



# Headache

## Diagnosis & Treatment of Headaches and Migraines

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- Proper Use of This Information..... 2
- Introduction..... 2
- Principles of headache diagnosis ..... 3
  - Use the International Headache Society classification..... 3
  - Classify headaches, not patients..... 3
  - Elicit headache characteristics and accompaniments..... 3
  - Tailor your physical and neurologic examinations to the patient ..... 4
  - Request the appropriate neuroimage..... 4
  - The main types of migraine in office practice ..... 4
- Migraine - Diagnosis..... 4
  - Diagnosing individual headaches versus a pattern of headaches..... 4
  - Migraine without aura ..... 5
  - Migraine with aura ..... 5
  - Comment on migraine diagnosis ..... 5
  - Migraine and the menstrual cycle ..... 6
- Migraine - Therapy ..... 6
  - Introduction..... 6
  - Alleviatives and Abortives..... 6
  - The drugs ..... 7
  - Preventives..... 13
  - Menstrual migraine therapy ..... 17
- Tension-Type Headache - Diagnosis ..... 18
  - The two kinds of tension-type headaches ..... 18
  - Episodic tension-type headache ..... 18
  - Chronic tension-type headache ..... 18
- Tension-Type Headache - Therapy..... 19
  - Alleviative Drugs ..... 19
  - Preventive Drugs..... 19
    - Episodic tension-type headache ..... 19
    - Chronic tension-type headache ..... 19
- Medication-Abuse (Rebound) Headache - Diagnosis..... 22
  - Why they occur and what they are..... 22

|  |    |
|--|----|
| Verifying diagnosis of analgesic-abuse headache .....                      | 23 |
| Medication-Abuse (Rebound) Headache - Therapy .....                        | 24 |
| Overview .....   | 24 |
| Out-patient withdrawal .....   | 24 |
| Withdrawal in hospital.....  | 26 |
| Administering DHE .....  | 26 |
| Prognosis .....  | 27 |
| Cluster Headache and Chronic Paroxysmal Hemicrania (CPH) - Diagnosis ..... | 27 |
| Prevalence and comparison.....   | 27 |
| Cluster Headache .....   | 27 |
| Chronic paroxysmal hemicrania .....  | 28 |
| Cluster Headache and Chronic Paroxysmal Hemicrania (CPH) - Therapy.....    | 29 |
| Abortive Medications .....   | 29 |
| Preventive Medications.....  | 30 |
| Chronic paroxysmal hemicrania .....  | 32 |
| Hospital therapy.....  | 32 |
| Surgical and radiation therapy.....  | 32 |
| Post-Traumatic Headache - Diagnosis .....                                  | 33 |
| Overview .....   | 33 |
| Chronic post-traumatic headache.....                                       | 33 |
| Post-Traumatic Headache - Therapy.....                                     | 34 |
| Overview .....   | 34 |
| Psychotherapy.....   | 34 |
| Drug therapy .....   | 35 |
| Effect of Litigation.....  | 35 |
| Additional Information Available at the Web Site of Dr. Haas.....          | 35 |

## Proper Use of This Information

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## Introduction

This text describes the current method of diagnosing and treating tension-type, migraine, medication-abuse (rebound), cluster, and post-traumatic (including post-"whiplash") headaches, which are the basic or core headaches of medical office practice. It also presents the diagnosis and treatment of most of the other headaches seen by physicians in their offices. In addition, it discusses the diagnosis and treatment of headaches seen in emergency rooms.

Although intended for physicians and medical students, this text is also accessible to laypersons. It's revised as needed to incorporate new information from the medical literature. It does not discuss (except for a few comments) the processes underlying headache production, because current knowledge of them is not useful clinically.

In the sections on the treatment of headaches, I do not discuss the mechanism of action of the drugs presented as headache preventives or alleviatives, because the available knowledge is not explanatory. Drugs are recommended if they have been shown to be effective by proper scientific studies.

## **Principles of headache diagnosis**

### ***Use the International Headache Society classification***

To diagnose a patient's headache is to place it into the most appropriate class within a headache classification. Only one headache classification exists, the one developed by the International Headache Society (IHS) and published in 1988 (Headache Classification Committee, 1988; Olesen, 1993). It's now being updated by committees of headache specialists. This classification is based primarily on the clinical features of headaches rather than on presumptions about etiologies or mechanisms of headaches. Thus, it contains no class called "stress headache" or "vascular headache."

### ***Classify headaches, not patients***

The IHS classification classifies headaches rather than patients. A patient may have more than one type of headache. The placement of headaches into the classes within the classification is based on operational diagnostic criteria listed for every class. This means that a headache's features must satisfy a certain number of the criteria listed for a class in order for the headache to be included in that class. The diagnostic criteria for the headache types presented in this primer are shown in the sections discussing headache diagnosis. Since its publication, the IHS classification has been subjected to validation studies, which have shown its strength and weaknesses. Its first revision, expected to be published in 1999, should incorporate the results of these studies.

### ***Elicit headache characteristics and accompaniments***

Most of the information needed to classify a headache is obtained by the clinical interview. From it the physician should know when the headache(s) began and whether the headache(s) is episodic or continuous (or nearly so). If episodic, the frequency and duration of attacks should be estimated. (Because some patients with continuous headaches speak only of their headache exacerbations, one must always ask patients if they have any headache in-between their headaches.) The physician should know the 4 main characteristics of the headache: its quality (pressing, throbbing, etc.), intensity (mild, moderate, or severe), location (unilateral, bilateral, etc.), and response to routine physical activities. He should know whether the headache has accompaniments, such as nausea, vomiting, hypersensitivity to light (photophobia) or noise (phonophobia), and auras (focal neurologic symptoms). He should obtain detailed information about the patient's use of analgesics, including non-prescription pills such as aspirin.

## ***Tailor your physical and neurologic examinations to the patient***

Physical abnormalities related to headache are rare in headache patients seen in physicians' offices. Hence, a thorough physical and neurologic examination is seldom indicated or beneficial. In general, the examination should answer questions raised during the interview. For example, the optic disks should be examined in an obese young woman with a new daily headache because she could have idiopathic intracranial hypertension (pseudotumor cerebri).

## ***Request the appropriate neuroimage***

Abnormalities on neuroimages (computed tomographic scans and magnetic resonance images) are rare in headache patients seen in physicians' offices. The decision to request a neuroimage should be based on the probability of finding intracranial abnormalities related to the headache. In general, a neuroimage should be obtained in patients with headaches of recent onset whose features deviate from the standard headache types, headaches associated with neurologic symptoms or signs, headaches poorly responsive to therapy, and posttraumatic headaches. "In adult patients with recurrent headaches that have been defined as migraine...with no recent change in pattern, no history of seizures, and no other focal neurologic signs or symptoms, the routine use of neuroimaging is not warranted" (The Quality Standards Committee of the American Academy of Neurology, 1994). The type of scan requested (plain or enhanced CT, plain MRI, MRI with enhancement, or MRA) should be appropriate for the condition sought. For instance, unenhanced CTs can reliably detect subdural hematomas, but not cerebral aneurysms. Sometimes neuroimages may be needed to reassure patients that serious intracranial disease is absent. Electroencephalograms are not helpful in the diagnosis of headaches in the absence of seizures.

## ***The main types of migraine in office practice***

Most migraines seen in physicians' offices are migraine without aura (formerly called "common migraine") and migraine with aura (formerly called "classic migraine" by some). Migraine aura without headache is also quite common, and is seen often by ophthalmologists. Neurologists and headache specialists often treat status migrainosus, characterized by a headache phase of over 72 hours. The other migraine types are listed in the left side bar and are fully described in the Headache Classification Committee's classification (1988).

The 1-year prevalence of migraine is about 10% (highest from 25-55 years). The female/male ratio is roughly 3. Migraine without aura is about twice as common as migraine with aura.

## **Migraine - Diagnosis**

### ***Diagnosing individual headaches versus a pattern of headaches***

Migraine is diagnosed by determining whether some of a person's recurrent headaches meet migraine criteria (listed below). Not every migraine needs to meet all of the migraine criteria. For example, a person may have a left-temporal throbbing headache of moderate intensity worsened by physical activity. These headache features meet migraine criteria. However, this headache may not be accompanied by nausea or hypersensitivity to light or noise and, therefore, not fulfill all the criteria for migraine. Yet, if some of this person's other headaches meet all the migraine criteria, then one can say that this headache is also a migraine.

## ***Migraine without aura***

**Description (IHS):** Idiopathic, recurring headache disorder, manifesting in attacks lasting 4-72 hours, in which headaches are typically unilateral, throbbing, of moderate to severe intensity, aggravated by routine physical activity, and accompanied by nausea and intolerance to brightness and noise. (See example of a patient with migraine without aura).

### **Diagnostic criteria (IHS) (abbreviated and slightly altered for clarity).**

At least 5 attacks.

Headache attacks lasting 4-72 hours.

Headache has at least two of the following four characteristics:

Unilateral location

Pulsating quality

Moderate or severe intensity (inhibits or prohibits daily activities).

Aggravation by walking stairs or similar routine physical activity.

During headache at least one of the following accompaniments:

Nausea and/or vomiting

photophobia and phonophobia

Other headache types not suggested or confirmed.

## ***Migraine with aura***

**Description: (IHS):** Idiopathic recurring disorder manifesting with attacks of neurological symptoms unequivocally localizable to cerebral cortex or brain stem, usually developing over 5-20 minutes and lasting less than 60 minutes, and followed or accompanied by migraine headache and its associated features.

### **Diagnostic criteria (IHS): Omitted here.**

### **Comment on auras**

Visual auras are the most common. They often appear in one visual field as a moving, expanding bright, curved, saw-tooth line with obscured vision in its wake. Some of these figures are strikingly colorful, whereas others are dull and monochromatic. Some bright colored figures have shapes that are not zig-zag lines. Visual auras consisting of absent or blurred vision in one or a part of one visual field are also common. Spreading numbness, in one side of the face or upper limb, or both, is the next most common aura. Mild hemiparesis and speech disturbances (dysphasia) are not rare.

### **Migraine aura status**

This term refers to a rare condition in which a visual aura persists for weeks, months or longer. It's not (yet) within the International Headache Society's classification of migraine. I devote a separate Web page to it.

## ***Comment on migraine diagnosis***

Chronic daily headaches, whether they be chronic tension-type headaches or analgesic-abuse headaches that developed from migraine (so-called transformed migraine), are often misdiagnosed as migraine, because their intensifications, which have migrainous features, are mistaken for individual migraine attacks. Metaphorically, migraines are storms with heavy rain and sometimes lightning, which pass and are replaced by clear skies, whereas chronic

tension-type and analgesic-abuse headaches are prolonged rains punctuated erratically by downpours and by brief partial clearing.

## ***Migraine and the menstrual cycle***

Many women state that they are more likely to have migraines close to or during their menstrual periods. A recent epidemiologic study by Stewart et al. (2000) has confirmed this belief and added some details to it. In their study, 81 female migraineurs kept detailed headache and menstrual diaries for up to 98 days. This data showed that "headaches were significantly more likely to occur in the 2 days before the onset of menses and the first 5 days following the onset of menses." Curiously, this increased prevalence pertained only to migraine without aura, not to migraine with aura. Tension-type headaches were also more common during this interval, but these headaches might have been mild migraines not meeting migraine diagnostic criteria. So-called true menstrual migraine (migraine occurring on the first day of menstruation or 2 days before or after and at no other time) occurred in 7.2% of this series of patients.

## **Migraine - Therapy**

For a presentation of the therapy of migraines occurring in relation to menses see my section in migraine therapy.

### ***Introduction***

Migraine therapy is largely based on the use of medications (drugs), although some patients may respond to other measures, such as stress reduction, exercise, discontinuation of an oral contraceptive, or avoidance of certain foods or beverages, most notably red wine. The drugs fall into two main classes: (1) the alleviatives and abortives and (2) the preventives (prophylactics). The former affect the headache, but not the neurologic symptoms. The latter decrease the frequency of migraine attacks whether they occur with or without neurologic symptoms (auras).

