



Headache: When is it an Emergency?

Headache is a common presenting chief complaint in the emergency department that can present diagnostic dilemmas when differentiating benign from deadly etiologies. The lecturer will present a systematic approach to the workup of headache and identify the appropriate management for each type of headache.

- Identify the different etiologies of headache seen in the emergency department.
- Describe the diagnostic workup required to rule out life-threatening etiologies.
- Discuss the current management of different etiologies of headache.

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FACULTY

Michael J Gerardi, MD, FACEP

Clinical Assistant Professor of
Medicine, University of Medicine
and Dentistry of New Jersey;
Director, Pediatric Emergency
Medicine, Children's Medical Center,
Atlantic Health System and Morrison
Memorial Hospital; Chair, ACEP
Pediatric Emergency Medicine
Committee

Headache: Benign or Deadly?

Michael J. **Gerardi**, M.D., FAAP, FACEP
Department of Emergency Medicine
Morristown Memorial Hospital
Morristown, New Jersey 07962
Michael.Gerardi@mmh.ahsys.org
973-971-7972

Goals and Objectives

1. Identify the different etiologies of headache in the emergency department.
 2. Describe the diagnostic work-up required to rule out life-threatening cases.
 3. Discuss the current management for specific types of headaches.
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INTRODUCTION & EPIDEMIOLOGY

Headache is a major public health problem.

- one of the top 10 presenting symptoms; 18 million outpatient visits
- over 1% of physician's office and ED visits are for headache
- among the most prominent causes of sickness absence from work
 - 638 million days of work lost per year
- 78% of women and 64% of men had experienced at least one headache in the year prior to one study
- 36% of women and 19% of men suffered from recurrent headaches

In a population of 100,000:

- 96,000 will have a headache in their lifetime (99% for women, 93% for men)
- 79,000-83,000 will have suffered a headache in the last year
- 24,000 will have suffered a headache sufficient to require an analgesic in the previous 14 days
- 9,100 will have had at least one "very severe or almost unbearable" HA in the past year
- 16 will have subarachnoid hemorrhage per year
- about 10 brain tumors will be diagnosed in the next year

Impact of common headache

- Can J Sci 1993;20:131-7: survey of Canadian households
- 16% have migraine, 29% tension HA
- 78% of migraine attacks impair daily activities
- 64% of migraine patients have ever sought medical attention (45% tension)
- 14% of migraine and 8% of tension had visited an ED

Only 0.004% of acute headache episodes are symptoms of underlying serious disease. Potentially *life-threatening* etiologies characterize patients presenting to the emergency department with a chief complaint of a severe headache in <5% of the cases.

In the ED, vascular headaches account for 4% to 20%. The vast majority of HA sufferers in ED will be tension type (muscle-contraction) headaches.

	Migrain	Tension-Ty Headache	Cold-stim Headache	Hangover Hea	Fever Headache
Lifetime prevalence women	16-25%	78%-88%	15%	67%	69%
men	8%	69%		72-75%	
Male:female ratio	1:3	4:5	1:1		57%
8-14 days per year	15%	23%			
> 14 days per year	9%	36%			
HA in last month	4%	48%			
Severe pain intensity	85%	1%			
Moderate pain intensity		58%			
Associations		Decrease with age	Migraines	Tension-type	Migraines

Secondary headache (i.e. headache caused by organic diseases) are uncommon, constitute less than 1% of headaches.

ED Goals in Headache Patients

1. Differentiate life-threatening/dangerous conditions from relatively benign causes
2. Initiate prompt treatment/diagnosis for malignant headache
3. Provide prompt pain relief for benign headache
4. Prevent **drug** seeking and refer for chronic pain treatment
5. Minimize resource utilization in the ED
6. Optimize patient use of the ED
7. Increase pre-ED treatment and reduce ED use.

HISTORY

Diagnosis

Establishing a diagnosis when a patient presents with a headache depends almost entirely on taking an accurate patient history.

