 to 200 mg. Effective for migraine as well as tension headache.
3. Caffeine: Either used by itself, or with an analgesic, caffeine is useful for tension and migraine headache. In children, soft drinks containing caffeine are helpful. Side effects are minimal when caffeine is used in very limited amounts.

Abortive Migraine Medications in Children (less than 11 years old)

1. Ibuprofen, Acetaminophen, Caffeine: Ibuprofen is effective and available as a liquid, but GI upset is relatively common. Acetaminophen is very safe, less effective than the other abortives, but easy to use, with liquid and chewable forms available. For children who are nauseated and cannot swallow oral medication, compounding pharmacists are able to formulate acetaminophen into a lozenge, to be kept in the mouth and absorbed by the buccal mucosa. This may be combined, in a lozenge, with an antiemetic such as Phenergan or Tigan. Caffeine decreases migraine pain in most children, and may be used alone, or in combination with other abortives.

2. Naproxen (Naprosyn, Naprelan, Anaprox, Aleve): Naproxen is an effective abortive that is non-sedating and available as a liquid. GI side effects are very common, however. Adding small amounts of caffeine, such as in soft drinks, may enhance the effectiveness. Aleve (OTC) = 220 mg. naproxen. Generic available.
3. Butalbital medications (Fioricet, Esgic, Phrenilin): One-half tablet to 1 tablet every 6-8 hours as needed. Sedating. See “Butalbital (Fiorinal) Compounds”, and also First Line Migraine Abortive Medications. Use in very limited amounts.
4. Triptans: Very low doses occasionally are used. Not FDA approved at this age.

Preventive Headache Medications in Children (less than 11 years old)

1. Cyproheptadine (Periactin): Cyproheptadine is a safe and mildly effective first line headache preventive therapy. Fatigue and weight gain may be a problem, but it is usually well tolerated. Cyproheptadine is not as useful after age 11. It may be dosed once a day, and a convenient liquid form is available.
2. NSAIDs (ibuprofen, naproxen): Ibuprofen and naproxen are available as a liquid, and the lack of sedation renders these very helpful for daily use. GI side effects are relatively common, and when these are used on a long-term basis, regular blood tests for hepatic and renal functions need to be done. Ibuprofen and naproxen may be utilized as daily preventives or as abortives for both tension and migraine headaches. Both are available OTC.
3. Propranolol (Inderal): Generally well tolerated, propranolol has been used for many years in children with migraine. Fatigue and decreased exercise tolerance may be a problem. With doses less than 60 mg. per day, we need to use propranolol twice per day, which is inconvenient for most children. Cyproheptadine or NSAIDs should usually be prescribed prior to propranolol.
4. Petadolex: The most effective natural remedy. See Natural Section (in migraine).
5. Feverfew or Magnesium: See section on Natural Herbs/Supplements. Relatively safe, these carry less risk than the standard preventatives. Doses have not been established in children; I prescribe 1 feverfew capsule per day, or 80 mg. to 150 mg. magnesium oxide per day, depending upon weight.
6. Amitriptyline: Low doses(5 to 25 mg.), at night. Similarly, Topamax has been used. See Migraine Preventive Section.

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Abortive Headache Medications in Adolescents (11 years and older)

1. At ages 11 and 12, the medications vary between those used for children and those for adults, depending upon weight and maturity. The NSAIDs (ibuprofen, naproxen), aspirin (with or without caffeine) and acetaminophen are most commonly utilized. MigraTen is used in adolescents. Triptans are being utilized with increasing frequency in adolescents. Many adolescents find the Zomig or Imitrex nasal spray, or the Maxalt MLT (on the tongue) tablets useful at school. See earlier section on first line migraine abortive medications, plus Instructions for Patients on each triptan. The triptans are not yet FDA approved for adolescents, but there have been a number of positive studies. Butalbital medications may be helpful, but must be limited. After age 13, the abortive meds are similar to those used in adults.

Headache Preventive Medications in Adolescents

1. Anti-inflammatories: Frequent GI upset is seen, but the NSAIDs usually do not cause fatigue or other cognitive effects. Ibuprofen (Motrin) and naproxen (Naprosyn, Aleve, Naprelan and Anaprox) are the NSAIDs most frequently utilized. Liquid preparations are available for both of these. Doses need to be kept to a minimum; hepatic and renal functions should be monitored via regular blood tests.
2. Depakote (Valproate): Useful for both migraine and CDH. Low doses (250 ER mg. once daily, or one Depakote ER 500 per day) are used. GI side effects, weight gain, or sedation may occur. Blood tests are done occasionally. See section on First Line Migraine Preventatives. The issue of polycystic ovarian syndrome in young women remains to be resolved. We usually avoid using Depakote in young women.
3. Topamax (topiramate): Extensively used (although not officially indicated for adolescent headache), Topamax avoids the weight gain, and is effective. See “First Line Preventive Medications for Migraine”.
4. Antidepressants: See Amitriptyline section, First Line Migraine Preventatives. Effective for migraine and daily headache. Nortriptyline (Pamelor), protriptyline (Vivactil), and amitriptyline (Elavil) are most commonly used. Usually well tolerated in low doses and safe for long term use. Cognitive side effects, dry mouth and dizziness are common. SSRI's and Effexor are useful, more for CDH than for migraine. The SSRI's are very helpful for comorbid anxiety and depression. See SSRI section. The small risk of suicidal thoughts, particularly in the 1st 30 days, must be understood by the patient and family. Risks/benefits need to be discussed. Used more when there is anxiety/depression.
5. Beta Blockers: See “First Line Preventative Medications for Migraine”. Effective for migraine, and occasionally for daily headache. Propranolol (Inderal) and nadolol (Corgard) are most commonly utilized. Beta blockers

may decrease exercise tolerance, which is a problem in this age range. Cognitive side effects, weight gain, and lethargy also limit the utility of beta blockers. Low doses should be used.

6. Verapamil: See First Line Preventative Medications for Migraine. Effective for migraine, and occasionally, daily headache. Generally well tolerated, with constipation common. Convenient once per day dosing with the sustained release form. Low doses should be used in this age range.
7. Feverfew, Petadolex or Magnesium (see section on natural headache herbs): These have proven to help prevent headaches; the usual dose is 1 or 2 capsules each day. Petadolex is the most effective, and is well tolerated. To order Petadolex, call 1-888-301-1084.

Depression and Anxiety

Depression

Depression usually profoundly affects your feelings and moods, as well as productivity and behavior. Depression often causes physical problems as well. Depression is a physical, medical illness, just like having asthma or diabetes. There is a very strong genetic basis, but not everybody has a family history of depression. Depression can occur once in a lifetime, or it may be ongoing on a chronic basis. Depression cuts across socioeconomic lines, and is a relatively common illness.

The symptoms in depression vary widely. There is usually a depressed mood, with feelings of helplessness, sadness, and hopelessness. Decreased motivation, and loss of interest in the usual pleasurable activities, often occurs. There may be sleep disturbances, sleeping too much or not enough. Easy awakening or difficulty going to sleep are common symptoms. Concentration problems are seen, with a difficult time making decisions. Often there is agitation and irritability, and fatigue is very common. Depression takes its toll on self-esteem, and people may feel that they are worthless. There may be no interest in sex, and weight can be increased (or decreased) due to appetite changes. A serious side effect of depression is suicidal thoughts, or actually committing suicide.

Along with depression, people often experience physical problems. These may include stomach cramps, diarrhea or constipation, backaches, headaches, or other pain syndromes. Depression may affect all ages. It does manifest itself somewhat differently in various age ranges.

Some people have a “major depression”, where they have at least 2 weeks of serious depression, while others have ongoing mild (or moderate) chronic depression. There is also the important category of bipolar depression (for this, please see the extensive bipolar section). Depression may be worse in certain seasons, such as in winter; Seasonal Affective Disorder is depression that is primarily related to a lack of sunlight, with the incoming late fall and winter. Light boxes may be very useful in treating Season Affective Disorder.

Stressful life events may trigger depression. Or, depression may cycle in and out of people’s lives, sometimes with certain seasons, regardless of stress. Chronic medical illnesses, or sickness in one’s family, may trigger depression. Financial difficulties may be a contributing factor. Hormonal changes may play a role, particularly with postpartum depression. It is crucial to recognize and treat postpartum depression.

The primary treatments are medication and psychotherapy. Exercise may help. The combination of meds plus therapy is ideal.