The U.S. Headache Consortium publishes evidence-based guidelines for migraine therapy in print and on the Web. Because the Web version is in PDF format, you will need Adobe Acrobat Reader to view it, but the reader can be downloaded free. My discussion here of the drug therapy of migraine is largely in agreement with the consortium's conclusions.

### ***Alleviatives and Abortives***

#### **Drug selection principles**

Migraine attacks vary in intensity from mild to excruciating among the population of sufferers and within individuals. Mild or even moderate headaches may be satisfactorily alleviated or even aborted in some folks by simple, inexpensive, non-prescription analgesics, such as aspirin, acetaminophen, ibuprofen, or naproxen sodium, or by compounds of inexpensive non-prescription analgesics such as those containing caffeine, acetaminophen, and aspirin. Severe headaches seldom respond to such medications. Relief from these generally requires use of a triptan, ergotamine, or dihydroergotamine, or an opioid (narcotic). Early fitting of the potency of the drug to the intensity of the patient's headache is referred to nowadays as "stratified" care, in contrast to "stepwise" care, in which prescribing starts with the cheapest and weakest and then ascends to more expensive and more potent drugs if the

lesser agents are ineffective. Stratified prescribing is more sensible and efficient and is favored by specialists.

When more-potent drugs than simple or compound analgesics are needed, then the triptans are usually preferable, if patients can afford them. These are discussed below. Dihydroergotamine (DHE) is an impressive migraine abortive as an injection, but is much less effective as a nasal spray, and is not available as a pill. Ergotamine, which is available as pills, sublingual tablets, and suppositories, is in general less effective and more productive of adverse effects than the triptans. The same is so for the compound containing isometheptene, dichloralphenazone, and acetaminophen.

The great majority of patients prefer the triptan tablets to sumatriptan injections or nasal spray (who likes "shots"?) and the spray has a disagreeable taste!). However, oral medications are unreliable for nauseated patients. For these patients and for others unsatisfied with the tablets, I recommend trying sumatriptan injections. Some of the responders to the injection then try the nasal spray, but few continue to prefer it to the injection, in my practice.

Patients poorly responsive to or unable to afford the triptans should be considered for trials of ergotamine, dihydroergotamine, or isometheptene compound.

Opioids, because of their potential for abuse and because they are generally not the most effective anti-migraine agents, should be prescribed last. However, they can be helpful back-up drugs whenever the more specific anti-migraine drugs do not provide adequate relief. In addition, some patients, we must admit, do not respond to any of the specific anti-migraine drugs, and therefore are justifiably candidates for opioids.

## ***The drugs***

**Aspirin with metoclopramide** has been shown in several double-blind studies (Tfelt-Hansen et al., 1995; Chabriat et al., 1997) to be superior to placebo and as effective as oral sumatriptan in alleviating migraine attacks. Most studies used 900 mg of aspirin (or its lysine acetylsalicylate equivalent) together with 10 mg of metoclopramide. This combination gave less side effects than sumatriptan. It is probably more effective than aspirin alone.

**Excedrin Migraine** (a non-prescription tablet) containing 250 mg acetaminophen, 250 mg aspirin, and 65 mg caffeine has been shown in 3 double-blind, placebo-controlled studies (Lipton et al., 1998) to be an effective alleviative for migraine attacks (without or with aura). Patients took 2 tablets of either Excedrin Extra Strength (with ingredients identical to those in the newer Excedrin Migraine brand) or placebo for a migraine of at least moderate intensity. Patients with incapacitating headaches were excluded from the study.

**Ibuprofen** in a "liquigel" formulation (capsules containing a solubilized form of the drug) has been shown to be more effective than placebo for migraine headaches. Despite the stated more rapid absorption of ibuprofen from the liquigel, we don't know whether this formulation has any clinical advantages over the standard tablets. Doses of 200, 400, and 600 mg were effective, but the latter two were more effective than the lowest dose. The differences between the two larger doses were minimal, but slightly favored the larger. Ibuprofen's effects were comparable to those reported for Excedrin (see above). Although about 70% of patients in this trial showed a headache response at two hours, only about 28% were free from pain.

**Ketoprofen**, a non-steroidal anti-inflammatory drug, was reported by Dib et al. (2002) to be much more effective than placebo and as effective as 2.5 mg zolmitriptan tablets in alleviating migraine headache attacks. These workers used dual-release formulations of 75 and 150 mg. The 75 mg dose was as effective as the 150 mg dose. In the U.S. we have immediate-release tablets of 25, 50, and 75 mg and also controlled-release tablets, which release the drug too-slowly to be used for acute pain.

**Ergotamine**, used for many decades before the arrival of the triptans, still has value for some migraineurs. Contraindications for its use are coronary artery disease, peripheral vascular disease, Raynaud's disease, and poorly controlled hypertension. It's too nauseating for many patients. Roughly one half of those who try it have their headaches lessened or eliminated within two hours. In the U.S.A. it is available as tablets containing 1 mg of ergotamine plus 100 mg of caffeine, as sublingual tablets containing 2 mg of ergotamine, and as suppositories containing 2 mg of ergotamine with 100 mg of caffeine. The tablets cost about \$1 each. Ergotamine abuse was known to induce daily rebound headaches decades before analgesic-abuse headaches were identified.

### **The triptans :**

The triptans are selective 5-hydroxytryptamine (5-HT, serotonin) agonists at 5-HT 1B receptors on intracranial arteries and 5-HT 1D receptors on the trigeminal-nerve terminals of these arteries. All are very effective in alleviating or aborting migraine headaches. In general, they are the preferred drugs for migraine sufferers. Sumatriptan, the first triptan on the market (1993 in the U.S.) was a major advance in migraine (and cluster) headache therapy. It was first available as an injection, later as a tablet and nasal spray. Subsequently, 6 more triptans have been marketed in the U.S. as tablets: zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan (in order of appearance).

Clinical trials and experience indicate that the newer triptans are in general more reliably effective than sumatriptan tablets, but some patients continue to prefer sumatriptan. Individual variation in response to the triptans is considerable. From a meta-analysis of 53 clinical drug trials, Ferrari et al. (2001) concluded that "at marketed doses, all oral triptans were effective and well tolerated. 10 mg rizatriptan, 80 mg eletriptan, and 12.5 mg almotriptan provide the highest likelihood of consistent success." Because individual responses to the triptans are considerable, when the first triptan tried isn't effective, one or two others should be tried before giving up on this drug class for any patient. Migraine recurrence within 24 hours of getting good relief from a triptan dose is common. The incidence of such recurrence is lower with some triptans than with others. From an analysis of published drug trials, Gerard et al. (2003) found an inverse correlation between triptan half-life and headache recurrence: the longer the half-life, the lower the incidence of recurrence. So, the triptans with the lowest recurrence rates were frovatriptan, naratriptan, and eletriptan, with half-lives of 25, 6, and 5 hours, respectively.

All the triptans are very expensive: Retail prices for usual adult doses, in December 2001, range from \$11 for one 12.5 mg almotriptan tablet to \$16 for one 2.5 mg naratriptan tablet. One injection of sumatriptan costs ~\$47. For up-to-date prices see Drugstore.com.

One of the triptans should be considered for patients who respond inadequately to aspirin-metoclopramide, analgesic-caffeine, or ergotamine tablets (see above sections on these

medicines), or who are not good candidates for them. The Drug Selection Principles section above gives advice on choosing the route of administration for the triptans.

Sumatriptan (Imitrex in the U.S.) is available as an injection, tablet, or nasal spray. Good relief (reduction from severe or moderate to mild or no headache) occurs in about 70% of patients 1 hour after a subcutaneous injection of 6 mg, the maximally effective dose for most patients (Subcutaneous Sumatriptan International Study Group, 1991), in about 65% of patients 2 hours after an oral dose of 100 mg, the maximally effective dose, (Tfelt-Hansen, 1993), and in about 62% 2 hours after nasal administration of 20 mg, the optimal dose for most adults (Ryan et al., 1997). (Only a small percentage of my patients prefer the spray, which tastes foul.) Many patients who get no relief from the tablet get excellent relief from the injection. Roughly 40% of the patients whose headaches are alleviated by sumatriptan experience a return of their headaches within 24 hours. But then another dose usually eliminates the attack.

Sumatriptan syringes come in "cartridge packs" containing 2 prefilled syringes (each with 6 mg of drug) for use in a "Statdose Pen." Patients learn to load a syringe into the pen and inject correctly in a few minutes. After buying the small case containing one pen and one cartridge containing two syringes, refills need be for the cartridge packs alone. Injectable sumatriptan is also sold in rubber-topped vials (5 per carton) of 6 mg in 0.5 ml of fluid for use with separate syringes. These are used by patients (children and some adults) who need to inject less than 6 mg.

Sumatriptan tablets of 25, 50, and 100 mg are sold in blister packs of 9 tablets. The 25 mg tablets are too weak for routine use in adults, who generally need 50 or 100 mg doses. The nasal spray is packaged in boxes of six individual "nasal spray devices" containing either 5 or 20 mg of the drug. The larger amount is needed for most adults.

Sumatriptan should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or Prinzmetal's angina. Because sumatriptan can give rise to increases in blood pressure (usually small), it should not be given to patients with poorly controlled hypertension. It should not be used concomitantly with ergotamines. It should not be prescribed for attacks of hemiplegic or basilar migraine, but it can be taken safely during attacks with standard migraine auras. Mild, brief, odd sensations (especially pressure in the chest or throat) are common after sumatriptan injections, less frequent after the other administration routes. Serious side effects are rare (Wilkinson et al., 1995). I have not seen anyone harmed by this drug or by any of the other triptans.

Zolmitriptan (Zomig) is available as regular or orally dissolving tablets of 2.5 or 5 mg in multiples of 3 tablets. Double-blind comparisons with placebo (Solomon et al., 1997) suggest it's slightly more potent than sumatriptan tablets, about as potent as sumatriptan nasal spray, and somewhat less potent than sumatriptan injections. Some of my patients prefer it to sumatriptan tablets, others not. Evaluations of the relationship between efficacy and tolerability indicate that 2.5 mg is the optimal initial dose for relief from a migraine attack (Rapoport et al., 1997). The graph below, made from the published data of Solomon et al. (1997), shows the percentages of patients who had satisfactory headache relief at 1, 2, and 4 hours after taking either 2.5 mg of zolmitriptan or a placebo pill.

The headache recurrence rate after a 2.5 mg dose is similar to the 40% recurrence rate after the use of sumatriptan. Adverse events are generally mild and similar to those after sumatriptan. Its contraindications are those for sumatriptan.

Naratriptan (Amerge) tablets are available as 1 or 2.5 mg tablets in blister packs of 9 tablets. Naratriptan has a half life of 6 hours, which was the longest of all the triptans until frovatriptan with a half-life of 26 hours came on the U.S. market--see below. For standard adult migraineurs, the 2.5 mg dose offers a better overall result without more side effects than the 1 mg dose (Mathew et al., 1997). If the first dose gives only a partial response or if the headache returns, then the dose can be safely repeated once after 4 hours, for a maximum dose of 5 mg in 24 hours, if the first was well-tolerated.

The percentage of patients experiencing good headache relief 4 hours after a 2.5 mg dose is essentially the same as that after a 2.5 mg dose of zolmitriptan (see above graph for zolmitriptan), and the headache recurrence rate in patients who got good relief from a 2.5 mg dose is comparable to that after relief with zolmitriptan. The potential side effects and the contraindications to its use are those for sumatriptan and zolmitriptan.

For sufferers stuck in a prolonged migraine state with daily fluctuating headache, twice daily administration of 2.5 mg of naratriptan for 3-4 consecutive days has been able to abort the state in my experience.