Age of onset

- benign syndromes usually begin before middle age
- ominous causes of headache occur more frequently with advancing with age (> 35 years old)

Duration of complaint

- sudden onset: subarachnoid hemorrhage or meningitis
- many years: migraine, tension-type headache

- recently developed over several days, weeks, or months
 - new-onset migraine or tension-type headache
 - temporal arteritis
 - increased intracranial pressure

Frequency and duration of each headache

- episodic: migraine and cluster
- chronic: tension-type or drug rebound

Site

- diffuse and bilateral: tension-type headaches
- unilateral: migraine (sometimes bilateral), cluster (always)

Quality

- cannot be relied upon due to variability and subjective aspects

Time of onset

- awaken from sleep: cluster

Associated phenomenon

- look for gastrointestinal symptoms, photophobia, neurological symptoms
- arthralgia, fever or malaise: signal presence of systemic disease such as temporal arteritis or infection

Aggravating and relieving factors

- intracranial: worse with cough or strains, or when adopting 'head low' position
- cluster: pacing around
- migraine: lie quietly in a darkened room

PERFORMING A PHYSICAL EXAM

FULL **neurologic** exam is **not** necessary. The exam below is adequate and should not take **more than 5 minutes**.

- Does the patient look ill?
- What is the body temperature?
- Is the patient mentally alert?
 - coherent, consistent account of themselves and their complaints
- Is there any evidence of meningeal irritation or increased intracranial pressure?
 - neck, optic **fundi**
- **Are the cranial nerves normal?**
 - pupils equal, face moves symmetrically, equal pin-prick sensation, normal voice and speech, tongue protrudes in mid-line
- Are strength, reflexes and coordination normal?
- General examination
 - cranium nl size and nl contours?
 - sore spots on the head or neck?
 - blood pressure normal?

INVESTIGATING HEADACHE

Is any special investigation warranted?

When there is diagnostic difficulty or when history suggests a serious disorder, investigation becomes obligatory.

Blood count and erythrocyte sedimentation rate (ESR)

- when symptoms of a systemic disorder or signs of infection or meningeal reaction are associated with headache
- ESR - patient over 50 years
High ESR: temporal arteritis, locus of infection, hidden malignancy, multiple myeloma, or subacute bacterial endocarditis

Lumbar puncture

- rule out meningitis, subarachnoid hemorrhage after CT; investigate infectious processes of the nervous system
- contraindicated if space-occupying lesion suspected

Electro-encephalography (EEG)

- High prevalence of false positives and false negatives; nonspecific. Therefore, not much value

Radio-isotope scanning

- Accumulates in lesions such as tumors and hematomas; can provide a rough estimate of blood flow through cerebral hemispheres.

Computerized tomographic (CT) brain scanning and magnetic resonance imaging (MRI)

- CT: brain tumor, cerebral atrophy, hydrocephalus, extradural or subdural hematoma, subarachnoid hemorrhage, cerebral hemorrhage
- MRI: better definition of brain structures; less sensitive for detecting areas of fresh intracranial bleeding

BUT: When should CT and/or more aggressive work-up be initiated?

Only 0.004% of acute headache episodes are symptoms of underlying serious disease

Chronic Isolated Headache: Most patients presenting with a headache most

frequently visit a physician to receive an explanation as to the cause of their headache, rather than for treatment alone (Packard RC, *Headache* 1979). Therefore imaging studies are frequently done to rule out mass lesions when patients present with chronic headaches. The stresses on emergency physicians to perform CT's are greater than on other physicians due to the more acute nature of presentation of headaches in our practices. Nevertheless, chronic isolated headaches do not need scanning when presenting to the ED.

Episodic Tension-Type Headache: 2 out of 5 adults (Schwartz, *JAMA* 1998);

Women (46.9%) and men (42.3%) age 30-39 had a higher prevalence; significant but modest impact on individuals; high societal impact due to prevalence.