Anxiety

Everybody feels somewhat anxious or worried at times, often increased by stressful events. Feeling very anxious or constantly worried **without stress**, and on a chronic basis, may be “Generalized Anxiety Disorder” (GAD). With GAD, there is usually unrealistic worrying and anxiety. Symptoms of GAD include some of the following: irritability, trouble concentrating, restlessness, constantly feeling keyed-up, loss of patience, muscle tension, a feeling of shortness of breath, increased sweating, difficulty with sleeping, trouble swallowing (or feeling as if there is a lump in the throat), and heartburn, reflux, or diarrhea. GAD is often accompanied by irritable bowel syndrome, and by headaches.

GAD may cycle in people’s lives, and certainly is worse with stress. There is almost always a family history of anxiety, and anxiety usually starts in childhood. Other anxiety disorders that may occur in childhood or adolescence include: obsessive-compulsive disorder, separation anxiety, and panic disorder.

As with depression, there are a number of differences in the brain, and nervous system, in people with anxiety. There are changes in certain neurochemicals or transmitters, and genetics has a major role to play. It is as much a physical disorder as asthma, headaches, or diabetes.

Certainly stressful events may trigger anxiety, but most people with GAD have an inherited physical and chemical difference in their brain.

Anxiety is eminently treatable with exercise, yoga, psychotherapy, biofeedback, and medication. The medications primarily involve use of the antidepressants and/or the “pure” anti-anxiety medications, in particular the benzodiazepines. Examples of antidepressants include the SSRI’s such as Prozac, Zoloft, etc., and the benzodiazepines include Xanax, Ativan, etc. While it is inconvenient, and somewhat expensive, to go to a psychotherapist on an ongoing basis, it is very helpful in the long run.

SSRI's (Selective Serotonin Reuptake Inhibitors)

Chronic anxiety is a problem in approximately 35% of migraine patients. Dysthymia or major depression are seen in 17% of migraineurs. Migraineurs are 12 times more likely to have panic disorder than those without migraine. The chronic anxiety or depression leads to a decreased quality of life in migraine patients. These comorbidities of anxiety or depression are a physical, genetic problem, just like migraines. The selective serotonin reuptake inhibitors (SSRI's) have been very effective in combating anxiety and depression. They also are somewhat helpful in preventing migraine or tension headache. Large-scale studies have not revealed SSRI's to be more than mildly helpful for preventing headaches. However, they continue to be widely used throughout the United States for headache patients because of the positive effect on anxiety and depression. The low incidence of adverse reactions is another factor in the widespread use of SSRI's.

The safety and efficacy of the major SSRI's (Prozac/Zoloft/Paxil/Celexa/Lexapro) in treating anxiety or depression is well established. Although SSRI's are not as effective as tricyclics (amitriptyline, nortriptyline, etc.) for pain, they have a very favorable side effect profile. The SSRI's have less of the dry mouth, constipation, weight gain and sedation seen with the tricyclics. SSRI's are also a safer choice in the elderly, primarily due to tolerability, and the lack of cardiac side effects.

Side Effects

The SSRI's do differ somewhat in their side effect profile. Some patients do extremely well with one SSRI, but not with another. The most common side effects are: nausea, spaciness, drowsiness or fatigue, dry mouth, anxiety, insomnia, decreased libido, impotence, asthenia, sweating, constipation, tremor, diarrhea and anorexia. Weight gain may be a major problem. These can decrease motivation. Many of the side effects are dose related. Minimizing the dose can, for instance, decrease the sedation or sexual side effects. One key to minimizing side effects is to begin with low doses. Compliance is enhanced when the SSRI's are slowly titrated. The initial anxiety seen with SSRI's often abates if low enough doses are utilized. Since any antidepressant can trigger hypomania or mania in bipolar patients, it is prudent to "start low and go slow". Weight gain and sexual side effects are the most common reasons for discontinuation.

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Seven Keys To Using SSRI's in Headache Patients

1. Start with very low doses. This minimizes sedation and anxiety and increases compliance. If the patient is bipolar, SSRI's are best avoided.
2. If patients are warned about the initial anxiety that may occur with SSRI's, they are more likely to be compliant and stay on the medication.
3. For most headache patients, lower doses are utilized than for severe depression.
4. If one SSRI does not help or causes side effects, it is very often worthwhile to try another. Patients have widely differing responses to these medications.
5. Slowly withdraw patients in order to avoid the withdrawal syndrome.
6. If the headaches are exacerbated, discontinue the SSRI.
7. Paroxetine (Paxil), fluoxetine (Prozac), and duloxetine (Cymbalta) have more drug interactions than the others. These are all 2D6 inhibitors. See section on "CYP 450 Enzyme System".

The SSRI's

Fluoxetine (Prozac): Prozac is available in 10 mg., 20 mg., 40 mg. pulvules; 10 mg. scored tablets; liquid=20 mg./5 ml. Prozac Weekly is a once a week capsule, equal to 20 mg. daily. A generic form of Prozac is now available. Prozac is the prototype SSRI, having been used in tens of millions of people. Prozac is a long-acting (elimination half-life=4 to 6 days, but the active metabolite, norfluoxetine, has an elimination half-life of 4 to 16 days) SSRI with a well- established track record. The long half-life is generally an advantage in avoiding the SSRI withdrawal syndrome. It is important to start with low doses of SSRI's; 5 or 10 mg. of Prozac is a good starting point. Many patients report initial anxiety (or even panic) from SSRI's, and if they are on a low enough dose, they are less likely to discontinue the medication. Patients can begin with 1/2 tablet of 10 mg. Prozac.

Over 4 to 10 days, the dose may be raised to 10 or 20 mg. The effective dose for migraine or tension headache varies widely, from 5 mg. per day to 60 mg. (or more). Most patients are on 20 mg. daily. Milder tension-type headache often responds to low doses (10 or 20 mg). As is true with tricyclics, lower doses of SSRI's are used for headache than for major depression. In some patients, SSRI's actually exacerbate headaches. Fluoxetine is an inhibitor of the 2D6 system, and to a lesser extent 3A4 as well.

Sertraline (Zoloft): Generic is available. Zoloft is available in 25 mg., 50 mg. and 100 mg. scored tablets. Zoloft is somewhat shorter-acting; elimination half-life=26 hours of the parent drug and 62 to 104 hours of the active metabolite. Because the half-life is shorter than with Prozac, patients are occasionally able to stop Zoloft for one or two days and alleviate the sexual side effects. However, with the shorter half-life, withdrawal syndrome is occasionally seen with Zoloft. I usually start with 25 mg., or 1/2 of a 25 mg. tablet, and slowly increase; the average antidepressant dose is 75 to 150 mg., but the usual headache dose is approximately 50 mg. While many patients are on 100 mg. or more for headaches, most patients are maintained on lower doses. The cost of the 50 mg. and 100 mg. tablets is approximately the same. In higher doses, Zoloft is a 2D6 and 3A4 inhibitor.

Paroxetine (Paxil): Generic is available. Paxil is conveniently available in 10, 20, 30 and 40 mg. tablets. Paxil CR (controlled release) is available in 12.5 and 25 mg. doses. The elimination half-life is 21 hours, with no active metabolite. Paxil is generally very well tolerated. I usually begin with 1/2 of a 10 mg. tablet and slowly increase to 10 or 20 mg.; many patients need 30 to 60 mg. for depression. Or, we start with 12.5 mg. CR and titrate as needed to 25 mg. CR. It is important to stop Paxil slowly in order to minimize withdrawal. Paxil (SSRI) withdrawal consists of one to several days (and occasionally longer) of flu-like symptoms, malaise, dizziness and asthenia. This often goes unreported to the physician. Managing the withdrawal can be difficult; at times, the addition of fluoxetine (Prozac) may help in weaning off of the short-acting SSRI. Paroxetine is a potent inhibitor of the 2D6 system and, to a lesser extent, 3A4. See section on CYP enzymes.

Citalopram (Celexa): Generic available. Celexa is available in 20 and 40 mg. tablets, which are scored. The mean terminal half-life is about 35 hours. Celexa has a clean profile with regard to cytochrome P450 enzymes. Celexa has been an outstanding antidepressant with a very good track record, and is well tolerated. Side effects are similar to the other SSRI's. As always, we start with low doses, half of a 20 mg. tablet for four to six days, then progress to 20 mg. per day. Withdrawal symptoms have been unusual with Celexa. Its use has mostly given way to Lexapro.

