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# MIGRAINE HEADACHE

- SUMMARY
- CLINICAL PRESENTATION
  - INTRODUCTION
    - ETIOLOGY
    - CLASSIFICATION [+]
    - EPIDEMIOLOGY
    - PATHOPHYSIOLOGY
    - PREDISPOSING FACTORS [+]
    - DIAGNOSTIC CRITERIA
  - ASSOCIATED CONDITIONS [+]
  - VITAL SIGNS [+]
  - PRESENTATION BY BODY SYSTEM [+]
  - COMPLICATIONS [+]
- LABORATORY DATA
- RADIOLOGIC DATA [+]
- DIFFERENTIAL DIAGNOSIS [+]
- TREATMENT
  - TREATMENT SUMMARY
  - NON-PHARMACOLOGIC TREATMENT [+]
  - PHARMACOLOGIC TREATMENT [+]
- DISPOSITION [+]
- REFERENCES
- AUTHOR INFORMATION

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## Summary

### 0.1 CRITICAL FOCUS

#### A. GENERAL:

1. Although uncomplicated migraine headache is benign and carries little morbidity except for pain and vomiting, it is important to differentiate this headache from more devastating headaches, eg, those associated with subarachnoid or cerebellar hemorrhage, meningitis, and intracranial masses.
2. Goals of treatment are amelioration of symptoms of an acute attack and prevention of further attacks. Most patients presenting to the ED with acute migraine usually require parenteral medication for control of symptoms. The individual patient's history of response to previous medication may be used as a guide for therapy.
3. Management of migraines in children differs from that of adult migraine, as not all therapies have been tested in the pediatric population; therapy should be instituted on an individualized basis, only after the diagnosis is certain.

#### B. ACUTE MIGRAINE - ADULTS:

##### 1. STATUS MIGRAINOSUS OR SEVERE MIGRAINE:

- a. PROCHLORPERAZINE: ADULTS: 10 mg IV over 2 to 3 min x 1. PLUS
- b. DIHYDROERGOTAMINE: ADULTS: 0.5 to 1 mg IV over 5 min; repeat 0.5 to 1 mg IV Q1H if headache still present; maximum dose, 3 mg/d. (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with triptans.)

##### 2. MODERATE TO SEVERE MIGRAINE:

- a. KETOROLAC: ADULTS: 30 to 60 mg IM.
- b. MEPERIDINE: ADULTS: 50 to 150 mg IM Q4H PRN.
- c. DIHYDROERGOTAMINE: ADULTS: IM: 1 mg; may repeat twice Q4H to total of 3 mg/attack. SC: 1 mg; may repeat Q1H to total of 3 mg/attack. IN: 0.5 mg; repeat after 15 min (maximum, 3 mg/24 h). (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with triptans.)
- d. SUMATRIPTAN: ADULTS: 6 mg SC Q1H or longer (maximum, 12 mg/24 h); 5 or 20 mg IN Q2H or longer (maximum, 40 mg/24 h); 25 or 50 mg PO Q2H or longer (maximum, 200 mg/24 h). (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with ergot alkaloids.)
- e. PROCHLORPERAZINE: ADULTS: 10 mg IV over 2 to 3 min x 1; 5 to 10 mg IM Q4H, alone or as adjunct therapy.

C. ACUTE MIGRAINE - CHILDREN:

1. ACETAMINOPHEN: CHILDREN: 15 mg/kg PO; repeat once after 2 h, then Q4-6H: maximum total dose, 100 mg/kg/d.
2. IBUPROFEN: CHILDREN: 10 mg/kg PO; repeat once after 2 h, then Q4-6H: maximum total dose, 40 mg/kg/d.
3. PROCHLORPERAZINE: May give alone or as adjunct therapy.
  - a. IM: CHILDREN LESS THAN 12 YEARS: 0.06 mg/lb IM.
  - b. PR: CHILDREN OVER 2 YEARS: 20 to 29 pounds: 2.5 mg PR QD or BID (maximum, 7.5 mg/day); 30 to 39 pounds: 2.5 mg PR BID or TID (maximum, 10 mg/day); 40 to 85 pounds: 2.5 mg PR TID or 5 mg PR BID (maximum, 15 mg/day).

D. IV FLUIDS: 1 to 2 L NS in dehydrated adult patients with excessive vomiting.

## 0.2 CLINICAL PRESENTATION

A. DEFINITION: Recurrent headaches with initial intracranial vasoconstriction followed by extracranial vasodilation.

B. TYPES: Migraine without aura, migraine with aura, migraine equivalents (basilar, ophthalmoplegic, hemiplegic migraine).

C. EPIDEMIOLOGY: Onset usually in childhood, adolescence, or early adulthood; more common in females; family history often present.

D. PATHOPHYSIOLOGY: Complex disorder involving many levels of brain and neurovascular physiology; generation of headache probably is related to inflammatory result of trigeminal activation.

E. PREDISPOSING FACTORS: Stress, premenstrual tension and fluid retention, drugs (eg, vasodilators, oral contraceptives, nitroglycerin), seasonal variation.

F. CLINICAL FINDINGS: Typical migrainous attack characterized by unilateral, throbbing moderate to severe headache in temporal, orbital, or frontal distribution that lasts several hours to 2 days and is aggravated by routine physical activity. Migraine with aura preceded by transient neurologic symptoms. Migraine equivalents associated with focal neurologic disturbances without headache or vomiting.

1. VITAL SIGNS: Fever (rare); tachycardia, hyperventilation possible.
2. SKIN: Pallor common.
3. HEENT: Hemianopic field defects, scotomas, scintillations that enlarge and spread peripherally (aura) are early signs; blurred vision, photophobia, scalp tenderness may be present; unilateral eye pain with limitation of extraocular movement (ophthalmoplegic migraine).
4. GI: Nausea, vomiting are common; abdominal pain and distention may be more common in children.
5. CNS: Headache (commonly unilateral, throbbing), vertigo, syncope, transient focal neurologic signs; ataxia, dysarthria (basilar artery migraine); motor deficits (hemiplegic migraine).
6. PSYCHIATRIC: Mood alterations, emotional changes.
7. MISCELLANEOUS: Weight gain (fluid retention), fatigue.

## 0.3 DIAGNOSTICS

A. LABORATORY:

1. Typically not helpful in the diagnosis and treatment of migraine headaches.

B. RADIOLOGY:

1. CT or MRI: Helpful in differentiating migraine symptoms from those of other entities, eg, aneurysm, mass lesion, or subdural hematoma. Consider in patients with nonacute headache and unexplained abnormal neurologic findings and in patients with atypical headaches or headaches that do not fulfill strict definition of migraine or other primary headache. Not usually warranted in patients with migraine and normal neurologic examination.

## 0.4 DIFFERENTIAL DIAGNOSIS

A. Includes other types of primary headaches (tension-type and cluster) and secondary organic headache disorders, including SAH, meningitis, sinusitis, glaucoma, cerebrovascular disease.

## 1.0 CLINICAL PRESENTATION

### 1.1 INTRODUCTION

#### 1.1.1 ETIOLOGY

##### A. DEFINITION:

1. GENERAL: Recurrent headaches usually characterized by unilateral pulsating pain of moderate to severe intensity lasting 4 to 72 hours and accompanied by nausea/vomiting and photophobia/phonophobia (Solomon, 1997; Skaer, 1996).
2. STATUS MIGRAINOSUS: Unremitting headache for 72 hours, despite self-administered treatment at home, or headache that causes patients to become dysfunctional from both psychological and physiologic standpoint (Dalessio, 1990). Associated with intractable nausea and vomiting (Silberstein, 1992).
3. COMPLICATED MIGRAINE: Syndrome in which neurologic or visual symptoms appear before the headache or aura phase or during the acute pain and last more than 24 hours after the headache subsides. Some patients have a stroke or permanent neurologic deficit.

#### 1.1.2 CLASSIFICATION

##### A. HEADACHE, MIGRAINE, WITHOUT AURA

1. GENERAL: Formerly known as common migraine. Defined in terms of attack duration and quality, and associated findings (Silberstein, 1992).
2. INCIDENCE: Accounts for 80% to 85% of migraine headaches (Rothner, 1986; Diamond, 1997).
3. GENDER: More common in females than males with a M:F ratio of about 1:2.2. Headaches often begin at menarche, and female preponderance is apparent only after menarche (Russell, 1996; Granella, 1993; Stang, 1992; Rasmussen, 1992).
4. CHARACTERISTICS:
  - a. Periodic; often precipitated by menstruation (Granella, 1993; Rasmussen, 1992) or emotional, environmental, occupational, dietary, or pharmacologic factors (Rubin, 1985). Some evidence suggests a genetic factor (Gervil, 1999).
  - b. Criteria for clinical diagnosis include headaches characterized by any 2 of the following: unilateral site, throbbing quality, nausea, photophobia, or phonophobia (Solomon, 1991a).
  - c. Vague and poorly defined premonitory symptoms, eg, yawning, fatigue, euphoria, depression, irritability, fluid retention, food-craving, or thirst, precede headache by hours to days in 50% to 80% of migraineurs, but neuro-ophthalmic symptoms are absent (Capobianco, 1996; Skaer, 1996; Diamond, 1997).
  - d. Headache often begins in early morning hours, waking patient from sleep (Skaer, 1996; Diamond, 1997).
  - e. Typically, pain is hemicranial and throbbing, but may become bilateral in 40% of patients; holocephalic pain is common in children (Capobianco, 1996; Diamond, 1997).
  - f. Associated with more severe and longer lasting headache than migraine with aura (Rasmussen, 1992).
  - g. Coexistent migraine with and without aura occurs frequently (Launer, 1999; Ferrari, 1998).
  - h. Usually improves during pregnancy (Granella, 1993).

##### B. HEADACHE, MIGRAINE, WITH AURA

1. GENERAL: Formerly known as classic migraine.
2. INCIDENCE: Accounts for 15% to 20% of all migraines.
3. DEFINITION:
  - a. Recurrent, periodic headache that is preceded or accompanied by transient visual (most common; over 50%), motor, sensory, or other focal cerebral symptoms (aura).
  - b. Migraines with and without aura may be due to the same disease process, and up to one third of patients experience both types of attacks over a lifetime (Ferrari, 1998; Ranson, 1991; Olsen, 1990). However, some studies have found epidemiologic differences in the two conditions, suggesting they are separate entities (Russell, 1996).
4. AGE: Average age of onset of migraine with aura is notably younger (by 3 to 5 years) than usual age at initial occurrence of migraine without aura (Stewart, 1991).
5. GENDER: Female preponderance less marked than in migraine without aura. One study found it equally common in men and women with migraine (Stang, 1992); another, however, found a M:F ratio of 1:1.5 (Russell, 1996).
6. CHARACTERISTICS (Diamond, 1997; Jensen, 1986; Bana, 1986; Rasmussen, 1992):
  - a. Characterized initially by disturbances of neurologic function, usually scotomata, or other sensory and/or motor prodromes that are sharply defined. Types of aura include homonymous visual disturbances, unilateral paresthesia or numbness, unilateral weakness, and aphasia or other speech difficulty (Silberstein, 1992).
  - b. Aura symptoms include visual phenomena in 99% of patients; these may be accompanied by sensory (31%), aphasic (18%), and/or motor (6%) manifestations (Ferrari, 1998).

- c. An acute confusional state may be the presenting sign in children (Ferrera, 1996; Capobianco, 1996).
- d. Aura symptoms are followed in a few minutes to several hours by hemicranial headache, nausea, and vomiting, which usually only last hours but may last a day or two.
- e. Some patients report an interval between the visual aura and headache onset in which they feel detached from the environment or other people and have fears, disturbances of thought or speech, or somatic symptoms (Blau, 1992).
- f. Coexistent migraine with and without aura occurs frequently (Launer, 1999; Ferrari, 1998).

#### C. HEADACHE, MIGRAINE, BASILAR

##### 1. DESCRIPTION:

- a. Type of complicated migraine characterized by paroxysmal throbbing occipital headache with aura symptoms originating from the brain stem or occipital lobes (Kuhn, 1997).
- b. Has been thought to represent vascular disturbances within the vertebrobasilar circulation (Diamond, 1997; Harker, 1987; Ganji, 1986; McDonald, 1990), although more recent evidence suggests such disturbances are secondary effects rather than primary causes (Ferrari, 1998; Noack, 1996; Capobianco, 1996).

2. AGE/GENDER: Occurs primarily in adolescents and young adults; females are affected in 75% of cases (Diamond, 1997).

##### 3. CHARACTERISTICS:

- a. Characterized by throbbing, bilateral, posterior head pain preceded or accompanied by tinnitus, hearing loss, vertigo, ataxia, dysarthria, and, occasionally, bilateral motor or sensory symptoms.
- b. In some cases, drop attacks, cranial nerve dysfunction, loss of consciousness, and transient global amnesia may occur.
- c. Neurologic defects may persist throughout and even after the headache, but permanent defects are rare (Kuhn, 1997).

4. COURSE: Usually benign; severe transient neurologic dysfunction or cerebral infarction may occur (Diamond, 1997; Harker, 1987; McDonald, 1990).

#### D. HEADACHE, MIGRAINE, HEMIPLEGIC

1. DESCRIPTION: One type of complicated migraine (Diamond, 1997; Kupersmith, 1987). The neurologic deficits are thought to be due to cerebral ischemia caused by intracranial vasospasm; decreased cerebral blood flow has been found in the regions corresponding to the neurologic manifestations (Tobita, 1987).

##### 2. CHARACTERISTICS:

- a. Rare migraine variant consisting of unilateral sensory and/or motor deficits that begin before or during the migraine attack and often do not resolve for days to weeks. A family history of hemiplegic migraine is common, but sporadic cases also occur (Diamond, 1997).
- b. Point mutations in genes coding for calcium channels have been identified in some kindreds with familial hemiplegic migraines, leading to the hypothesis that such migraines may stem from calcium channel dysfunction (Moskowitz, 1997).

#### E. HEADACHE, MIGRAINE, OPHTHALMOPLEGIC

1. DESCRIPTION: One type of complicated migraine (Diamond, 1997; Kupersmith, 1987; Hansen, 1990; van Engelen, 1991).

- a. The deficit is presumed to be caused by pressure on the oculomotor nerve by a swollen internal carotid artery within the cavernous sinus or by edema of the distal basilar artery.
- b. It may also be caused by ischemia produced by occlusion of the small arteries that supply the oculomotor nerve as they originate from the carotid artery (Rothner, 1986).

2. AGE: Children are affected more frequently than are adults.

##### 3. CHARACTERISTICS (Diamond, 1997; Rothner, 1986):

- a. Paresis of the extraocular muscles occurs, and diplopia developing during the course of a headache is the most common symptom. The third cranial nerve is involved in 80% of cases, but the sixth (12%) and fourth nerves also may be affected.
- b. Associated symptoms include unilateral orbital pain, ptosis, strabismus, and, occasionally, mydriasis.
- c. The ocular paresis may persist for days to weeks after cessation of the headache; rarely, it may become permanent (Diamond, 1997; Rothner, 1986).

#### F. HEADACHE, MIGRAINE, ABDOMINAL

##### 1. CHILDREN:

- a. Migraine-equivalent seen in children, most commonly in those who have a family history of migraine (Symon, 1986).

- b. Characterized by episodes of severe midline abdominal pain that typically begin in the morning and last six hours or longer; pallor, anorexia, nausea, and vomiting are typical associated symptoms (Symon, 1986).
  - c. Demographic and social characteristics, as well as trigger factors and associated symptoms, are similar in children with migraine and children with abdominal migraine (Abu-Arafeh, 1995a).
  - d. In one study, abdominal migraine accounted for nearly half of children with cyclic vomiting; many of these children had nocturnal onset and prodromal headache, photophobia, and vertigo, and about 70% had a family history of migraine (Pfau, 1996).
2. ADULTS: May be cause of some cases of functional abdominal pain in adults (Axon, 1991).

### 1.1.3 EPIDEMIOLOGY

#### A. INCIDENCE:

- 1. Occurs in 5% to 20% of the general population (Hu, 1999; Mitchell, 1998; CDC, 1991; Stewart, 1992; Winnem, 1992; Pryse-Phillips, 1992; Henry, 1992).
- 2. In US, estimated 23 million persons over 12 years suffer moderate to severe migraines (Noack, 1996; Capobianco, 1996). Another study found that migraineurs suffer a median of 12 attacks/year, with 25% having at least 2 attacks/month (Launer, 1999).
- 3. Incidence is increasing, particularly among males under age 45 (Stang, 1992) and in women of reproductive age (Rozen, 1999).

#### B. ONSET:

- 1. Usually is in childhood, adolescence, or early adult life; 50% of patients have migraine attacks by age 5 years (Rothner, 1986; Mortimer, 1992). Frequency of attacks tends to decrease with advancing age, generally declining after age 40 (Diamond, 1997; Honkasalo, 1993; Stewart, 1994); onset after age 50 years rare (Ferrari, 1998).
- 2. Average age of onset of migraine with aura is notably younger (by 3 to 5 yr) than usual age at initial occurrence of migraine without aura (Stewart, 1991). One study found a mean age of onset for migraine without aura of 16 yr in males and almost 19 yr in females; however, for migraine with aura, distribution appeared bimodal for both sexes, with an early group experiencing onset in the teenage years and a second group with onset during the 4th decade of life (Russell, 1996).

#### C. AGE/GENDER:

- 1. ADULTS: Prevalence varies considerably by both age and gender.
  - a. Two to four times more common in women than in men (10% to 20% vs 2% to 6%) (Hu, 1999; Stang, 1992; Honkasalo, 1993; Lipton, 1993; O'Brien, 1994). New cases of migraine are common in women in their late 20s but uncommon in men in this age group; initial onset of migraines begins at later age among females than among males (Stewart, 1991; Stang, 1992).
  - b. Highest prevalence in both sexes between ages 30 to 49 years (Hu, 1999; Ferrari, 1998; Honkasalo, 1993; Stewart, 1992; Stang, 1992, 1993; Henry, 1992). A US study using population-based data from several surveys estimated prevalence in men to be highest between ages 30 to 39 yr (8%) and lowest in men aged 20 to 29 yr (6%). In women, prevalence is highest between ages 30 and 49 (25%) and lowest at ages 20 to 29 yr (14%) (Rozen, 1999; Hu, 1999).
  - c. An Australian study of over 3500 migraineurs found that a past history of typical migraine was reported by 23% of people aged less than 60 and declined steadily with age to 9% of people over age 80 (Mitchell, 1998).
- 2. CHILDREN:
  - a. Estimated that 3% to 7% of the pediatric population suffers from migraine (Hernandez-Latorre, 2000). Accounts for about 16% of pediatric ED visits with chief complaint of headache (Burton, 1997).
  - b. In one study, about 25% of children with migraine had their onset before age 6 years and about 60% had onset between 6 and 10 years. Earlier the disease begins, the more likely is an unfavorable clinical evolution (Hernandez-Latorre, 2000).
  - c. Prevalence in boys is constant through ages 11 to 14 but reaches a peak in girls at age 12 (Diamond, 1997; Raieli, 1995; Stang, 1992; Mortimer, 1992).

D. RACE: Significantly more common in whites (Stang, 1993; Stewart, 1996).

E. SEASON: Some studies have reported an increase in number of attacks in the spring (Brewerton, 1990; Robbins, 1994), possibly related to seasonal variation in serotonin function (Brewerton, 1990).

F. ECONOMICS: US annual direct and indirect costs of migraine estimated between 10 and 18 billion dollars per year total (Tepper, 1996; Noack, 1996).

1. DIRECT COSTS: Direct costs of migraine, including health care resource utilization and prescriptions, are approximately \$1 billion/year; 60% of cost is due to physician office visits, 30% to prescription drugs, and less than 0.5% to emergency department visits. May represent only 10% of total migraine-related economic costs (Hu, 1999; Lofland, 1999; Stang, 1993).

2. INDIRECT COSTS:

a. Significant cause of short-term absenteeism from work, between 36 and 112 million migraine-related bedridden days per year (Hu, 1999; Lofland, 1999; Stang, 1993; Lipton, 1993; Pryse-Phillips, 1992; Winnem, 1992).

b. Total indirect costs (including lost work days, lost work day equivalents and reduced productivity while working with migraine) are estimated at between 1.4 and 13.3 billion dollars per year (Hu, 1999; Stang, 1993).

#### 1.1.4 PATHOPHYSIOLOGY

A. Despite recent advances, the pathophysiology of migraine remains incompletely understood.

1. Genetic factors appear to determine a threshold for a variety of internal and environmental stimuli, including hormonal fluctuation, stress/stress relief, fatigue, minor head trauma, barometric changes, and chemicals such as tyramine, nitrates, and phenylethylamine (Ferrari, 1998; Skaer, 1996; Capobianco, 1996).

