

# **HEADACHES: PRACTICAL MANAGEMENT**

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## **Introduction**

Headache is a nearly universal symptom. Migraine, and other headaches can be highly disabling, and impose a significant burden, both in economic terms and in personal suffering. For migraine alone, missed workdays and disability at work have been estimated to cost American employers approximately \$13 billion per year (Hu et al). Head pain is a common complaint by patients presenting to physicians' offices and emergency departments (Barton). The characteristics and treatment of the primary headache disorders including migraine, tension-type, and cluster will be discussed, as well as secondary headache disorders (including benign-appearing recurrent headache due to underlying disease). The recognition and treatment of chronic daily headache and its relationship to medication overuse will also be addressed.

## **Clinical Symptoms And Signs**

### **Approach To The Patient**

To properly diagnose a patient presenting with headache it is necessary to take a careful history and examine the patient. The history should include the date of onset, duration and timing of the headache attacks, as well as the frequency, severity, duration of pain episodes, triggers, quality of the pain, factors increasing and decreasing the pain, previous and current medications (including over-the-counter remedies), and family history. History of trauma, other medical conditions, and a psychiatric history should be obtained. A careful and complete history is important in earning the patient's confidence and in establishing the correct diagnosis. A complete medical and neurologic examination, based on clues from the history or other physical findings is performed. The results of this evaluation will dictate the physician's choice of additional investigations.

Neuroimaging (CT scanning or MRI), blood work, lumbar puncture, angiography, et cetera are necessary when a secondary headache, such as subarachnoid hemorrhage, meningitis, or giant cell arteritis is suspected. Testing is generally not indicated when history and examination suggest a primary (benign) headache disorder.

## **Secondary Headaches**

Secondary headaches include those headaches resulting from a known structural or pathological cause. The following case report is presented to stimulate thinking about secondary headaches that may mimic primary headache disorders.

## **Case Report**

A 20-year-old man came to the office complaining of pain over his forehead and into the left orbit. He rated the severity of his pain as a 10/10. He was previously seen in another office where he was given acetaminophen/caffeine/butalbital (Fioricet®), resulting in mild relief. He had continued pain. He had been given 28 Fioricet® of which only 7 remained after 20 hours. He complained of nausea and had vomited once at home. He denied photophobia, fever, ear or abdominal pain.

He has a history of asthma and had had an upper respiratory tract infection about two weeks prior to his presentation with stuffy nose, cough and tearing eyes. He had been coughing green-brownish material for the three days prior to his presentation in our office. Medications included albuterol (Proventil®) and acetaminophen (Tylenol®). His examination was

remarkable for equal pupils that were round and reactive to light without tearing, injection or nystagmus. He was able to read and count fingers in both visual fields. His fundi showed what was thought to be early papilledema. He had marked tenderness on palpation of his left frontal sinus and was non-tender to palpation over the other sinuses. He had a non-focal neurological examination. His initial temperature was 100.4 orally and vital signs were stable. A stat head CT scan without contrast was arranged and read as normal. The course and workup of this patient will be discussed (see below).

Thus far, this case illustrates the potential hazard of diagnosing a primary headache disorder too soon. A number of diagnostic problems in headache may occur. These problems may be grouped into four categories and are reviewed below (Mathew, 1994).

### **Organic Conditions Presenting With Acute Headache That May Cause Difficulty In Diagnosis**

Clues to diagnosing secondary (threatening) headaches include constant headaches (especially if a history of progressive frequency/severity is obtained), a deficit on neurologic examination (including abnormal mental status), abnormal vital signs, a history of trauma, onset of new headache (especially “the worst headache/first headache”), or a history of drug abuse.

#### **Intracranial aneurysms**

Unruptured

"sentinel headache" "thunderclap headache"

ruptured

Cerebral venous thrombosis

Encephalitis

herpes simplex encephalitis

Carotid artery dissection, vertebral artery dissection

Cerebral venous thrombosis

Subarachnoid hemorrhage from ruptured intracranial aneurysm or arteriovenous malformation is usually a dramatic clinical presentation. Some individuals collapse and expire immediately. Survivors generally have an explosive, severe headache with nausea and/or vomiting. Seizures may occur, as can stupor or coma. On examination, stiff neck (Brudzinski and Kernig signs), hypertension, and subhyaloid (preretinal) hemorrhages may be found, as well as focal neurologic deficits. Work-up proceeds promptly to a CT scan, which if negative (CT misses 10-15% SAH) is followed by a lumbar puncture. If SAH is confirmed, a 4-vessel cerebral angiogram is performed (up to 20% of aneurysms are multiple). Neurosurgical consultation is required.

Perhaps 1-2% of the general population harbors asymptomatic intracranial aneurysms. Unruptured intracranial aneurysms may cause symptoms due to sudden expansion (headache) or thrombosis (without leaking). Whether imaging with CT scan and lumbar puncture is sufficient to exclude the presence of intracranial aneurysm, is controversial. If sufficient clinical suspicion is present, magnetic resonance angiography (MRA) may be performed, or even conventional angiography. Investigation must be tailored to the particular clinical context and the degree of suspicion.

Patients with encephalitis or meningitis usually have fever (unless on antipyretics or steroids), and stiff neck (if in a deep coma, stiff neck may not be present). Headache is common, and focal neurologic deficits may develop. Seizures may occur, possibly followed by stupor and coma. CT scan or MRI is usually performed to rule out an abscess or other mass lesion, followed by a lumbar puncture.

Herpes simplex encephalitis, a progressive necrotizing encephalitis with a predilection for the temporal and frontal lobes, presents with fever, loss of sense of smell, and recent memory loss. Headache is common. MRI is positive early; polymerase chain reaction on CSF may be diagnostic. Treatment with acyclovir is initiated as soon as the diagnosis is suspected to try to limit the amount of brain damage. Neurologic and infectious disease consultation is appropriate.

Dissection of the carotid or vertebral arteries may occur spontaneously, or in the setting of trauma or underlying vascular disease. Symptoms include neck pain, headache, and neurologic deficits in the distribution of the involved blood vessel. The dissection may be revealed by ultrasound, MR angiography, or conventional angiography.

Cerebral venous thrombosis may be present with headaches, seizures, paraparesis (cortical parasagittal leg area), or other focal neurologic deficits. Predisposing conditions include pregnancy (or the immediate post-partum period), dehydration, cancer, coagulation disorders, or trauma.