Escitalopram (Lexapro): Lexapro is available in 5, 10 and 20 mg. tablets. Lexapro is metabolized primarily by the liver. Lexapro is a newer, more selective version of Celexa and has been fairly well tolerated. Lexapro has a favorable side effect profile, but side effects are similar to the other SSRI's. We start with 1/2 of the 10 mg. tablet for 4 to 6 days, and then increase to 10 mg. daily. Withdrawal symptoms are relatively unusual with Lexapro. It is fairly clean as far as drug interactions. Lexapro has risen to become one of the most prescribed antidepressants in the U.S.

Wellbutrin, Remeron, Effexor, and Cymbalta

Wellbutrin (bupropion, generic available): Wellbutrin is actually an older antidepressant that is in its own class (aminoketone). It is unlike tricyclics or SSRI's. Wellbutrin is available in lower doses. The XL form is once daily, 150 mg. or 300 mg. The usual dose is 100 or 150 mg. slow release tablets once per day. For moderate to severe depression, the doses are pushed to 300 mg. or more per day. Wellbutrin (bupropion) may work primarily through norepinephrine pathways. The advantages of Wellbutrin are that sedation, weight gain and sexual side effects are much lower than many of the other antidepressants. In fact, weight gain has been no more than placebo and the sexual side effects are exceedingly low. At higher doses, particularly at 300 mg. per day or more, people who are predisposed to seizures are at a slightly increased risk for seizure. This is dose related and is approximately .1 % (1 out of 1,000) at 300 mg. per day, increasing to .4% at 400 mg. per day. In treating headache patients, we usually use lower doses.

Wellbutrin is also utilized for smoking cessation (under the name Zyban). While it is not as anxiolytic as SSRI's, the lack of sexual side effects and weight gain render this an excellent antidepressant. The efficacy for anxiety is somewhat less than with the SSRI's and Effexor.

Remeron (mirtazipine): Remeron is available in 15 mg., 30 mg., and 45 mg. film coated tablets, and is also available in dissolving tablets. Generic is available. Remeron enhances noradrenergic and serotonergic activity. Remeron is also an antagonist of histamine, which helps to explain its sedative effects. The usual dose is 30 mg. per day; however, we start with 7.5 or 15 mg. at night for a period of time before increasing to 30 mg. Somnolence is very common, but this is an advantage in agitated depressed patients with insomnia. Weight gain is commonly seen, and is a major limiting side effect. Overall, Remeron has fewer side effects than the older tricyclics. While its primary use is in depression, for which it is a very effective medication, headache is sometimes improved with Remeron. Remeron is commonly used as an adjunctive medication for severe, refractory depression. Due to Remeron's 5HT3 antagonist activity, it helps some patients who have IBS with diarrhea.

Effexor XR (venlafaxine): The long-acting Effexor XR is available in 37.5 mg., 75 mg. and 150 mg. doses. Effexor has been an outstanding antidepressant because of efficacy and tolerability. Effexor is basically an SSRI in low doses; at higher doses, norepinephrine, then dopamine, are affected. It is very well tolerated, with less weight gain and sexual side effects than some of the other antidepressants. Effexor has few interactions with cytochrome P450 enzymes, rendering it a fairly clean medication. We usually begin with 37.5 mg. and progress to 75 mg., with a typical dose in headache patients being 75 mg. or 150 mg. Effexor XR is particularly well tolerated. It is very useful in headache patients who have concurrent anxiety and depression. Sustained elevation in blood pressure may occur at higher doses, particularly 250 mg. per day or more. The lower doses have not increased blood pressure. While headache is a potential side effect of Effexor (and all of the others), it has been no more than the rate of placebo in studies. Nausea, constipation, somnolence, dry mouth, dizziness, insomnia and agitation are seen more than in placebo. However, if doses remain low, Effexor has been well tolerated. While Effexor is less effective than tricyclic antidepressants for pain or headache, its efficacy in anxiety and depression, and its tolerability render it an extremely useful medication.

Cymbalta (duloxetine): Cymbalta has 2 official pain indications, and is a very effective antidepressant. Cymbalta increases both serotonin and norepinephrine. It is available in 20, 30, and 60 mg. capsules (which should not be split apart). Cymbalta may be helpful for headache, as well as for anxiety/depression. 60 mg. daily is the usual dose for depression; the starting dose is 20 or 30 mg., increasing over days to weeks. Side effects include, among others, nausea, dry mouth, anxiety, fatigue, lethargy, sexual effects, and weight gain. Use with caution in patients with glaucoma. Cymbalta is a moderate CYP 2D-6 inhibitor. See CYP enzyme system section.

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Bipolar Illness and Migraine

The comorbidity of migraine with anxiety and depression is well established, both in clinically based studies and in epidemiologic samples from community populations. The physiologic overlap between migraine and depression is considerable, and antidepressants or mood stabilizers often help both conditions. In the vast majority of migraine patients who suffer from depression, anxiety is a complicating factor. The anxiety disorder often precedes the age of onset of migraine, with depression following afterward.

It is possible that poorly controlled migraine headaches may fuel the onset of depression or depression may, at times, increase headache. However, it is more likely that shared environmental and genetic factors link migraine and depression.

The relationship between bipolar illness and migraine has not been as well studied as depression and migraine. However, in several studies bipolar I and bipolar II were found to be increased in migraineurs. In our initial study, (“The Bipolar Spectrum in Migraine Patients”, Robbins, L., Ludmer C., *American Journal of Pain Management*, October, 2000, Vol. 10, No. 4, pp. 167-170) we assessed 1000 consecutive migraineurs. The results were as follows: Bipolar I: 2.1 %; Bipolar II: 2.4%; Cyclothymic Disorder: 1.3%; Bipolar Disorder Not Otherwise Specified: 2.8%; Total Bipolar Spectrum: 8.6%. Recent studies have confirmed that at least 7% of headache patients fit into the bipolar spectrum. 40 to 50% of bipolar patients have migraines. In a recent study (available on headachedrugs.com), the above percentages were confirmed; about 4.5% of the general population fits into the Bipolar Spectrum.

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 to 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 / materials aimed at the milder end.

It is the milder end of the bipolar spectrum that tends to be missed; look for those 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 a clear hypomanic or manic episode. Soft bipolar signs include: early (teens) depression, severe depression, quick onset depression, “bipolar” reaction to certain meds (up all night, mind racing, etc.), agitated 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, when not diagnosed, often are given a number of antidepressants, with

predictable hypomanic (poor) results. The tricyclic antidepressants appear to have the highest propensity towards triggering mania, followed by the selective serotonin reuptake inhibitors (SSRI's). Any antidepressant can, over the short or long run, provoke hypomania (or mania) in someone who is bipolar. Some do well (particularly if they are on mood stabilizers) with antidepressants.

Once the bipolar diagnosis is established or suspected, mood stabilizers often are very helpful for the moods and headaches. Divalproex sodium (Depakote) is effective for mania, hypomania, depression associated with bipolar disorder, and for headache prevention. Divalproex sodium has been extremely well studied for these conditions, and has become one of the primary migraine and chronic daily headache preventives. Lithium carbonate is underutilized. It should be used more often. One or more of the newer antiepileptics may prove to be helpful for bipolar disorders and/or migraine. Carbamazepine (Tegretol) has some utility as a mood stabilizer, but not for migraine prophylaxis.

Topamax may improve moods in some patients. Trileptal (generic available) may prove to be one of the better mood stabilizers.

Lamictal is becoming one of the most commonly used mood stabilizers. It is one of the only effective medications for bipolar depression. Doses must be slowly titrated, due to the 1 out of 2000 severe allergic reaction. Lamictal may increase headache, but is usually well tolerated.

The Atypicals (see next section) are also used for bipolar. When a mood stabilizer is effective, the underlying agitation/anger/depression improves.

The recognition of an increased comorbidity between migraine and bipolar illness has important clinical implications. By broadening our concept of the bipolar realm, we can improve outcome in these patients. Recognition of the milder end of the bipolar spectrum is crucial, as the clinical stakes for missing bipolar illness are enormous.

Unfortunately, the medications are often more effective for the manic / hypomanic symptoms. The depression often goes untreated. Bipolar patients spend the majority of their time in depression, and we need better medications. Many patients need 2 to 4 meds (such as Lamictal, Lithium, and an antidepressant).