2. Data suggest that migraine patients have an increased state of cortical excitability, characterized by reduced threshold and increased responses. Mitochondrial oxidation defects, calcium channel dysfunction, low intracellular magnesium, and high levels of neurotoxic amines have all been proposed as the basis for this (Ferrari, 1998; Mauskop, 1998; Okada, 1998; Noack, 1996).

3. Positron emission scanning indicates the presence of a migraine generator in the dorsal raphe nucleus of the midbrain with increased blood flow to this area during attacks (Ferrari, 1998; Tepper, 1996).

B. Animal data suggest a spreading wave of cortical depression with transient failure of brain ion homeostasis and resultant efflux of excitatory amino acids and profound changes in cerebral blood flow may be responsible for aura symptoms (Ferrari, 1998; Noack, 1996).

C. Activation of the trigeminovascular system, which can be potentiated by spreading waves of cortical depression, appears critical in migraine attack (Ferrari, 1998; Noack, 1996; Moskowitz, 1993; Lance, 1993):

1. Depolarization of the trigeminal ganglion or its perivascular nerve terminals leads to central transmission of nociceptive information and retrograde release of vasoactive neuropeptides, including neurokinin A, substance P, and calcitonin-gene-related peptide, which mediate dural vasodilatation and plasma extravasation.

2. Pain is due to sterile neurogenic inflammation of cranial blood vessels, particularly meningeal vasculature, which is innervated by the trigeminal nerve. The trigeminal nerve transmits headache pain from blood vessels of the pia mater and dura mater.

3. Trigeminal afferents innervating these vessels become sensitized, and as pain signals proceed centrally, they are modulated by several different central nuclei.

D. Serotonin (5-HT) also plays a central role in migraine pathophysiology (Ferrari, 1998; Noack, 1996; Tepper, 1996; Friberg, 1991):

1. Migraine patients appear to have low 5-HT levels between attacks with increased levels during attacks. This may be related to activation of the dorsal raphe nucleus, whose neurons produce most of the 5-HT endogenous to the CNS.

2. Seven major classes of serotonin receptors have been identified. Of these, serotonin 1 receptors appear to be inhibitory, decreasing neurogenic inflammation of parameningeal vessels, while serotonin 2 receptors are excitatory, activating the trigeminal vascular system.

3. The efficacy of 5-HT derivatives that display potent and selective agonist activity at serotonin 1 receptors confirms the importance of serotonin in migraine attacks.

E. Increased sensitivity of migraineurs to dopamine and dopamine agonists and the beneficial effects of dopamine antagonists in the acute treatment of migraine suggest increased dopaminergic activity may play a role in the pathophysiology of migraine (Del Zompo, 1998; Peroutka, 1997). One study suggests an association between dopamine receptor genes and dopaminergic migraine (Del Zompo, 1998).

F. Magnesium deficiency, with low brain extracellular magnesium, also may play a role (Mauskop, 1998; Gallai, 1993; Welch, 1993a; Sarchielli, 1992). While one study found low blood magnesium levels unlikely to be related to migraine (Smeets, 1994), another found magnesium infusion produced relief in about half of migraine attacks and that low ionized magnesium levels were a predictor of response (Mauskop, 1998).

G. Nitric oxide and calcium channel dysfunction have been implicated in the pathophysiology of migraine, but their exact roles remain unclear (Ferrari, 1998).

### 1.1.5 PREDISPOSING FACTORS

#### A. OVERVIEW

1. A number of factors, including dietary, environmental, psychologic, and pharmacologic precipitants, may trigger migraine attacks. The main trigger factors are menstruation or ovulation in women, hunger, food additives, sleep (excess or deprivation), weather changes, light, noise, smells, alcohol, and relaxation after emotional stress. Certain trigger factors may be mutually related or additive (Skaer, 1996; Van den Bergh, 1987; Blau, 1992, 1992a).
2. Multiple environmental factors, including bright lights or sunshine, glare from snow or video display terminals, and certain strong odors such as perfume or cigarette smoke are implicated in migraine attacks (Diamond, 1997).
3. Changes in atmospheric pressure and high altitude may also induce migraine headaches (Diamond, 1997). Male migraineurs with permanent residence above 4300 meters (14,200 feet) had higher hemoglobin levels and chronic mountain sickness scores when compared with men without headaches residing at high altitudes (Arregui, 1994).

#### B. DIET

##### 1. GENERAL:

- a. Food additives (eg, sodium nitrite and monosodium glutamate (MSG)), as well as some substances occurring naturally in foods (eg, tyramine, dopamine, caffeine, phenylethylamine), trigger migraine headaches in 40% to 45% of patients (Diamond, 1997; Van den Bergh, 1987).
- b. In some patients, food allergy may provoke migraine attacks (Mansfield, 1987).
- c. Some evidence indicates that a low-fat diet can reduce headache frequency, intensity, duration, and medication intake (Bic, 1999).

##### 2. TYRAMINE (Diamond, 1997):

- a. Tyramine, an amino acid with sympathomimetic activity, causes cerebral vasoconstriction and subsequent rebound vasodilation.
- b. Evidence suggests that the ability to degrade tyramine to an inactive form may be altered in migraine patients. However, one study found that tyramine does not induce attacks (Blau, 1992a).
- c. Foods containing tyramine include aged cheeses, bananas, avocados, peanuts, pickled herring, and chicken livers.

##### 3. CAFFEINE:

- a. Sympathomimetic agent found in chocolate, coffee, tea, cola, and many over-the-counter and prescription analgesic agents (Diamond, 1997).
- b. In one double-blind parallel group study, chocolate ingestion was followed by a typical migraine episode in 42% of patients compared with none of controls; median time from ingestion to attack was 22 h (Gibb, 1991). However, another study found that chocolate does not induce migraine (Blau, 1992a).

##### 4. FOOD ADDITIVES (Diamond, 1997):

- a. As little as 5 to 10 mg of sodium nitrite, commonly used as a preservative and coloring agent in cured meats, may provoke a migraine attack in susceptible persons.
- b. MSG is found in varying amounts in many food products and meat tenderizers and is also commonly used in Chinese foods.

##### 5. ASPARTAME: Ingestion of the dietary sweetener aspartame may cause a significant increase in the frequency of migraine for some persons (Koebler, 1988).

##### 6. MISCELLANEOUS:

- a. Phenylethylamine, another sympathomimetic agent, is found in chocolate, and dopamine is present in fava beans (Diamond, 1997).
- b. Foods high in copper (eg, chocolate, nuts, wheat germ, and shellfish) may trigger migraine in susceptible individuals with abnormal copper metabolism (Harrison, 1986).

#### C. ALCOHOL CONSUMPTION

1. Triggers migraine headaches in up to 50% of patients (Van den Bergh, 1987).
2. Ethanol has vasoactive properties and can induce migraine in some persons regardless of the amount ingested (Diamond, 1997).
3. Persons in whom migraine is precipitated by ethanol ingestion are likely to have a number of other trigger factors, especially foods (Van den Bergh, 1987). In some patients, ethanol may increase permeability of the gut and potentiate the triggering effects of alimentary factors (Amery, 1987).
4. Red wine is a frequently cited migraine inducer. Contains a high content of tyramine as well as alcohol (Skaer, 1996). Provoked a typical migraine attack in 9 of 11 migrainous subjects, whereas none of the 8 subjects challenged with vodka had an attack (Littlewood, 1988).

## D. HORMONES

### 1. MENSTRUATION

- a. Trigger factor in approximately 60% of women with migraine. In about 50% of cases, the headaches occur just prior to or during menstruation, and about 10% of women relate their headaches to the time of ovulation; also may be associated with premenstrual syndrome (Stewart, 2000; Fettes, 1997; Van den Bergh, 1987; Granella, 1993; Rasmussen, 1992; Facchinetti, 1993).
- b. The results of a population-based study suggest that attacks of migraine without aura, but not migraine with aura, are significantly more likely to occur during the menstrual cycle (Stewart, 2000).
- c. The physiology of menstrual migraine is unclear; the natural withdrawal of estrogen with an increase in cerebral vasoreactivity to serotonin and hypersensitivity to dopamine is thought to be central, but prostaglandins also are involved (Fettes, 1997; Edelson, 1985).
- d. A change in platelet homeostasis, primarily evident in the luteal and perimenstrual phases of the cycle, also may play a role in the pathogenesis (Nattero, 1988).
- e. While most menstrual migraines follow a typical course, features resembling cluster headaches have been reported in some cases (Robbins, 1996).
- f. In some women, a depressive episode associated with the menstrual period may facilitate the development of a migraine attack (Amery, 1987; MacGregor, 1990).

### 2. CONTRACEPTIVES, ORAL

- a. May increase the frequency and severity of migraine headaches; women with and without a prior history of migraine are susceptible (Edelson, 1985; Granella, 1993).
- b. Women at particular risk of oral contraceptive-induced migraine include those over 30 years of age who have a menstrual migraine pattern, those with a menstrual interval over 30 days, and women who are multiparous (Edelson, 1985).

### 3. PREGNANCY

- a. Pregnancy influences the pattern of established migraine. While symptoms often improve during pregnancy, the response is highly variable. Reports of migraine occurring for the first time in pregnancy are uncommon (Granella, 1993).
- b. During the first trimester, migraine episodes may have their initial presentation or there may be an intensification of existing migraine (Edelson, 1985).
- c. In 70% to 80% of women, the incidence of migraine decreases during the second and third trimesters, which is probably associated with suppression of fluctuation of ovarian levels (Aube, 1999; Edelson, 1985; Chen, 1994).
- d. During the postpartum period, when estrogen and progesterone levels fall rapidly, there often is an increase in migraine attacks (Edelson, 1985).

### 4. MENOPAUSE

- a. In some women, there is a tendency for migraine headache to improve or remit with menopause, while in others (particularly those with a history of menstrual migraine), the headaches continue and even accelerate (Fettes, 1999).
- b. Fluctuating and falling estrogen levels during the perimenopausal years may increase frequency and severity of migraine. For women who are susceptible to fluctuations in estrogen and progesterone, initiation of cyclic hormone replacement therapy after menopause may exacerbate migraine (Fettes, 1999).

### 5. HORMONE REPLACEMENT THERAPY

- a. A significantly higher number of postmenopausal women taking HRT than women not on HRT gave a history of typical migraine (40% vs 26%) in an Australian study (Mitchell, 1998).
- b. For women who are susceptible to fluctuations in estrogen and progesterone, initiation of cyclic HRT after menopause may exacerbate migraine. Continuous combined therapy is the preferred approach, as it can stabilize the hormone milieu and relieve the migraine (Fettes, 1999).

## E. STRESS

1. Migraine trigger in about 50% of patients and is probably related to the somatic effects of states of excitement on the autonomic nervous system.
2. In some cases, stress may be an early prodromal sign rather than a real trigger factor (Van den Bergh, 1987). Frequently, the migraine does not occur until after the stressful episode has subsided (Diamond, 1997).
3. Emotional factors contribute to headache frequency and refractoriness in some, but not necessarily most, patients with headaches. Dealing with these factors may be essential. Many individuals who require psychologic intervention will accept help as long as it represents a component of a broad-treatment program, not the only form of therapy advised by the physician (Saper, 1989).
4. The results of a study of anxiety and life events in childhood migraine indicated that children with migraines are not more anxious or stressed than their peers. Normal amounts of stress and anxiety often lead to expression of a child's inherited migraine tendency; however, more anxious children with migraines have more frequent and severe headaches (Cooper, 1987).

5. Some epidemiologic studies have found an association between migraines and high levels of neuroticism. A prospective study found higher levels of neuroticism as measured by the Eysenck Personality Questionnaire predicted the onset of migraines in women aged 21 to 35 years (Breslau, 1996).

#### F. DRUG USAGE

1. Migraine may be provoked by vasodilators used to treat hypertension and coronary artery disease, by the antihypertensive agent reserpine, and by nitrates used for treatment of angina (Diamond, 1997).
2. More than 1/3 of patients attending a headache clinic suffered from chronic daily headache, where drug-induced headache was a prominent diagnosis (Sanin, 1994).
3. Frequent use of symptomatic headache remedies, including aspirin, acetaminophen, ergotamines, and narcotics, especially when combined with caffeine, can lead to the development of drug rebound headaches, characterized by increasing frequency and change in headache characteristics or chronic daily headache (Diener, 1998; Maizels, 1998; Ferrari, 1998).

#### G. EXERCISE

1. Migraine may be induced by physical activity, including anaerobic activities (eg, weightlifting) or aerobic exercise (eg, running, swimming) (Thompson, 1987).

#### H. TRAUMA, CERVICAL SPINE

1. Whiplash cervical injury may be a trauma-precipitated variant of migraine. Symptoms typically begin within minutes to hours following an acceleration injury (Winston, 1987; Weiss, 1991).
2. Basilar artery migraine after uncomplicated whiplash injury has been reported (Jacome, 1986).

#### I. SMOKING

1. The relationship between smoking and migraine headache is controversial. Although migraineurs are more likely to be smokers than are persons with no history of migraine, evidence suggests that smoking does not increase the frequency and/or severity of migraine headaches (Volan, 1976; Chen, 1987).
2. In some individuals with migraine, smoking may have the mild effect of reducing the need for using analgesics, possibly because smoking may reduce dysphoria and anxiety (Chen, 1987).
3. Smoking is a risk factor for ischemic stroke in younger women with migraines (Tzourio, 1993).

#### J. LIPOPROTEINS

1. The results of a study of lipids and lipoprotein cholesterol in children with severe migraine suggest that primary and familial lipoprotein abnormalities may be etiologically related to migraine, perhaps related to platelet hyperaggregability and/or increased likelihood of cerebral vascular instability (Glueck, 1986).

#### K. COCAINE ABUSE

1. Migraine-like headache as a sequela of cocaine bingeing has been reported. The headache appeared after a delay with cocaine administration and subsided immediately with the readministration of cocaine, suggesting a rebound or withdrawal phenomenon. The underlying mechanisms are uncertain but are consistent with cocaine's effect on central serotonin function (Satel, 1989).
2. May mimic aura of migraine. Patient with past history of migraine who developed migraine-like symptoms with aura 24 to 36 h after use of intranasal cocaine has been reported (Mossman, 1992).

#### L. TRAUMA, HEAD, BLUNT

1. Migraine attacks associated with complex neurologic disturbances can be triggered by direct blows to the head (often to top of head). Can occur in athletes during sporting activities such as "heading" a soccer ball or with straight-on, helmet-to-helmet collision (Plager, 1996).
2. Generally develop after a latent period. Clinical presentation can be identical to migraine with aura or complicated migraine (Plager, 1996; Ferrera, 1996; Salber, 1991; Weiss, 1991; Kennedy, 1991).
3. Some patients with trauma-triggered migraine also have spontaneous migraine attacks; the incidence of spontaneous attacks in these patients and in their families is significantly higher than in the general population (Haas, 1988).

#### M. DEPRESSION

1. Each disorder (major depression and migraine) increases the risk for first onset of the other (Breslau, 1994).

## N. WEATHER CHANGES

1. Evidence suggests an increased incidence of migraine headaches during Chinook (warm) wind weather conditions. Mechanism by which Chinook winds might trigger migraines is unknown but could be related to increased air positive ion concentrations (Cooke, 2000; Piorecky, 1997).

## O. GENETICS

1. Family history of migraine is reported in 55% to 90% of migraine patients. The genetics of migraine suggest inheritance as an autosomal dominant trait with incomplete penetrance (Diamond, 1997; Rasmussen, 1992).
2. A population-based study found a relative risk of 1.5 in first-degree relatives of migraine probands; relative risk was slightly higher for migraine with aura than for migraine without aura and increased for relatives of probands with significant migraine-related disability (Stewart, 1997). Data from another study also suggest a genetic factor in migraine without aura (Gervil, 1999).
3. About 75% of cases of pediatric migraine are associated with a family history of migraine (Hernandez-Latorre, 2000).
4. In some families, migraine presents with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, an adult onset hereditary disease affecting the tunica media of the small cerebral arteries. This rare but progressively worsening disease should be suspected in migraineurs with prolonged atypical (motor and aphasic) aura and white matter abnormalities on brain MRI (Ceroni, 2000).

### 1.1.6 DIAGNOSTIC CRITERIA

- A. Per the International Headache Society (Solomon, 1997a; Maytal, 1997):

#### 1. MIGRAINE WITHOUT AURA:

- a. At least five attacks fulfilling criteria.
- b. Headache attacks lasting 4 to 72 hours (2 to 48 hours in children) untreated or treated unsuccessfully.
- c. Headache has at least two of the following characteristics:
  - (1) Unilateral location.
  - (2) Pulsating quality.
  - (3) Moderate or severe intensity (inhibits or prohibits daily activities).
  - (4) Aggravation by walking stairs or similar routine physical activity.
- d. During headache at least one of the following:
  - (1) Nausea and/or vomiting.
  - (2) Photophobia and phonophobia.
- e. At least one of the following:
  - (1) History and physical and neurologic examinations do not suggest headaches secondary to organic or systemic metabolic disease.
  - (2) History and/or physical and/or neurologic examination do suggest such disorder, but it is ruled out by appropriate investigations.
  - (3) Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

#### 2. MIGRAINE WITH AURA:

- a. At least two attacks fulfilling criteria.
- b. At least three of the following four characteristics:
  - (1) One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction.
  - (2) At least one aura symptom develops gradually over more than four minutes or two or more symptoms occur in succession.
  - (3) No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
  - (4) Headache follows aura with a free interval of less than 60 minutes (it also may begin before or simultaneously with the aura).
- c. At least one of the following:
  - (1) History and physical and neurologic examinations do not suggest headaches secondary to organic or systemic metabolic disease.
  - (2) History and/or physical and/or neurologic examination do suggest such disorder, but it is ruled out by appropriate investigations.
  - (3) Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

- B. These criteria have been validated in a large population based study and are now widely accepted (Tepper, 1996; Solomon, 1997).

C. CHILDREN: Criteria were largely developed and validated in adults. Migraine with aura does not appear to differ significantly in children (Balottin, 1997), but a study of 88 children with the diagnosis of migraine without aura by a pediatric neurologist found the criteria had a specificity of 92% but a sensitivity of only about 27%. One major difference appeared to be a shorter duration of headache in children (less than 2 hours in 36%) (Maytal, 1997).

## 1.2 ASSOCIATED CONDITIONS

### A. MOTION SICKNESS

1. Accompanies migraines in 55% of adults and 45% of children. This may be due to central phenomenon in the brainstem or peripheral problems in the middle ear. Motion sickness may serve as a diagnostic criterion for childhood migraine (Barabas, 1983; Kayan, 1984; Mortimer, 1992).

### B. MITRAL VALVE PROLAPSE

1. There is a 15% to 37% incidence of MVP in female migraineurs and a 50% to 60% incidence of complicated migraine headache in MVP patients (Gamberini, 1984; Lanzi, 1986; Pfaffenrath, 1987, 1991). However, these and other cerebrovascular risk factors are not seen any more frequently in persons with migraine (Pfaffenrath, 1991).
2. A thorough cardiac evaluation and a CT scan should be performed in young patients with ophthalmoplegic or hemiplegic migraine to rule out MVP (Herman, 1987). However, because neither migraine with or without aura shows a significant difference with respect to the prevalence of MVP, it appears that a cardiac embolic cause for migraine with accompanying focal neurologic deficit is unlikely (Pfaffenrath, 1991).

### C. RAYNAUD'S PHENOMENON

1. An increased incidence of Raynaud's phenomenon has been noted in patients with migraines with and without aura. Both entities may be a manifestation of vasospasm (Zahavi, 1984; Kaiser, 1992).

### D. ANGINA, VARIANT

1. The occurrence of chest pain in patients with known migraine may represent coronary artery spasm and should be investigated with concurrent EKGs. The use of ergot preparations is contraindicated in such patients because exacerbation of chest pain and frank MI may result (Wayne, 1986).
2. Genetic factors may play a role in the etiology of variant angina and migraine in some cases (Fournier, 1986).

### E. ATHEROSCLEROSIS

1. Recurrent severe headache, which is primarily migraine, may be a risk factor or a marker for occurrence of atherosclerosis-related diseases (stroke, MI, diabetes, or hypertension) (Couch, 1989).
2. An Australian interview/survey study involving over 3500 elderly persons demonstrated significant associations in men between history of typical migraine and history of angina, MI, and stroke. In women, migraine was only significantly associated with MI (Mitchell, 1998).