Rizatriptan (Maxalt) is available as regular and orally dissolving tablets of 5 and 10 mg in multiples of 3 tablets. Because plasma levels of rizatriptan were increased and prolonged in healthy subjects taking 240 mg of propranolol daily, Merck recommends that patients on propranolol be given 5 mg doses of rizatriptan. However, I wonder whether the more usual lower doses of propranolol would give the same effect. Nadolol and metoprolol did not affect plasma levels of rizatriptan.

Rizatriptan was compared not only to placebo, but to 100 mg of oral sumatriptan by Visser et al. (1996) in a double-blind trial. The graph below made from their published data shows what percentage of patients in the 3 rizatriptan and in the sumatriptan and placebo groups experienced satisfactory headache relief 2 hours after taking their trial dose. Only the 40 mg rizatriptan dose was significantly more effective than 100 mg of sumatriptan. However, this dose produced much more frequent side effects than did sumatriptan, especially dizziness and drowsiness. On the other hand, all the doses of rizatriptan produced chest pain in a smaller percentage of subjects than did sumatriptan. Recurrence of headache within 24 hours of all the initial doses of rizatriptan was similar to that after sumatriptan (roughly 40%).

Almotriptan (Axert) is available in tablets of 6.25 and 12.5 mg. Most adults will get a better response without more bothersome side effects from the 12.5 mg dose. Side effects and contraindications are those for the other triptans. If the headache returns after the first dose, the dose may be repeated once after a two-hour interval with a 24-hour period, according to the manufacturer's recommendation. (Its mean half life is 3-4 hours.)

In a head-to-head, double-blind, randomized comparison of 12.5 mg almotriptan with 50 mg sumatriptan tablets by Spierings et al. (2001), the two drugs were similarly effective in alleviating and eliminating migraine headaches. The 24-hour recurrence rate was also similar: ~25% for both drugs.

Frovatriptan (Frova) came on the U.S. market in the summer of 2002. It's available as 2.5 mg tablets only, in blister cards of 9 tablets. Its half-life of 26 hours is much longer than the former triptan with the longest half life, naratriptan (6 hours). Whether this prolonged duration gives it superiority over the other triptans for prolonged migraine headaches or for those which recur when the shorter-acting triptans wear off remains to be determined. Despite its long half life, it's "not intended for the prophylactic therapy of migraine," although one may wonder whether it might be a more effective short-term preventive than naratriptan. The recommended dose is one tablet. "If the headache recurs after initial relief, a second tablet may be taken, providing there is an interval of at least 2 hours between doses. The total daily dose should not exceed 3 tablets."

Eletriptan (Relpax) came into the U.S. Market in the late winter of 2002/2003. It's marketed as 20 and 40 mg tablets. The latter is the usual dose for adults. Its half life is 4 hours. A second dose may be taken 2 or more hours after the first, if needed. Two doses per 24 hours is the maximal recommended by Pfizer. It's packaged in sheets of 6 tablets. A large, multi-center, head-to-head comparison of 40 mg eletriptan with 100 mg sumatriptan tablets found that the group who took eletriptan obtained better relief than those who took sumatriptan. The primary efficacy endpoint was improvement in headache intensity 2 hours after ingestion from moderate or severe pain to mild or no pain. For eletriptan this response rate was 67% and for sumatriptan 59%.

**Dihydroergotamine (DHE)**, by subcutaneous or intramuscular injection is comparable to subcutaneously injected sumatriptan in effectiveness. Some patients prefer one, some the other. DHE is more of a bother to inject than sumatriptan, because it's sealed in glass ampules, which must have their tops snapped off to be opened. Yet patients do this on their first attempt in my office when shown how to do it.

In a double-blind comparison of subcutaneous injections of dihydroergotamine and sumatriptan for migraine attacks (Winner et al., 1996) headache relief occurred in a significantly greater percentage of patients 1 and 2 hours after sumatriptan than after DHE, but not at 3 and 4 hours. 24 hours after injections, slightly more patients injected with DHE reported relief. (See graph.)

Headaches recurrences hours after injections were more frequent in the sumatriptan than in the DHE group (45% vs 18%), presumably related to the drugs' half lives: 2 hours for sumatriptan, 10 hours for DHE.

DHE is an extremely safe drug, although it, like sumatriptan, can constrict coronary arteries. Hence, it should be avoided in the presence of definite or suspected coronary artery disease. Its main side effect is nausea. I have never seen anyone harmed by this drug, even while receiving IV infusions in hospital, but have heard of anaphylactic reactions to it. The usual abortive injected dose is one ampule (1 mg in 1 ml), but an initial dose of 0.5 mg is recommended to judge the patient's sensitivity to the drug. One ampule's retail cost is ~\$20.

Intravenous injection of DHE should be standard therapy in emergency departments for patients with a history of poor response to sumatriptan. The drug may be injected directly into a vein over a period of 10-15 minutes or first diluted in 50 ml of 5% dextrose in water and then infused IV. Several IV administrations at roughly 6 hour intervals generally eliminate status migrainosus. Preceding the DHE administrations with 10 mg of metoclopramide IV is commonly done to lessen DHE's potential to induce nausea and vomiting.

DHE is also available as a nasal spray under the trade name "Migranal." Several double-blind, control studies show its effectiveness. Good migraine relief was experienced by 27% of patients 30 minutes after treatment with a 2 mg dose and by 70% at 4 hours (Gallagher et al., 1996). The spray solution is sealed in ampules, which must be snapped open in a special plastic case before being inserted into the throw-away sprayer. The recommended dose is one spray (0.5 mg) in each nostril followed 15 minutes later by another spray in each nostril. One ampule's retail price is ~\$18.

The **phenothiazines** (chlorpromazine and prochlorperazine), the **butyrophenones** (haloperidol and droperidol), or the related dopamine antagonist, **metoclopramide**, are injected IV or IM by some emergency-department physicians to alleviate migraines. This usage is supported by various blinded and open studies. These agents are a good choice for migraineurs with known or suspected coronary disease. These drugs are also effective anti-nauseants. A recent open-label pilot study of droperidol by Wang et al. (1997) showed it to be remarkably effective for prolonged migraine attacks, including those persisting for more than 72 hours (status migrainosus). They gave 2.5 mg IV push over 1 minute every 30 minutes until 3 doses had been given or the patient had been markedly relieved. Follow-up treatment with oral diphenhydramine was necessitated by the high incidence of akathisia (drug-induced restlessness).

**Opioids** can justifiably be used to alleviate migraine attacks in patients poorly responsive to the above drugs, but their use should be limited to a dose or two no more than 2 days a week. Codeine, hydrocodone, and oxycodone tablets are available, though most pharmacies carry brands combined with acetaminophen or aspirin. Meperidine, a more potent opioid, is sometimes needed. When nausea precludes absorption of pills, then butorphanol nasal spray, hydromorphone suppositories, or (rarely) meperidine injections may be needed.

**Intravenous valproate sodium** may be a rapidly effective alleviative for patients in the throes of an acute migraine attack, if the preliminary results of Mathew, Kailasam, et al. (2000) are confirmed. In their study 61 patients with moderate to severe migraine headaches were infused intravenously with 300 mg of valproate sodium dissolved in 100 ml of normal saline. 73% of the patients felt that the treatment gave "significant" relief: a reduction of pain from severe or moderate to mild or none, or a 50% reduction in headache intensity even though moderate headache persisted. Relief was judged at 30 minutes after the start of the infusion. If these results prove true, then this therapy would be especially suitable for patients for whom injected sumatriptan or DHE are ineffective or contraindicated. Of course the intravenous route limits use of this drug to patients seen in physicians' offices or hospital emergency departments.

**Isometheptene combined with dichloralphenazone and acetaminophen (Midrin capsules)** may be more effective than plain acetaminophen for some patients and is even preferred over other drugs by the occasional patient.

**Lidocaine** nose drops were reported (Maizels et al., 1996) as more effective than placebo drops in alleviating migraine headaches. 55% of the 53 patients in the lidocaine group had at least a 50% reduction of headache compared with 21% of the controls. Among those relieved after lidocaine, 42% experienced relapse of headache, usually within an hour after the treatment. The treatment method was the instillation of 0.5 ml of 4% topical lidocaine into the nostril on the headache side with the head hyperextended 45 degrees and turned 30

degrees toward the headache side. For bilateral headaches, both nostrils were treated. A repeat dose was given when the headache was more than mild 2 minutes after the first instillation. Seven of my patients asked for and tried this exact therapy after seeing glowing reports in the media, but none found it helpful. I no longer prescribe it.

## **Preventives**

### **Drug selection principles and comments**

Preventive medicines should be offered to patients whose quality of life is diminished by frequent migraine attacks. As few as two disabling attacks per month is an indication for preventive therapy for many patients. The choice of the initial and subsequent preventives to prescribe (from the list below) should be based on the patient's physical and mental condition and associated symptoms. For example, a patient subject to down moods and insomnia would be more suitable for amitriptyline than propranolol, for the former lifts mood and promotes sleep, whereas the latter may induce depression. Of course all choices should be based on scientific evidence of a drug's effectiveness. In general, the preventives are weak agents with common side effects, even though some folks are greatly helped by them. Not uncommonly we see patients not helped by or intolerant of all four of the validated drugs. Clinical drug trials of the effective agents usually show that the treated group has about 30% less-frequent migraine attacks than the placebo group.

### **Validated preventives**

At present, four preventives have been validated by clinical drug trials as effective.

**Propranolol** is a commonly prescribed migraine prophylactic. The Headache Consortium lists the quality of evidence supporting its effectiveness as "A". Metoprolol and nadolol probably have comparable preventive effects, but I see no advantage in prescribing them instead of propranolol. If the small initial dose of propranolol (generally 20 mg orally twice daily) is ineffective after several weeks, the dose should be slowly increased while monitoring the pulse and side effects, such as tiredness and depression. Doses larger than 60 mg twice daily are seldom needed. Propranolol is a particularly good choice for anxious patients. It's contraindicated for asthmatics.

**Amitriptyline** is a commonly prescribed migraine preventive. The Headache Consortium lists the quality of evidence supporting its effectiveness as "A". An initial small bedtime dose of 10 mg in women and 25 mg in men should be increased every few weeks as needed and tolerated. Common side effects are sedation, oral dryness, tachycardia, and weight gain. Amitriptyline is the preferred preventive for patients with down mood or insomnia and it seems to me to be the most effective preventive for children. It is given reluctantly to the obese. Nortriptyline is an effective substitute for some folks who are too sedated by amitriptyline.

**Divalproex (Depakote)**, a major anti-epileptic, is the most-recently validated migraine preventive. The Headache Consortium lists the quality of evidence for its efficacy as "A". The figure below shows the basic data from a representative study by Mathew et al., 1995

The recommended starting dose is 250 mg twice daily after a brief period of taking just one 250 mg tablet nightly. The main side effects are nausea, weight gain, hair loss, and tiredness, and these not uncommonly necessitate discontinuation of the drug. Because of rare reports of hepatotoxicity (liver damage), Abbott Laboratories recommends liver function tests before

therapy and at "frequent intervals thereafter, especially during the first 6 months." Disagreeing with this recommendation, Drs. Silberstein and Wilmore (1996) have emphasized the reliability of clinical monitoring and have advocated, after baseline tests, only sporadic monitoring of blood values when symptoms appear or when compliance is uncertain. Malaise, weakness, anorexia, and vomiting suggest the presence of hepatotoxicity.

**Methysergide**, the oldest of the preventives, ceased being manufactured by Novartis, its only manufacturer in the U.S. (and presumably elsewhere), in November 2002. It had been little prescribed for some time, in part because physicians were concerned about its potential for inducing an inflammatory fibrosis in the retroperitoneum, lungs, and heart valves. Some patients, however, responded better to it than to other preventives. The Headache Consortium lists the quality of evidence supporting its effectiveness as "A". For patients who had been doing well on this drug, prescribing methylergonovine (tablets of 0.2 mg), a semi-synthetic ergot alkaloid closely related to methysergide, should be considered.