## **2. Organic Conditions Associated With Recurrent Headaches Mimicking Primary Headache Disorders**

Symptomatic cluster headaches

Clue: the duration of the headache in symptomatic cluster may shorten progressively.

- Tumor
  - Parasellar meningioma
  - Pituitary adenoma
  - Carotid and vertebral artery aneurysm
  - Nasopharyngeal carcinoma
  - Ipsilateral large hemispheric arteriovenous malformation
  - Upper cervical meningioma
- Cerebral arteriovenous malformation
- Cough and exertional headache (including sex headache) due to organic intracranial lesions
- Antiphospholipid antibody syndrome
- Isolated CNS vasculitis
- Pheochromocytoma

The pain of cluster headache is so severe that patients are certain there must be an underlying mass lesion. Imaging is generally normal. However, in symptomatic cluster

headache a lesion may often be found in or near the cavernous sinus. The duration of the pain attacks may become progressively shorter, and a fixed neurologic deficit may appear.

Cough headache is usually a sudden head pain triggered by coughing or other Valsalva maneuvers. The headache is sudden in onset and severe, but only briefly so (seconds or minutes). It may be followed by a longer duration posterior or holocranial dull ache. Perhaps 10-20% are due to a posterior fossa lesion such as a Chiari malformation. MRI is indicated as part of the evaluation. If imaging is negative, treatment with indomethacin is usually dramatically effective. Lumbar puncture may also be therapeutic (Raskin, 1995).

Sex may trigger headaches in several ways. 1) Subarachnoid hemorrhage or sudden-onset migraine, (which may be clinically indistinguishable) may occur. CT, LP, even angiography, may be required. 2) Severe muscle contraction headache may be precipitated (gradual onset, without nausea or vomiting). 3) Postural headache may follow intercourse, presumably due to a nerve root sleeve tear with CSF leakage. The headache is relieved by recumbency and aggravated by standing.

Antiphospholipid antibodies (the lupus anticoagulant, anticardiolipin antibodies, antiphosphatidylserine antibody) may occasionally be associated with migraine with prolonged (1 hour) aura or migrainous infarction. A previous history of recurrent miscarriages or venous thrombosis should arouse suspicion. An elevated partial thromboplastin time (PTT) on routine coagulation testing and a false positive VDRL may provide a clue to their presence.

CNS vasculitis may be present with headaches, seizures, and focal neurologic deficits. Laboratory parameters consistent with collagen vascular diseases may be present, but may be absent if disease is confined to the CNS (a privileged area). Imaging may reveal strokes, CSF may contain red and white cells, and rising protein. Angiography may demonstrate beading of blood vessels and segmental narrowing or occlusions. Occasionally meningeal biopsy is performed. Rheumatologic, neurologic, and neurosurgical consultation may be necessary.

The headache of pheochromocytoma is generally paroxysmal -- sudden, but brief (less than one-hour duration). Dramatic elevations of blood pressure, with tremor and diaphoresis occur. The headache is often holocranial, pounding, and nausea/vomiting may be present. A 24-hour urine evaluation for products of the tumor (VMA, etc.) is diagnostic. **Tip -- mild essential hypertension is typically not associated with headache. Severe paroxysmal elevations of blood pressure, as occurs with pheochromocytoma or the tyramine reaction in patients on MAO inhibitors, is associated with headache.**

## **1. Organic Conditions Associated With Chronic Persistent Headache Or Facial Pain, Often Without Abnormal Physical Findings**

- Arnold-Chiari Malformation-Type 1
  - may eventually develop diplopia, vertigo, ataxia
- Adult aqueductal stenosis and hydrocephalus
  - Idiopathic intracranial hypertension (pseudotumor cerebri) without papilledema

Temporomandibular joint (TMJ) dysfunction

TMJ – Uncommon

- 3 components: 1. Clicking and popping.  
2. Pain on use.  
3. Limitation of jaw opening (to under 30 mm).

TMJ - Common.

Pain, crepitus. Responds to physical measures such as physical therapy, heat, massage, NSAID. Surgery usually best avoided.

Giant Cell Arteritis (temporal arteritis)

Giant cell arteritis is usually manifested as temporal pain, constant, sometimes with jaw claudication. The scalp and superficial temporal arteries may be tender. Most patients are over 50 years old and have an ESR over 50 mm/hr. Untreated, this disease carries a significant risk of blindness and stroke. If the diagnosis is suspected, prednisone is started immediately (60-80 mg per day initially), the patient is then sent for temporal artery biopsy (due to patchy involvement, a substantial length of vessel needs to be obtained. If one side is negative, the opposite side should be considered for biopsy).

## **2. Brain Tumor Occurring In A Patient With Established Migraine**

Carrying the diagnosis of a primary headache type, such as migraine, in no way prevents a patient from developing a second type of headache. Brain tumors certainly can occur in patients who also have primary headache disorders. Therefore, if a patient with an established headache disorder develops new or progressive signs or symptoms, or becomes refractory to previously effective therapy, the possibility of the presence of a second type of headache should be considered.

## **Diagnosis And Management Of Primary Headaches**

The International Headache Society diagnostic criteria are now used to classify and diagnose headache (IHS Headache Classification Committee). We will discuss the major primary headache disorders (migraine and tension-type) and their management. Patients often complain about headaches when they interfere with their routine- our goal is to keep this interference to a minimum.

### **MIGRAINE**

Migraine is a common problem, affecting approximately 6% of children, 6% of men, and 18% of women (Stewart). It is an episodic headache that is often a unilateral throbbing pain associated with photophobia, phonophobia, nausea and vomiting. It is made worse by exertion. If there are neurological symptoms associated with the headache it is called "migraine with aura" (IHS 1.2), without these symptoms it is known as "migraine without aura" (IHS 1.1).

The object of therapy is to ameliorate or terminate patients' migraine attacks, and when necessary, to reduce the frequency and severity of attacks via behavioral treatment, lifestyle changes, and preventative pharmacotherapy. Migraine is often precipitated by various triggers (ie, chocolate, cheeses, menses, sun glare, missing a meal, etc.). Therapy begins as these triggers are identified and subsequently avoided. Avoiding these is the first step.

Getting enough sleep and exercise, and dealing with stress is next. It is also important to be sure other medications are not contributing to headache causation, eg, hydralazine, nitroglycerine. The overuse of symptomatic medication can transform migraine into a chronic daily headache [see below].