The Use of “Atypicals” in the Headache Patient

These are poorly named drugs; the majority of patients on these never have psychosis. The newer “atypical” antipsychotics have been useful in several situations for selected headache patients. For a patient with a moderate or severe personality disorder, the atypicals may ease the anxiety and/or depression. They can be an effective mood stabilizer in bipolar. They also are helpful for insomnia. These medications may be useful as a headache abortive, primarily because of the induction of sedation and sleep. One commonly used atypical is quetiapine (Seroquel), 25-100 mg. qhs. It is very important to attempt to use as low a dose as possible. The doses for headache patients with severe anxiety or insomnia are much lower than the standard doses of these for schizophrenia. Seroquel is usually well tolerated, with sedation being the primary side effect the next day.

Because of the risk of long-term side effects, particularly tardive dyskinesia, and diabetes, these should only be used in the occasional selected patient where benefit outweighs risk. Patients must be aware of the possible side effects, such as weight gain. Olanzapine (Zyprexa) has also been utilized in a similar fashion. The usual dose is 2.5 or 5 mg. qhs. Occasionally, Seroquel or Zyprexa have been used on a prn basis with headache patients. While Olanzapine (Zyprexa) is very effective, it does cause more weight gain (and diabetes) than the other atypicals. Risperdal (generic available) has been very effective, and we usually use low doses (0.25 or 0.5mg daily). These help induce sleep, and may offset nausea as well. The other atypicals may also be useful. Ziprasidone (Geodon) and aripiprazole (Abilify) are also available, with much less tendency toward weight gain. While sedation is the most common side effect to all of these atypicals, the following are also seen relatively often: nausea, dizziness, restlessness, tremor, rash, diarrhea, or constipation. Hypomania may occur. While QT prolongation may occur with any of the antipsychotics, this may possibly be more of a concern with higher doses of Geodon. The potential for some of these newer “Atypicals” to possibly cause an increase in blood sugar is a serious concern that may limit these medications in certain patients. This is a very versatile group of meds, but they should be judiciously utilized, with informed consent. These meds may trigger a hypomanic reaction. Risperdal is associated (particularly with larger doses) with an increase in prolactin levels, which should be checked.

Attention Deficit Disorder (ADD)

4.7 % of adults have ADD. It tends to be underdiagnosed, and is one of the more undertreated conditions in the country. ADHD includes the "H" for hyperactivity, but most people lose the hyperactive, fidgety portion by age 20. ADD is the most genetic of all psychiatric conditions. We usually screen family members for ADD. It is not uncommon for a mom to present saying "my daughter was diagnosed with ADD and I think that I have it."

To have ADD as an adult, you must have had the condition as a child or adolescent. If you did not, the attention problem as an adult is not ADD, but is a combination of stress, insomnia, medication, or other factors. It is an attentional problem, not true ADD. The cost of untreated ADD is enormous, with a major increase in substance abuse, auto accidents, jail time, and broken or unfulfilled lives. Many people do compensate well for their ADD and achieve much in their lives, but they usually do better when they are treated.

Adults with ADD remember that they had difficulty handing in homework, with boring projects or reading assignments, and poor attention. They often remember working twice as much to achieve half the amount. While people do learn to compensate for the attentional problem, ADD still takes a great toll on quality of life, both for the person and the family.

The features of ADD include: difficulty with boring projects, careless mistakes, trouble starting projects or assignments, trouble or difficulty finishing assignments, irritability, impulsivity, and unfinished piles of materials laying about their room or house. In addition there may be a tendency to misplace things, being easily distracted, poor attention, and difficulty remembering appointments.

ADD often has other comorbid psychological conditions such as anxiety and depression. The attention problem interferes with life's functioning, and leads to more anxiety and depression. ADD itself creates anxiety and stress in people's lives.

We utilize the ASRS, Adult Self Report Scale, as a screening test for ADD in adults.

The scale is as follows:

	Never	Rarely	Some- times	Often	Very
1. How often do you make careless mistakes when you have to work on a boring or difficult project?	0	1	2	3	4
2. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?	0	1	2	3	4
3. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?	0	1	2	3	4
4. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	0	1	2	3	4

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5. How often do you have difficulty getting things in order when you have to do a task that requires organization?	0	1	2	3	4
6. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?	0	1	2	3	4
7. How often do you misplace or have difficulty finding things at home or at work?	0	1	2	3	4
8. How often are you distracted by activity or noise around you?	0	1	2	3	4
9. How often do you have problems remembering appointments or obligations?	0	1	2	3	4

Add up your score. The scoring is: 0-16: Unlikely to have ADD;
 17 -23: Likely to have ADD
 24 or greater: highly likely to have ADD

There are a number of good books in the bookstores on ADD. Sometimes they are general books that encompass child and adult, and there are books that just focus on adult ADD. The monthly magazine "ADDitude" is also a good resource. Outside of medication, behavioral treatments and therapies have been disappointing. Life coaches or therapists may be of some help, particularly with coexisting anxiety or depression. The primary mode of treatment has been medication, as the medications have been the most successful of all of the therapies. If you feel that you may have ADD, it is important to work with a doctor trained in dealing with patients who have ADD.

The "first-line" medications for ADD are the amphetamines (Adderall, Adderall XR, Vyvanse) and methylphenidates (Ritalin, Ritalin LA, Focalin, Focalin XR, Concerta). Adderall XR is a longer-acting, once-daily form; Ritalin LA, Focalin XR, and Concerta are also longer-acting. Side effects of these include, among others, anxiety, faster heart rate, and insomnia. These medications do, at times, help headaches and fatigue.

If Adderall or Ritalin-type medications are ineffective, or can't be used, the second-line drugs include Strattera, bupropion (Wellbutrin), nortriptyline, or desipramine. Other antidepressants have also been used. As usual, the idea with medication is to find an effective dose, but try and minimize medication.

Provigil (modafinil) is not indicated for ADD but is utilized as a 2nd-line ADD drug. It is expensive.

Personality Disorders

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 than others. In general, characteristics of personality disorders include: lack of insight, poor response to psychotherapy or other therapeutic interventions, difficulty with attachment and trusting, sense of entitlement, the creation of a great deal of chaos and distress in family and 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 that they have their sights set on. Personality disorder patients often create chaos and drama, which can vary from mild to severe. Comorbid substance abuse is common.

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 can improve naturally over time. One study of borderline personality disorder in adolescence indicated that by age 30, 1/3 of the people no longer had borderline personality. The following is a description of some of the more severe personality disorder types. Many people do not fit neatly into any of these categories, but have features of 2 or 3 personality disorder types.

Paranoid Personality Disorder: They tend to be non-trusting, suspicious, and they see the world as dangerous. They view themselves as constantly being mistreated. They are very secretive, and reluctant to confide in others. They doubt the loyalty of anybody around them, and believe they are being exploited or harmed, and these patients bear severe grudges against others. They become angry very easily and have a sense of entitlement. Paranoid personalities can become violent and dangerous, as most spree killers are paranoid personality disorders. Many terrible world leaders, such as Joseph Stalin or Saddam Hussein, were most likely paranoid personalities.

Antisocial Personality Disorder: These people generally have no regard for the rights of others; they are exploitative, they see themselves as better or superior, and are very opportunistic. They are deceitful, steal from people around them, and often have trouble with the law. They frequently engage in fraudulent activities, make very good 'scam artists', and tend to be irritable and impulsive. They often come in as a savior for a church, for example, and end up stealing everything. They generally have no remorse. Conduct disorder as a child often morphs into antisocial personality disorder. Examples include the Mafia 'Dapper Don' John Gotti, or Tony Soprano in 'The Sopranos'. TV shows such as Dateline or 20/20 are replete with stories revolving around antisocial personality disorders.

Borderline Personality Disorder: They have instability of mood, poor self image, and pervasive abandonment fears. There is an identity disturbance and major boundary issues. Borderlines usually demonstrate impulsiveness, suicidal behavior, and very quick shifts from depression to anxiety to irritability. There are usually chronic feelings of emptiness or severe "malignant" loneliness, plus anger and temper. Under stress they can become somewhat paranoid. Drug abuse or other addictive behaviors may occur. There are often sleep disorders with severe insomnia. Severe borderlines will react with a level-3 severe drama and create chaos for everybody around them. They tend to split, which is, they see people as wonderful or as terrible, with nothing in between. Examples include Princess Diana, Adolph Hitler, Marilyn Monroe, and Glenn Close's character Alex, in the movie "Fatal Attraction". Borderline Personality can vary from mild to severe, and may become better, or worse, over time. Suicide becomes more likely as patients get into their high 20's and 30's.