### F. INFECTION, HELICOBACTER PYLORI

1. GENERAL: Common in migraineurs and might have effect on migraine symptoms. Underlying pathogenetic mechanism may be reduction of vasoactive substances produced during H pylori infection (Gasbarrini, 1998).
2. ADULTS: In one study, H pylori was detected in 40% of patients affected by migraine and was eradicated successfully in 80%. Frequency, intensity, and duration of migraine attacks were significantly reduced in all eradicated patients (Gasbarrini, 1998).
3. CHILDREN: Does not appear to be factor in pediatric migraine. A case series found evidence of H pylori infection by 13C-urea breath test in only 1 of 36 children with migraine with aura (3%) vs 8% asymptomatic infection rate in same general population of schoolchildren (Caselli, 1999).

### G. PATENT FORAMEN OVALE

1. Increased prevalence of PFO has been noted in persons with migraine, particularly migraine with aura (Wilmshurst, 2000; Anzola, 1999; Del Sette, 1998).
2. Paradoxical microembolism could be involved in the aura of migraine attacks, or could be the reason that migraine with aura sufferers have a higher risk of stroke (Anzola, 1999).
3. Closure of the atrial defect may reduce or abolish migraine (Wilmshurst, 2000).

### H. GLAUCOMA

1. Results of one study suggest an association of normal-pressure glaucoma and migraine and a potential vascular etiology of both diseases (Cursiefen, 2000).

## I. DEPRESSION

1. Migraine sufferers have a much higher prevalence of depression than nonmigraineurs (47% vs 17% in a population-based case-control study) (Lipton, 2000; Breslau, 2000, 1994). In addition, migraine and depression each exert a significant and independent influence on health-related quality of life (Lipton, 2000).
2. In some women, a depressive episode associated with the menstrual period may facilitate the development of a migraine attack (Amery, 1987; MacGregor, 1990).

## 1.3 VITAL SIGNS

### A. TEMPERATURE

#### 1. TEMPERATURE, INCREASED

- a. Temperatures as high as 40 C occur occasionally in the absence of infection, especially in children (Saper, 1989).
- b. Fever in migrainous attacks is thought to result from disturbances in autonomic function (Saper, 1989)

### B. HEART RATE

#### 1. TACHYCARDIA

- a. Tachycardia accompanies migraine attacks in about 3% of patients (Saper, 1989).

### C. RESPIRATIONS

#### 1. RESPIRATIONS, INCREASED

- a. Hyperventilation has been described in patients during the headache phase. It is uncertain whether this occurs secondary to pain and anxiety or to a physiologic attempt to vasoconstrict dilated cerebral blood vessels by lowering PCO<sub>2</sub> (Blau, 1980).

## 1.4 PRESENTATION BY BODY SYSTEM

### 1.4.2 DERMATOLOGIC PRESENTATION

#### A. EDEMA, GENERALIZED

1. Edema may occur from fluid retention hours to days before a migraine attack (Saper, 1989).
2. Edema is asymptomatic in about 50% of patients, but it may be manifested by tightness of rings, shoes, or clothing, or by the presence of frank pitting edema (Saper, 1989).

#### B. PALLOR

1. May be noted in conjunction with peripheral vasoconstriction (Saper, 1989).

#### C. FLUSHING

1. Occurs occasionally, but facial pallor is more common (Saper, 1989).

### 1.4.3 HEENT PRESENTATION

#### A. TENDERNESS, SCALP

1. Occurs during or after headache in about 2/3 of patients; attributed to widespread distention of extracranial arteries or contraction of the scalp and neck musculature (Saper, 1989).
2. Tenderness of the superficial temporal artery also may be noted (Saper, 1989).

#### B. DISTENTION, VEIN, HEAD

1. Superficial veins over the forehead and temporal areas often are distended. This may reflect the opening of cranial arteriovenous anastomoses during a migraine attack (Saper, 1989).

#### C. ECCHYMOSIS, PERIORBITAL

1. May be seen when extracranial vasodilatation is profound (Saper, 1989).
2. Most likely a combination of vasodilation and release of vasoactive substances, including heparin, which have been observed to occur during attacks of migraine (DeBroff, 1990).

#### D. VISION, BLURRED

1. Reported by most patients. The mechanism is unknown, but it is not explained by concurrent lacrimation (Saper, 1989).
2. Persistent blurred vision should prompt a search for retinal artery occlusion (Gray, 1985).

#### E. PHOTOPHOBIA

1. Most patients report an abnormal intolerance to light (Saper, 1989).
2. The mechanism has not been defined, but at least two mechanisms could cause photophobia in migraine: sensitivity to glare may form part of a general hypersensitivity of the special senses, while bright light appears to exacerbate pain resulting from activation of trigeminal pain pathways during headache (Drummond, 1986).

#### F. PAIN, EYE

1. Unilateral eye pain is present with hemicranial migraine in patients who complain of retro-orbital pain (Saper, 1989).
2. Ophthalmoplegic migraine is associated with severe unilateral eye pain and a complete or incomplete third-nerve palsy (Rothner, 1986).
3. Eye pain may be due to segmental narrowing of the basilar artery between the origin of the posterior cerebral and superior cerebellar arteries caused by edema of the posterior cerebral vessel.

#### G. SCOTOMA

1. Visual hallucinations consisting of stars, spots, circles, angles, flashes of color, wavy lines, or heat waves are present in a majority of patients and precede the onset of migraine with aura (Saper, 1989).
2. Occur in 10% of patients (Manzoni, 1985). Usually appear bitemporally or across the entire visual field. Monocular in 5% of patients. Last 20 to 25 minutes prior to the onset of headache in over 80% of patients and rarely last over one hour (Manzoni, 1985).
3. Total visual aura associated with alterations in consciousness and various admixtures of vertigo, ataxia, dysarthria, tinnitus, and paresthesias represent the syndrome of basilar artery migraine (Saper, 1989).
4. Transient visual symptoms similar to the visual aura of migraine, often without headache, occur in about 1% of adults in mid or late life; episodes may occur for time after age 50. These symptoms do not appear to be associated with increased risk of stroke, and invasive diagnostic procedures or therapeutic measures generally are not indicated (Wijman, 1998).

#### H. VISUAL FIELD DEFICITS

1. Temporary visual field deficits can occur in migraine and may have disappeared by the time the patient is examined. Persistent deficits should be considered to be due to a more serious cause, eg, cerebral infarction (Kupersmith, 1987).
2. In one study, visual field loss was noted in 35% of 60 migraine patients; the prevalence of loss was greater with increasing age and duration of disease (Lewis, 1989).

#### I. AMAUROSIS FUGAX

1. Episodes of transient monocular blindness may occur (retinal migraine) (Diener, 1998; Tomsak, 1987).

#### J. CONGESTION, NASAL

1. Nasal stuffiness has been reported in 10% to 20% of patients during the course of a migrainous attack. It is caused by autonomic dysfunction (Saper, 1989) and is mediated at least in part by the greater superficial petrosal nerve (Dalessio, 1978).

#### K. AURA, OLFACTORY

1. Rare reports of prodromal smells prior to the onset of headache have occurred (Diamond, 1985; Schreiber, 1986; Fuller, 1987).

#### L. HEARING LOSS

1. Sudden hearing loss attributed to migraine with vasospastic cochlear damage has been reported rarely (Buchholz, 1996).

#### M. NOISE INTOLERANCE

1. The inability to tolerate loud sounds occurs in over 80% of patients who manifest otologic findings with migraines (Kayen, 1984).

### 1.4.4 NECK PRESENTATION

#### A. TENDERNESS, ARTERY, CAROTID

1. Tenderness of the common carotid artery on the more severely affected hemicranium is noted between attacks in over 50% of patients with frequent migrainous headaches (Saper, 1989).

## B. NUCHAL RIGIDITY

1. Atypical migraine presenting with meningeal signs, including meningismus, has been reported (Ulhaq, 1994).
2. Neck pain or stiffness was reported in 32 of 50 migraine patients, indicating possible extracerebral involvement of the migraine process (Blau, 1994).

## C. PAIN, NECK

1. Recurrent attacks of unilateral neck pain attributed to migraine have been reported (DeMarinis, 1996).

### 1.4.6 CARDIOVASCULAR PRESENTATION

#### A. PAIN, CHEST

1. The occurrence of chest pain in patients with known migraine may represent coronary artery spasm. These two entities may be related as part of a generalized vasospastic disorder (Wayne, 1986; Fournier, 1986).

### 1.4.7 GASTROINTESTINAL PRESENTATION

#### A. VOMITING

1. GENERAL: Occurs in about 50% of patients; may be central in origin, mediated through vagal regulation of gastric contractions (Saper, 1989).
2. CYCLIC VOMITING SYNDROME (CVS):
  - a. Disorder of primarily school-aged children and is considered by many to be a migraine equivalent (Li, 1999; Fleisher, 1999; Saper, 1989). Characterized by recurrent, severe, discrete episodes of vomiting that may be associated with abdominal pain, photophobia, headache, and nausea (Li, 1999; Rothner, 1986).
  - b. A retrospective review of 214 children with CVS found a family history positive for migraine headaches in 170 children and eventual progression to migraine headache in 61 (55 with family history, 6 without); overall, 82% of CVS was considered migraine related (Li, 1999). Other studies show a 50% to 75% association of CVS with migraine or progression to migraine (Pfau, 1996; Rothner, 1986).
  - c. A small retrospective case review reported that migraine-associated CVS (CVS with headache or migraine family history) responds significantly better to all types of migraine medications than nonmigraine-associated CVS, although these results were based on estimates of unblinded parents of reduction in child's symptoms (Li, 1999).
  - d. Children with CVS respond well to rescue medications for migraine (phenothiazines, isometheptene, sumatriptan), as well as to migraine prophylaxis medications (propranolol, amitriptyline, cyproheptadine) (Li, 1999; Fleisher, 1999). Response to serotonin agonists could be due either to a central action of serotonin or to gastric serotonin receptors that promote gastric atony (Li, 1999).
3. STATUS MIGRAINOSUS: Associated with intractable nausea and vomiting (Silberstein, 1992).

#### B. NAUSEA

1. Nausea is present in the vast majority of patients with migraine without aura (Saper, 1989). It was reported in over 50% of patients with migraine with aura (Manzoni, 1985).
2. STATUS MIGRAINOSUS: Associated with intractable nausea and vomiting (Silberstein, 1992).

#### C. DIARRHEA

1. About 15% of patients experience diarrhea, which may be mediated by serotonin - either released from intestinal mucosa or acting as a neurotransmitter in the mesenteric plexus (Saper, 1989).

#### D. PAIN, ABDOMINAL

1. MECHANISM: May be related to vagal- or serotonin-mediated increased GI motility (Saper, 1989).
2. ABDOMINAL MIGRAINE: Periodic abdominal pain is a migraine-equivalent seen in children, most commonly in those who have a family history of migraine. The syndrome is characterized by episodes of severe midline abdominal pain that typically begin in the morning and last six hours or longer; pallor, anorexia, nausea, and vomiting are typical associated symptoms (Fleisher, 1999; Symon, 1986).

#### E. DISTENTION, ABDOMINAL

1. Abdominal distention and flatulence commonly associated with migraine headaches; may be due to the altered peristalsis reported during migrainous attacks (Saper, 1989).

### 1.4.8 GENITOURINARY PRESENTATION

#### A. POLYURIA

1. May occur either immediately after onset of headache or during the period of diminishing headache intensity (Saper, 1989).

### 1.4.9 MUSCULOSKELETAL PRESENTATION

#### A. PAIN, MUSCLE

1. May occur as a prodromal symptom of the migraine attack (Saper, 1989).

### 1.4.10 NEUROLOGIC PRESENTATION

#### A. HEADACHE

##### 1. LOCATION:

- a. Commonly unilateral but may be bilateral in one third or more cases (Sjaastad, 1989; Saper, 1989); unilaterality alternating with bilaterality is common (42%) (Sjaastad, 1989).
- b. Pain in the temporal, orbital, and frontal regions is common, but parietal, occipital, and facial areas are also frequently involved (Saper, 1989).

2. DESCRIPTION: In the early stages the typical throbbing headache occurs, but it may become a dull ache as the attack evolves (Saper, 1989).

3. DURATION: Usually lasts 2 to 4 h (Winnem, 1992).

#### B. VERTIGO

1. May precede or occur during migrainous attacks (Kayam, 1984) and be accompanied by hearing loss, tinnitus, and ataxia (Buchholz, 1996). It is the principal symptom of basilar artery migraine (Harker, 1987).
2. Paroxysmal vertigo, a migraine equivalent, is characterized by transient episodes of unreal sensation of rotation of patient or surroundings and absence of a neurologic and auditory disorder (Abu-Arafeh, 1995).

#### C. SYNCOPE

1. Occurs in 10% of patients and may occasionally be the presenting complaint; may be an indication of basilar migraines.

#### D. PARESTHESIA

1. Abnormal sensations occurring with or independent of visual disturbances may involve the face, hand, and even the foot on the contralateral or unilateral side (Manzoni, 1985).
2. Migraine with aura has been associated with microcirculatory disorders of the upper limbs as measured by blood flow velocity using fingertip videomicroscopy showing increased vasospasm over normal controls.
3. Hemihyesthesias are not an infrequent finding (Saper, 1989).

#### E. HYPESTHESIA

1. Usually associated with hemiplegia, hemihyesthesia is ipsilateral to the side of the headache in one third of patients (Saper, 1989).

#### F. ATAXIA

1. Motor incoordination may be present with midbrain disturbances, as seen in basilar artery migraine (Saper, 1989).

#### G. ALTERED MENTAL STATUS

1. Altered consciousness may be associated with visual complaints and may precede onset of headache in some patients (Saper, 1989; Pietrini, 1987). Prolonged agitation and mental confusion characterize the headache attacks (Pietrini, 1987).
2. An impaired sensorium is associated with hemiplegia in one third of cases (Saper, 1989).
3. Atypical migraine presenting with meningeal signs and altered mental status has been reported (Ulhaq, 1994).
4. Transient global amnesia attributed to migraine has been reported (Buchholz, 1996).

#### H. NEUROLOGIC SIGNS, FOCAL

##### 1. OVERVIEW

- a. Focal neurologic signs may be associated with migraine headaches, but in most instances the deficits resolve within hours or days. On rare occasions there may be a residual effect, which may make the differentiation among complicated migraine, stroke, and transient ischemic attack with partial recovery a diagnostic dilemma.

##### 2. PALSY, OCULOMOTOR

- a. Paralysis of the eye muscles, a manifestation of ophthalmoplegic migraine, consists of ipsilateral ptosis progressing to complete third nerve palsy with occasional involvement of the sixth nerve. At times, attacks on alternating sides occur. Associated pupillary dilatation is usually present (Saper, 1989).
- b. Thought to be due to either compression of the involved nerve by an edematous carotid artery in the cavernous sinus or delayed ischemic neuropathy with border-zone infarction of the nerve (Crowell, 1982; Vijayan, 1980).

- c. May persist for several days after the headache ceases and usually resolves completely; however, after many attacks, some extraocular muscle paresis may persist (Saper, 1989).
- d. All patients with oculomotor nerve palsy, pupillary involvement, and headaches should be considered to have a cerebral aneurysm until proved otherwise (Crowell, 1982).

### 3. DYSARTHRIA

- a. May be present with the midbrain disturbances of basilar artery migraine origin.
- b. Also associated with hemiplegic migraine in 50% of cases (Saper, 1989).

### 4. HEMIPLEGIA

- a. Occurs uncommonly in association with migraine headaches. May precede, accompany, or follow the headache, but it most commonly begins with and then outlasts the headache by hours to days (Rothner, 1986). In one-third of cases, homonymous hemianopsia is associated with the hemiplegia (Saper, 1989).
- b. Hemiplegic migraine affects children and adolescents more commonly than adults; it occurs more often in females (Rothner, 1986).
- c. Diagnostic clues to hemiplegic migraine include (1) rapid spontaneous recovery from the acute neurologic deficit; (2) EEG abnormalities; (3) history of recurrent episodes; and (4) family history of migraines (Lai, 1982).
- d. If attacks occur on the same side consistently and/or other neurologic signs (eg, neck stiffness, retinal hemorrhages, localized bruit) are present, an underlying vascular malformation must be considered (Rothner, 1986).

### 5. HEMIANOPSIA, HOMONYMOUS

- a. Finding in one third of patients with hemiplegic migraine (Saper, 1989).

### 6. APHASIA

- a. May accompany hemiplegic migraine in 50% of cases (Saper, 1989).

### 7. DIPLOPIA

- a. Although monocular diplopia is usually functional in origin, it has been described in conjunction with migraine headaches. This may be due to occipital dysfunction (Drake, 1983).
- b. Characteristic manifestation of ophthalmoplegic migraine (Diamond, 1997).

## I. SEIZURES

1. Uncommonly, seizures may occur in association with migraine, particularly in patients with basilar artery migraine (Buchholz, 1996; Shuaib, 1987a). An increased incidence of migraines without aura and complex seizures has been noted in pediatric patients (Seshia, 1985).
2. Seizures in migraine patients may also be an early warning of cerebral infarction (Shuaib, 1987a).

## 1.4.14 PSYCHIATRIC PRESENTATION

### A. EMOTIONAL CHANGES

#### 1. OVERVIEW

- a. Mood alterations and emotional changes occur in most migraineurs. They may precede the headache by as much as a day or longer and generally occur with increasing severity of the headache.
- b. Changes that may be noted include the following: lethargy, anxiety, irritability, euphoria, poor judgment, impulsiveness, hostility, and confusion (Saper, 1989).
- c. Psychologic studies do not support the widely held view that the migrainous patient is likely to be more compulsive, inhibited, and prone to neurotic defenses (Rothner, 1986).
- d. However, a prospective study found higher levels of neuroticism as measured by the Eysenck Personality Questionnaire predicted the onset of migraines in women aged 21 to 35 years (Breslau, 1996).
- e. The personality and behavioral characteristics evident in children with migraine may be the result of recurrent chronic pain episodes rather than causative of the headaches (Cunningham, 1987).

## 1.4.15 MISCELLANEOUS SYMPTOMS

### A. WEIGHT GAIN

1. Weight gain of 2 to 5 pounds due to fluid retention is noted in over 95% of patients and may be manifested as frank pitting edema (Saper, 1989).

### B. FATIGUE

1. Most migraine patients complain of fatigue either as part of the prodrome or as the headache increases in severity (Saper, 1989).
2. After a migraine attack, patients typically report physical and mental tiredness that may last for several hours to days (Blau, 1991).

## 1.5 COMPLICATIONS

### A. OCCLUSION, ARTERY, CENTRAL RETINAL

1. Rare complication of migraine with aura. It should be suspected when there are persistent visual acuity problems (Gray, 1985).
2. Migrainous CRAO has been reported coincident with the initiation of propranolol therapy for migraine prophylaxis (Katz, 1986).
3. One case report showed branch retinal artery occlusion in a patient whose symptoms of retinal migraine persisted for months (Inan, 1994).

### B. CEREBROVASCULAR ACCIDENT

#### 1. GENERAL:

- a. Stroke is rare among patients who have migraine, but a significant proportion of strokes (up to 10%) in persons aged less than 50 years are migraine-related (Broderick, 1987; Featherstone, 1985; Rothrock, 1988; Bogousslavsky, 1988; Sacquegna, 1989; Gomez, 1991; Caplan, 1991; Tzourio, 1993; Buring, 1995).
- b. The majority of migraine-related strokes occur in females, most commonly women in their 30s (Broderick, 1987; Featherstone, 1985; Rothrock, 1988; Bogousslavsky, 1988; Sacquegna, 1989; Gomez, 1991; Caplan, 1991; Tzourio, 1993).
- c. The typical patient is a young adult with a prior migraine with aura or complicated migraine (Featherstone, 1985; Rothrock, 1988; Sacquegna, 1989); however, stroke has been reported in patients with migraine without aura (Narbone, 1996), and in one study 9 of 20 patients had had their strokes with their first migraine attack or had a history of prior migraine without aura (Broderick, 1987).
- d. Overall, patients with a history of migraine have 1.5 to 2 times the risk of stroke when compared with the nonmigrainous population. Migraine appears to be most significant as a risk factor in younger patients, especially women under 35 years, and in those with migraine with aura (Merikangas, 1997; Tzourio, 1997; Sacco, 1997; Carolei, 1996).
- e. A retrospective chart review and survey study of 291 women aged 22 to 40 yr with stroke found no significant difference in odds ratios for ischemic or hemorrhagic stroke in women with migraine with aura vs migraine without aura; a significantly increased odds ratio for women with any migraine for ischemic stroke but not for hemorrhagic stroke; and a significantly increased odds ratio for both ischemic and hemorrhagic stroke in women with a family history of migraine (Chang, 1999).
- f. The clinical pattern of stroke in migraine is consistent with a thromboembolic event (Featherstone, 1985; Cole, 1990). Intracerebral hemorrhage associated with migraine also has been reported (Furui, 1993).