In this situation prophylactic medication is ineffective and the offending medications must be stopped. Preventive pharmacotherapy is usually appropriate when patients need to use acute headache medications more than 2 days per week, if the headaches do not respond to abortive medications, (perhaps resulting in visits to the emergency room), or if the patient has had complicated migraine (a prolonged neurologic deficit, or migrainous infarction). Acute symptomatic therapy with medications is used to relieve headache attacks.

## **Prophylactic Treatment**

Prophylactic therapy is initiated to reduce the frequency, duration, and severity of migraine attacks. Ideally, the patient should not require the use of acute headache medication more than two days a week (an exception to this rule is made for menstrually-associated migraine attacks which can last several days). Limiting the use of acute medications reduces the likelihood of developing medication-induced (analgesic rebound) headaches.

Patients in the childbearing years requiring preventative treatment generally should be using an effective form of contraception. However, oral contraceptives may not be appropriate for some migraine patients.

It generally takes 2 to 3 months to ascertain medication's preventative effect. Typically, therapy starts "low, go slow". Start with the lowest dose and increase it slowly until headache control is achieved or unacceptable side effects are encountered. After the headaches are controlled for 6 months or more the medication may be gradually decreased and stopped, as tolerated.

**Tip: Choose a preventative migraine therapy based on co-morbid/co-existent conditions such as mitral valve prolapse, Raynaud's phenomenon, epilepsy or, depression. Choose a drug that might help both.**

The major classes of prophylactic drugs include beta-blockers, anticonvulsants, calcium channel drugs, and heterocyclic antidepressants. There are also several miscellaneous drugs, which are sometimes useful (Ward, 2000).

## **Antidepressants**

### **Amitriptyline, Nortriptyline, Doxepin**

Many patients with migraine have co-morbid depression. If sleep disturbance is prominent, consider using a heterocyclic antidepressant. Amitriptyline (Elavil®, others) has the most support in the literature. Its effect on migraine is separate from its effect on depression. Its mechanism of action appears to be through modulation of serotonergic pathways. Symptoms of fibromyalgia may also be alleviated. Start patients on a 10mg or 25mg bedtime dose and increase the dose slowly to achieve headache control. Doses of 150mg or less are generally employed. Side effects include weight gain, dry mouth, cardiac arrhythmias, urinary retention, blurred

vision, and constipation. The medication should be avoided in patients with untreated glaucoma and prostatic hypertrophy. The dry mouth side effect can be managed by using hard sugarless candies or with pilocarpine (Salagen®) 5-10mg tid.

**Tip-Medications within the same pharmacologic group produce various side effects that are more, or less, acceptable to each individual patient. If one agent is poorly tolerated, consider either a lower dose or a trial of another agent in the same family.**

Nortriptyline (Pamelor®, others) may be tried if the side effects of amitriptyline are unacceptable. It causes less drowsiness. Again, the initial dose is generally 10-25 mg hs, but as it is also available in a liquid formulation, even lower doses can be employed if necessary. Doxepin (Sinequan®) is another potential option, and is also available in a liquid form. Heterocyclic antidepressants are contraindicated in patients with cardiac arrhythmia, narrow angle glaucoma, prostatism, and uncontrolled seizures (Saper).

### **Beta-Adrenergic Antagonist Drugs**

#### **Propranolol, Timolol, Metoprolol, Nadolol, Atenolol.**

The beta-blockers are widely used for the prevention of migraine. They were discovered to have an effect serendipitously, and are now thought to work via an effect on 5-HT<sub>2</sub> receptors, preventing the generation of nitric oxide. Propranolol (Inderal®) and timolol (Blocadren®) have FDA indications for migraine prevention. Propranolol is often the first choice and is used in doses ranging from 40-320 mg daily, in divided doses. It is also available in several extended-release forms that can be given once or twice daily. Nadolol (Corgard®) can be given once daily, as can atenolol (Tenormin®). Side effects are common and include hypotension, bradycardia, fatigue, weight loss, and bronchospasm (Welch). This class of medications is contraindicated in patients with asthma, diabetes, Raynaud's phenomenon, depression, and sometimes heart failure. Some authorities avoid beta-blockers in migraine with aura.

## **Calcium-Channel Blocking Drugs**

### **Verapamil, Diltiazem, Amlodipine.**

This class of drugs is especially useful in those migraineurs suffering from Raynaud's. Verapamil (Calan®, Isoptin®, others) is the best studied. Like other preventative agents, benefit may not become apparent for weeks to months (Welch). Verapamil is usually started at doses of 80mg twice or three times a day. It may be increased to 480mg per day as tolerated. There are sustained-release formulations (Calan SR®, others) that may be used once or twice daily, to enhance compliance. Common side effects include constipation, hypotension, and pedal edema. The vasodilation associated with some drugs in this category (particularly nifedipine [Procardia®]) occasionally causes a migraine-like headache.

## **Nonsteroidal Anti-Inflammatory Drugs (Nsaids)**

### **Naproxen, Naproxen Sodium, Others.**

These drugs have a role in both acute and preventative migraine therapy (see below). Naproxen (Naprosyn®) has been demonstrated to be an effective prophylactic in clinical trials. It decreases the intensity and duration of headache, nausea, vomiting, and other analgesic use. It may be particularly useful for predictable menstrually-associated migraine attacks. The initial dose is 550mg naproxen sodium (Anaprox DS®) BID beginning 2 days prior to the expected onset of headache and continued through the usual time of headache susceptibility (Raskin, 1988). Patients may be switched to another NSAID to find the most effective and tolerable relief. There are many choices including ketoprofen (Orudis®), and newer agents such as rofecoxib (Vioxx®) and celecoxib (Celebrex®).

## **Aspirin**

Aspirin is useful in migraine prophylaxis (Welch). A single 325 mg dose daily may reduce the frequency of migraine attacks. Side effects of aspirin and other NSAIDs are well known and include dyspepsia, gastritis, and GI hemorrhage.

**Tip - These side effects can be ameliorated with concurrent treatment with misoprostol (Cytotec®). It is given as 200 mcg tablets 4 times a day, with meals. The dose may be reduced if necessary to 100 mcg 4 times a day.**

## **Anticonvulsants**

### **Valproic Acid, Gabapentin, Topiramate.**

Migraine is known to be co-morbid with epilepsy. Valproic acid (Depakote®, others) has an FDA indication for migraine prevention. It is usually administered as the enteric-coated formulation, Depakote® with superior GI tolerability. The initial dosage is usually 250 mg BID. After 6-8 weeks, the dose may be increased to 500 mg BID, and eventually to 750 mg BID. The most important parameter to monitor is headache control. Blood levels do not correlate with clinical effect. Side effects include GI irritation, tremor, hair loss, weight gain, and hepatic dysfunction. Pancreatitis occurs rarely. Spina bifida may occur during pregnancies in fetuses exposed to valproic acid.