### **Unproven preventives**

**Verapamil**, a calcium-channel blocker, is commonly used by physicians as a migraine preventative, often as the first drug prescribed--but this is not advisable. The Headache Consortium lists the quality of evidence supporting its effectiveness as "B" and the consortium's clinical impression of its effect is 1+ out of 3+. My clinical impression is that it's not effective. In contrast, it's clearly an effective preventive for cluster headaches.

**Gabapentin (Neurontin)** has been prescribed for migraine prevention since Mathew and Lucker's preliminary open-label study in 1996 suggested that daily doses of 900 to 1800 mg could reduce migraine frequency and intensity. A subsequent double-blinded, controlled study by Mathew et al. (2001) has indicated that a stable daily dose of 2400 mg daily (800 mg 3 times daily) reduces migraine frequency more than does placebo. Patients took gabapentin in increasing doses for 4 weeks and then in stable doses for the final 8 weeks of the trial. The primary outcome measure of migraine attack frequency during the final 4 weeks of the trial for patients taking 2400 mg of gabapentin or an equivalent number of placebo capsules was statistically significantly better for the gabapentin group ( $P=0.006$ ). However, the effect was clinically modest and the dropout rate high. In the gabapentin group the median headache frequency decreased from 4.2 to 2.7 per 4 weeks, and in the placebo group it decreased from 4.1 to 3.5. Of 98 patients who received gabapentin, only 56 had maintained a stable dose of 2400 mg daily for the final 4 weeks.

A secondary outcome measure was the percentage of patients whose migraine frequency declined by at least 50% from baseline to the last 4 weeks. For those who maintained the requisite dose during the last four weeks, the results favored the gabapentin group: 46% on gabapentin vs. 16% on placebo had at least a 50% decrease in migraine frequency ( $p<0.01$ ). This result suggests that a limited proportion of migraine sufferers may obtain considerable relief from a large dose of gabapentin.

**Topiramate (Topamax)**, a relatively new anti-epileptic, is being used as a migraine preventative. A double-blind placebo-controlled study of its effect on the frequency of migraine attacks has been published by Storey et al. (2001). They reported that during the 8 weeks of the study the 19 patients randomized to the topiramate group averaged 3.31 migraine attacks per 28-day period, while the 21 patients randomized to the placebo group averaged 3.83 attacks per 28-day period. Although this difference was statistically significant

at  $P=.002$ , it seems unimpressive clinically. In the topiramate group 26.3% experienced a 50% or greater reduction in attack frequency, while in the placebo group only 9.5% had such a decrease. This difference was not statistically significant. This study suggests that topiramate lowers migraine attack rates for some folks, but that it's not in general a powerful preventive. The doses used in this study were close to optimal. The initial dose of 25 mg nightly was increased by 25 mg increments weekly to the target dose of 100 mg twice daily or to the maximum tolerated dose. The mean end-of-study dose was 125 mg daily. Adverse events were more common in the topiramate group (paresthesia, weight loss, memory impairment, etc.), but only 3 patients dropped out of the study.

**Magnesium** has bested placebo in some clinical trials. The Headache Consortium lists the quality of evidence supporting its effectiveness as "B". Its clinical impression of magnesium's effectiveness is 1+ out of a possible 3+. I've not found it helpful and no longer recommend it. Its laxative effect indicates that it's given in adequate doses.

**Cyproheptadine** is used as a migraine prophylactic, but its effect remains questionable. Few adults tolerate it, because it's quite sedating, but children are relatively resistant to its sedative effects, though they can be susceptible to its tendency to induce weight gain. I rarely prescribe it for adults. The Headache Consortium lists the quality of evidence supporting its effectiveness as "C".

**Fluoxetine (Prozac)** and similar antidepressants in the selective serotonin re-uptake inhibitor class are prescribed by some physicians to prevent migraines, but the data supporting such use is meagre. I no longer prescribe it. The Headache Consortium lists the quality of evidence supporting fluoxetine's effectiveness as "B" but the consortium's clinical impression of its effect is only 1+ out of 3+.

A retrospective study of **Venlafaxine (Effexor)**, a selective serotonin re-uptake inhibitor, has suggested that it may be a prophylactic for both migraine and chronic tension-type headaches. Venlafaxine was prescribed for 114 migraine sufferers, most of who had failed to respond to standard preventives. Among the 101 patients for whom adequate follow-up information was obtained, the mean number of headaches per month declined from 16 to 11 during an average treatment period of 6 months (median most effective dose was 150 mg daily). 27% of the patients discontinued the drug for side effects or lack of efficacy. The authors rightly called for a blinded, controlled study to determine whether the drug is efficacious.

Aspirin and other non-steroidal anti-inflammatory drugs are prescribed by some physicians as migraine preventives. The Headache Consortium lists the quality of evidence supporting aspirin and other NSAIDs as "B" but the consortium's clinical impression of their effect is only 1+ out of 3+. I don't prescribe NSAIDs as preventives.

**Riboflavin (vitamin B2)** has been reported by Schoenen et al. (1998) to decrease the frequency of migraine attacks. Their 3-month-long, double-blind, placebo-controlled study compared patients receiving 400 mg of riboflavin daily with patients receiving placebo. This is a very large dose, but adverse effects were seen in only two patients in the riboflavin group (diarrhea in one and excessive urination in the other). The decrease in headache frequency in the treated group was significant only during the third month of the trial, when the mean monthly frequency had dropped to 1.83 from a baseline frequency of 3.83 attacks. The attack frequency in the placebo group remained stable at 3.71/month. In their paper, the authors

discuss how riboflavin might ameliorate one of the possible abnormalities in migraineurs. The Headache Consortium lists the quality of evidence supporting vitamin B2 as "B" and the consortium's clinical impression of its effect is 2+ out of 3+.

**Injection of botulinum toxin type A (Botox)** into the scalp muscles has been tested in several clinical trials. But only one trial was double-blinded, controlled, and fully published, by Silberstein, et al. (2000). Subjects received 11 injections of the toxin or the solution in which the toxin was dissolved (the control group) into scalp muscles in the forehead and temples. The total toxin dose was either 25 or 75 units. The result was that, as a group, the subjects who received 25 units had a significantly greater decrease in the number of moderate-to-severe migraines per month at the second and third months after the injections than did the controls. Curiously, those injected with 75 units did not fare better than the controls. No adequate explanation was given for this disparity. Moreover, the authors did not discuss whether the subjects could tell whether they had been injected with the toxin or the plain solution. Despite the paucity of information supporting a preventive effect of botulinum toxin for migraines, many neurologists and headache specialists are providing this therapy to patients. Double-blind, controlled studies of scalp-muscle injections of botulinum toxin for chronic tension-type headache have, so far, not shown any therapeutic effect of the toxin.

**Lisinopril**, an "angiotensin converting enzyme inhibitor" used for the treatment of high blood pressure, has been found to have a preventive action against migraine in one blinded, controlled, crossover study by Schrader et al., (2001). Among the 47 patients who completed 12 weeks on lisinopril (one 10 mg tablet daily for one week and then two tablets daily for 11 weeks) and 12 weeks on placebo, their mean percentage reduction in hours with headache, days with headache, and days with migraine while on lisinopril as compared to placebo was 20, 17, and 21 percent, respectively. The (well-known) main side effects were coughing (13%), dizziness (12%), and faintness (5%). Because "angiotensin converting enzyme inhibitors are known to cause fetal and neonatal morbidity and mortality in the second and third trimesters of pregnancy," say the authors, this drug should be prescribed cautiously to women in the childbearing years.

**Tizanidine**, a drug in use for years to relax spastic muscles in patients with multiple sclerosis or spinal-cord injuries, has been tested for its effects on chronic tension-type headache and, more recently, on "chronic migraine," a type of migraine that is essentially a chronic daily headache with definite migrainous features. Chronic migraine develops from episodic migraines from overuse of alleviative drugs or it can develop spontaneously. When it is the former type, it's called by various names, such as "rebound migraine," "transformed migraine," and "medication-abuse migraine."

In a double-blind, placebo-controlled study of tizanidine's effect on the spontaneous form of chronic migraine, Saper, et al. (2002) reported that the drug had some beneficial effects. The primary endpoint was a comparison of headache indices (a measure of headache frequency, intensity, and duration) for the last four weeks of the trial, which was either from weeks 9 through 12, or if patients dropped out before this, from weeks 5 through 8. Although the P value for the difference between the tizanidine and placebo groups was 0.0025, the clinical difference was slight: an index of 1.2 for the tizanidine group and 2.1 for the placebo group from a beginning index for both groups of 2.6. In addition, the indices for the patients who completed all 12 weeks of the trial were closer: 1.2 for tizanidine, 1.7 for placebo, suggesting a diminution of "effect" over time. The dropout rates were high in both groups (~30%) and considerable numbers of patients taking tizanidine had side effects, mostly somnolence,

dizziness, oral dryness, and tiredness. At the end of the trial, the mean daily dose of tizanidine was ~18 mg, given in 3 divided doses daily.

### ***Menstrual migraine therapy***

For a definition of menstrual migraine see its section in Migraine Diagnosis, and for a recent review of therapy see Granella et al., 1997.

The standard abortive drugs for migraines, presented above on this page, are also effective for menses-related migraines, but the standard preventive drugs (discussed above) are less effective for menstrual migraines. For women whose migraines are limited to the peri-menstrual period and respond well to abortive drugs, daily preventive medications, taken either each day of the month or just during the peri-menstrual period, are seldom indicated. But for those who respond poorly to abortives and have prolonged severe attacks, or more than one attack during menses, the taking of a preventive medication during the peri-menstrual period makes good sense. The problem is finding one that works well and gives no notable side effects.

Good results have been reported for estrogen supplementation from shortly before and during menses. This therapy is based on the evidence that the natural declining estrogen level before menses triggers migraine. In the most successful (placebo-controlled) study, by Lignieres and coworkers in Paris in 1986, women applied estradiol (a synthetic estrogen) gel daily to the skin 48 hours before an expected migraine and then for the following 6 days. Results were impressive, but have not been solidly confirmed. Results with the transdermal delivery of estradiol by adhesive skin patches were favorable in one study, but only with the 100 microgram patches. One patch was applied 4 days before the expected menses and then another at the onset. My results with this therapy have been disappointing, and I am no longer seeing reports of success with such estrogen therapy in the medical literature.

One uncontrolled trial of continuous bromocriptine therapy reported impressive results (Herzog, 1997). One 2.5 mg pill was given thrice daily after building up to this dose by daily increments of 1.25 mg. I have not had success with this therapy, and I've seen no further reports of this therapy in the medical literature.

The relatively long-acting triptan, naratriptan, was reported to have some effect as a short-term migraine preventive for menstrual migraine. In this double-blinded study by Newman and co-workers (2001), naratriptan tablets of either 1 or 2.5 mg or placebo tablets were taken twice daily by the subjects from two days before expected onset of menstruation for a total of five days. This was done for four consecutive periods. The primary efficacy end point was the number of menstrually associated migraines that occurred during the four menses. The group of patients treated with the 1 mg naratriptan tablets, but not those treated with the 2.5 mg naratriptan tablets, had significantly fewer menstrual migraines, whether they were or were not taking an oral contraceptive. The ineffectiveness of the 2.5 mg doses, which one would expect to be more effective, casts doubt on the effectiveness of this therapy. Yet, naratriptan is being used with success as a short-term migraine preventive for patients who get runs of frequent migraines. Frovatripan, which came on the market after the naratriptan study, might also be studied, since it has a much longer half-life than naratriptan (25 vs. 6 hours).

# Tension-Type Headache - Diagnosis

## ***The two kinds of tension-type headaches***

Tension-type headaches are either episodic or chronic. The 1-year prevalence of all tension-type headaches is about 74%. That of frequent (more than 1 per month) tension-type headaches is roughly 20-30%, and that of the chronic variety is about 3%. The female/male ratio for tension-type headache is approximately 1.4/1.