Narcissistic Personality Disorder: This is less common, and the people see themselves as being above others, they are grandiose, have a lack of empathy, and they feel self-important. There is a true sense of entitlement. They may be very vain and constantly require admiration. They are envious, arrogant, exploitative, and can be very angry. Examples include General George Patton, Nicole Kidman's character in the movie "To Die For", Michael Douglas' character, Gordon Gekko, in the movie "Wall Street", Kelsey Grammer's character in "Frazier", and the Chief of Medicine, Dr. Robert Romano on the TV show "ER".

There are a number of other personality disorders that are not as dangerous for the people around them or for health care providers. Personality disorder characteristics in people are often overlooked, and health care clinics may react and treat these patients in a dysfunctional manner. Many patients do not have all of the characteristics of one particular personality disorder, but it is a spectrum with several characteristics of a number of personality disorders.

Treatment consists of maintaining limits and boundaries on the person, encouraging therapy with somebody who is experienced with personality disorders, and encouraging the therapy to go on weekly for a very long time. Medications may help the anxiety and depression aspects, but there are no specific medications that are very successful for personality disorder characteristics. We attempt to avoid addicting medicines and primarily utilize mood stabilizers / antidepressants.

For more information on personality disorders, an excellent resource is Dr. Gregory Lester's tapes and booklets. "Personality Disorders in Social Work and Health Care" and "Borderline Personality Disorder" are available from:

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Insomnia

Insomnia is commonly seen in migraine and chronic daily headache patients. The following are Rules for Better Sleep:

Sleep as much as needed to feel refreshed and healthy during the following day, but not more. Curtailing the time in bed seems to solidify sleep; excessively long times in bed seem related to fragmented and shallow sleep.

A regular awakening time in the morning strengthens circadian cycling and, finally, leads to regular times of sleep onset.

A steady daily amount of exercise probably deepens sleep. Yoga may be helpful. Deep breathing / relaxation exercises may help.

Occasional loud noises (e.g. aircraft flyovers) disturb sleep even in people who are not awakened by noises and cannot remember them in the morning. Sound attenuated bedrooms may help those who must sleep close to noise. White noise sound machines (such as at Brookstone and Sharper Image) help to blunt outside sounds. Consider ear plugs (Hearos, 33db, is a particularly good brand). These are also helpful on a plane, or on vacation.

Although excessively warm rooms disturb sleep, there is no evidence that an excessively cold room solidifies sleep.

Hunger may disturb sleep; a light snack may help sleep.

An occasional sleeping pill may be of some benefit, but their chronic use is ineffective in most insomniacs. However, some people do well on sleeping pills for months or years.

Caffeine in the evening disturbs sleep, even in those who feel it does not.

Alcohol helps tense people fall asleep more easily, but the ensuing sleep is then fragmented.

People who feel angry and frustrated because they cannot sleep should not try harder and harder to fall asleep, but should turn on the light and do something different.

The chronic use of tobacco disturbs sleep.

Go to bed only when sleepy.

Keep a night light in the bathroom (bright lights will awaken your brain). Keep the lights in the bedroom down low (even prior to sleeping).

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Use the bed only for sleeping; do not read, watch television or eat in bed.

If unable to sleep, get up and move to another room. Stay up until you are really sleepy, then return to bed. If sleep still does not come easily, get out of bed again. The goal is to associate bed with falling asleep quickly. Repeat this step as often as necessary throughout the night.

Set the alarm and get up at the same time every morning, regardless of how much you slept during the night. This helps the body acquire a constant sleep/wake rhythm.

Useful websites include: www.sleepfoundation.org, and www.soundsleepsolutions.com.

The primary sleep aids utilized have been: Ambien and AmbienCR, Lunesta, and Sonata. Ambien has been the most-preferred, and is available in 5mg. and 10mg. tabs that may be split. Generic is available. The AmbienCR is an excellent, longer-lasting formulation, with doses of 6.25 and 12.5 mg.(that should not be split). With any sleep med, fatigue or cognitive effects may be seen the next day. Minimizing the dose with any sleep med is important. Lunesta has a similar mechanism of action to Ambien, primarily GABA. The usual dose is 2 or 3mg. at night; some do well on 1/2 tablet. SE's are similar to those of Ambien. Lunesta is not as well tolerated, and bad taste is common. Sonata is shorter-acting, and is effective for some in the middle of the night. Some pts. may take Sonata at 3am and not be tired at 8am. While relatively safe, any of the above meds can be abused. Rozerem is a newer 'melatonin agonist', similar (but stronger) to the OTC melatonin. While non-addicting and relatively safe, Rozerem is relatively mild in it's effect. Rozerem may be used with another sleep medicine.

In addition to the above, the atypical antipsychotics are occasionally utilized in selected patients. These are particularly helpful in those patients with bipolar illness, or very severe anxiety. The usual medication would be Seroquel 25 mg. 1/2 or 1, or 2, qhs, or Zyprexa 2.5 mg. or 5 mg. qhs. Risperdal, 0.25 to 0.5mg, may also help. Fatigue may occur with both of these the next day, and weight gain is seen relatively often with Zyprexa. These atypicals do have the possibility for long term side effects (tardive dyskinesia, diabetes), and therefore are used only in selected patients where the benefit may outweigh the risk.

Certain muscle relaxants may aid sleeping. Zanaflex, (tizanidine) 4 mg., 1/2 or 1, is not addicting, and may be helpful in preventing the headaches the next day. Cyclobenzaprine (Flexeril) is also sedating, not addicting, and helpful for those with neck or back pain.

Benzodiazepines are not the first-line meds, but do play a role in selected patients. The chronic use of benzodiazepines may actually increase pain or headache the next day.

The older antidepressants, particularly trazodone, often are very useful. The Trazodone dose varies from 50 mg. to 300 mg. The tricyclics (such as amitriptyline or nortriptyline) may help sleep and headache.

Fatigue

Fatigue is a symptom commonly reported by headache patients. Causes such as anemia or hypothyroidism need to be ruled out. Two studies have indicated that 50% of migraine patients report significant “excessive daytime sleepiness”. Unfortunately, little is understood about its cause. The following medications are sometimes utilized to treat fatigue.

1. **Provigil** (modafinil): This fairly safe medication is classified as a wake-promoting agent. Usual doses start at 100 mg. daily and occasionally are increased up to 400 mg. a day if needed. Most patients are on 200 mg. a day. The most common side effects with this medication are headache, nausea and anxiety. Unfortunately, Provigil may actually increase headache: it is expensive, and not “FDA indicated” for general fatigue.
2. **Stimulants** (dextroamphetamine, methylphenidate, Adderall): These medications may be helpful for fatigue, as well as concurrent ADD/ADHD. They may help to decrease pain or headache as well. Some of these medications come in short-acting and long-acting preparations, which is helpful. The main side effects consist of decreased appetite, anxiety, insomnia and dry mouth. Adderall XR is a good long-acting preparation, usually dosed once daily.
3. **Wellbutrin** (bupropion, generic available): This medication is an antidepressant which is beneficial due to its activating nature. The doses are available in SR slow-release tablets 100 mg., 150 mg., and 200 mg. tablets, along with a once-daily XL form, which comes in 150 mg. and 300 mg. dosage. Depending on comorbid anxiety and depression, the dose range may vary from 100 mg. up to 300 mg. per day. The advantages of Wellbutrin are that sedation, weight gain and sexual side effects are much lower than with many of the other antidepressants. See previous section on Wellbutrin.
4. **Caffeine**: While caffeine may offset fatigue, it is not ideal due to its short-acting activity. Caffeine may help headache, but overuse leads to more headaches. Doses should be limited to 200mg per day (at most). See previous section on “Sources of Caffeine”.

The CYP 450 Enzyme System

We have tried to be accurate, but different reference sources vary as to these systems.

Drug-Drug interactions are important to understand prior to starting a new medication. All medications go through various routes of elimination. A subset of enzymes found in the liver, known as CYP isoenzymes, are responsible for metabolism of many common medications. Some medications are substrates for one of these enzymes, in many cases meaning that they are converted into a less active form than the parent compound. Various medications may act as inducers or inhibitors of these enzymes. The inducers “speed up” the action of these enzymes. The inhibitors “slow down” the action of these enzymes. Thus, inducers may decrease the effectiveness of particular drugs that are substrates for the same isoenzyme while inhibitors have the opposite effect.