Gabapentin (Neurontin®) and topiramate (Topamax®) have been reported to have efficacy in selected migraine patients (Ward, 2000). Neurontin is not hepatically-metabolized and has little potential for drug interaction. Dosing typically begins at 300 mg tid, and may be

slowly raised as high as 1200 mg tid. Topiramate is actually associated with weight loss, which may be of benefit to some migraineurs. For migraine prevention, dosing is begun at 15-25 mg at hs, and slowly raised to as high as 100 mg BID. This drug is a weak carbonic anhydrase inhibitor, and therefore should not be given to patients with a history of renal stones. Higher doses are often associated with significant sedation.

## **Miscellaneous Headache Preventative Agents**

### **Methysergide, Cyproheptadine.**

Numerous other drugs have been used as for migraine prophylaxis, with variable success, and often limited support in the literature. Methysergide (Sansert®) has an FDA indication for migraine prevention. It is highly and rapidly effective, but its use is limited by rare but serious side effects including retroperitoneal, cardiac valvular, and pulmonary fibrosis. Therefore it cannot be given for longer than 6 months without a “drug holiday” of at least one month. Other side effects are related to vasoconstriction and include: chest pain, abdominal pain, cold numb painful extremities with or without paresthesiae, and diminished or absent pulses. These effects usually regress when the medication is stopped. Nausea and vomiting may also occur. The medication may make patients feel strange (chemically similar to LSD), especially at the initiation of therapy. Many of these side effects can be avoided by gradually increasing the dose. The 2 mg tablet is started once daily for 3-4 days, then increased slowly to tid or qid. Methysergide's major usefulness is for episodic cluster headache.

**Tip- this drug has a rapid onset of action and may be a useful temporary choice to achieve rapid reduction in headaches.**

Cyproheptadine (Periactin®) is an agent with anti-serotonergic, antihistamine, and calcium channel blocking properties. It has been advocated particularly as a preventative agent for children with migraine. The usual starting dose is 2mg (1/2 a 4mg tablet) twice or thrice daily. The dose may be increased slowly, usually to 4 mg twice or three times daily. It is available as syrup as well, enabling lower dosage titration. Side effects include sedation and weight gain.

## Symptomatic Migraine Treatment

### Simple Analgesics

#### **Aspirin, Acetaminophen, BAC (Butalbital, Aspirin (Or Acetaminophen), Caffeine)**

Both aspirin and acetaminophen are superior to placebo in decreasing migraine pain (Welch). Aspirin is the most commonly used non-prescription analgesic selected by patients for the management of headache pain. An initial dose of 975 - 1000 mg is recommended at the onset of the attack. Subsequent doses of 650 - 1000 mg every 4 hours may be given as needed (maximum 4-6 grams in a 24-hour period). Buffered and effervescent forms of aspirin may reduce gastric irritation. Although these forms are more rapidly absorbed, a corresponding onset of action is not always seen. Delayed absorption with enteric-coated aspirin precludes the use of this product in acute pain management. Aspirin is also available for rectal administration. It has been used intravenously with good results (Welch) but is only available outside of the U.S.A.

Acetaminophen is a non-prescription alternative in patients who cannot tolerate aspirin. Several pain models demonstrate the equivalent analgesic efficacy of aspirin and acetaminophen on a milligram to milligram basis. A study in patients with tension and tension-vascular headaches observed no difference between 1000 mg acetaminophen and 650 mg aspirin in relieving headache pain.

Gastric stasis during a migraine attack impedes the absorption of medications, such as aspirin and acetaminophen. **Tip-Concomitant administration of metoclopramide (Reglan®) significantly increases serum concentrations of both these agents, by increasing gastrointestinal motility. (Volans) [see below for further discussion].** Oral medications may be limited in their utility by their incomplete absorption and the frequent vomiting accompanying migraine. The use of the rectal route of administration is available for aspirin and acetaminophen. Codeine and other drugs may also be prepared in this fashion by pharmacists (Ward). Dependence can occur in patients who use these products uninterrupted for 48 hours or more. Unless withdrawal is carried out, such patients are unlikely to benefit from other antimigraine therapy.

Aspirin and acetaminophen are commonly combined with caffeine and butalbital to enhance analgesic activity. These combinations are called BAC (butalbital, aspirin or acetaminophen, caffeine) and are sold as Fiorinal®, Esgic® and Fioricet® (with acetaminophen). This combination works for many patients with headache.

**Tip-Sometimes patients have an adverse reaction to the caffeine in this combination. Phrenilin® combines acetaminophen and butalbital, avoiding this problem.** BAC may be abused in chronic headache patients, complicating their treatment. It is important to detoxify these patients from all rebound-producing medications, including simple analgesics, when using excessive quantities (eg, more than 2 days a week). An effective BAC detoxification protocol to do this has been published (Sands).

## **Nonsteroidal Anti-inflammatory Drugs (Nsaid)**

### **Naproxen Sodium, Ketorolac**

Nonsteroidal anti-inflammatory drugs (NSAID) may be considered the drugs of choice in first line abortive therapy of migraines, due to their effectiveness and lack of a dependency cycle. Naproxen (Naprosyn®) is the most frequently studied NSAID for the treatment of migraine. Naproxen and naproxen sodium (Anaprox/Anaprox DS®) achieve peak plasma concentrations after 2 and 1 hour, respectively. **Tip-Naproxen sodium is preferred for abortive therapy because onset of analgesic activity corresponds with its earlier peak plasma concentration.**

Ketorolac (Toradol®), the first parenteral NSAID available in the United States, has modest effects in the treatment of migraine. However, relief from pain and disability with I.M. ketorolac are significantly less than the combination of IV DHE 45® and metoclopramide. Keterolac may also be administered intravenously.