## ***Episodic tension-type headache***

**Description (IHS):** Recurrent episodes of headache lasting minutes to days. The pain is typically pressing or tightening in quality, of mild to moderate intensity, bilateral in location and does not worsen with routine physical activity. Nausea is absent, but photophobia or phonophobia may occur. (These latter two terms are poorly defined by the IHS, but are generally taken to mean bothersome hypersensitivity to light and noise, respectively.)

### **Diagnostic criteria (IHS) (abbreviated and slightly altered for clarity)**

At least 10 previous headaches fulfilling criteria below.

Number of days with such headache should be less than 15/month.

Headaches lasting from 30 minutes to 7 days.

At least 2 of the following pain characteristics:

Pressing (non-pulsating) quality

Mild or moderate intensity (may inhibit, but does not prohibit activities)

Bilateral location

No aggravation by walking stairs or similar routine physical activity

Both of the following:

No nausea or vomiting

Photophobia and phonophobia are absent, or only one is present

Secondary headache types not suggested or confirmed

Comment: This most common headache seldom needs a specialist's attention, because it is generally mild, infrequent, and responsive to non-prescription analgesics. Physicians should instruct patients with this headache in the proper use of analgesics in order to prevent analgesic-abuse headache. If analgesics are needed several days per week for several weeks, then a preventive medication or other therapies should be prescribed.

## ***Chronic tension-type headache***

**Description (IHS):** Headache present for at least 15 days per month for at least 6 months. The pain is typically pressing or tightening in quality, of mild to moderate intensity, bilateral in location, and does not worsen with routine physical activity. Nausea, photophobia, or phonophobia may occur.

### **Diagnostic criteria (IHS) (abbreviated and slightly altered for clarity)**

Average headache frequency of more than 15 days per month for over 6 months.

At least 2 of the following pain characteristics:

Pressing (non-pulsating) quality

Mild or moderate intensity (may inhibit, but not prohibit activities)

Bilateral location

No aggravation by walking stairs or similar routine physical activity

Both of the following:

No vomiting

No more than one of the following: nausea, photophobia, phonophobia

Secondary headache types not suggested or confirmed

Comment: Although this headache is generally continuous, it is seldom disabling. It fluctuates in intensity. During moderate or severe exacerbations, it often has mild migrainous features, such as throbbing, nausea, and mild hypersensitivity to light. Its persistence makes it hard to endure. It commonly persists for many years, although preventive medications often provide considerable relief (see Tension-Type Headache Treatment).

## **Tension-Type Headache - Therapy**

### ***Alleviative Drugs***

Episodic tension-type headaches generally respond to simple analgesic pills, such as aspirin, acetaminophen, or ibuprofen. Some evidence suggests that the addition of caffeine (roughly 100 mg, the amount in a strong cup of coffee) enhances the effect of the analgesic.

Analgesics are, in general, poor therapy for chronic tension-type headaches, because they alleviate the pain little. Moreover, when taken daily or almost daily, they inhibit the effects of preventive medications and may add a degree of analgesic-abuse headache to the primary headache. However, a few analgesic doses a week for particularly marked flare ups of headache can give welcome temporary relief.

### ***Preventive Drugs***

#### **Episodic tension-type headache**

Preventives are seldom needed for episodic tension-type headache, because its frequency of occurrence is, by definition, less than 15 days per month, its intensity is not disabling, and its response to analgesics is usually satisfactory. However, when this headache becomes so frequent, intense, and long-lasting as to and disturb a person's activities, then a prescription for amitriptyline, or a similar tricyclic drug, such as nortriptyline or protriptyline, should be considered. Unexpectedly, an open study of amitriptyline in episodic and chronic tension-type headache showed no significant lessening of the episodic type (Cerbo et al., 1998).

#### **Chronic tension-type headache**

##### **The tricyclic anti-depressants**

Preventive drugs are the main therapy for chronic tension-type headache. Unfortunately, the choices are very limited. In fact, amitriptyline (a tricyclic antidepressant) is the only drug shown by clinical drug trials to ameliorate this headache (Bendtsen et al., 1996). It lessens the headache in most patients, but seldom eliminates it. Those who respond well have days without headache and have less-intense headache when it is present. Some are even without headache on many more days per month than they are with headache. A controlled, blinded trial published in 2001 confirmed the effectiveness of amitriptyline (see discussion below).

Clinical experience clearly shows that nortriptyline, closely related to amitriptyline, is also effective against chronic tension-type headache. I use it when amitriptyline is too sedating or induces too-much weight gain at headache-effective doses.

A recent uncontrolled-unblinded study by Cohen (1997) of protriptyline (10-40 mg every morning) in 22 women with chronic tension-type headache suggests that this tricyclic drug may be comparable in effectiveness to amitriptyline without producing its common side effects of drowsiness and weight gain (from increased appetite). My subsequent experience with this drug jibes with his results. Its most common side effect at headache-effective doses has been tachycardia, generally not recognized by the patient. I have had to withdraw many patients from protriptyline because of this side effect. I prefer amitriptyline for the many patients with insomnia, but for obese patients without insomnia, I have been initiating therapy with protriptyline.

### **The selective serotonin re-uptake inhibitors (SSRIs)**

The SSRIs, such as fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft) are much used by physicians despite the absence of demonstrated effectiveness against chronic tension-type headache in high-quality drug trials. My experience is in line with the trials. I have seen hundreds of treatment failures and hardly any partial successes. However, a recent retrospective study of venlafaxine (Effexor) use for patients with chronic tension-type headaches and migraines suggested some efficacy against both headache types. The median "effective" dose was 150 mg daily. For the 56 treated patients with tension-type headaches, the mean number of headaches per month declined from 24 to 15 during the second and third months of therapy. 30% of the patients discontinued the drug for side effects or lack of efficacy. The authors rightly called for a blinded, controlled study to determine whether the drug is efficacious.

Here is the evidence against the SSRIs:

Bendtsen, Jensen, and Olesen (1996) compared the very selective SSRI citalopram to amitriptyline and placebo in a double-blind 3-way crossover trial. Patients were on each of the 3 for 8 weeks. 40 patients entered and 34 completed the study. Amitriptyline was very significantly more effective than placebo ( $P=0.002$ ), but citalopram was not ( $P=0.68$ ). However, while taking citalopram, patients did show lower headache scores than when on placebo. In considering this, the authors stated that conceivably a larger study might have shown a significant difference between citalopram and placebo, but they concluded that, even if such could be shown, it would not likely be clinically relevant.

Langemark and Olesen (1994) compared paroxetine (a SSRI) in a dose of 30 mg daily to sulpride (a dopamine antagonist) in a double-blinded pilot study without the use of a placebo. Each treatment group contained 25 patients initially. Those who showed no response after 8-weeks of treatment or had intolerable side effects were "crossed over" to the alternative drug. After 8-weeks of treatment, patient-evaluation scores were not significantly different in the two groups, both of which showed significant improvement compared to baseline. As the authors stated, this effect could have been a drug effect, but could also have been a placebo or time-related effect. By the various measures used in this study, sulpride was somewhat more effective. However, according to the authors, the effect of neither drug was impressive enough to suggest it would have much of an impact on chronic tension-type headache.

Saper et al. (1994) reported a double-blind trial of fluoxetine in "chronic daily headache," but did not use diagnostic criteria for this label which fit those for chronic tension-type headache. Hence, this study's results can't be applied to a sample with unequivocal chronic tension-type headache. Overall headache status (quite a subjective measure, if I read it correctly) was significantly better for the fluoxetine-treated group than the placebo group, but only during the last 4 weeks of the 12-week trial. However, daily headache diaries, the more direct

measure of headache, showed no difference in headache-free days between fluoxetine and placebo: for fluoxetine, headache-free days increased from 1.57/week during the single-blind placebo baseline to 2.67/week during the third month, whereas for placebo the increase was from 1.12 to 2.27/week.

Walker et al. (1998) compared fluoxetine and desipramine in the treatment of chronic tension-type headache. They thought that this comparison might determine whether headache relief from amitriptyline is due to the inhibition of serotonin re-uptake (which fluoxetine shares with amitriptyline) or from inhibition of noradrenaline re-uptake (which desipramine, a tricyclic antidepressant, shares with amitriptyline). No placebo was used. The dropout number was high: 12 of 37 who entered. The remaining 25 subjects took adequate doses of either drug (12 on fluoxetine, 13 on desipramine) for 12 weeks. No significant difference in improvement was found between the two drugs: Among the fluoxetine group, 9 had mild or good improvement, as determined by their weekly grading of their headache on a 0-10 scale, while among the desipramine group, 6 did. The authors thought that the effectiveness of these drugs was probably related to an effect on the patients' mood. Although they realized that their results could be mere placebo responses, they discounted this because they were convinced that Saper et al. (see paragraph above) had shown fluoxetine to be effective. My opinion of this trial is that it gives no scientifically valid result, and that it certainly does not indicate that fluoxetine is effective for chronic tension-type headache.

### **Buspirone**

A recent open, randomized, 12-week clinical trial by Mitsikostas et al., (1997) compared buspirone (a mild anti-anxiety drug) with amitriptyline. The results suggested that buspirone may be an effective preventive for some patients. My limited experience with this drug suggests that a minority of patients may have less headache on it.

### **Tizanidine**

Tizanidine (Zanaflex in the U.S.A., Sirdalud in Finland), a drug for spasticity, was slightly more effective than placebo in a double-blind, crossover trial of 37 women by Fogelholm and Murros (1992). The median values of the visual-analogue and verbal-rating scales for headache were significantly lower in the tizanidine periods, but the 95% confidence values overlapped a lot. Side effects of tizanidine (mostly drowsiness and dry mouth) made the tolerability of this drug less than good for 38% of the patients. The doses used were 2 to 6 mg three times daily. However, in a second study of (modified-release) tizanidine by Murros (2000), one of the authors of the first trial, doses of 6 or 12 mg daily were no more effective than placebo in alleviating chronic tension-type headache.

### **Dextroamphetamine**

During the past several years, when I have been faced with a patient unresponsive to tricyclics or buspirone, I have often prescribed dextroamphetamine tablets. A considerable percentage of the treated have had long-lasting lessening of headache frequency and intensity. Beginning doses are either 5 or 10 mg at breakfast and at lunch, and therapeutic doses have ranged from 10 to 80 mg daily. A controlled, double-blinded pilot study of this drug is nearing completion.

### **Psychological and Biofeedback Therapy**

Although I have referred many patients to experienced, skilled psychologists with an interest in headaches, I have rarely seen patients gain sustained headache relief from either psychological or biofeedback therapy, or both together. However, reports of benefit from

cognitive-behavioral therapy and biofeedback therapy have been appearing for many years. In 2001 Holroyd et al. reported the results of a randomized, placebo-controlled trial of the response of chronic tension-type headache to tricyclic antidepressants (amitriptyline or nortriptyline) or stress management therapy, or both. 203 subjects with chronic tension-type headaches were recruited. 53 were assigned to receive tricyclic antidepressants (up to 100 mg of amitriptyline or 75 mg of nortriptyline nightly), 49 were assigned to receive stress management therapy (3 sessions and 2 telephone contacts) plus placebo, 53 were assigned to receive stress management plus antidepressants, and 48 were assigned to receive placebo. Drop outs were considerable. The numbers who finished the 6-month study were 44, 34, 40, and 26 subjects, respectively.

The mean headache-index scores (a measure of daily pain ratings) declined identically in the antidepressant and the antidepressant plus stress-management groups during the first 3 months of the study, and were no different at the 3-month juncture. They were both significantly less than the scores for the placebo group and the stress management plus placebo group. This latter group's scores had, however, declined significantly more than the placebo group's scores. At the end of the study five months later, the index scores for the antidepressant and the antidepressant plus stress management groups had not changed notably from the 3-month state, but the stress management plus placebo groups' index had now dropped further to equal that of the two groups receiving antidepressants. The placebo group showed no decrease.