#### 2. PREDISPOSING FACTORS:

- a. Include vasospasm and hyperaggregable platelets in combination with other abnormalities of blood vessels and/or plasma coagulability (Featherstone, 1985; Rothrock, 1988; Cole, 1990). However, the results of one study showed no increased coincidence of migraine with potential vascular risk factors, eg, MVP, EKG changes, increased platelet aggregation, or raised thromboxane B2 levels (Pfaffenrath, 1991).
- b. In one study, patients with migraine stroke had longer previous attacks of migraine and their infarct was more frequently in the territory involved during the attacks than the controls. These data support the hypothesis that a prolongation of the migrainous process beyond usual limits may explain most migraine strokes (Bogousslavsky, 1988).
- c. A controlled study found that while the risk of ischemic stroke is increased in migraine patients, an underlying disorder other than prolonged vasospasm may be responsible. Thus migraine with aura may be a marker for patients at increased risk for ischemic stroke unrelated to a migraine attack (Henrich, 1989).
- d. Because neither migraine with or without aura shows a significant difference with respect to the prevalence of MVP, it appears that a cardiac embolic cause for migraine with accompanying focal neurologic deficit is unlikely (Pfaffenrath, 1991).
- e. Migraine may be an early and prominent symptom in the antiphospholipid antibodies syndrome, which may increase risk of ischemic stroke (Silvestrini, 1993). However, a large study failed to find an increased frequency of anticardiolipin antibodies in migraineurs (Tietjen, 1998).
- f. Transient visual symptoms similar to the visual aura of migraine, often without headache, occur in about 1% of adults in mid or late life; episodes may occur for time after age 50. These symptoms do not appear to be associated with increased risk of stroke, and invasive diagnostic procedures or therapeutic measures generally are not indicated (Wijman, 1998).
- g. A retrospective chart review and survey study of 291 women aged 22 to 40 yr with stroke showed a significantly (multiplicatively) increased odds ratio for stroke in migrainous women who smoked. Oral contraceptive use and history of high blood pressure in and outside pregnancy were not contributing factors (Chang 1999).

3. **PATHOPHYSIOLOGY:** In patients with migraine-associated intracerebral hemorrhage, vasospasm associated with severe migraine attacks may result in ischemia of intracranial vessel walls, leading to necrosis and subsequent vessel rupture when perfusion pressure is restored (Cole, 1990).
4. **LOCATION:**
  - a. The largest percentage of infarcts occur in the distribution of the posterior cerebral artery, although in some reports, strokes in the middle cerebral artery distribution predominate. In one series involving six patients, all strokes occurred in the occipital lobe (Sacquegna, 1989).
  - b. The high percentage of posterior circulation infarcts in migrainous strokes is contrary to the majority of anterior circulation infarcts occurring in thrombotic and embolic strokes in general, as well as in patients under 40 years of age (Broderick, 1987; Bogouslavsky, 1988).
5. **CLINICAL FEATURES:**
  - a. The stroke is typically preceded by an increase in headache activity and may be sudden or gradual in onset (Featherstone, 1985; Cole, 1990). A study of 291 women with strokes reports that more than twice the number of women with migraine than women without migraine report headache in the 3 days prior to the stroke, with up to 40% of strokes in migraineurs evolving directly from a migraine (Chang, 1999).
  - b. Usually characterized by a hemiparesis or hemiplegia, often with related abnormalities of vision, sensation, and/or speech (Featherstone, 1985; Cole, 1990).
  - c. Seizures in migraine patients may be an early warning of a cerebral infarction (Shuaib, 1987).
6. **PROGNOSIS:**
  - a. The majority of patients with migraine-related strokes have apparently mild functional impairment; 25% to 50% of survivors show return to normal function (Featherstone, 1985; Rothrock, 1988).
  - b. Recurrent strokes occur in approximately 1% to 2% of patients (Broderick, 1987).
  - c. Overall mortality is 5% (Featherstone, 1985; Rothrock, 1988).
  - d. A large study examining the prevalence and role of anticardiolipin antibody in young people with migraine and transient focal neurologic events noted that in a 3-yr follow-up period, in which approximately half of both aCL+ and aCL- groups took some form of antiplatelet therapy, there was only one clinically verified stroke that occurred during carotid endarterectomy (Tietjen, 1999).

## **2.0 LABORATORY DATA**

### **2.1 GENERAL DISCUSSION**

- A. Laboratory studies generally not helpful in diagnosis and treatment of migraine headaches.

## **3.0 RADIOLOGIC DATA**

### **3.1 GENERAL DISCUSSION**

- A. **PRINCIPLES FOR DIAGNOSTIC IMAGING** (Silberstein, 2000, per US Headache Consortium practice guidelines):
  1. Testing should be avoided if it will not lead to a change in management.
  2. Testing is not recommended if the patient is not significantly more likely than a person in the general population to have a significant abnormality.
  3. Testing that is not normally recommended may make sense in individual cases, eg, in patients who are excessively worried about a serious problem as the cause of their headaches.
- B. **INDICATIONS:** Helpful in differentiating migraine symptoms from those of other entities, eg, aneurysm, mass lesion, or subdural hematoma (Silberstein, 2000, per US Headache Consortium practice guidelines):
  1. Consider neuroimaging in patients with nonacute headache and an unexplained abnormal finding on the neurologic examination (Grade B recommendation; some evidence from randomized trials but scientific information not optimal). This recommendation is based on finding that an abnormal neurologic examination increases likelihood of intracranial pathology (eg, brain tumor, AV malformation, hydrocephalus). Absence of abnormalities on neurologic examination reduces odds of an abnormality on CT or MRI.
  2. Because of insufficient evidence, no recommendations are made regarding neuroimaging in the presence or absence of neurologic symptoms (Grade C recommendation). While data suggest that headache worsened by the Valsalva maneuver, headache that awakens the patient, new-onset headache in older patients or progressively worsening headache increases likelihood of significant intracranial pathology, the absence of such signs and symptoms is less reliable than their presence.
  3. Neuroimaging is not usually warranted in patients with migraine and normal findings on neurologic examination (Grade B recommendation). A lower threshold for CT or MRI may be applicable in patients with atypical features or with headaches that do not fulfill the definition of migraine (Grade C recommendation). These recommendations are based on the finding that an abnormality is unlikely to be found on CT or MRI in patients with migraine and a normal neurologic examination.

4. Because of insufficient evidence, a recommendation regarding neuroimaging in patients with tension-type headaches cannot be made (Grade C recommendation). In two studies, no lesions were found in patients with tension-type headaches and normal neurologic examination. Because of insufficient evidence, recommendations regarding the comparative sensitivity of MRI and CT cannot be made (Grade C recommendation). The guidelines state that the greater resolution of MRI appears to be of little clinical importance in the evaluation of nonacute headache. No comparative data exist for the effectiveness of CT scanning with and without enhancement.

### **3.5 CT SCANS**

#### **A. COMPUTED TOMOGRAPHY, HEAD**

1. GENERAL: Following symptoms significantly increase likelihood of finding an abnormality on neuroimaging. (NOTE: Absence of these features does not significantly lower odds of finding a neuroimaging abnormality) (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Rapidly increasing headache frequency.
  - b. History of lack of coordination.
  - c. History of localized neurologic signs or of subjective numbness or tingling.
  - d. History of headache causing awakening from sleep.
2. INDICATIONS: Helpful in differentiating migraine symptoms from those of other entities, eg, aneurysm, mass lesion, or subdural hematoma (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Patients with nonacute headache and unexplained abnormal finding on neurologic examination (Grade B recommendation; some evidence from randomized trials but scientific information not optimal).
  - b. Patients with atypical headache features or headaches that do not fulfill strict definition of migraine or other primary headache disorder (or have some additional risk factor, eg, immunodeficiency) (Grade C recommendation; consensus achieved in absence of relevant randomized controlled trials).
  - c. Not usually warranted in patients with migraine and normal neurologic examination (Grade B recommendation).
3. CT VS MRI: There is insufficient evidence to make recommendations regarding the comparative sensitivity of MRI and CT (Grade C recommendation). Greater resolution of MRI appears to be of little clinical importance in the evaluation of nonacute headache. MRI may be more sensitive than CT in identifying clinically insignificant abnormalities, but MRI may be no more sensitive than CT in identifying clinically significant pathology. No comparative data exist for effectiveness of CT scanning with and without enhancement (Silberstein, 2000, per US Headache Consortium practice guidelines).

### **3.7 MAGNETIC RESONANCE IMAGING**

#### **A. IMAGING, MAGNETIC RESONANCE, HEAD**

1. GENERAL: Following symptoms significantly increase likelihood of finding an abnormality on neuroimaging. (NOTE: Absence of these features does not significantly lower odds of finding a neuroimaging abnormality) (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Rapidly increasing headache frequency.
  - b. History of lack of coordination.
  - c. History of localized neurologic signs or of subjective numbness or tingling.
  - d. History of headache causing awakening from sleep.
2. INDICATIONS: Helpful in differentiating migraine symptoms from those of other entities, eg, aneurysm, mass lesion, or subdural hematoma (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Patients with nonacute headache and unexplained abnormal finding on neurologic examination (Grade B recommendation; some evidence from randomized trials but scientific information not optimal).
  - b. Patients with atypical headache features or headaches that do not fulfill strict definition of migraine or other primary headache disorder (or have some additional risk factor, eg, immunodeficiency) (Grade C recommendation; consensus achieved in absence of relevant randomized controlled trials).
  - c. Not usually warranted in patients with migraine and normal neurologic examination (Grade B recommendation).
3. CT VS MRI: There is insufficient evidence to make recommendations regarding the comparative sensitivity of MRI and CT (Grade C recommendation). Greater resolution of MRI appears to be of little clinical importance in the evaluation of nonacute headache. MRI may be more sensitive than CT in identifying clinically insignificant abnormalities, but MRI may be no more sensitive than CT in identifying clinically significant pathology. No comparative data exist for effectiveness of CT scanning with and without enhancement (Silberstein, 2000, per US Headache Consortium practice guidelines).

## 5.0 DIFFERENTIAL DIAGNOSIS

### 5.1 GENERAL DISCUSSION

A. GENERAL: Includes other types of primary headaches (tension-type and cluster) and secondary organic headache disorders, as listed in the following table (Silberstein, 1992).

1. ACUTE SINGLE HEADACHE:
  - a. Encephalitis
  - b. Glaucoma
  - c. Meningitis
  - d. Optic neuritis
  - e. Postconcussion/posttraumatic syndrome
  - f. Pressor reaction
  - g. Subarachnoid hemorrhage
  - h. Sinusitis
  - i. Systemic infection
2. ACUTE RECURRENT HEADACHE:
  - a. Cerebral neoplasm
  - b. Cerebrovascular insufficiency
  - c. Cluster HA
  - d. Hydrocephalus, intermittent
  - e. Pseudotumor cerebri
  - f. Pheochromocytoma
  - g. Trigeminal neuralgia
  - h. Tension-type headache

### 5.2 TRAUMA

#### A. HEADACHE, POSTTRAUMATIC

1. History will indicate a constant dull headache, variable in location, usually occurring within 24 hours of head injury and worsening over a period of days to weeks, and then gradually improving over a similar time course. It may or may not be associated with loss of consciousness at the time of head injury.
2. Physical examination may show ecchymoses, hematomas, and/or abrasions.
3. Post-traumatic headache is not associated with anatomic CNS lesions. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BLUNT HEAD TRAUMA)

#### B. HEMATOMA, SUBDURAL

1. There will usually be a history of mild-to-moderate head injury, although the trauma may be so trivial as to be forgotten.
2. Physical examination may show ecchymoses, hematomas, and/or abrasions.
3. CT-scan will usually demonstrate a hematoma and (where available) is the initial procedure of choice. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BLUNT HEAD TRAUMA)

### 5.3 INFECTIOUS

#### A. MENINGITIS, BACTERIAL

1. History will usually indicate headache with fever and neck pain. Meningitis is often associated with otitis media.
2. Physical examination may show neck stiffness and a positive Kernig sign. Retro-orbital pain markedly exacerbated by the slightest eye motion may be distinctive. Cranial nerve involvement may be present, resulting in inequality of pupils, paresis or paralysis of eye movement, and strabismus. A diminished level of consciousness may be present.
3. Atypical or complicated migraine presenting with signs and symptoms of meningeal irritation, projectile vomiting, and altered mental status has been reported (Ulhaq, 1994).
4. CSF analysis reveals leukocytosis, hypoglycorrhachia, and/or positive Gram stain or culture results. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BACTERIAL MENINGITIS)

#### B. ABSCESS, CEREBRAL

1. History will often indicate cyanotic congenital heart disease, mastoiditis, sinusitis, lung abscess, bronchiectasis, or subacute bacterial endocarditis. Vomiting may be a complaint.
2. Physical examination may reveal papilledema, neck stiffness, and variable focal neurologic signs, depending on the site of the lesion.
3. CT-scan will establish a diagnosis of abscess. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BRAIN ABSCESS)

## 5.4 INFLAMMATORY

### A. ARTERITIS, TEMPORAL

1. Primarily a disease of persons over age 50. Sudden loss of vision is common (50% of cases) and is often preceded by amaurosis fugax.
2. The complaint that leads the patient to seek medical attention is headache, which may be nonspecific and is sometimes worse at night or aggravated by exposure to cold.
3. Multiple systemic clues may be present such as low-grade fever, weight loss, anorexia, and anemia.
4. Ocular problems may precede or follow onset of systemic symptoms, but often the diagnosis is not made until loss of vision occurs.
  - a. The optic disc may be gray-white and elevated; small hemorrhages may be present.
  - b. Pain in or around the eye has been reported, as well as diplopia, photophobia, ptosis, conjunctivitis, and occlusion of branch retinal arteries.
5. Physical examination reveals a tender, indurated superficial temporal artery. Jaw or lingual claudication is probably pathognomonic. Erythrocyte sedimentation rate is usually 50 to 100 mm or more per hour. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: TEMPORAL ARTERITIS)

## 5.5 METABOLIC

### A. HYPERCAPNIA

1. History will indicate chronic obstructive lung disease, bronchiectasis, pulmonary infection, or the hypoventilation of extreme obesity. Physical exam shows evidence of one of these pulmonary diseases.
2. Arterial blood gases show increased CO<sub>2</sub> tension.
3. Headache improves with improved ventilation.

## 5.6 VASCULAR

### A. HEMORRHAGE, SUBARACHNOID

1. History indicates onset of sudden, severe headache, usually in the occipital area, regardless of the site of aneurysmal rupture. Rapid loss of consciousness occurs in 20% of patients. Neck stiffness is present in almost all patients unless they are in profound coma.
2. Pre-existing hypertension may be a predisposing factor.
3. Subhyaloid hemorrhages may be seen.
4. Lumbar puncture shows grossly bloody fluid under increased pressure.
5. CT-scan is almost 100% accurate in demonstrating extravasated blood if done within 5 to 7 days posthemorrhage. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: SUBARACHNOID HEMORRHAGE)

### B. HEADACHE, HYPERTENSIVE

1. Headache is usually frontal, orbital, fronto-temporal, or temporal; it is unilateral in only 10% of patients.
2. It typically begins between midnight and 4 AM, reaching peak intensity about daybreak or shortly before arising, then commonly diminishing in intensity after the patient arises and assumes daily activities.
3. This type of headache is statistically more common in hypertensive patients when the diastolic blood pressure exceeds 140 mmHg. It improves more frequently when the systolic blood pressure is reduced by 60 mmHg than when it is reduced by 35 mmHg.

### C. CEREBROVASCULAR ACCIDENT

1. A CVA may be difficult to differentiate from complicated migraine with unresolving focal neurologic deficits (Olsen, 1991). Patients with certain migraine equivalents will have no headache, thus further complicating the distinction.
2. The deficits in migraine usually precede the headache, whereas in a CVA the headache (if present) usually precedes the onset of focal signs.
3. History of migraine attacks may delay diagnosis of such potentially treatable conditions as dissection of the internal carotid artery; careful attention should be paid to focal signs, history of a different pattern of headache, or new clinical characteristics (Duyff, 1997; Ganesan, 1997; Diamond, 1997).
4. CT scans can be utilized to diagnose most CVAs and should be done if focal signs are present.
5. Stroke related to migraine is rare but occurs in significant proportion of patients under 50 years who have a stroke (Broderick, 1987; Featherstone, 1985). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: THROMBOEMBOLIC STROKE)

### D. AMAUROSIS FUGAX

1. Patients with migraine may experience a variety of visual phenomena as the prodrome to their attack. Transient unioocular visual loss, though uncommon, has been described in migraine. Thromboembolism from atheroma in the carotid artery must be ruled out, especially in older patients (Sandercock, 1990).

## E. DISSECTION, CAROTID ARTERY

1. May be misdiagnosed as recent onset migraine. Important to identify correctly to avoid delay in treatment (Mirza, 1998).

## 5.7 NEOPLASTIC

### A. NEOPLASM, CEREBRAL

#### 1. TYPES:

- a. PRIMARY: Include gliomas (50%), meningiomas, pituitary adenomas, and neurofibromas.
- b. METASTATIC: Most common source is carcinoma of the lung; other primary sites are breast, kidney, and GI tract.

2. CLINICAL PRESENTATION: Characterized by generalized or focal disturbances of cerebral function, or both, and signs and symptoms of increased ICP.

#### a. GENERALIZED:

(1) May include personality changes, intellectual decline, emotional lability, seizures, headache, nausea, malaise, slowly progressive weakness on one side, visual changes, aphasia, vomiting, mental changes. Papilledema occurs in 25% of patients and may not be early sign; vital signs are normal.

(2) Increased ICP may cause herniation, most commonly tentorial, characterized by ipsilateral pupillary dilatation, followed by stupor, coma, decerebrate posturing, and respiratory arrest.

- b. FOCAL: Due to localized destruction or compression of nerve tissue or to altered endocrine function; depend on tumor location.

3. DIAGNOSIS: Neuroradiologic evidence of space-occupying lesion. CT or MRI may detect lesion and also may define its location, shape, and size; extent to which normal anatomy is distorted; and degree of any associated cerebral edema or mass effect. CT and MRI are particularly indicated in patients with headache and hemiplegic, basilar, or ophthalmoplegic symptoms, or in whom history or clinical examination reveals any unusual features.

## 5.8 TOXICOLOGIC

### A. POISONING, CARBON MONOXIDE

1. History indicates exposure to fumes of oil, gas, gasoline, coal, wood, or charcoal combustion, or to fumes of paint removers containing methylene chloride (Steward, 1976).
2. Headache is usually frontal and bandlike.
3. The serum carboxyhemoglobin level will confirm the diagnosis of CO exposure.

### B. HEADACHE, HANGOVER

1. History indicates headache following heavy ingestion of ethanol.
2. Headache usually occurs when blood ethanol level has fallen to minimal levels (several hours after maximum alcohol concentration).

## 5.9 PHYSICAL AGENTS

### A. HEADACHE, HIGH ALTITUDE

1. History indicates a headache associated with unacclimatized high altitude exposure - usually over 8000 feet.
2. Physical exam may show cyanosis, evidence of pulmonary edema, papilledema, and retinal hemorrhages.
3. Low arterial O<sub>2</sub> tension will help confirm diagnosis.
4. Headache is not always improved with oxygen therapy. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: HIGH ALTITUDE ILLNESS)

## 5.10 MISCELLANEOUS

### A. GLAUCOMA

1. Past history will indicate mild, transient attacks, particularly at night, when in darkness, or in association with atropine-like drugs. Patients will report seeing a halo-effect about lights.
2. Physical exam reveals an ipsilateral mid-dilated pupil and a steamy cornea.
3. Tonometry reveals increased intraocular pressure. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: GLAUCOMA)

### B. HEADACHE, CLUSTER

1. Cluster headaches are characterized by paroxysmal, explosive, unilateral, periorbital pain that is frequently nocturnal and occurs in cluster cycles lasting weeks, with pain-free intervals lasting weeks to months.
2. Individual headaches within the cluster period usually last several hours.
3. Attacks are characterized by ipsilateral nasal stuffiness, soft tissue swelling, lacrimation, hyperemic eye, and Horner's syndrome.

4. Alcohol sensitivity occurs during cluster cycles.
5. There will be no family history of migraine.
6. Majority of cases occur in men, with onset in middle age. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: CLUSTER HEADACHE)

#### C. HEADACHE, TENSION

1. Tension type headache is bilateral in 90% of patients, with the majority of patients experiencing head pain daily and constantly. Vomiting is not a common symptom.
2. Idiopathic headaches may be on a continuum from tension to migraine. The crossover in symptoms, signs and therapy is at times difficult.
3. Features that occur significantly more often in patients with migraine without aura than in those with chronic daily headache include nausea, vomiting, unilateral site, throbbing quality, photophobia or phonophobia, increase with menstruation, and a family history of migraine (Solomon, 1988).
4. Patients with a history of migraine and frequent consumption of painkillers (often over-the-counter) and caffeine may develop chronic daily headaches related to drug use (Maizels, 1998; Ferrari, 1998; Diamond, 1997).