The most common isoenzymes that have relevance to our practice are: CYP 2D6, CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2B6.

The lists below are not complete. Prior to starting a new medication not listed below, one should consult the PDR for interactions.

CYP 2D6

Bold = strong effect

Substrates

Amitriptyline
Aripiprazole (and 3A4)
Atomoxetine
Captopril
Chlorpromazine
Clomipramine (and 1A2, 2C19)
Codeine
Desipramine
Dextroamphetamine
Doxepin (and 1A2, 3A4)
Duloxetine
Fluoxetine (and 2C9)
Hydrocodone (a prodrug)
Haloperidol
Imipramine (and 2C19)
Labetalol
Methylphenidate
Metoprolol
Mirtazapine (and 1A2, 3A4)
Nortriptyline

Inhibitors

Bupropion
Celecoxib
Cimetidine
Citalopram
Chlorpromazine
Clomipramine
Cocaine
Desipramine
Dexamethasone
Diphenhydramine
Doxepin
Duloxetine (Cymbalta)
Fluoxetine
Haloperidol
Hydroxyzine
Imipramine
Ketoconazole
Methadone
Miconazole
Midodrine

Inducers

None

CYP 2D6 continued

Substrates

Oxycodone (a prodrug)
(converted to active
metabolite-inhibitors
decrease overall efficacy
of Oxycodone)
Paroxetine
Pindolol
Promethazine (and 2B6)
Propranolol (and 2C19, 1A2)
Protriptyline
Risperidone
Tamoxifen
Timolol
Tramadol (a prodrug)
Venlafaxine (and 3A4)

Inhibitors

Metoclopramide
Paxil (Paroxetine)
Rifampin
Sertraline (if > 150 mg.)
Trazodone

Interestingly, 14% of patients are “poor metabolizers”. The CYP 2D6 enzyme doesn’t work as efficiently, in those patients.

Also, tramadol, hydrocodone, and oxycodone are metabolized to various active forms. So, 2 D6 Inhibitors may decrease effect. Oxycodone→ oxymorphone (15% of parent, weaker met), inhibitors to CYP 2D6 have unknown significance, have not been identified.

Oxycodone→ noroxycodone not metabolized by CYP2D6.

Tramadol→ M1 metabolite (active form of drug), inhibitors may decrease analgesic effects.

Hydrocodone→ hydromorphone (active form of drug), same as tramadol: inhibitors may decrease effect.

The above opioids are “prodrugs”, and need 2D6 in order to be metabolized to the active compound.

CYP 3A4

Substrates

Alprazolam
Amlodipine
Aripiprazole (and 2D6)
Astemizole
Atorvastatin
Buprenorphi

Inhibitors

Antiretrovirals
Caffeine
Cimetidine
Ciprofloxacin
Clarithromycin
Desipramine

Inducers

Phenobarbital
Phenytoin
Rifampin
St. John’s Wort
Tegretol

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CYP 3A4, continued

Substrates

Buspirone
Cerivastatin
Cisapride
Chlordiazepoxide
Clarithromycin
Clonazepam
Diazepam (and 2C19)
Dihydroergotamine
Diltiazem
Doxepin (and IA2, 2D6)
Eletriptan
Erythromycin
Escitalopram (and 2C19)
Estrogens (and IA2)
Fentanyl
Lansoprazole (and 2C 19)
Losartan (and 2C9)
Lovastatin
Methadone
Mirtazapine (and IA2, 2D6)
Modafinil
Montelukast (and 2C9)
Nifedipine
Ondansetron
Pimozide
Quetiapine
Quinine
Sertraline (and 2B6, 2C9, 2C19)
Sildenafil
Simvastatin
Tamoxifen (+ 2D6)
Tiagabine
Trazodone
Triazolam
Venlafaxine (and 2D6)
Verapamil
Vincristine
Zaleplon
Zolpidem (partial)
Zonisamide

Inhibitors

Diltiazem
Doxycycline
Erythromycin
Fluconazole
Grapefruit Juice
Itraconazole
Ketoconazole
Metronidazole
Miconazole
Nefazodone
Norfloxacin
Norfluoxetine
Sertraline
Tetracycline
Verapamil

Inducers

Trileptal
(?>1200)
Topiramate (Topamax)

*Pravastatin has multiple pathways...may want to use if pt is on CYP 3A4 inhibitor

CYP 1A2

Substrates

Clomipramine (and 2C19, 2D6)
Clozapine
Cyclobenzaprine
Doxepin (and 2D6, 3A4)
Estrogen
Frova
Imipramine
Mirtazapine (and 2D6, 3A4)
Naproxen
Olanzapine
Propranolol (and 2C19, 2D6)
Tacrine
Theophylline
Zomig

Inhibitors

Broccoli / Brussel sprouts
Caffeine
Cimetidine
Ciprofloxacin
Diclofenac
Gemfibrozil
Insulin
Ketoconazole
Miconazole
Modafinil(Provigil)
Nifedipine
Norfloxacin
Omeprazole
Prozac
Rofecoxib
Tobacco

Inducers

Broccoli
Caffeine
Phenytoin/PB
Smoking (tobacco)
Tegretol

CYP2C9

Substrates

Fluoxetine (and 2D6)
Losartan
Montelukast (and 3A4)
NSAIDS
Phenytoin
Tamoxifen
Sertraline (and 3A4, 2B6,2C19)
Sulfamethoxazole
Warfarin

Inhibitors

Amiodorone
Fluconazole
Flurbiprofen
Fluvastatin and Lovastatin
Gemfibrozil
Ibuprofen
Indocin
Ketoconazole
Losartan
Lovastatin
Miconazole
Omeprazole
Pantoprazole
Provigil
Rifampin
Sulfamethoxazole
Sertraline
Zafirlukast

Inducers

Phenobarb
Phenytoin
Tegretol

CYP 2C19

Substrates

Amitriptyline
Clomipramine (and 1A2, 2D6)
Diazepam (and 3A4)
Escitalopram (and 3A4)
Esomeprazole
Imipramine (and 2D6)
Indomethacin
Lansoprazole (and 3A4)
Omeprazole**
Pantoprazole
Phenobarbitone
Phenytoin
Progesterone
Propranolol (and 1A2, 2D6)
Sertraline (and 3A4, 2B6, 2C9)

Inhibitors

Cimetidine
Fluconazole
Fluoxetine
Gemfibrozil
Ketoconazole
Lansoprazole
Loratadine
Miconazole
Modafinil
Omeprazole
Oxcarbazepine
Prednisone
Rabeprazole
Sertraline
Tegretol
Topamax (Topiramate)

Inducers

Phenytoin
Rifampin
Tegretol

** Try Prevacid, Axid, Aciphex, Pepcid or Protonix instead

CYP 2B6

Substrate

Cyclophosphamide
Methadone
Promethazine
Wellbutrin

Inhibitors

Desipramine
Paroxetine
Rifampin
Sertraline

Inducers

Orphenadrine
Phenytoin
Phenobarbital
Tegretol

Instructions For Patients: Maxalt (Rizatriptan)

The earlier it is taken, the better Maxalt works. Maxalt is a well-tolerated, effective triptan. Maxalt is available in 5 mg. and 10 mg. strengths. Maxalt MLT are tablets that dissolve in seconds on the tongue. In general, the side effects have been found to be minimal. Side effects are very similar to those of Imitrex. These include nausea, chest heaviness or pressure, pressure in the throat, shortness of breath, rash, tingling sensation, heat sensation or heaviness, tiredness, drowsiness, dizziness, etc. The symptoms are usually short-lasting. They go away, but, if they are more than mild, Maxalt should not be taken again until you speak with the physician. We are careful with Maxalt (and all triptans) in patients who have major risk factors for heart problems. Maxalt should not be used in people with hardening of the arteries or who have had past heart attacks. However, in all of the studies and previous experience with Maxalt, it has generally been a safe medication. See Imitrex side effect section.

How To Use Maxalt Tablets

The earlier one uses Maxalt for a migraine, the better. Maxalt, 10 mg., may be taken one every three to four hours, as needed, three in a day at most. Most patients have only needed one tablet. The tablets are generally limited to 10 tablets per week at most. The very first time you use it, try 1/2 tablet only to see how you will react. Maxalt MLT tablets should be put on the tongue (they dissolve in seconds). Patients usually like the MLT tablets because of convenience; these do not require water.