Although the headache-index scores were for all 3 treatment groups were not significantly different at the end of the trial at 8 months, the combined antidepressant/stress management therapy group had a greater proportion of patients with a clinically significant (at least 50%) reduction in headache index scores than did the groups treated with the antidepressant or with stress management alone: 64% vs. 38 % and 35%. This suggests that combined therapy may have advantages over either alone. the slow response of the subjects treated with stress management alone makes this an impractical treatment for all but those persons highly committed to it.

#### Botulinum toxin injections

At least 3 placebo-controlled, double-blind studies of injections of botulinum toxin into the muscles of the scalp (Schmitt et al., 2001; Rollnik & Dengler, 2002) or the scalp and neck (Rollnik et al., 2001) of patients with chronic tension-type headache have been published. None showed the toxin to be more effective than the placebo solution in alleviating headache, although the injections do diminish the scalp's EMG (muscle contraction) activity (Rollnik et al., 2001).

## **Medication-Abuse (Rebound) Headache - Diagnosis**

### ***Why they occur and what they are***

Folks who take analgesics, ergotamine, triptans, or any other type of drug frequently for several consecutive weeks to alleviate migraines or episodic tension-type headaches risk inducing a chronic daily headache. In general, the more potent the drug, the less often it need be taken to induce such a headache state. Opioids (narcotics), such as tablets with codeine or hydrocodone, may be used only three times a week for several weeks before the headache becomes daily, whereas tablets of acetaminophen may need to be taken almost daily to induce such a state. When the headache becomes daily, folks need more frequent dosing to

keep it suppressed enough to function. We see patients who take, for example, 100 Excedrin tablets a week to maintain some degree of headache suppression. Such large doses are more typical for patients whose original headaches were migraines.

Headache is more likely to develop or flare up when the medication level in the body is waning (hence the term "rebound headache"), but it can also occur despite heavy medication levels. When doses are missed or delayed, the headache generally flares up, since the headache mechanism is no longer suppressed by medication. Hence, patients become convinced that their alleviators are necessary for headache control, not realizing that the alleviators have induced the daily headache state. In some as yet unknown way, too-frequently suppressing headaches by drugs makes the brain more likely to generate headache.

Daily headaches induced by excessively frequent use of alleviative medicines are called rebound headaches or medication-abuse headaches whether they develop from migraines or episodic tension-type headaches. When they develop from migraines, they are commonly also referred to as transformed migraines, meaning that naturally occurring episodic migraine attacks have been transformed into a chronic daily headache with migrainous features.

Many patients with chronic tension-type headache also take analgesics daily. Such use may worsen the headache and make it less responsive to preventive medicines.

### ***Verifying diagnosis of analgesic-abuse headache***

Although frequent use of alleviative medications strongly suggests that a chronic daily headache is from drug abuse, the diagnosis must be verified by seeing the headache lessen notably after a period (generally one to several months) of complete abstinence from the abused drug(s) without substituting other drugs taken as alleviators. After such a period, patients with transformed migraines generally return to having intermittent migraines, and those whose daily headaches developed from episodic tension-type headaches generally experience the latter type once again. Those whose original headaches were the chronic tension-type continue to have a chronic daily headache, but it generally lessens in severity and shows responsiveness to standard preventives not present during heavy analgesic use.

### **Diagnostic criteria of the International Headache Society**

These are omitted here because they are (frankly) outdated. Recently published criteria for transformed migraine better reflect current thinking about the degree of analgesic or ergotamine use leading to its development (Silberstein et al., 1994). These criteria (not validated) state that migraine can be transformed into chronic daily headache with any of the following abuses for at least one month:

**Simple analgesic use:** over 1000 mg of aspirin or acetaminophen, or an equivalent of another drug, more than 5 days per week.

**Compound analgesic use:** over 3 tablets per day more than 3 days per week.

**Opioid use:** over 1 tablet per day more than 2 days per week.

**Ergotamine use:** 1 mg more than 2 days per week (rebound headache from excessive use of ergotamine was recognized long before analgesic-abuse headache was identified).

Similar analgesic use can change episodic tension-type headache into chronic daily headache or worsen chronic tension-type headache, as stated above.

Subsequent to these estimations, headache specialists have recognized that too-frequent use of the triptans, such as sumatriptan (Imitrex), can also induce chronic daily headache of the transformed-migraine type.

What they are, in a nutshell

Episodic migraines may be transformed into a chronic daily headache by excessive use of analgesics (pain pills), ergotamine, or any of the triptans, such as sumatriptan (Imitrex in the USA)--hence the label "transformed migraine". Similarly, episodic tension-type headache may be changed into a chronic daily headache by excessive use of analgesics. Most of the medication-abuse, chronic-daily headaches seen in practice are transformed migraines, and most develop from excessively frequent use of analgesics, such as Excedrin, butalbital compounds, acetaminophen, or ibuprofen. Medication-abuse headaches are also called rebound headaches, since the headaches tend to flare up as the medicine doses are wearing off.

Excessively frequent analgesic use also seems to worsen chronic tension-type headache and make it less responsive to the beneficial effects of preventive drugs.

## **Medication-Abuse (Rebound) Headache - Therapy**

### ***Overview***

The basic therapy for rebound headaches is discontinuation of all alleviative drugs (those taken when the headache "calls" for them) and abstention from them for roughly 8 to 12 weeks. Most patients can discontinue medications as outpatients, given a proper plan; some with transformed migraine need hospitalization to be withdrawn from them.

Among the outpatients, some can discontinue medications abruptly, whereas others do better with a slow stepwise cessation during a period of a few weeks. During this stepwise withdrawal, the drugs should be taken during set times (by the clock), not when patients feel the need to take them to suppress headache. The reason for this is that taking medications as preventives by the clock does not perpetuate (or induce) rebound headache, whereas taking them to suppress worsening headache does perpetuate the rebound state and is what induced this state.

Discontinuation is difficult for patients, not because they have become addicted to their drugs (aside from rare exceptions), but because their headaches worsen when they do not take them. After withdrawal of the abused drugs, almost all patients' headaches become intermittent within a few weeks to a few months and then return to their natural frequency, whatever that may be.

### ***Out-patient withdrawal***

During and for some time after discontinuation of alleviative drug use, patients with transformed migraine need a strong preventive medicine for short-term use to decrease the occurrence of headache flare ups. Short term preventives are less important for patients whose rebound headaches arose from episodic tension-type headaches, because flare ups of tension-type headache are less severe than those of migraines.

In general, the most reliable short-term preventive drug to use during withdrawal of alleviatives for patients with rebound migraine is dihydroergotamine (DHE), although some

patients can get by with naratriptan. DHE must be injected by the patient, but all my patients learn to do this in one 10-minute session in my office. I usually prescribe injections every 12 hours for one to two weeks, and then decrease the injection frequency to once a day for the next week or two before discontinuing preventive injections. The period needed for preventive injections varies greatly among patients. When a patient is without headache of note for 2-3 consecutive days, then the DHE dose can be decreased from twice to once daily, and when headaches do not occur for 2-3 consecutive days on the once-daily schedule, then preventive injections can be discontinued. Thereafter, either DHE or one of the triptans can be used to suppress severe migraine attacks, but such use should be limited to 3 days per week, lest overly frequent use perpetuate the rebound headache. Thus, patients may need to endure less than severe headaches without taking any alleviative medication for some weeks at least.

Unfortunately, the standard migraine preventives for long-term use, such as propranolol and amitriptyline, are not potent or reliable enough to be used as the sole preventive during withdrawal from alleviative medications for patients with transformed migraines.

Naratriptan in a dose of one 2.5 mg tablet twice a day is a fair substitute for DHE for some good responders to triptans. This triptan is preferable to the others because its longer duration of action gives better sustained preventive effects (its mean half life is 6 hours).

A retrospective study by Timothy Smith of 55 patients with rebound migraines treated with abrupt withdrawal of analgesics (or triptans if they were abused) along with tizanidine and a long-acting non-steroidal anti-inflammatory drug (such as naproxen) as short-term preventives reported that the patients' former chronic daily headaches had resolved in 62% of the sample by 12 weeks. The tizanidine doses were relatively low (2 to 16 mg) and were taken at bedtime (it's a sedating drug). Of course in a retrospective study such as this with more than one variable, one can't attribute the therapeutic successes to tizanidine. Yet, it may have helped the patients abstain from taking their customary alleviatives, which is what seems to perpetuate the rebound-headache state.

Although the standard migraine preventive pills for long-term use can not substitute for DHE injections or naratriptan tablets during withdrawal from alleviative drugs, most patients should be started on one of them in the early phase of withdrawal to combat their strong migraine tendency. The best choice is usually amitriptyline, given as a single nightly dose. It has the added benefit of promoting sleep, often hard to come by during the withdrawal phase. In fact, many patients do better with an added sleeping pill, such as zolpidem (Ambien) or temazepam (Restoril).

Short-term preventives that I've used successfully during analgesic withdrawal in patients with rebound headaches that developed from episodic tension-type headache are naproxen sodium, 220 to 440 mg twice daily, or cyclobenzaprine, 10 mg thrice daily.

Once the chronic daily rebound headache is replaced by a natural, intermittent headache pattern, the use of short-term preventives can be gradually eliminated. Then, alleviative drug use can be resumed, but with strict limits on the frequency of such use, lest patients slip back into a rebound headache state. If the patient's post-rebound headache frequency warrants the taking of a long-term preventive, then one should be found for the patient. These and other preventive measures for migraine are presented in my Web page on migraine therapy, and

the preventive measures for episodic tension-type headache are presented in my page on tension-type headache therapy.

Patients who have been taking compounds containing butalbital, such as Fiorinal and Esgic Plus, may need to take a substitute barbiturate to control restlessness if they are withdrawn quickly from their medication. I generally prescribe declining doses of phenobarbital at lunch and at bedtime for a few weeks when the butalbital compound is discontinued.

Patients who were abusing weak opioids, such as propoxyphene or codeine, can generally be weaned from them as outpatients, and even those on more potent opioids, such as oxycodone and meperidine, can generally be so weaned. I ask patients to abstain from taking opioids on an as-needed basis and prescribe doses at set intervals unrelated to the state of the headache. I often prescribe one of the long-acting opioid tablets to be taken two to three times per day at set times. I've often used long-acting oxycodone (OxyContin) and morphine (MS Contin). Every week or so, the dose is gradually decreased until it is low enough to be discontinued without withdrawal symptoms developing. For some patients, taking oral prednisone for a week or two might make withdrawal from opioids easier: see (Markley, 1994).

### ***Withdrawal in hospital***

Hospitalization is not needed for patients whose rebound headaches developed from excessively frequent use of analgesics to suppress episodic tension-type headaches. Hospitalization may be needed for certain patients with rebound migraine who have been heavily using strong opioids, butalbital compounds, or ergotamine. In hospital, those on opioids or butalbital can be monitored for withdrawal symptoms during gradual discontinuation of the offending substances, while their migraines can be suppressed by infusions of DHE. Those on ergotamine can be withdrawn abruptly from their tablets or suppositories under DHE infusions. Patients who tried but failed outpatient withdrawal from any offending substance should also be hospitalized. During and after hospitalization, the use of long-term preventives to suppress the migraine tendency is the same as it is for outpatient withdrawal, as noted above.

### **Administering DHE**

This drug is usually pushed into an arm vein directly from a syringe over the course of 5 to 10 minutes. However, the doses can be diluted in 50 ml of 5% dextrose in water in an IV infusion bag and, without delay, dripped in over the course of 15 minutes or so. My initial dose is 0.3 mg (ml). If this does not produce notable side effects, then larger doses up to 1 mg are infused on a t.i.d. (3 times a day) schedule. Doses are then adjusted to give maximal headache suppression while avoiding notable side effects, which are nausea (sometimes with a brief bout of emesis), diarrhea, leg pains, and tight uncomfortable feelings in the chest. The first 3 are common, the latter infrequent. Either tablets of hydroxyzine or metoclopramide or IV infusions of metoclopramide can be administered about one hour before each DHE infusion to lessen DHE-induced nausea, but the best treatment for the nausea is lowering the DHE doses. I've yet to see a serious side effect from DHE. However, because it can constrict coronary arteries, it should not be given to anyone with known or probable coronary artery disease. I rarely hospitalize patients for DHE for more than 5 days, in part because patients' medical insurers won't pay for longer admissions.