#### D. NEURALGIA, TRIGEMINAL

1. Trigeminal neuralgia, with an episodic recurrent, unilateral pain syndrome, occurs chiefly in persons over age 50 and seldom before age 30 years.
2. Pain is primarily experienced in tissues supplied by the second - and to a lesser extent in those supplied by the third and first - divisions of the fifth cranial nerve, but it is never experienced below the ramus of the mandible or in back of the ear and rarely in the entire distribution of the fifth nerve at one time.
3. The aching and burning pain may occur spontaneously, but it is often initiated by cold air or a light touch on the skin of the cheek (powder puff, veil, kiss, towel, etc), by biting, chewing, swallowing, laughing, talking, yawning, sneezing, blowing the nose, or drinking cold water.
4. Pain is usually a high-intensity jab of 20 to 30 seconds duration followed by a period of relative freedom from pain of a few seconds to a minute, to be followed again by another jab of high intensity pain. The attack usually lasts one or more hours. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: TRIGEMINAL NEURALGIA)

#### E. PSEUDOTUMOR CEREBRI

1. CLINICAL PRESENTATION: Pseudotumor cerebri may present with headache, focal and transient effects on vision similar to migraine headaches (Mathew, 1996).
2. REFRACTORY MIGRAINE HEADACHES: Elevated intracranial pressure was documented in 12 of 85 patients with refractory migraine headaches; none of the 12 had papilledema or visual field defects. Previous prophylactic antimigraine agents were only partially effective in controlling headaches; addition of acetazolamide and furosemide improved control (Mathew, 1996).
3. PATHOPHYSIOLOGY: Further studies are needed to determine if these two entities share common pathophysiology (Mathew, 1996). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: PSEUDOTUMOR CEREBRI)

## 6.0 TREATMENT

### 6.1 TREATMENT SUMMARY

#### A. GENERAL:

1. Although uncomplicated migraine headache is benign and carries little morbidity except for pain and vomiting, it is important to differentiate this headache from more devastating headaches, eg, those associated with subarachnoid or cerebellar hemorrhage, meningitis, and intracranial masses.
2. Goals of treatment are amelioration of symptoms of an acute attack and prevention of further attacks. Most patients presenting to the ED with acute migraine usually require parenteral medication for control of symptoms. The individual patient's history of response to previous medication may be used as a guide for therapy.
3. Management of migraines in children differs from that of adult migraine, as not all therapies have been tested in the pediatric population; therapy should be instituted on an individualized basis, only after the diagnosis is certain.

#### B. ACUTE MIGRAINE - ADULTS:

##### 1. STATUS MIGRAINOSUS OR SEVERE MIGRAINE:

- a. PROCHLORPERAZINE: ADULTS: 10 mg IV over 2 to 3 min x 1. PLUS
- b. DIHYDROERGOTAMINE: ADULTS: 0.5 to 1 mg IV over 5 min; repeat 0.5 to 1 mg IV Q1H if headache still present; maximum dose, 3 mg/d. (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with triptans.)

## 2. MODERATE TO SEVERE MIGRAINE:

- a. KETOROLAC: ADULTS: 30 to 60 mg IM.
- b. MEPERIDINE: ADULTS: 50 to 150 mg IM Q4H PRN.
- c. DIHYDROERGOTAMINE: ADULTS: IM: 1 mg; may repeat twice Q4H to total of 3 mg/attack. SC: 1 mg; may repeat Q1H to total of 3 mg/attack. IN: 0.5 mg; repeat after 15 min (maximum, 3 mg/24 h). (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with triptans.)
- d. SUMATRIPTAN: ADULTS: 6 mg SC Q1H or longer (maximum, 12 mg/24 h); 5 or 20 mg IN Q2H or longer (maximum, 40 mg/24 h); 25 or 50 mg PO Q2H or longer (maximum, 200 mg/24 h). (Avoid in patients with risk for cardiovascular disease or thrombosis; do not use with ergot alkaloids.)
- e. PROCHLORPERAZINE: ADULTS: 10 mg IV over 2 to 3 min x 1; 5 to 10 mg IM Q4H, alone or as adjunct therapy.

## C. ACUTE MIGRAINE - CHILDREN:

1. ACETAMINOPHEN: CHILDREN: 15 mg/kg PO; repeat once after 2 h, then Q4-6H: maximum total dose, 100 mg/kg/d.
2. IBUPROFEN: CHILDREN: 10 mg/kg PO; repeat once after 2 h, then Q4-6H: maximum total dose, 40 mg/kg/d.
3. PROCHLORPERAZINE: May give alone or as adjunct therapy.
  - a. IM: CHILDREN LESS THAN 12 YEARS: 0.06 mg/lb IM.
  - b. PR: CHILDREN OVER 2 YEARS: 20 to 29 pounds: 2.5 mg PR QD or BID (maximum, 7.5 mg/day); 30 to 39 pounds: 2.5 mg PR BID or TID (maximum, 10 mg/day); 40 to 85 pounds: 2.5 mg PR TID or 5 mg PR BID (maximum, 15 mg/day).

D. IV FLUIDS: 1 to 2 L NS in dehydrated adult patients with excessive vomiting.

## 6.2 NON-PHARMACOLOGIC TREATMENT

### A. ENVIRONMENTAL STIMULATION, DECREASED

1. If possible, environmental stimulation should be decreased by allowing the patient to rest in a quiet, darkened room (Saper, 1989).

### B. BEHAVIORAL THERAPY

1. INDICATIONS: Treatment option for prevention of migraine in patients who have one or more of the following characteristics (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Poor tolerance or poor response to drug therapy.
  - b. Medical contraindication to drug therapy
  - c. History of long-term, frequent, or excessive use of analgesics or other acute medications.
  - d. Significant stress or deficient stress-coping skills.
  - e. Pregnancy, planned pregnancy, or nursing.
2. TECHNIQUES: Include relaxation training, biofeedback therapy, and cognitive-behavioral (stress management) training. Relaxation techniques and biofeedback may be combined with preventive drug therapy (ie., propranolol or amitriptyline) to achieve additional clinical improvement (Silberstein, 2000, per US Headache Consortium practice guidelines).

### C. COMPRESSION, ARTERY

1. Common carotid artery compression may transiently diminish headache intensity on the ipsilateral side in 50% to 70% of patients examined during an attack (Saper, 1989).
2. Temporal artery pressure occasionally relieves the headache as well. Use of an elastic headband to apply local pressure has been described (Vijayan, 1993).

## 6.3 PHARMACOLOGIC TREATMENT

### A. OVERVIEW

1. GOALS OF ACUTE MIGRAINE MANAGEMENT (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. Treat attacks rapidly and consistently and eliminate recurrence of attack.
  - b. Restore patient's ability to function.
  - c. Minimize use of back-up and rescue medications.
  - d. Optimize self-care and reduce subsequent use of resources.
  - e. Institute cost-effective approaches for overall management.
  - f. Minimize or avoid adverse events.

2. DRUGS OF CHOICE: Headaches of different types and severity respond to specific agents, even though no data support this impression (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - a. MIGRAINE-SPECIFIC MEDICATIONS: Patients with more severe migraine and those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine.
    - (1) TRIPTANS: Appropriate initial treatment choice with patients with moderate to severe migraine. Do not use with ergots.
    - (2) ERGOTS (dihydroergotamine (DHE), ergotamine): Moderate to severe migraine; less severe migraine when nonopiate medications fail. DHE IV plus an antiemetic is used for status migrainosus and is therapy of choice in the ED. Do not use with triptans.
  - b. NONSPECIFIC MEDICATIONS:
    - (1) ANTIEMETICS: Adjunct therapy; may be choice for acute therapy. An antiemetic should not be limited to patients who have vomiting or who are likely to vomit because nausea is one of the most disabling symptoms of a migraine attack. Combination of an antiemetic and an oral migraine drug may be appropriate in some patients. Prochlorperazine IM/IV adjunct first-line therapy in ED.
    - (2) NSAIDS/NONOPIATE ANALGESICS: First-line treatment choice for mild to moderate attacks. Consider ketorolac in ED.
    - (3) OPIATE ANALGESICS: Moderate to severe migraine; rescue therapy. Parenteral opiates reserved for ED use or rescue therapy.
    - (4) STEROIDS (IV): Given with antiemetic for rescue therapy in status migrainosus.
3. ROUTE: Select a nonoral route of administration for patients whose migraines are characterized by nausea or vomiting early in course of attack (Silberstein, 2000, per US Headache Consortium practice guidelines).
4. RESCUE MEDICATION: Consider use of a self-administered rescue medication for patients with severe migraines that fail to respond well to other treatments. A rescue medication is used at home when other migraine treatments fail to provide relief. While a rescue medication may not completely eliminate the pain, it can provide relief and obviate the need for the patient to visit the physician's office or ED (Silberstein, 2000, per US Headache Consortium practice guidelines).
5. MEDICATION-OVERUSE HEADACHES: Acute therapy should be reserved for those patients who regularly have two or more headache days per week. Preventive therapy may be considered in patients suspected of medication overuse (Silberstein, 2000, per US Headache Consortium practice guidelines).

## B. ANTIEMETICS

### 1. OVERVIEW

- a. INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - (1) Migraine associated with nausea and/or vomiting. Antiemetics should not be limited to patients who have vomiting or who are likely to vomit because nausea is one of the most disabling symptoms of a migraine attack. Combination of an antiemetic and an oral migraine drug may be appropriate in some patients.
  - (2) Treatment of status migrainosus, in combination with IV dihydroergotamine (DHE); a therapy of choice in ED.
- b. ROUTE: Intravenously, intramuscularly, or per rectum; oral antiemetics may be used as adjunct in treatment of migraine-associated nausea (Silberstein, 2000, per US Headache Consortium practice guidelines).
- c. DRUGS OF CHOICE (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - (1) Prochlorperazine IM/IV is adjunct first-line therapy in ED; PR route is adjunct in treatment of acute migraine with nausea and vomiting.
  - (2) Chlorpromazine IM/IV is adjunct therapy; may be first choice for acute therapy.
  - (3) Metoclopramide IM/IV/PR is adjunct therapy; may be first choice for acute therapy; IV route may be considered as monotherapy for migraine pain relief.
  - (4) Serotonin receptor (5-HT<sub>3</sub>) antagonists may be considered as adjunct therapy to control nausea in select patients with migraine attacks, but are not effective as monotherapy for migraine pain relief.

### 2. PROCHLORPERAZINE

- a. INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - (1) Parenteral prochlorperazine is adjunct first-line therapy in ED (Grade B recommendation - some evidence from randomized clinical trials support recommendation but scientific support not optimal). Statistical and clinical benefits are proven and pronounced for IV route and moderate for IM and PR routes.
  - (2) Intravenous prochlorperazine plus IV dihydroergotamine (DHE) is appropriate treatment choice for severe migraine (including status migrainosus) and a therapy of choice in emergency department (Grade B recommendation, as above).

(3) Consider rectally as adjunct in treatment of acute migraine with nausea and vomiting (Grade C recommendation - consensus on recommendation in absence of relevant randomized controlled trials.)

b. RECOMMENDATION:

(1) INTRAVENOUS: ADULTS: 10 milligrams intravenously over 2 to 3 minutes once (Dalessio, 1990), PLUS/MINUS dihydroergotamine. As a wide range of doses may be effective (3.5 to 30 mg), it is recommended that prochlorperazine be titrated to effect (Ducharme, 1999).

(2) INTRAMUSCULAR:

(a) ADULTS: 5 to 10 milligrams intramuscularly every four hours PRN (Dalessio, 1990).

(b) CHILDREN LESS THAN 12 YEARS: 0.06 milligram/pound deep intramuscularly.

(3) RECTAL:

(a) ADULTS: 25 milligrams rectally twice a day PRN (Dalessio, 1990).

(b) CHILDREN OVER 2 YEARS 20 to 29 pounds: 2.5 milligrams rectally once or twice daily (maximum, 7.5 milligrams/day); 30 to 39 pounds: 2.5 milligrams rectally two or three times a day (maximum, 10 milligrams/day); 40 to 85 pounds: 2.5 milligrams rectally three times a day or 5 milligrams twice a day (maximum, 15 milligrams/day).

c. AVAILABLE FORMS: Compazine(R) (injection, suppository).

d. DOSING IN SPECIAL SITUATIONS: Reduce dose in severe liver disease; dose reduction not required in renal insufficiency.

e. MAJOR ADVERSE REACTIONS: Extrapyramidal reactions (dystonias that may mimic tetanus); hepatotoxicity; blood dyscrasias (granulocytopenia, thrombocytopenia); adverse reactions with prolonged use.

f. PRECAUTIONS: Contraindicated in severe hypotension and in patients with bone marrow depression; caution in glaucoma, hepatic dysfunction, and prostatic hypertrophy.

g. MONITORING PARAMETERS: Monitor for dystonic reactions.

h. EFFICACY:

(1) The results of a randomized, double-blind trial suggest that IV prochlorperazine alone is an effective treatment for patients with severe vascular headaches who present to the ED; of the 23 patients with migraine, 74% had complete relief within 50 minutes of a 10-mg the injection (Jones, 1989).

(2) Rectal prochlorperazine (25 mg) provided excellent pain relief within 2 hours in one study (Jones, 1994).

(3) Relieves headache and tends to improve nausea more effectively than metoclopramide (Ducharme, 1999; Coppola, 1995).

(4) Produced greater decrease in pain scores than IV ketorolac (Seim, 1998).

3. CHLORPROMAZINE

a. INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) Adjunct in treatment of acute migraine with nausea and/or vomiting (Grade B recommendation - some evidence from randomized clinical trials support recommendation but scientific support not optimal). Statistical and clinical benefits are proven and pronounced for IV route and moderate for IM route.

(2) Intravenous chlorpromazine plus IV dihydroergotamine (DHE) is appropriate treatment choice for severe migraine (including status migrainosus) and a therapy of choice in emergency department (Grade B recommendation, as above).

b. RECOMMENDATION: Orthostatic hypotension is much greater with IV dosing but can be minimized by pretreatment with a 500-mL bolus of NS or 5 mL/kg IV fluid (Ducharme, 1999; Dalessio, 1990).

(1) INTRAVENOUS (status migrainosus): ADULTS: 7.5 to 10 milligram intravenous boluses over three minutes every seven to ten minutes; maximum total dose, 30 milligrams (Dalessio, 1990), or 0.1 milligram/kilogram intravenously over one to two minutes every fifteen minutes to maximum of three doses (Cameron, 1995), PLUS dihydroergotamine.

(2) INTRAMUSCULAR:

(a) ADULTS: 25 milligrams intramuscularly; if no hypotension occurs, then 25 to 50 milligrams may be given every three to four hours as needed until vomiting stops

(b) CHILDREN 6 to 11 years: 0.5 milligram/kilogram intramuscularly every six to eight hours (maximum daily dose, 40 to 75 milligrams, depending on age).

c. AVAILABLE FORMS: Thorazine(R) (injection, suppository).

d. DOSING IN SPECIAL SITUATIONS: Caution in patients under 18 years and over 60 years of age; reduce dose in hepatic insufficiency and in severe renal failure.

e. MAJOR ADVERSE REACTIONS: Blood dyscrasias; orthostatic hypotension; extrapyramidal reactions; hepatotoxicity; adverse reactions with prolonged use.

f. PRECAUTIONS: Caution in patients with epilepsy, glaucoma, liver disease, and in pregnancy; absorption decreased with concomitant antacids; may enhance effects of phenytoin, antidepressants, propranolol; may reduce effects of guanethidine, levodopa.

g. MONITORING PARAMETERS: Blood pressure prior to and after parenteral administration.

h. EFFICACY:

(1) INTRAMUSCULAR: A prospective, randomized, double-blind, placebo-controlled study found that IM chlorpromazine provides some relief from migraine but is less effective than suggested by earlier reports; it is most effective in improving the nausea that often accompanies migraine (McEwen, 1987).

(2) INTRAVENOUS:

(a) A randomized, double-blind, controlled study of chlorpromazine vs meperidine with dimenhydrinate suggests IV chlorpromazine is an effective treatment in the ED for fixed migraine headaches and avoids the potential problems of narcotic addiction/abuse (Lane, 1989).

(b) A single-blind, randomized study in the ED comparing chlorpromazine, dihydroergotamine, and lidocaine favored chlorpromazine in measures of headache relief, incidence of headache rebound, and patient satisfaction with therapy (Bell, 1990).

(c) A double-blind trial comparing chlorpromazine with metoclopramide found similar efficacy and adverse effects (Cameron, 1995).

#### 4. METOCLOPRAMIDE

a. INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) PARENTERAL: IM/IV route is adjunct to control nausea (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials) and may be considered as IV monotherapy for migraine pain relief (Grade B recommendation - some evidence from randomized clinical trials support recommendation but scientific support not optimal). Statistical and clinical benefits are moderate for IV route; evidence is conflicting or inconsistent for IM route.

(2) RECTAL: Adjunct to control nausea (Grade B recommendation, as above). Evidence for efficacy is conflicting or inconsistent.

b. RECOMMENDATION: ADULTS: 10 milligrams intravenously (over 15 minutes) or intramuscularly every three to four hours PRN (Dalessio, 1990); or 0.1 milligram/kilogram intravenously over one to two minutes every fifteen minutes (maximum, three doses) (Cameron, 1995).

c. AVAILABLE FORMS: Reglan(R) (injection); generic injection.

d. MAJOR ADVERSE REACTIONS: Central nervous system (dizziness, restlessness, fatigue, extrapyramidal reactions, drowsiness, anxiety), gastrointestinal (nausea, diarrhea), and hypertension. Children under 12 years of age may have a lower threshold for extrapyramidal effects (Diener, 1998).

e. PRECAUTIONS: Contraindicated when stimulation of GI motility might be dangerous (hemorrhage, perforation, obstruction), in hypersensitivity, and in epileptics or patients receiving drugs likely to cause extrapyramidal reactions.

f. EFFICACY:

(1) Was shown effective in the treatment of both pain and nausea in double-blind studies in patients with acute migraine (Tek, 1990; Ellis, 1993).

(2) Combination of metoclopramide and DHE was more effective than an IM narcotic plus an antiemetic for treatment of severe migraine (Klapper, 1993).

(3) Metoclopramide IV and chlorpromazine IV are similarly effective in acute migraine (Cameron, 1995).

(4) A combination of lysine acetylsalicylate (equivalent to 900 mg aspirin) with 10 mg metoclopramide PO was as effective as 100 mg sumatriptan PO for migraine but more effective in treatment of nausea and better tolerated (Tfelt-Hansen, 1995).

### C. ERGOTS

#### 1. OVERVIEW

a. INDICATIONS: Moderate to severe migraine. Combination of an antiemetic and an oral migraine drug may be appropriate in some patients (Silberstein, 2000, per US Headache Consortium practice guidelines).

b. DRUGS OF CHOICE (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) DIHYDROERGOTAMINE (DHE): Migraine-specific medication for patients with moderate to severe migraine (including those with nausea and vomiting) or with less severe migraine when nonopiate medications fail. IV DHE plus antiemetics is a therapy of choice in ED, including patients with severe migraine/status migrainosus.

(2) ERGOTAMINE (with/without caffeine): Select patients with moderate to severe migraine.

- c. ROUTE: Select a nonoral route of administration for patients whose migraines are characterized by nausea or vomiting early in course of attack (Silberstein, 2000, per US Headache Consortium practice guidelines).
- d. CONTRAINDICATIONS: Ergot alkaloids and derivatives induce sustained coronary artery and peripheral arterial contraction and are contraindicated in patients with coronary artery or peripheral vascular disease, Raynaud's disease, hypertension, and pregnancy (Ducharme, 1999; Diener, 1998). Therapeutic plasma concentrations of these drugs do not reach levels likely to cause myocardial ischemia in patients with normal coronary arteries (Maassen VanDenBrink, 1998). Do not use with triptans.