Other NSAIDs found to be effective in the treatment of migraine include diclofenac sodium, flufenamic acid, flurbiprofen, ibuprofen and mefenamic acid (See **Table 1**). The most common adverse effect with all NSAIDs is dyspepsia. Diclofenac was better than placebo, but relieved only 27 % of migraine attacks. (Lance)

### **Table 1: Dosing Guidelines For Nsaids For Treating Migraine**

Naproxen sodium (Anaprox®)

550 mg-850 mg BID

275, 550 mg tablets

Diclofenac sodium (Voltaren®)

50-100 mg in 2 divided doses

25, 50, 75 mg enteric coated tablets

Flufenamic acid

Not available in the United States

Flurbiprofen (Ansaid®)

300 mg in 2-4 divided doses

50, 100 mg tablet

Ibuprofen (Motrin®)

600-800 mg TID

300, 400, 600, 800 mg tablet

Mefenamic acid (Ponstel®)

500 mg, then 250 mg every 6 hours

250mg

Tolfenamic Acid

Not available in the United States

## **Antiemetics**

### **Metoclopramide, Chlorpromazine, Prochlorperazine, Promethazine**

Antiemetics are useful in the management of disabling nausea and vomiting frequently associated with migraine headaches. In addition to antiemetics properties, metoclopramide (Reglan®) can also reverse the gastric stasis accompanying migraine attacks. Metoclopramide enhances the effectiveness of analgesics such as aspirin, acetaminophen, naproxen as well as ergotamine in migraine by improving absorption (Raskin, 1988). **Tip-For maximum effectiveness, metoclopramide 10 mg should be administered at the onset of the migrainous episode either with or followed by the analgesic agent 15 - 20 minutes later.**

Metoclopramide should be used sparingly as it may cause dystonia and akathisia, especially in adolescents (Welch). Keeping the dose below 30 mg per day decreases the chance such a reaction will occur. Patients should be warned of the potential dystonic reaction and have 25 mg of diphenhydramine (Benadryl®) available.

Administration of a narcotic analgesic (eg, meperidine-Demerol®) or anticholinergic agents may antagonize increased gastrointestinal motility produced by metoclopramide

Metoclopramide provided pain relief in 67% of patients after one hour compared to 19% for placebo, in a controlled, double blind study (Text cited in Raskin 1988).

Recent studies suggest that some antiemetics may be useful as single agents in the treatment of migraine attacks.

Controlled studies have shown intravenous chlorpromazine (Thorazine®) 0.1 mg/kg and prochlorperazine (Compazine®) 10 mg effectively terminate migraine attacks (Lane/Jones cited in Raskin 1988) Chlorpromazine may be useful when treating migraine with intravenous dihydroergotamine (DHE-45®) (Welch).

Chlorpromazine and prochlorperazine may cause tardive dyskinesia that occasionally is irreversible.

Promethazine (Phenergan®) suppositories (12.5mg-25 mg-50mg) are effective in treating nausea and vomiting, with little likelihood of dystonia.

## **Isometheptene**

Isometheptene (Midrin®) is suitable for patients to try for mild to moderate migraine attacks. It is generally well-tolerated. Adverse reactions are unusual. Isometheptene is a vasoconstrictor possessing antispasmodic activity. Midrin® contains isometheptene in combination with dichloralphenazone (a sedative) and 325 mg of acetaminophen. It was more effective in treating mild to moderately severe migraine in a placebo-controlled trial (Raskin 1988). In a comparative trial, no difference in headache duration was observed between Midrin® and ergotamine\caffeine (Cafergot®). However, the incidence of nausea and vomiting was significantly lower with Midrin® (6.5% versus 24.6%). The recommended dose for Midrin® is 2 capsules at the onset of the attack, followed by 1 capsule every hour as needed, up to a maximum of 5 capsules per 12 hours.

## **Ergot Preparations**

### **Ergotamine Tartrate, Dihydroergotamine.**

Ergotamine tartrate was a very important medication for symptomatic treatment of migraine. It is available in oral, rectal, and sometimes sublingual forms. Availability of some of these formulations has been intermittent. Dihydroergotamine (DHE-45®) is the only parenteral ergot available. The absorption rates of ergotamine are variable, depending on the route of administration. Caffeine enhances ergotamine's absorption. Metoclopramide is likely to improve absorption of oral ergotamine (Welch). Parenteral treatment is most effective, rectal ergotamine achieves higher serum levels than the oral route. Therapeutic responses will, of course, vary among different patients and route and dose of medication. Oral ergotamine (Cafergot®, Wigraine®, and others) is given initially as two 1 mg tablets followed by 1 tablet every 30 minutes until relief occurs. The dose is limited to 6 tablets daily and 10 tablets weekly. Nausea and vomiting are common side effects of the medication. **Tip - Ergotamine is most effective when given in a subnauseating dose.** We suggest that patients try the medication when they do not have a headache to determine the nauseating dose. For example, if they become nauseated after using 5 ergotamine tablets then they should establish 4 ergotamine tablets as their personal limit. Metoclopramide can also be used to help control the nausea and vomiting associated with ergotamine.

Rectal ergotamine (Cafergot® or Wigraine®) is available in 2 mg suppositories. **Tip - It is useful to take one-quarter to one-half a suppository initially, followed by one-quarter every 30 minutes as needed to a maximum daily dose of two suppositories or 4 mg.** Again, patients should determine the subnauseating dose when they are headache-free. Since patients using rectal ergotamine appear to be at higher risk for developing a dependency on ergotamine, there is a weekly limit of 5 suppositories.

Gradual overuse of oral or rectal ergotamine may lead to dependency and the development of ergotamine headache. The patient develops a rebound or withdrawal ergotamine headache that is successfully treated with another dose of the drug. The total daily dose may slowly increase over years transforming a migraine headache into a chronic daily headache (Mathew, 1993). Other side effects include nausea, vomiting, abdominal pain, diarrhea, muscle cramps, paresthesias of the extremities, vasoconstriction and loss of pulses, and angina.

Dihydroergotamine (DHE-45®) is effective in aborting migraine, and is more effective than meperidine plus hydroxyzine and utorphanol (Raskin, 1986) (Silberstein, 1990) (Welch). Up to 90 % of migraines treated with intravenous DHE 45® abated - it is also useful in treating drug-induced headache (Sands) (Silberstein 1990). Patients can be taught to give themselves subcutaneous or intramuscular injections. DHE-45® comes in ampules (1mg in 1 ml) - the dose may be titrated between 0.5-1.0 mg twice daily, as needed. The goal is to use the smallest effective dose.