Maxalt With Other Medication

Maxalt should not be taken in the same day as Imitrex, Amerge, Axert, Frova, Replax, or Zomig. Pain medications (such as aspirin, Aleve, ibuprofen, Fiorinal, Vicodin, Tylenol, etc.) may be used, even at the same time. In some patients, this increases efficacy. Anti-nausea medications may also be used at the same time. Generally, there are relatively few interactions between Maxalt and other medications.

How Long Does It Take To Work?

Maxalt can take anywhere from 30 minutes to two hours to help.

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Instructions for Patients: Relpax (Eletriptan)

The earlier in a migraine, the better Relpax works. Relpax is an effective and well-tolerated triptan. It is available in 20 and 40 mg. strengths. The side effects have, in general, been found to be fairly minimal. They are similar to Imitrex's. These include possible nausea, pressure in the throat, dizziness, and tiredness or weakness. Although chest pressure/pain/tightness may occur with Relpax, these symptoms have not been seen very often (only 1 to 2% of patients). In long-term studies, only 8.3% of patients discontinued the Relpax due to side effects. Relpax has had an excellent cardiac safety profile (in studies). See Imitrex side effect section.

Who Should Not Use Relpax

As with any other triptan, the following conditions should mitigate against the use of Relpax: 1. hypertension that is not well controlled, 2. past history of a stroke, 3. history of heart disease, 4. circulatory problems, 5. basilar or hemiplegic migraine, and 6. Relpax should not be used with nefazodone (Serzone), Nizoral, Sporonox, verapamil, TAO, Biaxin, Norvir and Viracept. These medicines may increase the concentration of Relpax; a few other medications are contraindicated, please check the PI for the list. Any triptan can cause a short-term increase in blood pressure. Serious cardiac events have occurred following the use of triptans.

How To Use Relpax

The tablets are available in 20 and 40mg. The usual dose is 40 mg, which may be repeated in 2 to 4 hours, if needed. 80 mg. per day (2 of the 40 mg tablets) is the recommended maximum. The very first time that patients use a triptan such as Relpax, I usually recommend that they take 1/2 tablet only, then repeat the other half in 30 to 45 minutes. After the initial time, we usually utilize the whole tablet.

Relpax With Other Medication

Relpax should not be used in the same day as ergotamines (Migranal) or other triptans (Imitrex, Zomig, Maxalt, Axert, Frova). Nefazodone (Serzone) and a few other CYP3A4 inhibitors are contraindicated with Relpax.

Pain medications (such as aspirin, Aleve, ibuprofen, Fiorinal, Vicodin, Tylenol, etc.) may be used even at the same time as Relpax. Combining these with Relpax will, at times, increase efficacy. Anti-nausea medications may also be used at the same time.

How Long Does Relpax Take To Work?

Relpax may take from 30 minutes to 2 hours to become effective. After a 40 mg. dose, 55% to 65% of patients have mild or no headache after 2 hours.

Instructions For Patients: Zomig Tablets and Nasal Spray (N.S.)

Zomig N.S. is a fast-acting triptan. It is very effective, and may work as soon as 15 to 25 minutes. SE's are similar to the tabs; a mildly unpleasant taste may occur.

Zomig tabs are very similar to Imitrex tablets. It is available in 2.5 mg and 5 mg. tablets. The Zomig ZMT (on the tongue) is 2.5 mg or 5 mg. The side effects have, in general, been found to be minimal. Side effects are very similar to those of Imitrex. These include chest heaviness or pressure, pressure in the throat, nausea, shortness of breath, rash, swelling of the face or lips, tingling, heat or a sensation of heaviness, tiredness, drowsiness, dizziness, etc. Most of these symptoms are not seen with Zomig, or, if they occur, they are short lasting. They go away and, if they are more than mild, the Zomig should not be taken again until you talk with your physician. We are careful with Zomig or Imitrex in patients who have major risk factors for heart problems. Zomig should not be used in people with hardening of the arteries or who have had past heart attacks. However, in all of the studies and previous experience with Zomig, it has generally been a safe medication. The earlier Zomig is used for a migraine, the better. See Imitrex side effect section.

How To Use Zomig Tablets and Nasal Spray

Zomig 5 mg. tablet or the 5 mg. ZMT (dissolvable tablet on the tongue) may be taken every three to four hours as needed. Many patients need 5 mg. at a time, every three to four hours, as needed, with 10 mg. per 24 hours at most (or two of the 5 mg. tablets per 24 hours at most). The tablets are limited to 10 tablets per week at most. The ZMT (dissolvable) has a pleasant orange taste. The Zomig N.S. is dosed at 1 spray every 3 hours, as needed, 2 sprays (10mg) in a day at most.

Zomig With Other Medication

Zomig should not be taken in the same day as Imitrex or other triptans. Pain medications, such as aspirin, naproxen, ibuprofen, Fiorinal, Vicodin, Tylenol, etc, may be used, even at the same time as Zomig. Anti-nausea medication may be used at the same time. Generally, there are relatively few interactions with Zomig.

How Long Does Zomig Take To Work?

From 15 minutes to 2 hours; the nasal spray is the form that works faster.

Instructions For Patients: Axert

The earlier Axert is used for a migraine, the more effective it is. Axert is a well tolerated triptan, available in 6.25 mg. and 12.5 mg. tablets. The side effects are generally mild, and include: possible nausea, pressure in chest or throat, shortness of breath, tingling sensation, fatigue, dizziness, etc. The side effects, if experienced, usually resolve within 1/2 hour. If you have more than mild side effects, do not take Axert again until you speak with your physician. As with other triptans, people with major risk factors for coronary artery disease should be screened prior to using Axert. Axert has generally been a safe medication. See Imitrex side effect section.

How To Use Axert

Axert, 12.5 mg., may be taken every 2 hours, as needed, 2 in a day at most. The tablets are usually limited to 10 per week at most. The very first time you use it, try 1/2 tablet to see how you will react. Axert usually takes 1/2 hour to 1 hour to help. The earlier one uses Axert for a migraine, the better.

Axert With Other Medications

Axert should not be taken in the same day as triptans (Imitrex, Amerge, Maxalt, Replax, Frova, Zomig). Pain medications and OTC's (such as aspirin, ibuprofen, Aleve, Fiorinal, Vicodin, etc.) are OK to use with Axert, even at the same time. Sometimes using ibuprofen or naproxen (Aleve) with a triptan such as Axert increases the effectiveness. Anti-nausea medications may be used at the same time. Axert has relatively few medication interactions.

Instructions For Patients: Frova (Frovatriptan)

The earlier in a migraine that Frova is used, the more effective. Frova is usually well tolerated. The long (26 hours) half-life is advantageous for those with prolonged migraines. Mean maximal blood concentrations are seen approximately 2 to 4 hours after a dose of Frova. Frova has been particularly useful for those with slower-onset moderate or moderate to severe migraines. Frova is available in 2.5 mg tablets. Side effects are similar to those of Imitrex. See Imitrex side effect section.

Who Should Use Frova?

Frova is most useful for migraines that are of slower onset; if one awakens with a very severe migraine with severe nausea, Frova may not be the optimal choice. It is common for migraineurs to experience prolonged moderate or moderate to severe migraines. Menstrual migraines are often of long duration. Frova, with its extended duration of action, is an ideal triptan for these patients. As with any migraine abortive, early intervention with the medication is best.

Who Should Not Use Frova?

As with other triptans, the following conditions should mitigate against the use of Frova: 1. hypertension that is not well controlled; 2. past history of a stroke; 3. history of heart disease; 4. circulatory problems; and 5. basilar or hemiplegic migraine. Any triptan can cause a transient increase in blood pressure.

How to use Frova Tablets

Frova is available in 2.5 mg tablets. The usual dose is 2.5 mg every 2 to 4 hours as needed, 3 tablets in 24 hours at most.

Frova With Other Medications

As with other triptans, Frova may be used in conjunction with most other medications such as nsoids or analgesics. At times, I do sometimes suggest to patients that they combine an nsaid (such as naproxen) with a triptan, in an attempt to prevent headache recurrence. Antiemetics are safe with Frova.

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Frova should not be used in the same day as other triptans (Imitrex, Amerge, Axert, Zomig, Maxalt).