HEADACHE DANGER SIGNALS

On History

- sudden onset of new severe headache; “first or worst” the patient has ever experienced (especially if onset is acute or associated with **neurologic** symptoms)
- headache is subacute in onset but worsens progressively over days or weeks
- onset with exertion, coughing, straining, and/or sexual activity
- headache is accompanied by fever, nausea, and vomiting that cannot be explained by systemic illness
- associated symptoms such as:
 - drowsiness, confusion, memory loss
 - chronic malaise, myalgia, arthralgia
 - progressive visual disturbances
 - weakness, clumsiness, loss of balance
- onset of the first headache after the age of 50 years
- headache has no obvious identifiable etiology

Physical Exam Red Flags

- abnormal vital signs, especially fever or hypertension
- altered consciousness or cognition
- papilledema or **fundal** hemorrhage
- pupils unequal and/or poorly reactive
- weakness or sensory loss in face or limbs
- reflex asymmetry or abnormal **plantar** response
- clumsiness or loss of balance
- tender, poorly-pulsate cranial arteries
- meningeal irritation / meningismus (physical finding)
 - true involuntary resistance to passive **flexion** of the neck
 - Kernig's or **Brudzinski's** sign may be present

versus

- neck stiffness
 - subjective and characteristic of several benign headache disorders
 - cervical hyperextension or cervical disk injury or muscle contraction
- Fever
- Hypertension
- Chronic malaise
- Myalgia
- Arthralgia
- Weight loss

Headache Danger Signs Suggesting the Need for Further Evaluation

Sudden, explosive, thunderclap onset

Onset of HA after 40 years of age

Onset of a new or different headache

Worst headache ever experienced

Onset of subacute headache that progressively worsens over time

Onset of headache with exertion, sexual activity, coughing, or straining

History of head trauma, cancer, anticoagulation

Immunosuppressed

Headache associated with neurologic change, such as:

Drowsiness

Confusion

Memory impairment

Weakness

Ataxia

Loss of coordination

Sensory loss

Asymmetry of pupillary response,

DTRs

Progressive visual or neurologic change

Diagnostic Dilemmas

- basilar migraines
- migraines with unilateral neurologic deficits
- migraine in the elderly and children
- persistent neurologic deficits

NEUROIMAGING: When do you do CT when evaluating headache?

We would hope to not miss **brain tumors** but the following studies demonstrate that they rarely present acutely solely as a headache.

Criteria for Ordering Neuroimaging

Suspicion of **cerebellar** hemorrhage or infarct

Developing cerebrovascular accident or completed stroke with emergency use of anticoagulants

History and neurologic examination **indicate** presence of intracerebral hemorrhage or mass lesion

Acute clinical signs of increased intracranial pressure

Patient at risk for cerebral abscess but requires lumbar puncture

Blunt head **trauma with signs of increased intracranial pressure**

Depressed or open skull fracture

Penetrating head injury

Head injury and Glasgow Coma Scale less than 14 to 15

Medical Conditions that Commonly Present with Headache

Fever

Pheochromocytoma

Chronic renal failure

Hyperthyroidism

Malignant hypertension

Systemic lupus erythematosus

Polyarteritis nodosa

Giant cell arteritis

Vasculitis

Fibromyalgia

Sleep apnea syndrome

Conditions that are Comorbid with Migraine

Hypertension

Aspirin-sensitive asthma

Stroke

Depression

Coronary vasospasm

Raynaud's disease

Mitral valve prolapse

Epilepsy

1. Snyder H et al: Signs and symptoms of patients with brain tumors presenting to the Emergency Department. *J Emerg Med* 1993;11(3):253.

Age range: 3 days to 88 years; average 43 years old

Duration of symptoms: < 1 month in 60%; less than a week in 22%

Initial misdiagnoses: stroke, vasculitis, tension or vascular headache, hysterical headache, and sinusitis

Presenting Symptoms	Percentage of Patients	Presenting Signs	Percentage of Patients
headache	55	motor weakness and ataxia	37
altered mental status	50	papilledema	28
ataxia	41	cranial nerve palsy	26
nausea or vomiting	31	visual changes	20
motor weakness	27	sensory abnormalities	19
seizures	24	Babinski's sign	18
visual changes	23	speech deficits	12
speech deficits	21		

2. Weingarten S. The effectiveness of cerebral imaging in the diagnosis of chronic headache. *Arch Intern Med* 1992;152:2457-2462.