## 2. DIHYDROERGOTAMINE

- a. INDICATIONS: A migraine-specific agent such as dihydroergotamine (DHE) should be used in patients with moderate to severe migraine or whose mild to moderate headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine. All routes are of proven pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).
- b. ROUTE (Silberstein, 2000, per US Headache Consortium practice guidelines):
  - (1) DHE IV PLUS ANTIEMETICS: Severe migraine (including status migrainosus); a therapy of choice in emergency department (Grade B - some evidence from randomized clinical trials support recommendation but scientific support not optimal).
  - (2) DHE SC/IV/IM: Moderate to severe migraine or when less severe migraine when nonopiate medications fail; treatment option for patients with nausea and vomiting (Grade B - as above).
  - (3) DHE NASAL SPRAY: Moderate to severe migraine or when nonopiate analgesics fail; treatment option for patients with nausea and vomiting. (Grade A - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings).
- c. RECOMMENDATION:
  - (1) INTRAVENOUS: ADULTS: Approximately 10 minutes after pretreatment with an antiemetic, give 0.5 to 1 milligram intravenously slowly over three to four minutes; if necessary, repeat 0.5 to 1 milligram in one hour to a maximum dose of 2 milligrams; not to be repeated in less than four days; do not exceed 5 milligrams/week (Maizels, 1998; Raskin, 1990a; Dalessio, 1990).
  - (2) INTRAMUSCULAR: ADULTS: 1 milligram intramuscularly at first sign of headache; may repeat twice at one-hour intervals to a total of 3 milligrams/attack (Med Lett, 1998a).
  - (3) NASAL SPRAY: ADULTS: 0.5 milligram per nostril (single spray); repeat after 15 minutes (2 milligrams/dose; maximum, 3 milligrams/24 hours) (Bartleson, 1999; Med Lett, 1998a).
  - (4) SUBCUTANEOUS: ADULTS: 1 milligram subcutaneously may repeat at one-hour intervals to total dose of 3 milligrams/attack.
- d. AVAILABLE FORMS: DHE 45(R) (injection); Migranal(R) (nasal spray).
- e. MAJOR ADVERSE REACTIONS: Nausea, vomiting, diarrhea; pale or cold hands or feet; blisters on hands/feet; numbness/tingling; swelling of feet or lower legs; rhinitis (with nasal administration).
- f. PRECAUTIONS: Contraindicated in patients with ischemic or vasospastic coronary artery disease, uncontrolled hypertension, or who are receiving concurrent ergotamine-containing preparations within 24 h; caution in patients at high risk of unrecognized coronary disease or with hemiplegic or basilar migraine. Do not use with triptans.
- g. EFFICACY:
  - (1) Onset of action occurs in 15 to 30 minutes following IM administration and persists for three to four hours (Saadah, 1992a).
  - (2) Dihydroergotamine plus prochlorperazine or metoclopramide is a safe and effective treatment of acute migraine in the ED and a useful alternative to narcotics (Maizels, 1998; Callahan, 1986; Klapper, 1993).
  - (3) In a randomized, single-blind study, only 53% of patients treated with IV dihydroergotamine had persistent relief of headache 12 to 24 h after treatment compared with 89% of patients treated with IV chlorpromazine (Bell, 1990).
  - (4) DHE SC provides less pain relief than sumatriptan SC at 1 h but not at 3 or 4 h; DHE has lower rate of headache recurrence within 24 h (Maizels, 1998). DHE SC by home injection is effective in over 2/3 of patients, although side effects are main reason for stopping the drug (Becker, 1996; Klapper, 1992).
  - (5) DHE nasal spray is less effective than SC sumatriptan for acute self-treatment of migraine (Touchon, 1996).

## 3. ERGOTAMINE

- a. INDICATIONS: Oral and rectal ergotamine (and caffeine combination) may be considered in select patients with moderate to severe migraine (Grade B - some evidence from randomized clinical trials support recommendation but scientific support not optimal). Evidence for efficacy for both routes is conflicting or inconsistent (Silberstein, 2000, per US Headache Consortium practice guidelines).

b. RECOMMENDATION (Bartleson, 1999; Med Lett, 1998a; Dalessio, 1990):

(1) ORAL:

(a) ADULTS: 2 tablets orally at onset of attack, then 1 tablet every 30 minutes times four; maximum: 6 tablets/24 hours.

(b) CHILDREN: 1 milligram orally at onset of pain; repeat every 30 minutes, up to three doses in children less than twelve years and no more than six doses per headache regardless of age.

(2) SUBLINGUAL: ADULTS: Place 1 tablet (2 milligrams) under tongue at onset of attack; may repeat every 30 minutes times two PRN; maximum: 6 milligrams (3 tablets)/24 hours.

(3) RECTAL:

(a) ADULTS: 1 suppository (2 milligrams) rectally; may repeat once after 60 minutes if necessary; maximum: two suppositories/24 hour.

(b) CHILDREN less than 12 years: 1 suppository (2 milligrams) rectally once.

c. AVAILABLE FORMS: Ergostat(R) (tablets); Ergomar(R) (sublingual tablets); Cafergot(R) (tablets, suppository; contains 100 mg caffeine).

d. MAJOR ADVERSE REACTIONS: Nausea and vomiting; diarrhea; cramping; paresthesias; peripheral vascular insufficiency; gangrene of extremities (rare); angina; ergotism in large doses.

e. PRECAUTIONS: Contraindicated in peripheral vascular disease, severe hypertension, angina, peptic ulcer; avoid in renal or hepatic disease, pregnancy, and sepsis; dependence may occur with prolonged use. Do not use with triptans.

f. MONITORING PARAMETERS: Symptoms of angina or peripheral ischemia.

## D. TRIPTANS

### 1. OVERVIEW

a. INDICATIONS: Migraine-specific medication for patients with moderate to severe migraine (including those with nausea and vomiting) or for migraine of any severity when nonopiate medications fail to provide adequate relief (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials). All agents/routes are of proven pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

b. DRUGS OF CHOICE: Initial treatment with any triptan is a reasonable choice (Silberstein, 2000, per US Headache Consortium practice guidelines). Options include sumatriptan (subcutaneous, oral, intranasal), zolmitriptan (oral), naratriptan (oral), rizatriptan (oral).

(1) Sumatriptan nasal spray or SC injection preferred for patients if fast onset of action is particularly important or when nausea/vomiting is significant.

(2) Naratriptan preferred for patients if recurrent headache is a problem.

(3) Zolmitriptan and rizatriptan have consistent efficacy across different migraine types (menstrual, with or without aura).

(4) Rizatriptan is available in both conventional and orally disintegrating tablets.

### 2. SUMATRIPTAN

a. INDICATIONS: Migraine-specific medication for patients with moderate to severe migraine or for migraine of any severity when nonopiate medications fail to provide adequate relief (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials.) (Silberstein, 2000, per US Headache Consortium practice guidelines). Useful for both ED treatment and self-treatment (Med Lett, 1998a; Diamond, 1997; Mathew, 1997).

b. ROUTE:

(1) Subcutaneous injection and intranasal routes preferred for patients if fast onset of action is particularly important (ie, severe migraine) and for those experiencing nausea and vomiting (Ryan, 1997; Mathew, 1997; Rapoport, 1997).

(2) Oral administration useful in patients who are unwilling/unable to self-administer injection or who have relatively less severe migraine symptoms and those with slow-onset migraine (Mathew, 1997).

c. RECOMMENDATION:

(1) SUBCUTANEOUS: ADULTS: 6 milligrams subcutaneously in lateral thigh; may repeat in one hour, up to 12 milligrams/24 hours (Med Lett, 1998; Diamond, 1997). May be autoinjected by patient (upper lateral quadrant of gluteal area may be more suitable injection site, especially in males) (Frid, 1997)).

(2) INTRANASAL: ADULTS: 5 or 20 milligrams intranasally; may repeat once after two hours; maximum, 40 milligrams/24 hours (Med Lett, 1998a, 1998).

(3) ORAL: ADULTS: 25 or 50 milligrams orally; may repeat in two hours; maximum dose, 200 milligrams/24 hours (Bartleson, 1999; Med Lett, 1998a, 1998).

- d. AVAILABLE FORMS: Imitrex(R) (injection, tablets, nasal spray).
- e. MAJOR ADVERSE REACTIONS: Tingling, dizziness, warm/hot/burning sensation, injection site reactions, drowsiness, sedation, flushing, weakness, neck pain or stiffness; chest, jaw, neck tightness (less frequent with nasal form), nasal discomfort (with intranasal administration), loss of vision.
- f. PRECAUTIONS: Contraindicated for IV use and in patients with ischemic heart disease or vasospastic coronary artery disease, uncontrolled hypertension, or who are receiving concurrent ergotamine-containing preparations; caution in patients at high risk of unrecognized coronary disease. Do not give to patients with hemiplegic or basilar migraine.
- g. EFFICACY: Safe and effective abortive antimigraine agent with minimal side effects; relieves headache of migraine with and without aura; also decreases nausea and vomiting. Multiple headache recurrence is major limitation (recurs within 24 h in 35% to 45% of initial responders) (Visser, 1996).

(1) SUBCUTANEOUS:

- (a) Single 6-mg dose high effective, rapid-acting, and well tolerated; overall response rate of 70% to 80% in 1 hour (Gobel, 1999; Akpunonu, 1995; Cady, 1991; Subcutaneous Sumatriptan Intl Study Group, 1991; Schoenen, 1994; Visser, 1992; Hay, 1994; Portuguese Sumatriptan Auto-injector Study Group, 1994; Sheftell, 1994).
- (b) Administration of sumatriptan too early (ie, during aura phase) is strongest indicator for nonresponse (Visser, 1996a).
- (c) Self-administration at beginning of headache significantly reduces productivity loss in the workplace (Schulman, 2000; Bartleson, 2000; Cady, 1998).
- (d) When used according to labeled directions, is unaffected by concomitant drugs (Putnam, 1999).

(2) ORAL:

- (a) Relieves headache in about 70% of patients within 4 h of dosing (Ryan, 1997; Oral Sumatriptan Intl Multiple-Dose Study Group, 1991). Also maintains efficacy in repeated episodes of migraine (Cady, 1993; Ferrari, 1994).
- (b) Appears less effective in children, indicating that children may respond differently to oral sumatriptan than do adults (Hamalainen, 1997a).
- (c) A small retrospective chart review and prospective treatment study of 50 migraineurs with frequent recurrence after oral sumatriptan showed that tolfenamic acid (200 mg PO) given with sumatriptan reduced headache recurrence from 62% to 24% (significance unknown) (Krymchantowski, 1999).

(3) INTRANASAL:

- (a) Compared with SC and PO form, nasal spray provides intermediate route of administration. Lower response rate and slower onset of action than SC formulation; overall response rate of 55% to 70% at 2 h (Gallagher, 1996; Finnish Sumatriptan Group and Cardiovascular Clinical Res Group, 1991). Onset of pain relief may be slightly sooner than with PO form.
- (b) More effective than intranasal dihydroergotamine for acute self-treatment of acute migraine (Boureau, 2000; Touchon, 1996).
- (c) Has been found effective in relieving migraine pain in children (Ueberall, 1999) and adolescents (Winner, 2000), with minimal adverse effects.

h. ECONOMICS (Lofland, 1999):

- (1) A moderate-sized prospective and retrospective study by the manufacturer showed a significant decrease in the number of primary care office visits (by 40%) and ED (by 80%) in the 6 mo following the first sumatriptan prescription vs the prior 6 mo.
- (2) Reported missed workdays, time worked with migraine symptoms, reported days missed from nonwork activities, and days of nonwork activities done with migraine symptoms were all decreased at 6 mo after starting sumatriptan. Total disability time after sumatriptan fell from 16 to 8 days over 3 months.

### 3. ZOLMITRIPTAN

- a. INDICATIONS: Migraine-specific medication for patients with moderate to severe migraine or for migraine of any severity when nonopioid medications fail to provide adequate relief (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials). Of proven and pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines). Some patients who fail to respond to sumatriptan may respond to zolmitriptan (Med Lett, 1998).
- b. RECOMMENDATION: ADULTS: 2.5 or 5 milligrams orally initially (tablet can be broken in half); may repeat in two hours; maximum dosage, 10 milligrams/24 hours (Med Lett, 1998a, 1998).

- c. AVAILABLE FORMS: Zomig(R) (tablets).
- d. MAJOR ADVERSE REACTIONS: Paresthesias, nausea, dizziness, malaise, drowsiness most common; cardiac events (rare).
- e. PRECAUTIONS: Contraindicated in patients with history of cardiac, cerebrovascular, or peripheral vascular syndromes, or underlying cardiovascular diseases. Caution in patients with impaired liver function.
- f. MONITORING PARAMETERS: Relief of headache symptoms; periodic interval cardiovascular evaluation recommended.
- g. EFFICACY: In double-blind, placebo-controlled trials involving 1326 patients with moderate to severe migraine, response rates with zolmitriptan were 44% at 1 h, 62% to 65% at 2 h, and 74% at 4 hr (Rapoport, 1997a; Solomon, 1997).

#### 4. NARATRIPTAN

- a. INDICATIONS: Migraine-specific medication for patients with moderate to severe migraine or for migraine of any severity when nonopiate medications fail to provide adequate relief (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials) (Silberstein, 2000, per US Headache Consortium practice guidelines). Of proven and pronounced statistical and clinical benefit. Because of longer half-life (6 h) than other triptans, recurrence rate is lower.
- b. RECOMMENDATION: ADULTS: 1- or 2.5-milligram tablet orally with fluid; may repeat once after four hours; maximum dosage, 5 milligrams/24 hours (Med Lett, 1998a; Mathew, 1997a).
- c. AVAILABLE FORMS: Amerge(R) (tablets).
- d. MAJOR ADVERSE REACTIONS: Paresthesias, nausea, dizziness, malaise, drowsiness most common; angina, myocardial infarction; colonic ischemia; dyspnea; cerebral vascular accident; subarachnoid hemorrhage; anaphylaxis/anaphylactoid reactions.
- e. PRECAUTIONS: Contraindicated in patients with history of cardiac, cerebrovascular, or peripheral vascular syndromes, or underlying cardiovascular diseases. Caution in patients with severe renal or liver impairment.
- f. MONITORING PARAMETERS: Relief of headache symptoms. Liver and renal function tests should be determined prior to and during prolonged treatment. Periodic interval cardiovascular evaluation recommended.

#### 5. RIZATRIPTAN

- a. INDICATIONS:
  - (1) Migraine-specific medication for patients with moderate to severe migraine or for migraine of any severity when nonopiate medications fail to provide adequate relief (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials). Of proven and pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).
  - (2) Effective in treatment of menstrual migraine; relieves pain, associated migraine symptoms, and functional disability, and reduces need for rescue medications (Silberstein, 2000a).
- b. RECOMMENDATION: ADULTS: 5- or 10-milligram tablet or wafer; may repeat in 2 hours if needed; maximum dosage, 30 milligrams/24 hours (15 milligrams/24 hours for patients using propranolol) (Med Lett, 1998a).
- c. AVAILABLE FORMS: Maxalt(R) (tablets); Maxalt-MLT(R) (orally disintegrating tablets).
- d. MAJOR ADVERSE REACTIONS: Dizziness, drowsiness, fatigue, paresthesias, nausea, dry mouth, syncope.
- e. PRECAUTIONS: Contraindicated in patients with hypersensitivity to rizatriptan, ischemic heart disease or Prinzmetal's angina, uncontrolled hypertension, or who are receiving concurrent ergotamine-containing preparations or MAO inhibitors. Caution in patients at high risk of unrecognized coronary disease, asthma, pregnancy, renal or hepatic insufficiency. Do not give to patients with hemiplegic or basilar migraine.
- f. EFFICACY:
  - (1) Randomized, double-blind, placebo-controlled trial found rizatriptan given in 10- or 20-milligram doses as effective as 100-milligram dose of sumatriptan and superior to placebo. Although rizatriptan given in 40-milligram dose is superior to placebo and sumatriptan, 40-milligram dose is poorly tolerated due to high frequency of adverse reactions (Visser, 1996b).
  - (2) In a controlled, multicenter, outpatient study, onset of action was seen as early as 30 minutes after 10-mg oral dose. Pain relief was apparent in 70% of patients at 2 h; in patients with recurrent headache, a second 10-mg dose provided further pain relief in 80%, with complete relief in 50% (Teall, 1998).
  - (3) Tolerability and efficacy of rizatriptan 10 mg is maintained uniformly over a series of attacks (Kramer, 1998).
  - (4) In women with menstrual migraine, rizatriptan effectively relieved migraine in 70% vs 44% of placebo patients (Silberstein, 2000a).

## E. ANALGESICS

### 1. OVERVIEW

a. INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) NONOPIATE ANALGESICS:

(a) ORAL: The favorable tolerability of oral NSAIDs and combination products make these agents a reasonable first-line treatment choice for mild to moderate migraine attacks or severe attacks that have been responsive in the past to similar NSAIDs or nonopiate analgesics. (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings.)

(b) IM: Ketorolac is an option that may be used in a physician-supervised setting, although conclusions regarding clinical efficacy cannot be made at this time. (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials.). Consider for use in ED.

(2) OPIATE ANALGESICS:

(a) ORAL COMBINATIONS: May be considered for use in acute migraine when sedation side effects will not put patient at risk and/or risk for abuse has been addressed (Grade A recommendation, as above).

(b) PARENTERAL: May be considered for rescue therapy in a supervised setting when sedation side effects will not put patient at risk and when risk of abuse has been addressed (Grade B recommendation - some evidence from randomized trials but scientific information not optimal).

(c) BUTORPHANOL NASAL SPRAY: Treatment option for some patients with migraine (Grade A recommendation, as above). May be considered when other medications cannot be used or as a rescue medication when significant sedation would not jeopardize the patient (Grade C recommendation, as above). Limit use due to increased risk of headache rebound and dependency.

### 2. MEPERIDINE

a. INDICATIONS: Reserved for ED use or as rescue medication. Limit use due to increased risk of headache rebound and dependency. May be considered for rescue therapy in a supervised setting when sedation side effects will not put patient at risk and when risk of abuse has been addressed (Grade B recommendation - some evidence from randomized trials but scientific information not optimal). Of moderate statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

b. RECOMMENDATION: ADULTS: 50 to 150 milligrams intramuscularly or subcutaneously every four hours; maximum, 400 milligrams (Bartleson, 1999).

c. AVAILABLE FORMS: Demerol(R) (injection).

d. DOSING IN SPECIAL SITUATIONS: Reduce dose in patients with hepatic disease. Geriatric patients should be initiated on reduced doses and titrated according to response. Reduce dose (usually by 25% to 50%) when administering concomitantly with phenothiazines and other tranquilizers.

e. MAJOR ADVERSE REACTIONS: Respiratory depression; hypotension; respiratory arrest or cardiac arrest (with rapid IV doses); tachycardia; nausea and vomiting.

f. PRECAUTIONS: Contraindicated in patients with respiratory depression or coma unless intubated and in patients receiving MAO inhibitors. Use with caution in the presence of convulsions, shock, asthma, renal failure, COPD, atrial flutter, or supraventricular tachycardia.

g. MONITORING PARAMETERS: Respiratory and cardiovascular parameters following parenteral administration.

h. EFFICACY:

(1) Studies concerning the efficacy of meperidine in migraine treatment and relative efficacy compared with other migraine drugs are conflicting. There is no good study that supports routine use (Ducharme, 1999).

(2) Nonopiate therapies such as IM dihydroergotamine and IV chlorpromazine are of equal or superior efficacy to meperidine and avoid common problems with opioids such as dizziness, dependence, respiratory depression, and requests for their use (Ducharme, 1999; Carleton, 1998).

(3) When combined with promethazine or hydroxyzine, potentiation of analgesia and addition of antiemetic effects occur.

### 3. BUTORPHANOL

a. INDICATIONS: Limit use due to increased risk of headache rebound and dependency (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) NASAL SPRAY: Treatment option for patients with moderate to severe migraine (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings.). May be considered when other medications cannot be used or as a rescue

medication when significant sedation would not jeopardize the patient (Grade C - consensus achieved in absence of relevant randomized controlled trials). Of proven and pronounced statistical and clinical benefit. Poor tolerance is often limiting factor for routine use, with adverse psychotropic effects, nausea and vomiting, and dizziness often rated as intense (Ducharme, 1999; Rapoport, 1997).

(2) IM: Reserved for ED use or as rescue medication. Limit use due to increased risk of headache rebound and dependency. May be considered for rescue therapy in a supervised setting when sedation side effects will not put patient at risk and when risk of abuse has been addressed (Grade B recommendation - some evidence from randomized trials but scientific information not optimal). Of moderate statistical and clinical benefit.

b. RECOMMENDATION:

(1) NASAL SPRAY: ADULTS: 1 milligram (1 spray in one nostril); may repeat in other nostril if adequate pain relief does not occur within 60 to 90 minutes. Sequence may be repeated four hours after last spray (maximum, 3 to 4 sprays/24-hour period) (Med Lett, 1998a; Rapoport, 1997).