Initially metoclopramide or another antiemetic should be taken prior to DHE-45® to help control drug-induced nausea and vomiting. Many patients later find the metoclopramide is no longer necessary. The side effects of DHE-45® are similar to those of ergotamine but less severe. An intranasal formulation, Migranal®, is also available.

The ergots are contraindicated in patients with severe hypertension, peripheral vascular disease, ischemic heart disease and thrombophlebitis. They should be used cautiously in patients with peptic ulcer disease, bradycardia, renal and hepatic abnormalities. The ergots can not be used with “triptan” drugs ( sumatriptan (Imitrex®), zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®)) within 24 hours.

## **Sumatriptan**

Sumatriptan (Imitrex®) is the first medication engineered to work at the 5-HT receptor to treat migraine. It is an effective treatment and has been used extensively since it became available in the United States in 1993. Sumatriptan is currently available for patients orally, intranasally, and with an autoinjector for subcutaneous injection. The autoinjector is well accepted because the needle is not seen. Sumatriptan suppositories are available in some countries outside the USA. Physicians may administer the drug without the use of an autoinjector. Subcutaneous sumatriptan reaches peak plasma level within 15 minutes. Extensive clinical trials have shown marked relief of head pain, nausea, vomiting, phonophobia, and photophobia within 1-2 hours after treatment with 6 mg in approximately 80% of patients. A second 6 mg injection did not prove to be more effective. The short half-life of sumatriptan possibly led to headache recurrence in 38-46 % of patients, within 24 hours (Welch). This formulation is most effective for headache occurring early in the morning (upon awakening), those which escalate to maximum severity rapidly, and those attacks with vomiting. Oral sumatriptan (25,50, and 100 mg) produces relief less rapidly, within 2 to 4 hours, with recurrent headache in up to 44 percent of subjects within 24-48 hours. Sumatriptan produced better relief from nausea and vomiting than ergotamine and had a similar effect to aspirin with metoclopramide. Intranasal sumatriptan is available in 5mg and 20mg single use devices (20mg BID prn is the usual adult dose). It is another option for use during attacks with vomiting. The side effects of subcutaneous, nasal, and oral sumatriptan are similar. Most common is an injection site reaction after subcutaneous administration. Also, flushing, heat sensation, chest pressure, heaviness, tingling and neck pain. Occasional patients report chest pressure with pain going into the left arm suggestive of myocardial ischemia. After 3 million documented headache attacks treated with sumatriptan, 4 patients had documented myocardial ischemia (Welch). More extensive data suggests the occurrence of serious cardiac events is rare. Usually side effects are mild to moderate in severity, short-lived, and resolve on their own. They do not usually change with continued use of the drug; the patients eventually get used to the reactions. Some authorities advocate giving the initial dose of “triptans” under medical supervision. It is contraindicated to use “triptans” in patients with previous myocardial infarction, ischemic heart disease, Prinzmetal's angina, or uncontrolled hypertension. They should only be used 24 hours before or after an ergot preparation is ingested. They should be avoided when patients are taking methysergide because of the vasoconstrictor properties of both medications.

Other “triptan” drugs available include zolmitriptan (Zomig®), naratriptan (Amerge®), and rizatriptan (Maxalt®). In the USA, these agents are presently available only as oral

treatments. Other triptans (eg, eletriptan, almotriptan, frovatriptan), and other formulations (nasal sprays, injections) will likely become available in the future. Failure to respond to one triptan does not preclude a successful response to another (Ward 2000). These agents give superior results if used as early in the migraine attack as possible.

## **Narcotics**

### **Butorphanol, Codeine, Oxycodone, Hydrocodone, Meperidine, Others.**

Codeine has been shown to be superior to placebo in aborting a migraine attack (Raskin 1988). Butalbital, aspirin or acetaminophen, and caffeine (BAC) combinations (see above) may become more effective in selected patients when codeine is added (Kunkel). BAC is potentially addictive: the addition of codeine increases the risk and severely limits its utility. Oxycodone (Percodan®) and hydrocodone (Vicodin®) have similar effects and concerns. Parenteral meperidine (Demerol®) is often used for the emergent treatment of migraine. It should be limited to those patients with infrequent attacks that cannot be treated effectively with another agent. This includes patients with peripheral vascular or coronary artery disease and pregnant women (Welch).

It is important to note that the efficacy of oral meperidine is approximately 25 % of the IM preparation. Oral meperidine should be used in a very limited way for selected patients with severe migraine and as a rescue medication when other measures fail. Medication use should be closely monitored.

Transnasal butorphanol (Stadol NS®) has been used in the treatment of migraine. While US regulatory agencies formerly did not view it as a narcotic, it does contain the morphine molecule, and its major side effect is sedation. As a mixed agonist-antagonist, it may have less addiction potential. Nonetheless, overuse may occur, and it seems capable of causing rebound (Ward, unpublished observations). The initial dose of 1 mg = 1 puff in one nostril is approximately equipotent to 5 mg of morphine. Onset of action is rapid (minutes). **Tip: Transnasal butorphanol is potent and very rapid in onset of action. It is an alternative to the patient reporting to the emergency department for parenteral narcotics. The patient is advised to take one puff, then go to bed. If this is too strong for the patient, yet relieves head pain, physicians may direct the pharmacist to dilute it in half with an equal volume of normal saline. Again, medication use should be closely monitored.**

**Tip - pregnant migraine patients: There are very few medications that can be safely used, including acetaminophen, and meperidine. Combination analgesics are to be avoided. Oral meperidine can be titrated to produce the appropriate effect. Fortunately many migraineurs experience fewer headaches during pregnancy.**

## **TENSION-TYPE HEADACHE**

Previously known as muscle contraction headache and tension headache, the IHS classified it as tension-type headache: episodic (IHS 2.1) and chronic (IHS 2.2). The episodic type is the headache that almost everyone experiences and usually responds to simple analgesics. The chronic type (more than 15 days per month) may be difficult to treat. We will discuss the symptomatology and treatment.