In a study of 89 patients scanned for chronic isolated headache, **none** of the scans provided any new information. In addition, upon review of patients with brain tumors, no patient had headache alone at the time of diagnosis and only 5% presented for headache alone.

3. Mitchell CS, Osborn RE, Grosskreutz SR. Computed tomography in the headache patient: Is routine evaluation really necessary? *Headache* 1993;33:82-86

350 patients of headache, regardless of presence or absence of physical or **neurologic** signs, referred for CT. 7 (2%) had clinically significant findings. 25 (7%) had positive CT findings. All pts. with clinically significant CT findings had (1) abnormal physical or neuro exam or (2) unusual clinical symptoms: Case 1. awoke with H/A: ameliorated sitting up; Case 2: hypersomnolence and "going crazy"; Case 3: nonlocalized headache awoke him 4 of last 4 nights with 9/10 pain. Unusual symptomatology in patients with **normal** CT scans: worst H/A-26; Nausea, vomiting-9; rapid increase in severity or frequency-8; awakening from sleep-3; dizziness-1; subjective tingling -1. Likelihood of positive CT increased 500% with no misses when only patients with (+) neuro or physical exams or unusual clinical symptomatology are examined with CT.

4. **Reinus** WR et al: Unenhanced emergency cranial CT: Optimizing patient selection with univariate and multivariate analyses. *Radiology* 1993;186(3):763.

In a study of 1,074 ED patients undergoing emergent unenhanced CT; 26 clinical variables evaluated for their ability to identify patients most likely to have CT abnormalities.

Variables associated with an abnormal CT:

- unresponsiveness
- focal neurologic deficits
- hypertension

Statistically less likely to have an abnormal CT scan than study population at large:

- blurred vision
- trauma
- loss of consciousness
- headache
- dizziness

After multivariate analysis, predictors of a positive CT scan:

- focal neurologic deficits
- unresponsiveness
- intoxication and amnesia in setting of a normal exam

Limiting studies to this group: 91% sensitivity; would have reduced scanning by 54% and increased yield from 16% to 31% (positive predictive value).

Negative predictive value: 97%

Summary of **CT**:

Little role beyond ruling out occult lesions such as neoplasms, hemorrhages, vascular malformations, brain abscesses, hydrocephalus, or congenital malformations (Arnold-Chiari malformations)

-miss pseudotumor **cerebri**, meningitis, other infections, glaucoma, metabolic or toxic causes

In headache clinics, less than 1% of headaches have organic cause. However, benefits of CT stem from it being reassuring

If SAH suspected is superior to MRI scan for identifying subarachnoid blood

- CT can be normal in 5%-10% of patients initially presenting with SAH; less false negative with new generation CT (**NGCT**)

MRI superior to CT:

- tumors
- changes in brain tissue
- vascular lesions (**AV** malformations, cerebral venous thrombosis, venous angiomas)

SIJBARACHNOID HEMORRHAGE

- Annual incidence of **16/100,000** population (about 33,600 cases/year) in the U.S.
- 54% are secondary to ruptured AAA
- Without treatment, 40% of aneurysm patient have recurrent bleeding within 8 weeks
- An aneurysm patient who survives initial rupture and is treated conservatively has a 50% chance of **surviving** for 1 year
- Warning leaks in 50%
- Vasospasm and rupture follow in weeks
- CT misses up to 10% small leaks
- Suspect if > 35 years, no hx previous headache, no fading of headache, came on with exertion, altered LOC or **neuro deficitr**, stiff neck
- Unconscious and abnormal ECG c/w MI: suspect SAH (Lambermont '98)

- Rare but an important cause of maternal mortality. Physiologic changes in pregnancy may predispose to aneurysm formation and rupture (Stoodley '98)

Sames et al 1996: The sensitivity of NGCT scans for SAH was 93.1% for Group 1 (symptoms < 24 hours); 83.8% for Group 2 (symptoms > 24 hours).
A "normal" HGCT does not reliably exclude the need for LP.