Side Effects

Frova has usually been exceptionally well tolerated. As with other triptans, certain patients will experience 20 to 30 minutes of mild side effects. These include dizziness, paresthesias, flushing and fatigue. In addition, feelings of hot or cold, dyspepsia, skeletal pains, dry mouth, or (brief) headache may occur. All triptans may provoke chest pain, which is rarely of cardiac origin.

The serious side effects of triptans, as a class, include myocardial infarction and stroke. Over 80 million patients have taken triptans, and serious adverse events are extremely rare. Prior to triptan use, patients should be screened for risk factors associated with coronary artery disease or spasm. If moderate to severe chest pain does occur after the use of any triptan, it is prudent to discontinue use, at least until appropriate cardiac evaluation is accomplished.

Instructions For Patients: Amerge (Naratriptan)

Amerge is a smooth, long-acting triptan, extremely well tolerated. It is available in 1 mg. and 2.5 mg. strengths. In general, the side effects have been found to be minimal. These include possible nausea, chest heaviness or pressure, pressure in the throat, shortness of breath, rash, tingling sensation, head sensation or heaviness, tiredness, drowsiness, dizziness, etc. Most of these symptoms have been minimal and actually are more common with other triptans than with Amerge. The symptoms usually are short-lasting. However, if they are more than mild, Amerge should not be taken again until you speak with your physician. We are careful with all triptans in patients who have major risk factors for heart problems. Amerge should not be used in people with hardening of the arteries or who have had past heart attacks. However, in all of the studies and previous experience with Amerge, it has generally been a safe medication. See Imitrex side effect section.

How To Use Amerge Tablets

The earlier one uses any triptan, the better. Amerge, 2.5 mg. may be taken one every three to four hours, as needed, two in a day at most. Most patients have only needed one tablet. However, 5 mg., or two tablets in 24 hours, is the most that we want to use. The tablets are generally limited to 10 tablets per week at most. The very first time you use it, try $\frac{1}{2}$ tablet to see how you will react.

Amerge With Other Medication

Amerge should not be taken in the same day as Imitrex, Migranal, Zomig, Relpax, Maxalt, or Axert. Pain medications (such as aspirin, Aleve, ibuprofen, Fiorinal, Vicodin, Tylenol, etc.) may be used, even at the same time as Amerge. This can increase efficacy. Anti-nausea medications may also be used at the same time. Generally, there are relatively few interactions with medications and Amerge.

How Long Does It Take To Work?

Amerge can take anywhere from 30 minutes to two hours to help. While Amerge does take somewhat longer to take effect, it lasts longer than most of the others in its class.

Instructions For Patients: Imitrex (Sumatriptan)

The earlier Imitrex is utilized, the better it works. Imitrex is an extremely effective migraine abortive medication. Side effects have, in general, been found to be minimal. Imitrex is effective for approximately 70% of patients. The gold standard in headache abortive treatment. Imitrex tabs are now “fast-dissolving” in the stomach, leading to a quicker onset of action. Over 50 million patients have used Imitrex.

Who Should Use Imitrex?

Imitrex is excellent for migraine patients who are not at risk for coronary artery disease (CAD). Tablets of Imitrex can be used in patients in their 50's, or 60's, but with caution, and only in those patients who have been screened for CAD. Imitrex should not be a “last resort”; it is helpful for moderate as well as more severe migraines.

How To Use Imitrex Tablets

The earlier one uses any triptan the better the effect. Imitrex comes in 25 mg., 50 mg. and 100 mg. tablets. Most patients require 50 mg. or 100 mg. I start with 25 or 50 mg. every three to four hours, to assess how people will react to the drug. If they do not have adverse side effects, we have the patient take 50 or 100 mg., every three to four hours, up to a maximum of 200 mg. per day. Many patients will require 100 mg. per dose; all attempts are made, however, to minimize the dose.

How To Use Imitrex Nasal Spray

Imitrex Nasal Spray is available in 5 mg. and 20 mg. sizes. Each unit dose is for one-time use only. Almost all patients use the 20 mg. spray. Side effects are generally mild.

Patients should limit the nasal spray to two 20 mg. sprays per day at most, separating them by at least two hours. We use only one spray and two tablets in a day at most.

The nasal spray is very easy to use. The instruction sheet for patients is easy to follow; keep the head in an upright position, close one nostril, insert the nozzle of the nasal spray into the open nostril, and press the blue plunger on the Imitrex.

The nasal spray, of course, is very convenient. The nasal spray is usually sold in a box of six sprays at a time. A bad taste is the most common side effect. Keeping the head upright can help, do not lean the head back; patients have found that drinking a carbonated beverage prior to the spray, or sucking on a hard candy (particularly butterscotch) may alleviate the bad taste.

How To Use The Imitrex Injection

Imitrex injections are most often available in the STATdose injector form, which is simple to learn and comes in a convenient hard case. This carrying case fits into a purse and renders transportation of the injections (which many patients do carry around with them) very easy. While the usual dose has been 6mg, the 4mg STATdose is usually effective. The injections are dosed at one every three to four hours as needed, but limited to no more than two in a day at most. The tablets are usually limited to ten tablets per week, and the injections to four per week. There are exceptions where we will use Imitrex daily for periods of time, particularly with cluster headaches. The vials of Imitrex, 6 mg per 0.5 cc, are also available. The patient draws up 0.25 cc (3 mg. Imitrex) or 0.5 cc (6 mg.) into an insulin syringe. Many patients prefer this route, and it allows the patient to use a lower dose; this is effective for many people.

Mild Side Effects

Side effects are milder with the tablets than with the injections. Many people will not have side effects with Imitrex tablets. With the injections, they do often sense a “rush” into their head. Feeling heat in the head or numbness is relatively common. Chest heaviness or pressure, or pressure in the throat is also common. This is rarely from cardiac origin. If chest heaviness is moderate or severe, or is associated with arm pain, the patient should not use it again prior to clearance with the physician. Nausea is also common, as is fatigue, but these side effects tend to be short lasting. Most side effects resolve by 30 minutes.

Occasionally patients will feel weak or dizzy. Tingling in the fingers or feet may be experienced, particularly with daily high dose usage of Imitrex. Again, the tablets are usually much better tolerated (and convenient).

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Serious Side Effects

With Triptans, the two serious side effects have been myocardial infarction and (possibly) stroke. Stroke has occurred in a number of cases, but it is unclear whether this was due to Imitrex or was a random event. Millions of people have had Imitrex now, and Imitrex has been used to treat over 500 million migraines. The issue of myocardial infarction and coronary ischemia is very important with the use of triptans. Imitrex does decrease coronary artery blood flow by approximately 17% for one hour or so. These effects are more marked with the injections than with the tablets. Patients at any age should be screened for coronary artery disease at least by history, and patients over the age of 40 should possibly have an appropriate workup (if indicated). The tablets have only been associated with rare cardiac events. However, in studies investigating Imitrex tablets, patients who have coronary artery disease or who have ventricular arrhythmias can have some ischemia. While Imitrex has generally been a very safe medication, it is important to screen these patients. After moderate or severe chest symptoms, it is prudent to discontinue use. Patients must be informed of possible adverse events. Over the past 18 years, as a class the triptans have had a good record of safety.

Imitrex With Other Medication

Pain medications and OTC's (such as aspirin, Tylenol, Aleve, Vicodin, Fiorinal, etc.) are OK to use in the same day or even at the same time as Imitrex. This may enhance efficacy in some patients. Antiemetics such as Phenergan, Reglan, Compazine, etc. are safe with Imitrex. Midrin, which is a mild vasoconstrictor, should not be used within eight hours of Imitrex. While all indications are that they are probably safe, other triptans and Imitrex have not been cleared for use in the same day. Do not use other triptans the same day as Imitrex.

Imitrex With Pregnancy/Breastfeeding

Imitrex should not be used during pregnancy. With breastfeeding, with consent, Imitrex has been utilized (the lower the dose, the better).

Other Uses Of Imitrex

Occasionally, Imitrex will be useful for preventing headache, particularly menstrual migraines. Sometimes we will use one tablet twice a day for three or four days for severe menstrual migraines. However, in general, Imitrex is too short-acting to be used as a preventative. Imitrex is also extremely effective in cluster headache and approximately 80% of cluster patients receive excellent relief from Imitrex. The longer-acting triptans, such as Amerge, may be better suited for prevention of headache.