Patients often complain of a dull ache across their forehead or in the back of their neck or both. The pain or pressure may be at the vertex, as well. It may feel as if a tight band is compressing the head. The pain location may vary and may even be unilateral at times. The neck muscles are usually tight. Patients do not often complain of photophobia, nausea or vomiting. Routine activity is generally not impaired, and there is less disability associated with headache episodes than there is with migraine. In primary tension-type headache the neurologic examination is normal, except for possible tightness/spasm in pericranial and cervical muscles. When the headache is chronic, depression and anxiety may be present. **Tip-tension-type headache in patients who also have migraine may respond differently to treatment than in those patients who do not also have migraine. “Fibromyalgia” is often seen in migraine patients, and sometimes in those also having tension-type headache. This condition may be treated with physical measures, exercise, trigger point injections, muscle relaxants, and amitriptyline. Sleep disturbances are often prominent.**

Tension-type headache often may coexist or blend with episodic migraine headache, along a clinical spectrum. Chronic tension-type headache may also be exacerbated by drug-induced or rebound headache caused by increasing symptomatic medication use over time. It is important to find out exactly how much medication the patient uses. **Tip-ask about over-the-counter, and herbal, remedies, as well as prescription medications.**

### **Treatment of Tension-Type Headache**

Episodic tension-type headache may respond to the medications discussed for the symptomatic relief of migraine. Acetaminophen, aspirin, NSAIDs, and the isometheptene combination are the mainstays of episodic treatment. Chronic tension-type headache is difficult to treat. It is important that symptomatic medications are not overused leading to rebound headache. If so the patient must be withdrawn from the offending medications. This often causes the patient to have a brief exacerbation of headache (“withdrawal headache”). DHE-45 may be used to treat this withdrawal headache (Raskin, 1986) (Sands) (Silberstein). It takes approximately 8 to 12 weeks for the abused analgesics to “wash out” of the patient. (Rapoport): only then may prophylactic medication, if necessary, become fully effective.

Caffeine, present in medications, beverages and foods, often causes rebound headache. If the patient is taking over 500 mg daily, it is useful to slowly taper the caffeine ingestion. When the patient reports that caffeine ingestion provides headache relief within 1 hour, it virtually confirms the diagnosis of caffeine withdrawal headache.

Amitriptyline, nortriptyline or doxepin can be used for prophylactic therapy (see above). **Tip- Elderly patients often cannot tolerate the smallest dose tablets or capsules because of their increased sensitivity to medication.** Doxepin (Sinequan®) comes in a concentrate that may be added to juice or other drink. This gives precise control over the dose and permits these patients to be successfully treated. Nortriptyline is also available in liquid form.

Non-pharmacological treatments may also be useful. Biofeedback seems helpful, especially in combination with relaxation training and psychotherapy (Kunkel). Physical therapy and, if appropriate, an exercise program may be useful.

## **CLUSTER HEADACHE**

Cluster headache occurs predominantly in men and occurs daily in approximately 50% of patients, twice a day in 33 %, and more often in the remainder. Attacks range in frequency from 8 (or more) a day to one every other day. The attack may last from 15 minutes to 3 hours, although the mean duration is 45 minutes. The attack often awakens the patient from sleep, occurring with the first stage of REM sleep (Kudrow). It is described as an extremely severe, boring pain that begins in or above one eye radiating to the frontal or temporal regions. The pain may also radiate into the teeth or the neck. It is associated with autonomic phenomena including ipsilateral rhinorrhea and lacrimation, nasal stuffiness, and conjunctival injection. A partial Horner's syndrome may occur with the attack (miosis and ptosis). Kudrow states that "inability to lie still during an attack is pathognomonic of cluster headache pain" (Kudrow).

The headaches of cluster patients occur typically in episodes or bouts lasting 2 to 4 months. During this time the attacks occur spontaneously or may be provoked by alcohol, histamine, or nitroglycerin). The time between bouts is a "remission" that may last from 1 month to 20 years, in episodic cluster headache. Occasionally, remissions are permanent. Some patients have chronic cluster headache, without remission (fewer than 14 days per year without attacks).

### **The Differential Diagnosis Of Cluster Headache Includes:**

- Migraine
- Trigeminal neuralgia
- Temporal arteritis
- Pheochromocytoma
- Raeder's syndrome/cervical carotid arterial dissection
- Chronic and episodic paroxysmal hemicrania

### **Treatment Of Cluster Headache**

During cluster bouts, treatment starts by explaining to the patient how to avoid triggers, most importantly alcohol and nitroglycerin. Prolonged exposure to solvents, gasoline and oil-based paints may also trigger an attack. Altitude-induced relative hypoxemia may occur above 5000 feet (such as airplane travel) and can lead to a cluster headache. Ergotamine 2 mg taken 1 hour prior to take-off may prevent a cluster headache. If an attack occurs in flight, 100% oxygen inhalation at 7 l/min or more may produce complete relief (Kudrow).

### **Symptomatic Treatment Of Cluster Headache**

As in migraine, symptomatic treatment is the second line of defense against attacks, if prophylactic therapy fails (Ward 1997, 1998). Oxygen inhalation is effective and safe. The patient should be given 100 percent oxygen at 7 or more liters/minute via a facemask (non-rebreather). It has been effective in 90 % of patients within 15 minutes (Kudrow). Ergotamine in the sublingual form may be tried. DHE-45® (1 mg) may be given IV to provide relief (preceded by an antiemetic such as metoclopramide 10 mg). Sumatriptan (Imitrex®) subcutaneously is

highly effective in treating cluster attacks. Caution is advised, as many cluster patients are middle-aged males with multiple risk factors for coronary artery disease, a contraindication to the use of sumatriptan. Transnasal butorphanol (Stadol NS®) is another option.

### **Prophylactic Treatment Of Cluster Headache**

Many of the prophylactic treatments for cluster are similar to those for migraine. Patients with episodic cluster are in tremendous pain. Vigorous attempts to prevent the attacks are warranted. Treatment with prednisone will usually stop the bout or decrease its severity within 24 hours. The initially dose is 60- 80 mg daily instituted immediately. Then after 2 to 3 days at this level the dose is slowly tapered over 10-14 days. This immediate control permits the initiation of another medication that will be safer over the long-term than prednisone.

**Tip-Prednisone causes immediate bone loss, even when given for a short time.** This concern is especially important for women. Bone loss may be prevented by taking Vitamin D 50,000 units weekly and calcium, one gram per day. One inexpensive and easy way to achieve this intake of calcium is to take 4 Tums daily. Other measures to protect the stomach (such as H2 blockers, antacids, or proton pump inhibitors) may be advisable.

Methysergide (Sansert®) is used as described under the treatment of migraine (see above). It tends to be most effective early in the course of the disease. It has been reported to have an efficacy of 65 % (Kudrow).