Patients who respond well to DHE in hospital are taught to inject themselves into the top of their thighs. Patients are surprised by how easily they learn to break the glass ampule, draw up the fluid into a syringe (3 ml with a 5/8" 25 gauge needle) and stick themselves with the needle. Injections can be subcutaneous, intramuscular, or a bit of both--it doesn't matter. When armed with this ability, they have good control over migrainous flare ups of headache after discharge. I generally recommend that, for the first few days or week after discharge, patients inject themselves with DHE twice daily on a regular schedule as a migraine preventive. Then, the injection frequency is decreased to one per day for a week before the drug is used as needed to suppress developing migraines.

### ***Prognosis***

Over 90% of patients who discontinue their use of analgesics, opioids (narcotics), ergotamine, or triptans and who continue to abstain from the offending drug(s) have their headache return to a natural episodic pattern, whatever this may be, within several months. These patients are very grateful for and often amazed at their recovery from daily headaches. Even patients with many years (even decades) of rebound headache can be relieved from their chronic daily headache.

## **Cluster Headache and Chronic Paroxysmal Hemicrania (CPH) - Diagnosis**

### ***Prevalence and comparison***

Cluster headaches are rare in the population. A rough estimate of the prevalence is about 70 persons with cluster headache among a population of 100,000 persons, or 0.07% of the population. CPH is considerably rarer. Over 80% of patients with cluster headaches are males and roughly 70% of patients with CPH are females. Both types of headaches have the same location, pain intensity, and associated features, but the former are longer lasting and less frequent (see descriptions and diagnostic criteria for both headache types below).

### ***Cluster Headache***

**Description (IHS)** (abbreviated and slightly altered): Attacks of severe unilateral pain in the orbit or surrounding areas, or both, lasting 15-180 minutes, recurring from once every other day to 8 times per day, and accompanied by one or more of the following symptoms: ipsilateral (on the headache side) conjunctival injection (reddened eyeball), lacrimation (excessive tears from the eye), nasal congestion (stuffy nose), ptosis (lowered upper eyelid), miosis (smaller pupil) and facial sweating. Attacks occur in series lasting for weeks or months separated by remissions lasting for months or years--hence the name cluster headache.

### **The two subclasses of cluster headache**

#### ***Episodic cluster headache***

This label is used for the cluster headache which disappears for over 14 consecutive days after less than one year of repeated attacks. Roughly 90% of patients have this type.

#### ***Chronic cluster headache***

This term designates the cluster headache which does not remit for a year or more, or which remits for less than 14 consecutive days within the year. Some 10% of patients have this type.

These two varieties are not fixed for any patient, in that episodic cluster headache can become chronic or vice versa. See description of a patient with episodic cluster headache.

**Diagnostic criteria (IHS) (abbreviated and slightly altered)**

At least 5 attacks

Severe unilateral pain in the orbit or surrounding areas, or both, lasting 15-180 minutes untreated

Headache is associated with at least one of the following signs on the side of the pain:

conjunctival injection (reddened eyeball)

lacrimation (excessive tears from the eye)

nasal congestion (stuffy nose)

rhinorrhea (runny nose)

facial sweating

miosis (smaller pupil)

ptosis (lowered upper eyelid)

eyelid edema (lids become puffy)

Frequency of attacks: from 1 every other day to 8 per day

Secondary headache types neither suggested nor confirmed

**Comment:** Cluster headaches are easy to recognize because their features are so uniform among their victims. They are frequently excruciating. Rather than lying down or sitting still during attacks as patients do during severe migraines, patients with cluster headaches generally pace the floor, or sit and rock their head and trunk up and down. Alcoholic beverages generally trigger a cluster headache when patients are within a cluster series. Essentially all patients with cluster headaches have some of their headaches begin during sleep. Most are smokers, yet the cessation of smoking does not bring relief.

I recommend that all patients felt to have cluster headaches, or CPH (see below), have a magnetic resonance image (MRI) of the head to exclude the rare presence of a benign tumor inducing cluster-like headaches. These are most likely to be located in the vicinity of the internal carotid artery. Computed- tomographic (CT) scans do not reliably show tumors in this region.

***Chronic paroxysmal hemicrania***

**Description (IHS):** Attacks with largely the same characteristics of pain and associated symptoms and signs as cluster headache, but they are shorter lasting, more frequent, occur mostly in females, and there is absolute effectiveness of indomethacin, as shown in the description of a patient with chronic paroxysmal hemicrania.

**Diagnostic criteria (IHS) (abbreviated and slightly altered)**

At least 50 attacks

Attacks of severe unilateral orbital, supraorbital and/or temporal pain always on the same side lasting 2 to 45 minutes

Attack frequency above 5 per day for more than half of the time

Pain is associated with at least one of the following symptoms on the pain side:  
conjunctival injection (reddened eyeball)  
Lacrimation (excessive tears from the eye)  
Nasal congestion (stuffy nose)  
Rhinorrhea (runny nose)  
Ptosis (lowered upper eyelid)  
Eyelid edema (lids become puffy)  
Absolute effectiveness of indomethacin (150 mg per day or less)  
Secondary headache types neither suggested nor confirmed

**Comment:** Just as cluster headache has both an episodic and chronic form, so does paroxysmal hemicrania. Its episodic form is called episodic paroxysmal hemicrania. Its first identification was just before the IHS published its headache classification in 1988. It's rarer even than the chronic form. Its individual headache attacks are identical to those of the chronic form, from which it differs only by its remissions of months to years between bouts of attacks. Goadsby and Lipton (1997) have reviewed the literature on the paroxysmal hemicranias and proposed diagnostic criteria for both forms.

The IHS requires disappearance of the headache attacks of chronic paroxysmal hemicrania during indomethacin therapy, in a dose of 150 mg or less per day, for the diagnosis to be established. But this criterion has been challenged, in view of reports of a few patients whose headaches responded partially or not at all to indomethacin, even though their headaches were otherwise typical of chronic paroxysmal hemicrania.

## **Cluster Headache and Chronic Paroxysmal Hemicrania (CPH) - Therapy**

### ***Abortive Medications***

#### **Cluster headache and CPH**

Subcutaneously injected sumatriptan (6 mg in 0.5 ml) (Imitrex in the U.S.A.) is the most effective, reliable, and rapid abortive therapy for cluster headache attacks. An injection (easily given by the patient) eliminates or markedly diminishes cluster headaches within 15 minutes in essentially all patients at every attack. Some of my patients have had headaches eliminated in 7 minutes! This effect does not lessen with continued use. Some patients have had satisfactorily rapid results with sumatriptan nasal spray. The oral triptans are less effective, but some especially good responders with relatively milder and slower-developing headaches may prefer this route of administration. A blinded/controlled study of oral zolmitriptan reported that 10 mg of the drug (a big dose) reduced pain considerably at 30 minutes in 47% of patients with episodic cluster headache. This number was significantly greater than the 29% response rate for the placebo group. 5 mg of zolmitriptan was not significantly better than placebo. In addition, patients with chronic cluster headache did not get better headache relief from zolmitriptan than from placebo.

Breathing 100% oxygen from a tight-fitting mask at a flow rate of 7 liters per minute for about 15 minutes diminishes or eliminates the headache in the majority of patients, but it's less effective and reliable than sumatriptan injections and is difficult to use outside of the home, although small, portable oxygen tanks are available. Of course, it may be the primary therapy for patients who should not take sumatriptan or dihydroergotamine because of their coronary artery disease.

Dihydroergotamine (DHE) can alleviate a cluster headache. When injected intramuscularly or subcutaneously its action is slower than that of subcutaneously injected sumatriptan. This and the lack of a self-injector gadget for DHE, in contrast to the easy-to-use StatDose Pen for sumatriptan, has deterred me from prescribing DHE as an abortive for cluster headache attacks.

No abortive treatment is known for chronic paroxysmal hemicrania (CPH) or its variant, episodic paroxysmal hemicrania. Since the attacks of these paroxysmal hemicranias last less than an hour, and generally about 10 to 15 minutes, any abortive therapy would have to act with dramatic swiftness to be of value.

## ***Preventive Medications***

### **Cluster headache**

#### ***Established preventives***

Most series of episodic cluster headaches are reduced within a few days by oral prednisone. Once the headaches cease or markedly diminish in frequency and severity, the initial dose of 60 to 80 mg every morning should be progressively decreased over the next few weeks. Prednisone is not generally prescribed for chronic cluster headaches, because it's less-effective for this variety and is too toxic for prolonged use.

Verapamil, lithium, methysergide, and, to a lesser degree, ergotamine, are effective preventives (for some patients) for prolonged use, but their effects are less rapid than prednisone's.

A common and effective practice is to prescribe verapamil together with prednisone at the beginning of a new cluster period. After 2-3 weeks of this therapy, the verapamil generally exerts a sufficient preventive effect to permit most patients to rapidly wean off prednisone without suffering a flare up of their cluster headaches. The starting dose of verapamil is 80 mg (one tablet) 3 times a day. The dose may need to be doubled, tripled, or even quadrupled (to 960 mg daily), if tolerated, to adequately suppress the appearance of cluster headaches. Verapamil's major side effect is constipation. Verapamil is effective against both episodic and chronic cluster headaches (which are just different patterns of the same entity).

Methysergide had been sold as 2 mg pills, but Novartis, the only manufacturer in the U.S. and presumably elsewhere, discontinued production in November of 2002. Perhaps methylergonovine, a semi-synthetic ergot alkaloid closely related to methysergide, will be an adequate substitute. An open study of this drug suggested that it too can decrease the frequency and severity of cluster headaches (Mueller et al., 1997). One 0.2 mg tablet is given 3-4 times daily. Although it has less side effects than methysergide, drug holidays for a month every six months are recommended for it, as they had been for methysergide. Prolonged use of this latter sometimes produced an inflammatory fibrosis in the abdominal retroperitoneal space, in the lungs, or in the heart valves. Monitoring for this by questioning for symptoms, by palpating foot pulses, and by checking a sedimentation rate, at the least, is indicated several times a year.

lithium carbonate is effective for many patients with either episodic or chronic cluster headache. The usual doses are 300 mg (one tablet or capsule) 2-3 times daily. Lithium levels should be checked and kept within, or even slightly below, the therapeutic range for bipolar disorder, namely 0.5 to 1.5 milliequivalents per liter.

Ergotamine, an ergot alkaloid commonly used to abort migraine, has long been used with considerable success to prevent cluster headaches. It can be effective when prescribed alone or when added to prednisone, verapamil, or perhaps lithium. However, one would not prescribe it together with the other ergot derivatives, methysergide and methylergonovine. In the U.S.A., it can be prescribed as 2 mg tablets designed for sublingual absorption (which may be swallowed) or as tablets containing 1 mg of ergotamine with 100 mg of caffeine. 2 to 4 mg daily in two divided doses are the doses I have used. One worries whether patients on ergots should use sumatriptan to abort headaches, because of the added potential constrictive effect on coronary arteries. However, I have as yet seen no adverse effects from this practice. Ergotamine should probably be reserved for patients who fail to respond to verapamil, methysergide, methylergonovine, or lithium, and should be used for relatively short periods. Hence, it's not a good choice for folks with the chronic form of cluster headache. It is often used successfully as a nightly dose to prevent nocturnal attacks of cluster headache, either alone or together with standard doses of verapamil or lithium.