(2) IM: ADULTS: 2 milligrams intramuscularly, repeated every three to four hours as necessary.

c. AVAILABLE FORMS: Stadol NS(R) (nasal spray); Stadol(R) (injection).

d. MAJOR ADVERSE REACTIONS: Somnolence, dizziness, nausea and/or vomiting, nasal congestion, insomnia.

e. PRECAUTIONS: In patients with history of drug abuse; respiratory difficulty caused by uremia, severe infection, medication, asthma, obstructive respiratory conditions, or cyanosis; acute myocardial infarction, ventricular dysfunction, or cardiac insufficiency; head injuries; hepatic or renal impairment; hypertension; opioid-dependency.

f. MONITORING PARAMETERS: Withdrawal effects such as flushing and chills (may be precipitated in opioid-dependent persons at approximately one half the analgesic dose).

4. ANTI-INFLAMMATORY DRUGS, NONSTEROIDAL

a. OVERVIEW

(1) INDICATIONS (Silberstein, 2000, per US Headache Consortium practice guidelines):

(a) ORAL: Favorable tolerability makes these agents a first-line choice for treatment for mild to moderate migraine attacks and for severe attacks that have been responsive in the past to nonopioid medications (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings).

(b) IM: May be used in a physician-supervised setting, although conclusions regarding clinical efficacy cannot be made at this time (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials). Consider for use in ED.

(2) DRUGS OF CHOICE (Silberstein, 2000, per US Headache Consortium practice guidelines):

(a) ORAL: Most consistent evidence exists for aspirin, ibuprofen, and naproxen sodium; limited or inconsistent evidence exists for other NSAIDs (eg, diclofenac K, flurbiprofen, piroxicam). Choice should be governed by both drug and patient characteristics (Capobianco, 1996).

(b) IM: Ketorolac.

b. KETOROLAC

(1) INDICATIONS: Option that may be used in a physician-supervised setting, although conclusions regarding clinical efficacy cannot be made at this time (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials) (Silberstein, 2000, per US Headache Consortium practice guidelines). Of moderate statistical and clinical benefit. Consider for use in ED (Shrestha, 1996; Davis, 1993; Duarte, 1992; Harden, 1991).

(2) RECOMMENDATION (SINGLE-DOSE TREATMENT):

(a) ADULTS UNDER 65 YEARS: 60 milligrams intramuscularly or 30 milligrams intravenously as single dose.

(b) ADULTS OVER 65 YEARS, REDUCED RENAL FUNCTION, WEIGHING LESS THAN 50 KILOGRAMS: 30 milligrams intramuscularly or 15 milligrams intravenously as single dose.

(3) AVAILABLE FORMS: Toradol(R) (injection).

(4) DOSING IN SPECIAL SITUATIONS: Reduce dose in geriatrics, patients with reduced renal function, patients weighing less than 50 kg.

(5) MAJOR ADVERSE REACTIONS: Headache; dizziness; nausea and vomiting; pain on injection; acute renal failure with prolonged (over 5 day) use.

(6) PRECAUTIONS: Contraindicated if previous hypersensitivity (nasal polyps, angioedema, bronchospastic activity) to aspirin or NSAID, history of peptic ulcer disease or GI bleeding, presence of renal impairment or volume depletion.

(7) EFFICACY:

(a) In two studies, 75% to 100% of ED patients in headache crisis improved sufficiently to require no further emergent treatment following treatment with ketorolac (Harden, 1991; Davis, 1993).

(b) Was as effective as meperidine plus hydroxyzine (Duarte, 1992), IV chlorpromazine (Shrestha, 1996), and meperidine plus promethazine (Davis, 1995). However, in other studies, was found less effective than prochlorperazine (Seim, 1998), meperidine alone (Larkin, 1992), or DHE plus metoclopramide (Klapper, 1992).

c. IBUPROFEN

(1) INDICATIONS:

(a) Favorable tolerability makes oral NSAIDS such as ibuprofen a first-line choice for treatment for mild to moderate migraine attacks and for severe attacks that have been responsive in the past to nonopiate medications (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings). Of proven and pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

(b) Effective treatment for moderate to severe migraine attacks in children (Hamalainen, 1998, 1997).

(2) RECOMMENDATION:

(a) ADULTS: 600 to 1200 milligrams orally at onset, then 400 to 600 milligrams orally in one hour; maximum, 2.4 grams/day (Moore, 1997; Dalessio, 1990; Kloster, 1992).

(b) CHILDREN: 10 milligrams/kilogram orally; repeat once after two hours, then every four to six hours; maximum total dose, 40 milligrams/kilogram/day (Hamalainen, 1998).

(3) AVAILABLE FORMS: Motrin Migraine Pain(R) (tablets, gels, caplets); Motrin(R) (tablets); Nuprin(R) (tablets, caplets); Advil Migraine Liqui-Gels(R) (gelcaps); Advil(R) (tablets); Medipren(R) (tablets), or equivalent NSAID.

(4) DOSING IN SPECIAL SITUATIONS: Increase dosage interval in renal failure.

(5) MAJOR ADVERSE REACTIONS: Tinnitus; hearing loss; GI bleeding; cholestatic jaundice; anaphylaxis.

(6) PRECAUTIONS: Contraindicated in patients hypersensitive to aspirin or other NSAIDS; caution in active peptic ulcer disease, renal insufficiency, hepatic dysfunction, and patients with compromised cardiac function (edema); potentiates effects of warfarin; concomitant antacid administration may reduce absorption.

d. NAPROXEN

(1) INDICATIONS:

(a) Favorable tolerability makes oral NSAIDS such as naproxen a first-line choice for treatment for mild to moderate migraine attacks and for severe attacks that have been responsive in the past to nonopiate medications (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings). Statistical and clinical benefit are proven and pronounced for naproxen sodium and moderate for naproxen (Silberstein, 2000, per US Headache Consortium practice guidelines).

(b) Effective treatment for moderate to severe migraine attacks in children (Hamalainen, 1998, 1997).

(2) RECOMMENDATION:

(a) ADULTS: 275 to 825 milligrams orally loading dose, followed by 275 milligrams orally every four hours (maximum daily dose: 1250 milligrams) (Dalessio, 1990).

(b) CHILDREN: 5 to 7 milligrams/kilogram orally; repeat once after two to four hours; maximum total dose, 10 to 15 milligrams/kilogram/day (Hamalainen, 1998).

(3) AVAILABLE FORMS: Naprosyn(R) (tablets); Anaprox(R) (tablets), or equivalent.

(4) DOSING IN SPECIAL SITUATIONS: Dose reductions not required in liver disease.

(5) MAJOR ADVERSE REACTIONS: Tinnitus; hearing loss; GI bleeding; cholestatic jaundice; anaphylaxis.

(6) PRECAUTIONS: Contraindicated in patients hypersensitive to aspirin or other NSAIDS; caution in active peptic ulcer disease, renal insufficiency, hepatic dysfunction, and patients with compromised cardiac function (edema); potentiates effects of warfarin; concomitant antacid administration may reduce absorption.

e. ASPIRIN

(1) INDICATIONS: Favorable tolerability makes oral NSAIDS such as naproxen a first-line choice for treatment for mild to moderate migraine attacks and for severe attacks that have been responsive

in the past to nonopioid medications (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings). Of proven and pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

(a) May be used alone or in various combinations with caffeine, sedatives, and anti-anxiety agents (Lipton, 1998; Gilkey, 1996; Dalessio, 1990).

(b) Combination of acetaminophen, aspirin, and caffeine highly effective for treatment of mild to moderate migraine; also alleviates nausea, photophobia, phonophobia, and functional disability associated with migraine attacks (Lipton, 1998). FDA-approved for mild, moderate, and severe migraine pain and associated symptoms of the full migraine syndrome.

(c) Aspirin combined with codeine should be reserved for moderate attacks. One study showed no significant difference between the efficacy of aspirin 1000 mg and that of acetaminophen 400 mg with codeine 25 mg (Boureau, 1994).

(d) Intravenous aspirin (available in Europe) combined with IV metoclopramide had similar effectiveness to sumatriptan in migraine in two studies. Where available, aspirin (500 to 1000 mg) and metoclopramide as a combination are recommended as a first-line therapy for severe migraine (Diener, 1998).

(2) RECOMMENDATION:

(a) ADULTS: 500 to 1000 milligrams orally every four to six hours; maximum daily dosage, 4 grams (Bartleson, 1999; Moore, 1997).

(b) CHILDREN 6 to 11 years: 60 milligrams/year of age orally every four hours; maximum, 650 milligrams/dose.

(c) COMBINATION PRODUCT (aspirin, acetaminophen, caffeine): ADULTS & CHILDREN OVER 12 YEARS: 2 tablets or caplets orally every six hours while symptoms persist, not to exceed 8 tablets or caplets in 24 hours, or as directed by a physician. Do not take for more than 48 hours for the pain of migraine.

(3) AVAILABLE FORMS: Ecotrin(R); Bufferin(R), many other preparations; Excedrin Extra-Strength(R) (tablets, gels, caplets), Excedrin Migraine(R) (caplets) (acetaminophen, aspirin, and caffeine). Do not use enteric-coated ASA for migraine because of delayed onset of action.

(4) DOSING IN SPECIAL SITUATIONS: Dose reductions not required in impaired renal function but may exacerbate uremic symptoms; avoid in severe hepatic insufficiency.

(5) MAJOR ADVERSE REACTIONS: Increased bleeding time and potential bleeding episodes; hypersensitivity reaction (urticaria or anaphylaxis); hepatotoxicity with high doses; overdose toxicity (tinnitus); adverse reactions with prolonged use.

(6) PRECAUTIONS: Contraindicated in bleeding disorders, in last month of pregnancy, hypersensitivity to aspirin, and in viral illness (eg, influenza and chickenpox) in children because of possible association with Reye's syndrome; caution in asthma, nasal polyps, ulcers, and in patients receiving anticoagulants; many drug interactions.

## 5. ACETAMINOPHEN WITH ASPIRIN AND CAFFEINE

a. INDICATIONS: FDA-approved for mild, moderate, and severe migraine pain and associated symptoms of the full migraine syndrome.

(1) Favorable tolerability makes this combination drug a first-line treatment choice for mild to moderate migraine attacks and for severe attacks that have been responsive in the past to nonopioid medications (Grade A recommendation - evidence from multiple well-designed randomized clinical trials yielded consistent pattern of findings). Of proven and pronounced statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

(2) Also alleviates nausea, photophobia, phonophobia, and functional disability associated with migraine attacks (Lipton, 1998).

b. RECOMMENDATION: ADULTS & CHILDREN OVER 12 YEARS: 2 tablets or caplets orally every six hours while symptoms persist, not to exceed 8 tablets or caplets in 24 hours, or as directed by a physician. Do not take for more than 48 hours for the pain of migraine.

c. AVAILABLE FORMS: Excedrin Extra-Strength(R) (tablets, gels, caplets); Excedrin Migraine(R) (caplets).

d. DOSING IN SPECIAL SITUATIONS: Dose reduction not required in renal failure or geriatric patients; avoid in severe hepatic insufficiency.

e. MAJOR ADVERSE REACTIONS: Aspirin: increased bleeding time and potential bleeding episodes; hypersensitivity reaction (urticaria or anaphylaxis); hepatotoxicity with high doses; overdose toxicity (tinnitus). Acetaminophen: hepatotoxicity in overdose (adults); thrombocytopenia; hemolytic anemia (rare); adverse reactions during prolonged use. Caffeine: GI disturbances, nervousness, diuresis, irritability, tachycardia, tremulousness, tachypnea, muscle twitching, arrhythmias, palpitations, hyperventilation, flushing; may

interact with drugs that are substrates for, are inhibited by, or induce cytochrome P450 1A2 (CYP1A2).  
f. PRECAUTIONS: Aspirin contraindicated in bleeding disorders, in last month of pregnancy, hypersensitivity to aspirin, in viral illness (eg, influenza and chickenpox) in children because of possible association with Reye's syndrome; caution in asthma, nasal polyps, ulcers, and in patients receiving anticoagulants; many drug interactions. Use acetaminophen with caution in patients with G-6-PD deficiency. Limit use of caffeine-containing medications, foods, or beverages while taking this product.

## 6. ACETAMINOPHEN

### a. INDICATIONS:

- (1) Acetaminophen alone is not recommended for migraine but may be considered for use in children and pregnant women (Grade B recommendation -some evidence from randomized trials but scientific information not optimal). Proven to be statistically or clinically ineffective (Silberstein, 2000, per US Headache Consortium practice guidelines).
- (2) Combination of acetaminophen, aspirin, and caffeine highly effective for treatment of mild to moderate migraine; also alleviates nausea, photophobia, phonophobia, and functional disability associated with migraine attacks (Lipton, 1998). FDA-approved for mild, moderate, and severe migraine pain and associated symptoms of the full migraine syndrome. Of proven and pronounced statistical and clinical benefit.
- (3) Isometheptene mucate compound (isometheptene mucate 65 mg, dichloralphenazone 100 mg, and acetaminophen 325 mg) may be used in patients with mild to moderate migraine (Diamond, 1997; Dalessio, 1990). Of moderate statistical and clinical benefit
- (4) Acetaminophen with codeine may be used to treat moderate to severe migraine, but its use should be limited due to increased risk of headache rebound and dependency. Of moderate statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

### b. RECOMMENDATION:

- (1) ADULTS: 500 to 1000 milligrams orally every four to six hours; maximum daily dosage, 4 grams (Bartleson, 1999; Moore, 1997).
- (2) CHILDREN: 15 milligrams/kilogram orally; repeat once after two hours, then every four to six hours; maximum total dose, 100 milligrams/kilogram/day (Hamalainen, 1998).
- (3) COMBINATION PRODUCT (acetaminophen, aspirin, caffeine): ADULTS & CHILDREN OVER 12 YEARS: 2 tablets or caplets orally every six hours while symptoms persist, not to exceed 8 tablets or caplets in 24 hours, or as directed by a physician. Do not take for more than 48 hours for the pain of migraine.

c. AVAILABLE FORMS: Tylenol(R); many other preparations. Excedrin Extra-Strength(R) (tablets, gels, caplets), Excedrin Migraine(R) (caplets) (acetaminophen, aspirin, and caffeine).

d. DOSING IN SPECIAL SITUATIONS: Dose reduction not required in renal failure or geriatric patients.

e. MAJOR ADVERSE REACTIONS: Hepatotoxicity in overdose (adults); thrombocytopenia; hemolytic anemia (rare); adverse reactions during prolonged use.

f. PRECAUTIONS: Use with caution in patients with G-6-PD deficiency.

## 7. ISOMETHEPTENE

a. INDICATIONS: Isometheptene containing compounds (isometheptene mucate 65 mg, dichloralphenazone 100 mg, and acetaminophen 325 mg) may be used in patients with mild to moderate migraine (Grade B recommendation -some evidence from randomized trials but scientific information not optimal). Of moderate statistical and clinical benefit (Silberstein, 2000, per US Headache Consortium practice guidelines).

b. RECOMMENDATION: ADULTS: Two capsules at the onset of headache, then one capsule every hour until headache is gone; maximum dose, 8 capsules/24 hours (Bartleson, 1999; Dalessio, 1990).

c. AVAILABLE FORMS: Midrin(R) (capsules).

d. MAJOR ADVERSE REACTIONS: Agranulocytosis (due to dichloralphenazone component in Midrin(R) component); dizziness, palpitations, GI distress, sedation.

e. PRECAUTIONS: Contraindicated in glaucoma, severe renal disease, hepatic disease, and in patients receiving MAO inhibitors; caution in cardiovascular disease; Midrin(R) may potentiate effects of warfarin.

## 8. NITROUS OXIDE

a. May be efficacious in short-term treatment of migraine in the emergency department, but no large studies with follow-up periods greater than 1 h have been attempted (Triner, 1999).

b. A small (n=22) prospective, randomized, double-blind pilot study of adults showed that inhaling a 50%/50% mix of NO/O<sub>2</sub> for 20 min decreased pain significantly (on average 48 points on a 100-point Visual Analog Scale) as compared with inhaled 100% O<sub>2</sub> alone, which did not significantly decrease pain. Significantly fewer in the NO group did not require rescue medication in the 20 min following therapy (80% vs 17%). No follow-up beyond 20 min after therapy was done, so persistence of relief is unknown (Triner, 1999).

## F. LIDOCAINE

1. Evidence is insufficient to establish a defined role for intranasal or IV lidocaine in the management of acute migraine headache (Grade B recommendation -some evidence from randomized trials but scientific information not optimal). Evidence is of moderate statistical and clinical benefit for IN route, but IV route is proven to be statistically or clinically ineffective (Silberstein, 2000, per US Headache Consortium practice guidelines).

## G. STEROIDS

### 1. DEXAMETHASONE

#### a. INDICATIONS:

(1) A treatment choice for rescue therapy for patients with status migrainosus (Grade C recommendation - consensus achieved in absence of relevant randomized controlled trials) (Silberstein, 2000, per US Headache Consortium practice guidelines). First choice in some centers and may be used as an alternative to DHE when DHE is ineffective or contraindicated (eg, pregnancy, patients with coronary artery disease).

(2) Early administration of steroids has been reported to decrease the severity and duration of ophthalmoplegic migraine and to prevent or ameliorate the ophthalmoparesis (Smith, 1986).

#### b. RECOMMENDATION: Pretreat with an antiemetic, eg, prochlorperazine or metoclopramide.

(1) LONG-ACTING PREPARATION: ADULTS: 16 milligrams intramuscularly; limit to one dose (Dalessio, 1990; Freitag, 1991).

(2) INJECTABLE: ADULTS: 8 to 20 milligrams intravenously or intramuscularly; limit to one dose (Dalessio, 1990).

#### c. AVAILABLE FORMS: Decadron Injectable(R); Decadron LA(R).

#### d. DOSING IN SPECIAL SITUATIONS: Dosage adjustments may be required in patients with cirrhosis because of possible enhanced steroid effects.

#### e. MAJOR ADVERSE REACTIONS: Peptic ulceration may occur with high doses; fluid retention may precipitate CHF in susceptible patients.

#### f. PRECAUTIONS: Contraindicated in presence of systemic fungal infections; adrenal suppression may occur with administration of high doses for prolonged periods; large doses may induce hypokalemia, which is accentuated by concomitant therapy with diuretics.

#### g. EFFICACY:

(1) Dramatic improvement has been reported with the use of steroids in patients suffering prolonged, severe migrainous attacks (Saper, 1989).

(2) The results of a prospective study of 162 patients who were treated with and without steroids for intractable migraine indicated that the inclusion of a steroid may be of some benefit (Gallagher, 1986).

#### h. MECHANISM: One postulated mechanism is through activation of tryptophan hydroxylase, an important step in the synthesis of serotonin. Another postulated mechanism is reduction in the sterile inflammation often found around the affected dilated vessels and noted in migraine attacks lasting over 24 hours (Dalessio, 1990).

## H. INTRAVENOUS FLUID

### 1. DEHYDRATION

#### a. INDICATIONS: Patients with protracted vomiting and evidence of dehydration, particularly those with status migrainosus (Dalessio, 1990).

#### b. RECOMMENDATION:

(1) 1 liter normal or one-half normal saline over 60 to 90 minutes is usually sufficient; patients with dry mucous membranes or orthostatic hypotension may require more fluid (Dalessio, 1990).

(2) A bolus of 500 to 750 cc NS, or 5 cc/kg NS, prior to intravenous chlorpromazine therapy may prevent associated orthostatic hypotension in up to 20% of patients (Ducharme, 1999; Dalessio, 1990).

## I. PROPHYLAXIS, MIGRAINE

### 1. OVERVIEW

#### a. GOALS OF PREVENTIVE THERAPY (Silberstein, 2000, per US Headache Consortium practice guidelines):

(1) Reduction in frequency, severity, and duration of attacks.

(2) Improvement in patient's responsiveness to treatment of acute attacks

(3) Improvement in patient's function and reduction in disability from migraine attacks.

b. GUIDES TO MANAGEMENT DECISIONS (Silberstein, 2000, per US Headache Consortium practice guidelines);

- (1) Presence of recurrent migraines that interfere with the patient's daily routine despite treatment of acute attacks.
- (2) Frequent headaches.
- (3) Contraindications to acute therapy
- (4) Failure or overuse of acute therapy.
- (5) Adverse effects from acute therapy.
- (6) Cost of acute and preventive therapies
- (7) Patient's preference
- (8) Presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura or migrainous infarction (to prevent neurologic damage, as based on expert consensus).

c. INDICATIONS: Patients experiencing more than 2 or 3 severe migraine attacks per month in whom abortive agents are ineffective or contraindicated; patients with prolonged aura symptoms; patients using daily symptomatic therapy (Med Lett, 1998a; Maizels, 1998; Noble, 1997; Klapper, 1991a; Welch, 1993; Schulman, 1992).

d. DRUGS OF CHOICE:

(1) Beta blockers (drug of choice), calcium channel blockers, antidepressants, anticonvulsants, NSAIDs, and serotonin antagonists are major classes of drugs used. NSAIDs are drugs of choice for menstrual migraine prophylaxis (Med Lett, 1998a; Fettes, 1997; Noble, 1997; Klapper, 1991a; Schulman, 1992; Jensen, 1994).