Verapamil (Calan®, others) has been effective in several studies. Patients may require up to 480 mg per day (egg, as Calan SR 240 BID) or, cautiously, even higher doses. Adding oral ergotamine 2 mg 1 hour prior to bedtime increases the effect of the verapamil (Kudrow). Lithium is effective in episodic cluster and chronic cluster. The dose has to be gradually built up to avoid untoward reactions. This dose escalation takes place while controlling the cluster with the prednisone treatment. Lithium can be prescribed at 300 mg daily for 3 days then increased every 3 days until it is taken three times daily. It is necessary to follow the lithium serum level to monitor for toxicity. The concomitant use of diuretics, NSAIDS, and severe sodium -restricted diets are contraindicated, since this may cause toxicity. The symptoms of lithium toxicity include tremor, polyuria and mild nausea initially. Diarrhea, vomiting, drowsiness, muscular weakness, and incoordination occur with greater lithium intoxication. Stopping the lithium and monitoring the patient is necessary in this situation.

Valproic acid (Depakote®) appears to be another treatment option in the treatment of cluster headache (Ward 2000). Recent studies suggest that for refractory cases, gabapentin (Neurontin®), and topiramate (Topamax®) might be useful. Combinations of verapamil and lithium, or verapamil and valproic acid, for example, may be effective when monotherapy fails.

When all medical treatment fails surgical treatment may be appropriate. Currently the procedure of choice is percutaneous radiofrequency lesions directed against the trigeminal ganglion. This tends to produce the highest success rate and the least complications.

## Case Report (Part 2)

Examination of the patient's CSF showed 3 mononuclear cells with protein 22, glucose 77, and later, negative cultures. His blood WBC was 15,000. Later in the evening, after the results of the brain CT became available, he was diagnosed as having migraine or cluster headache. The next morning his temperature reached 102.5 (rectal) and he complained of chills: subsequently his temperature rose to 104.1 (oral) with normal vital signs. His left eyelid and conjunctiva became swollen, with tenderness to percussion over the left frontal sinus.

He was admitted and treated with nafcillin 2 grams and cefuroxime 1.5 grams, intravenously. Acetaminophen and ibuprofen were prescribed for his pain. Repeat CT scan of the brain this time with additional views of the paranasal sinuses showed fluid collections in both maxillary and ethmoid sinuses, as well as the left frontal and sphenoid sinuses.

He underwent bilateral intranasal antrostomies, a left intranasal ethmoidectomy and a left sphenoidotomy. Subsequently his WBC normalized and he did well.

## Question For Discussion

Which symptoms and signs would lead to the diagnosis of sinusitis?  
Does the quantity of analgesic taken have any significance?

The case is presented to sensitize you to the fact that not all headache is migraine or cluster. Also, many routine brain CT protocols do not include adequate views of the paranasal sinuses. Therefore, if clinically appropriate, these additional views should be obtained.

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## Self-Assessment

1. A 35-year-old woman, with a past history of occasional migraine, has sudden onset of severe generalized headache and nausea, causing her to stop her activities and lie down. The headache persists and her family takes her to the emergency room. The primary diagnostic consideration for the examining physician is:
  - A. migraine headache
  - B. subarachnoid hemorrhage
  - C. posttraumatic headache
  - D. cluster headache
  - E. none of the above.
2. The above individual undergoes a noncontrast CT scan of the head which is read by the radiologist as negative. The next step for the examining physician is:
  - A. administer an analgesic and observe for headache resolution.
  - B. lumbar puncture.
  - C. refer to a neurologist for his next available appointment.
  - D. schedule for an outpatient MRI and MRA of the brain.
  - E. administer 6 mg of sumatriptan subcutaneously.
3. The following organic conditions can mimic recurrent primary headache disorders:
  - A. pituitary adenoma
  - B. cerebral arteriovenous malformation
  - C. isolated CNS vasculitis.
  - D. pheochromocytoma
  - E. all of the above.
4. A 68-year-old female presents with a three week history of severe unilateral headache and scalp tenderness. She has had one episode, the day prior, of transient ipsilateral monocular visual loss, which has completely resolved. A stat sedimentation rate is 65 mm/hr. The following steps should be instituted:
  - A. schedule cerebral angiography.
  - B. start prednisone, 60 -80 mg/daily immediately
  - C. obtain a stat CT scan of the brain.
  - D. schedule for a temporal artery biopsy
  - E. A, B, C
  - F. B, C
5. Pick the one true statement among the following:

- A. oral or rectally administered ergotamines rarely lead to dependency, despite frequent use.
  - B. the ergotamines or sumatriptan cannot be used concomitantly within 24 hours of each other.
  - C. ergotamine or sumatriptan can be used safely during pregnancy.
  - D. sumatriptan can be used safely six months after myocardial infarction.
  - E. dihydroergotamine has only marginal benefit in the treatment of migraine headache.
6. The mainstay drug(s) for treatment for episodic tension-type headache are:
- A. ergotamines, sumatriptan.
  - B. beta-adrenergic antagonist drugs.
  - C. calcium channel blockers
  - D. steroids.
  - E. aspirin, acetaminophen, non-steroidal anti-inflammatory drugs.
7. Overuse of medications which symptomatically treat tension-type headache may lead to:
- A. transformed migraine.
  - B. cluster headache
  - C. chronic daily headache.
  - D. rebound headache
  - E. classic migraine.
8. The following medication should not be used for migraine prophylaxis:
- A. valproic acid (Depakote®)
  - B. verapamil
  - C. nadolol
  - D. nortriptyline
  - E. butorphanol.
9. Label the following statements True (T) or False (F):
- A. valproate serum levels correlate with clinical effectiveness in migraine prophylaxis.
  - B. metoclopramide (Reglan®) may enhance analgesic absorption during a migraine attack.
  - C. oxygen inhalation is a safe and effective treatment for cluster headache attacks.
  - D. nonsteroidal anti-inflammatory drugs are an effective first line abortive therapy for mild to moderate migraine headaches.
  - E. fronto-maxillary headache with associated local tenderness is almost always due to a benign headache disorder.
10. New-onset headache, followed shortly by confusion and/or seizures, may be secondary to:
- A. encephalitis
  - B. brain abscess
  - C. subdural empyema
  - D. aseptic meningitis
  - E. a,b,c.

## Answers

1. B
2. B
3. E
4. F
5. B
6. E
7. C
8. E
9. A is False  
B is True  
C is True  
D is True  
E is False
10. E