### *Unestablished preventives*

Naratriptan (Amerge in the U.S.), one of the triptans used to abort migraines, has been tried with apparent success as a preventive for both episodic and chronic cluster-headache in an unblinded, uncontrolled study of 9 patients by Mulder & Spierings (2002). A dosage of 2.5 mg twice daily reduced or eliminated attacks in 7 of the patients, all of whom had also been taking verapamil as a preventive. The drug was well tolerated in all. The authors cautioned that patients who take naratriptan daily should not inject sumatriptan for headaches that do occur.

Divalproex (Depakote) may have preventive effects in both episodic and chronic cluster headache, as suggested by 2 small "open-label" trials and 2 case reports (Wheeler, 1998) of patients whose cluster headaches remitted for prolonged periods on this drug after having been refractory to all the standard medications. The author of the case reports suggested that the presence of migrainous features (vomiting, photo- or phono-phobia) might indicate responsiveness to divalproex. The remissions were slow to occur: "within 2 months" in each patient.

Melatonin may have some preventive action against cluster headache, as suggested by a pilot study by Leone et al. (1996). The trial dose was 10 mg nightly for 14 days. Five of the 10 treated patients reported a decline in attack frequency after 3-5 days of treatment, and then experienced no further attacks until melatonin was discontinued.

Baclofen, a drug used primarily to alleviate spasticity in conditions such as multiple sclerosis, was reported by Hering-Hanit and Gadoth in 2001 to have eliminated cluster-headache episodes within a week or two in 13 of 16 patients given 15 to 30 mg daily in 3 divided doses. Three of these patients subsequently had another cluster period, and all three again had their periods eliminated by baclofen. Blinded-controlled studies are needed to confirm these striking results.

Topiramate (Topamax) was reported to induce remissions in cluster headache episodes in one uncontrolled small study. The doses used were small: 50-125 mg daily in two divided doses.

Civamide nasal installation has been reported by Saper et al. (2002) to perhaps be "modestly effective" in the prevention of episodic cluster headaches. The authors reported the results of

a multicenter, double-blinded, controlled pilot study in which 18 subjects took civamide and 10 just the vehicle in which the civamide was dissolved. The subjects installed with a dropper 0.1 ml of solution in one nostril daily for 7 days. The primary efficacy end point was change in headache frequency from baseline during the post-treatment period of 20 days. The civamide group recorded a change from 12.5 to 4.9 headaches/week for the whole 20-day period, a decrease of 61%, whereas the control group reported a decrease from 10.8 to 7.2 headaches/week, a decrease of 31%. The P value for this difference was 0.054. This study has certain weaknesses. One is that civamide ("a synthetic isomer of capsaicin," the irritating agent in hot red peppers) burns the nostril, whereas the vehicle doesn't. Hence, it would be expected to give a stronger placebo effect. Another weakness is that the baseline headache frequencies were obtained from the subjects' retrospective estimates of the number of attacks during the 3 days prior to the study. Such estimates are unlikely to be accurate. If the slightly higher number of baseline attacks in the civamide group were falsely elevated, then the change with therapy would have been less. More and better blinded studies will be needed before civamide can be judged to be effective or not.

### ***Chronic paroxysmal hemicrania***

Almost all patients with chronic or episodic paroxysmal hemicrania have their headaches eliminated by indomethacin, which for CPH generally has to be taken for years. Sometimes large doses (200 mg per day) are needed to suppress the attacks. Indomethacin, like other non-steroidal anti-inflammatory drugs (NSAIDs) can produce intolerable dyspepsia, which may or may not be alleviated by antacids, such as cimetidine, and it can cause perforated or bleeding stomach or duodenal ulcers. When indomethacin is not tolerated (or effective) other drugs should be tried. One case report (Warner et al., 1994) stated that a patient with CPH unresponsive to indomethacin had her headaches suppressed by acetazolamide (Diamox) in a dosage of 250 mg three times daily. More recently, Mathew et al. (2000) reported a woman with CPH who had to discontinue indomethacin for intolerable gastric symptoms due to multiple ulcers. She was then treated with celecoxib (Celebrex), a drug in a new class of NSAIDs which decrease prostaglandin synthesis by inhibiting the enzyme cyclo-oxygenase-2 (COX-2) without affecting cyclo-oxygenase-1, as does indomethacin and the older NSAIDs such as aspirin, ibuprofen, etc. On a dose of 200 mg twice daily, her headache attacks remitted within 3 days and remained absent for the 3-month follow up--and without gastric symptoms.

### ***Hospital therapy***

#### **Cluster headache**

In-hospital infusions of intravenous dihydroergotamine should be considered for patients whose cluster headaches do not respond to any of the preventive drugs noted above and who are having multiple, severe, daily attacks. Mather, et al. (1991) reported that all 54 of their refractory patients who received this treatment had complete headache relief, usually within two days. Moreover, a very high percentage of these patients remained free from headaches for prolonged periods. For information at this Web site on in-patient DHE use see my sections "Withdrawal in hospital" and "Administering DHE" in the page "Treatment of analgesic-abuse headaches".

### ***Surgical and radiation therapy***

#### **Cluster headache**

Surgical procedures and radiotherapy are rarely done or needed for cluster headache, even the chronic form. The various procedures have not been compared and are difficult to evaluate. Among the procedures are glycerol injection into the cistern of the trigeminal ganglion, microvascular decompression of the trigeminal nerve, and so-called gamma-knife radiotherapy of the trigeminal ganglion. The only patient of mine who had one of these procedures had a glycerol injection twice without it having an effect on his headaches. For a review of such non-medicinal therapies see Dodick et al. (2000).

## **Post-Traumatic Headache - Diagnosis**

### **Overview**

Roughly 50% of patients who are stunned or knocked out by a blow to the head experience headache soon afterwards. The International Headache Society (IHS) calls this headache an "acute post-traumatic headache." However, as acute suggests "severe" and "brief," which are inaccurate adjectives for many of these headaches, I prefer "early post-traumatic headache." Most of these headaches are not severe and require only simple analgesics for relief. These early headaches occur just as commonly in people whose heads have been jerked during automobile accidents. (The inappropriate metaphorical term "whiplash" is commonly used to refer to these movements of the head and the neck.) These headaches disappear within a few weeks in about 70% of the sufferers, but the other 30% (or 15% of persons subjected to head trauma or "whiplash") continue to have headaches for years. The IHS calls these chronic post-traumatic headaches.

No correlation exists between the severity of the trauma and the chance of developing a chronic post-traumatic headache (Haas, 1993). This well-established fact suggests that this headache is not caused by brain damage. Instead, as other evidence suggests, the headache is most likely related to a person's reaction to the traumatic event. Some cultural determinants of these reactions are discussed in the section on "whiplash".

My recent study (Haas, 1996) found that about 75% of chronic post-traumatic headaches had the features of the naturally occurring (non-traumatic) chronic tension-type headache and about 25% had the features of naturally occurring migraine without aura. Among the former, roughly 25% were probably adversely affected by analgesic abuse.

Patients with chronic post-traumatic headaches after head trauma or "whiplash") often have other symptoms, such as dizziness, insomnia, and impaired memory and concentration, which together with the headache are commonly referred to as the post-traumatic (or post-concussion) syndrome. To believe that these symptoms are from traumatic brain injury, in the usual case, is a mistake in my opinion. Instead, the symptoms are most likely related to altered psychological states, as are the headaches. However, patients who have suffered brain damage may be mentally impaired. Sometimes, neuropsychologic examinations are needed to distinguish between these two types of altered mentation. Exactly what changes in a person's psychological state account for the post-traumatic symptoms has not yet been adequately explained.

### ***Chronic post-traumatic headache***

#### **Diagnostic criteria**

The 1988 International Headache Society criteria are in need of revision, in my opinion (Haas, 1994). They were based on the assumption that the headaches were

related to intracranial disturbances. I suggest the following criteria for the category of chronic post-traumatic headache.

Headache should begin within 3 months of a traumatic event.

Headache should be present for more than 3 months after its onset.

Subdural hematoma or traumatic hydrocephalus should be absent.

Headaches meeting these criteria are ostensibly related to the traumatic event, but not by means of a subdural hematoma or traumatic hydrocephalus. At our current level of understanding, coding a headache as "chronic post-traumatic" should not imply that it is related to brain injury or other structural intracranial or cervical abnormalities.

Chronic post-traumatic headaches can be subdivided into the following classes.

Chronic headache after head trauma.

Chronic headache after head movement without a blow to the head ("whiplash movement").

Chronic headache after accidents without head trauma or notable head movement

Although the headaches in these three categories are identical both symptomatically and etiologically in my opinion, I favor coding them by antecedent events, since the prevalent view is that these headaches are distinct entities.

After coding a chronic post-traumatic headache as one of the three above types, I advocate coding it for the class of natural (non-traumatic) headache in which it fits--in other words as chronic tension-type, or as migraine without aura, or as whatever other headache class it resembles.

## **Post-Traumatic Headache - Therapy**

### ***Overview***

Chronic post-traumatic headaches are notoriously resistant to therapy, and if present beyond 3 months from the head trauma tend to persist for years. Opinions vary on the cause of these headaches. I see the evidence as indicating that they are not generated by brain damage or other intracranial derangements, even when present, but instead are manifestations of psychological alterations induced by the traumatic event in its entirety (Haas, 1996). (See Diagnosis of post-traumatic headaches)

### ***Psychotherapy***

I think the bedrock of therapy should be psychological. However, our poor understanding of the psychological foundations of these headaches has hindered the development of properly directed therapy. My current belief is that patients should be directed toward re-establishment of their life's activities and away from rumination on the injury suffered and their symptoms. Therapy for depression, so common among these patients, is important. Reassuring patients that brain damage (whether evidence for it is present or not--generally not) is not the cause of their symptoms may be helpful. Patients who also suffer from post-traumatic stress disorder can have this set of symptoms ameliorated by psychotherapy. Sometimes the headache lessens with such therapy.

## ***Drug therapy***

The medications prescribed should be appropriate for the patient's headache type. Thus, post-traumatic headaches with the features of chronic tension-type headache are probably more likely to respond to amitriptyline than to other drugs. If amitriptyline is poorly tolerated, then similar tricyclic drugs, such as nortriptyline or protriptyline, may be worth prescribing. These tricyclics are also anti-depressants and thus can serve a double function for patients with post-traumatic headaches who are depressed. Amitriptyline is especially useful for the many patients with insomnia. In fact, its success in promoting sleep is in general better than in alleviating headache. I have seen headaches diminish and moods improve on dextroamphetamine given at breakfast and at lunch. I generally begin with doses of 10 mg.

Post-traumatic headaches meeting migraine criteria should be treated with the standard migraine preventives and abortives. Sumatriptan is as effective for post-traumatic migraine as for natural migraine.

Patients with definite or suspected analgesic abuse should be withdrawn from analgesics in the manner advocated for patients with non-traumatic analgesic-abuse headaches.

## ***Effect of Litigation***

Patients in litigation for monetary remuneration may be more refractory to therapy than those who are not, yet headaches persist after successful conclusions of litigation and disappear before verdicts are rendered. Moreover, even in our litigious society, a fair percentage of patients with post-traumatic headaches do not initiate litigation.

## **Additional Information Available at the Web Site of Dr. Haas**

The above information is extracted from the Web site of David C Haas, MD (<http://www.upstate.edu/neurology/haas/>) who periodically updates the information at this Web site. Please note that the above information does not contain all the information available at this Web site.

Specifically, the above extract does not contain:

- A section on "Other Headaches of Office Practice" that includes information on Brain-tumor headaches, Brief spontaneous headaches (Idiopathic stabbing headache, SUNCT syndrome, Chronic paroxysmal hemicrania), "Cervicogenic" headaches, Children's Headaches, Cough headaches (benign and symptomatic), Exertional headaches, Hemicrania Continua, Postural headaches from spinal taps, dural rents, or shunts, Sexual headaches, Sinus headaches, Temporal (Giant-cell) arteritis, "Whiplash" headaches from car crashes.
- A section on Headache Emergencies.
- A reference list of articles in medical journals and chapters in medical books cited in the cybertext.

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