(2) Strength of evidence for clinical benefits of specific drugs (Silberstein, 2000, per US Headache Consortium practice guidelines):

(a) GROUP 1: Proven high efficacy; mild to moderate adverse effects:

Amitriptyline  
Divalproex sodium  
Propranolol and timolol  
Fluoxetine  
Gabapentin

(b) GROUP 2: Lower efficacy than group 1; mild to moderate adverse effects:

Aspirin alone  
Atenolol  
Fenoprofen  
Feverfew  
Flurbiprofen  
Fluoxetine (racemic)  
Gabapentin  
Guanfacine  
Ketoprofen  
Magnesium  
Mefenamic acid  
Metoprolol  
Nadolol  
Naproxen  
Naproxen sodium  
Nimodipine  
Verapamil  
Vitamin B 2

(c) GROUP 3: Clinically efficacious based on consensus and clinical experience but no scientific evidence of efficacy:

Cyproheptadine  
Diltiazem  
Doxepin  
Fluvoxamine

Ibuprofen  
Imipramine  
Methylergonovine (concerns about side effects)  
Mirtazapine  
Nortriptyline  
Paroxetine  
Phenelzine (concerns about side effects)  
Protriptyline  
Sertraline  
Tiagabine  
Topiramate  
Venlafaxine

(d) GROUP 4: Proven efficacy but frequent or severe adverse effects:

Methysergide

(e) GROUP 5: Proven to have limited or no efficacy:

Acebutolol  
Carbamazepine  
Clomipramine  
Clonazepam  
Clonidine  
Indomethacin  
Nicardipine  
Nifedipine  
Pindolol

e. MEDICATION USE: Initiate therapy with lowest effective dose. Begin with low dose and increase dose slowly until clinical benefits are achieved in absence of adverse events or until adverse events limit the dose. Evidence of clinical benefit may take as long as 2 to 3 months. Avoid medications that may interfere with efficacy of preventive therapy, eg, as overuse of drugs used in acute therapy. A long-acting formulation may improve compliance.

f. EFFICACY: Prophylactic medications rarely more than 55% to 65% effective in significantly reducing attack frequency (Maizels, 1998; Ferrari, 1998; Capobianco, 1996).

## 2. BETA ADRENERGIC BLOCKERS

### a. OVERVIEW

(1) INDICATIONS: A first choice for preventive migraine therapy; reduce headache frequency; do not reduce headache aura but can be used in patients with and without aura (Med Lett, 1998a; Maizels, 1998; Noble, 1997; Capobianco, 1996).

(2) DRUGS OF CHOICE:

(a) Propranolol and timolol (both FDA-approved for this indication) both have proven high efficacy, with mild to moderate adverse effects; atenolol, metoprolol, and nadolol are less effective but also mild to moderate adverse effects ((Silberstein, 2000, per US Headache Consortium practice guidelines). Agents with sympathomimetic activity (eg, acebutolol, pindolol) are ineffective.

(b) Failure to respond to one beta blocker does not preclude successful use of another beta blocker in same patient (Med Lett, 1998a; Maizels, 1998; Noble, 1997; Capobianco, 1996).

(3) DOSING: Begin with low dose and increase dosage slowly; underdosing is major cause of therapeutic failures (Noble, 1997).

### b. PROPRANOLOL

(1) INDICATIONS: A drug of first choice for preventive migraine therapy; has proven high efficacy, with mild to moderate adverse effects; reduces headache frequency but does not reduce aura (Silberstein, 2000, per US Headache Consortium practice guidelines; Med Lett, 1998a; Noble, 1997).

(2) RECOMMENDATION:

(a) ADULTS: 80 milligrams/day orally initially; maintenance, 160 to 240 milligrams/day orally in 2, 3, or 4 divided doses. Long-acting form: 80, 120, or 160 milligrams orally in a single daily dose.

(b) CHILDREN: 10 to 20 milligrams/day orally initially; increase by 10 to 20 milligrams/day each week until a dosage of 1 to 4 milligrams/kilogram/day is achieved or relief of symptoms occurs.

(3) AVAILABLE FORMS: Inderal(R) (tablets); Inderal LA(R) (long-acting form).

(4) DOSING IN SPECIAL SITUATIONS: Reduce dose in renal insufficiency and chronic hepatic disease.

(5) MAJOR ADVERSE REACTIONS: CHF; bronchospasm; cardiac arrest; severe bradycardia; peripheral arterial insufficiency; adverse reactions with prolonged use.

(6) PRECAUTIONS: Contraindicated in bronchial asthma, COPD, bradycardia, CHF, cardiogenic shock, right ventricular failure secondary to pulmonary hypertension; abrupt withdrawal may precipitate angina or acute MI; many drug interactions.

#### c. TIMOLOL

(1) INDICATIONS: A drug of first choice for preventive migraine therapy; has proven high efficacy, with mild to moderate adverse effects; reduces headache frequency but does not reduce aura (Silberstein, 2000, per US Headache Consortium practice guidelines; Med Lett, 1998a; Noble, 1997).

(2) RECOMMENDATION: ADULTS: 10 milligrams orally twice a day, up to 20 milligrams twice a day; may wish to start at lower dose to reduce side effects.

(3) AVAILABLE FORMS: Blocadren(R) (tablets); Timolide 10/25(R) (combination with hydrochlorothiazide) (tablets).

(4) DOSING IN SPECIAL SITUATIONS: Reduce dose in hepatic insufficiency and severe renal failure.

(5) MAJOR ADVERSE REACTIONS: Bradycardia; bronchial spasm; heart failure; AV dissociation and cardiac arrest (in patients with AV block); Raynaud's phenomenon; hallucinations; psychotic reactions.

(6) PRECAUTIONS: Contraindicated in bronchial asthma or history of bronchial asthma, COPD, sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock; caution in heart failure, impaired hepatic function, nonallergic bronchospasm, diabetes mellitus and thyrotoxicosis; drug withdrawal in coronary artery disease may be followed by recurrence of unstable angina, ventricular tachycardia, or myocardial infarction (reduce dose gradually); cimetidine may increase bioavailability; indomethacin may antagonize hypotensive effects; hypertension and bradycardia with combined epinephrine use; avoid concomitant use with antidiabetic agents.

(7) MONITORING PARAMETERS: Blood pressure; symptoms of congestive heart failure.

(8) EFFICACY: Timolol significantly decreased headache frequency compared with placebo in one study of 107 patients with migraine without aura or migraine with aura. The number of patients with a 50% or greater reduction in headache frequency was greater with timolol, and both physicians and patients rated timolol as significantly more effective than placebo (Stellar, 1984).

#### d. METOPROLOL

(1) INDICATIONS: May be of benefit as an alternative to propranolol or timolol for prophylaxis in patients with migraine with and without aura (Noble, 1997; Kangasniemi, 1987; Steiner, 1988; Grottemeyer, 1990). Has lower efficacy than propranolol and timolol but also mild to moderate adverse effects (Silberstein, 2000, per US Headache Consortium practice guidelines).

(2) RECOMMENDATION:

(a) ADULTS: 50 milligrams orally twice a day (starting dose); up to 200 milligrams/day (Steiner, 1988)

(b) CHILDREN: 2 to 6 milligrams/kilogram/day orally (Igarashi, 1992).

(3) AVAILABLE FORMS: Lopressor(R) (tablets).

(4) DOSING IN SPECIAL SITUATIONS: Consider reduction of dose in severe hepatic disease.

(5) MAJOR ADVERSE REACTIONS: Hypotension; Raynaud's phenomenon; bradycardia; congestive heart failure; CNS toxicity (insomnia, dizziness); diarrhea (5% of patients); bronchospasm.

(6) PRECAUTIONS: Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure; caution in asthmatic patients (bronchospasm), diabetic patients, and in patients with history of heart failure and thyrotoxicosis; theophylline may antagonize therapeutic effects of metoprolol; impaired cardiac function may occur with verapamil; reduced effects may be seen with antacids and indomethacin; ranitidine may increase metoprolol's half-life.

(7) MONITORING PARAMETERS: Heart rate; blood pressure.

(8) EFFICACY: Metoprolol is significantly more effective than placebo for migraine prophylaxis (Andersson, 1983; Langohr, 1985; Kangasniemi, 1987; Steiner, 1988). It has been shown to be equal to propranolol (Olsson, 1984) and superior to clonidine (Louis, 1985) in clinical efficacy.

### 3. CALCIUM ANTAGONISTS

#### a. VERAPAMIL

- (1) INDICATIONS: Recommended for migraine prophylaxis in patients with coexistent stroke or for prolonged or atypical migraine aura. Has lower efficacy than other agents (eg, propranolol, amitriptyline, divalproex) but has mild to moderate adverse effects (Silberstein, 2000, per US Headache Consortium practice guidelines).
- (2) RECOMMENDATION: ADULTS: 80 to 160 milligrams orally three to four times a day (Markley, 1991).
- (3) AVAILABLE FORMS: Calan(R) (tablets); Isoptin(R) (tablets).
- (4) DOSING IN SPECIAL SITUATIONS: Reduce dose by 30% to 50% in hepatic insufficiency; reduce dosage in severe renal insufficiency.
- (5) MAJOR ADVERSE REACTIONS: Severe hypotension, bradycardia, ventricular standstill in digitalized patients, asystole, hepatotoxicity (long-term use), respiratory failure.
- (6) PRECAUTIONS: Contraindicated in advanced heart failure, second or third degree AV block, cardiogenic shock, severe hypotension, sick sinus syndrome, left ventricular dysfunction; caution in hepatic or renal impairment, heart failure, atrial flutter/fibrillation, AV block, hypertrophic cardiomyopathy with high pulmonary capillary wedge pressure; increases digoxin serum levels of toxicity; hypotension with quinidine in patients with hypertrophic cardiomyopathy. Calcium chloride or gluconate is specific antagonist for toxic effects (10 ml of 10% solution for 5 minutes).

### 4. ANTIDEPRESSANTS

#### a. AMITRIPTYLINE

- (1) INDICATIONS: Only antidepressant that has shown fairly consistent efficacy in the prevention of migraine (also has been evaluated more frequently than other antidepressant). Of proven high efficacy, with mild to moderate adverse effects. Particularly useful in patients with migraine and tension headache and in those with depression (Silberstein, 2000, per US Headache Consortium practice guidelines).
- (2) RECOMMENDATION:
  - (a) ADULTS: Effective dosage varies from 10 to 300 milligrams/day orally (Maizels, 1998); 90% of patients achieve optimal effect with 50 to 75 milligrams/day or less. Therapy usually begins with 10 milligrams at bedtime and is increased in 10-milligram increments at 1- to 3-week intervals (Maizels, 1998).
  - (b) CHILDREN: 0.1 to 2 milligrams/kilogram/day orally; increase every two weeks; divide dosages over 1 milligram/kilogram/day into two doses (Hamalainen, 1998).
- (3) AVAILABLE FORMS: Elavil(R) (tablets).
- (4) DOSING IN SPECIAL SITUATIONS: Dose adjustments not required in renal failure; reduce dose in severe liver disease and in elderly patients.
- (5) MAJOR ADVERSE REACTIONS: Orthostatic hypotension; tachycardia; granulocytopenia; confusional reactions; convulsions (normal doses); hepatotoxicity; dry mouth.
- (6) PRECAUTIONS: Many contraindications (see formulary); use with caution in elderly, hyperactive patients, epilepsy and ischemic heart disease; caution with concomitant MAO inhibitor use; may reduce effect of guanethidine, clonidine, reserpine; may enhance effects of warfarin, phenothiazines, thyroid, sympathomimetics.

#### b. NORTRIPTYLINE

- (1) Although less well studied than amitriptyline, nortriptyline may be useful in patients in whom sedative effect is undesirable (Maizels, 1998; Tepper, 1996).
- (2) Effective dosage varies from 10 to 75 milligrams/day orally (Maizels, 1998); most patients require less than 50 milligrams daily (Tepper, 1996).

### 5. SEROTONIN ANTAGONISTS

#### a. CYPROHEPTADINE

- (1) INDICATIONS: Antihistamine with mild to moderate peripheral serotonin-antagonist activity. May be useful in patients who cannot tolerate, or who have contraindications, to propranolol or methysergide. Children with migraine may have an excellent response to cyproheptadine (Noble, 1997).
- (2) RECOMMENDATION:
  - (a) ADULTS: 4 to 16 milligrams/day orally in two doses.
  - (b) CHILDREN: 0.2 to 0.4 milligram/kilogram/day orally in three to four divided doses.
- (3) AVAILABLE FORMS: Periactin(R) (tablets, syrup).
- (4) DOSING IN SPECIAL SITUATIONS: Dose adjustments not required in renal insufficiency; reduce dose in hepatic insufficiency.

(5) MAJOR ADVERSE REACTIONS: Increased appetite and weight gain; extreme drowsiness; hepatotoxicity; mouth dryness.

(6) PRECAUTIONS: Contraindicated during the breast feeding period; use with caution in pregnancy; additive sedation with CNS depressants.

## 6. ANTICONVULSANTS

### a. DIVALPROEX

(1) INDICATIONS: Of proven high efficacy for migraine prophylaxis, with mild to moderate adverse effects (Silberstein, 2000, per US Headache Consortium practice guidelines). Particularly effective prophylactic agent in patients with severe migraine or prolonged or atypical migraine aura (Noble, 1997). Decreases frequency of attacks by 40% to >50% in 50% to 85% of patients (Gidal, 1996).

(2) RECOMMENDATION:

(a) ADULTS: 250 to 1500 milligrams/day orally. Begin with 125 to 250 milligrams orally twice daily; increase dosage gradually by 125 to 250 milligrams weekly. Average dosage, 250 to 500 milligrams three times daily (Noble, 1997).

(b) CHILDREN: 15 to 30 milligrams/kilogram/day orally in divided doses (Hamalainen, 1998).

(3) AVAILABLE FORMS: Depakote(R) (tablets).

(4) DOSING IN SPECIAL SITUATIONS: Teratogenic; effective contraception in women of child-bearing age essential; discontinue drug 1 to 2 months before a planned pregnancy.

(5) MAJOR ADVERSE REACTIONS: Nausea or vomiting, asthenia, somnolence, tremors, hair loss.

(6) PRECAUTIONS: Monitor liver function tests and drug levels.

### b. LAMOTRIGINE

(1) A small (n=24) open label longitudinal trial for migraine with aura showed a highly significant reduction in attack frequency in the treatment phase, with over half of subjects having migraine attacks completely abolished by month 3 (D'Andrea, 1999).

(2) In a small (n=15) open longitudinal trial examining length and frequency of migraine aura (2 of 15 with aura without migraine), lamotrigine significantly reduced both aura frequency and aura duration from baseline during treatment period. When drug was withdrawn, all subjects had significant increases in aura frequency and duration back to baseline (Lampl, 1999).

## 7. ANTI-INFLAMMATORY DRUGS, NONSTEROIDAL

### a. NAPROXEN

(1) INDICATIONS:

(a) Has lower efficacy than other agents (eg, propranolol, amitriptyline, divalproex) for migraine prophylaxis but has mild to moderate adverse effects. May be useful in migraine patients with arthritis (Silberstein, 2000, per US Headache Consortium practice guidelines).

(b) May be effective in preventing migraine attacks in women with menstrual migraine (Fettes, 1997; Sances, 1990; Bellavance, 1990).

(2) RECOMMENDATION:

(a) ADULTS: 250 to 375 milligrams orally two to three times a day. For menstrual migraine prophylaxis, 550 milligrams orally twice a day beginning seven days before onset of menses and continued throughout menses (Fettes, 1997).

(b) CHILDREN: 5 to 10 milligrams/kilogram/day orally in two divided doses; a break is recommended after two to four weeks (Hamalainen, 1998).

(3) AVAILABLE FORMS: Naprosyn(R) (tablets); Anaprox(R) (tablets).

(4) DOSING IN SPECIAL SITUATIONS: Dose reductions not required in liver disease.

(5) MAJOR ADVERSE REACTIONS: Tinnitus; hearing loss; GI bleeding; cholestatic jaundice.

(6) PRECAUTIONS: Contraindicated in aspirin intolerance; use with caution in patients with peptic ulcer; may potentiate effects of warfarin and phenytoin; absorption reduced by antacids.

## 8. FEVERFEW

a. Herbal medication that may be helpful for prevention of migraine (Murphy, 1988; Johnson, 1985), although strength of evidence is limited (Silberstein, 2000, per US Headache Consortium practice guidelines; Pittler, 2000; Vogler, 1998). (FOR FURTHER INFORMATION: SEE ALTMEDDEX(R) EVALUATION: FEVERFEW)

## 9. VITAMIN B2

a. In a randomized, controlled trial, high-dose (400 mg/d) riboflavin (vitamin B2) was significantly superior to placebo for migraine prophylaxis in both reducing attack frequency and headache days (Schoenen, 1998).

## 10. MAGNESIUM SULFATE

a. Studies of effectiveness have been contradictory; however, use of serum ionized magnesium levels may allow selection of patients likely to respond (Mauskop, 1998).

b. Patients with low ionized magnesium levels may respond to 600 milligrams of chelated magnesium diglycinate or magnesium oxide orally daily. If response is limited by malabsorption or diarrhea, intravenous magnesium replacement may be effective (Mauskop, 1998).

## 11. ESTROGEN

- a. Women with menstrual migraines may respond to stabilization of estrogen levels (Fettes, 1997).
- b. Percutaneous estrogen gel or estradiol transdermal patches may be used for one week beginning two to three days before expected headache (Fettes, 1997).

## 12. TRIPTANS

### a. SUMATRIPTAN

- (1) Results of an open-label pilot study suggest that sumatriptan may be useful in intermittent prophylaxis of menstruation-related migraine. Reduced frequency and severity of migraines; breakthrough headaches were rare and significantly reduced in severity (Newman, 1998).
- (2) Double-blind, placebo-controlled trials are indicated to confirm these results (Newman, 1998).

## 13. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

### a. SERTRALINE

- (1) Not as effective as conventional migraine prophylactic agents but may play role in treatment of patients with comorbid depression who have failed conventional therapy (Landy, 1999).

## 14. LEUKOTRIENE RECEPTOR ANTAGONISTS

### a. MONTELUKAST

- (1) A prospective open-label study reported potential of montelukast as an effective, well-tolerated prophylactic agent in migraine. Double-blinded, placebo-controlled studies are warranted (Sheftell, 2000).

## 7.0 DISPOSITION

### 7.1 ADMISSION CRITERIA

- A. Severe, intractable pain.
- B. Intractable vomiting.
- C. Persistent neurologic deficits.
- D. Focal neurologic deficit without past history of similar deficit.
- E. Lack of home support.

### 7.2 HOME CRITERIA

- A. All U.S. emergency department patients must be screened, stabilized, and discharged in accordance with the EMTALA (COBRA) law.
- B. Patients may be discharged home under the following circumstances:
  1. Mild to moderate pain controlled with oral or rectal medications.
  2. Vomiting controlled.
  3. Can take fluids by mouth.
  4. Family or friend at home for support.
  5. Diagnosis definitely established either through past history of similar headaches or present signs/symptoms consistent with migraines.
- C. Some data suggest need for follow-up period of at least 72 h after ED treatment, particularly among patients not obtaining complete headache relief in the ED (Ducharme, 1998).

### 7.3 CONSULT CRITERIA

- A. For headache with persistent alteration in level of consciousness, a consultation with a neurologist or neurosurgeon should be made in the emergency department.
- B. For headache with persistent neurologic deficit, a consultation with a neurologist or neurosurgeon should be made in the emergency department or inpatient service.
- C. For severe headache where diagnosis is in question but with no neurologic deficit, an emergency department or inpatient consultation should be made with a neurologist, neurosurgeon, or internist.
- D. For typical migrainous headache of mild to moderate intensity with no past history of similar headaches, an outpatient consultation may be made with a neurologist, neurosurgeon, or internist.

## 7.4 TRANSFER CRITERIA

A. All U.S. emergency department patients must be screened, stabilized, and discharged in accordance with the EMTALA (COBRA) law.

B. Either ground or air transport is acceptable for both intra- and inter-city transfer, depending upon which method provides the least environmental stimulation.

C. Minimum requirements for both intra- and inter-city transfer include the following: (1) stable patient or as stable as possible, depending on the resources of the transferring institution; (2) appropriate IV fluids for dehydrated patients; (3) transfer acceptable to patient and family; and (4) transfer accepted by receiving institution.

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