Sidman et al 1996: The sensitivity of CT in the diagnosis of nontraumatic SAH when performed at or before 12 hours of symptom duration was 100% (80/80) and 81.7% (49/60) after 12 hours of symptom duration (95% CI 95-100% and 69.5 - 90.4%, respectively; $p < 0.0001$). 11 of the 140 patients had a negative CT and positive spinal fluid analysis, yielding an overall sensitivity of 92.1% (129/140).

Morganstern et al 1998: Modern CT imaging is sufficient to exclude 97.5% of SAH in patients presenting to the ED with "worst headache" symptoms. 2 of 107 patients (2.5%, 95% CI, 0.3% to 8.8%) had (+) CSF with (-) CT.

What about an LP first and "can the (CT) scan?"

Schull et al Feb 1999: Theoretical analysis of LP first for lone acute sudden headache (LASH): For every 100 patients: 79 - 83 fewer CTscans and only 7 to 11 additional LPs.

With LASH criteria, (1) more efficient use of resources (2) minimal additional morbidity and (3) equal diagnostic accuracy.

CAUSES OF PEDIATRIC HEADACHE

Burton *Ped Emerg Care* 1997

- Looked at 696 visits; 1.3% to pediatric ED for headache
- viral illness - 36%, sinusitis 16%, migraine 16%, post-traumatic 7%, strep pharyngitis, 5%, tension headache 4%
- no tumor or bacterial meningitis; 5% viral meningitis
- 1 each of shunt malfunction, hydrocephalus, lymphoma, traumatic hemorrhage
- (+) Tests: sinus films 46%, LPs 61%, brain imaging 19%

Vomiting after Head Injury in Children

Jan et al; *J Pediatr* 1997

- 66% of observed children vomited after head injury
- Increased likelihood with history of:
 - recurrent headache
 - previous migraine
 - family history of migraine
 - history of motion sickness

If more than one risk factor, 100% probability

Brain Imaging in Children with Headaches

Maytal 1995: very limited value in evaluating HAs in children without clinical evidence of an underlying structural lesion.

Medina et al 1997: Brain tumors in children are often associated with HA (60% at time of diagnosis)

- annual incidence about 3/100,000
- studied 314 children; spaceoccupying lesion (SOL) in 28 (9%); surgical lesions 13(4%)
- multivariate analysis, independent predictors of a surgical space occupying lesion:
 - awaking patient from sleep or present on waking (OR 25.8)
 - absence of family history of migraine (OR 20.3)
 - concomitant vomiting (OR 16.4)
 - history of headache for less than six months (OR 15.2)
 - confusion (OR 12.4)
 - abnormal neurologic findings (OR 8.0)
- 3 or more of these characteristics were present in all 13 with surgical SOL

DIFFERENTIAL DIAGNOSIS OF HEADACHE

	SUBARACHNOID HEMORRHAGE	MENINGITIS	TEMPORAL ARTERITIS
Onset	Acute	Acute or chronic	Acute or chronic
Location	Global	Global	Localized
Associated symptoms	N,V, LOC, meningismus, focal neurologic symptoms	N,V,fever, photophobia, meningismus, focal symptoms, seizures	Weight loss, PMR, fever, decreased vision, jaw claudication
Pain characteristics	Worst ever	Severe throbbing	Severe throbbing over affected area
Duration	Brief	Brief	Prolonged
Prior history	(-)	(-)	(-)
Diagnostic tests	CT 80%-90%	LP (+), CBC	WSR (+)
Physical examination	Focal signs, decreased LOC, meningismus	Meningismus, decreased LOC, irritability, rash	Tender temporal arteries, myalgias, fever

	HYPERTENSIVE	MIGRAINE	CLUSTER	MUSCLE CONTRACTION
Onset	Acute or Chronic	Acute	Acute	Chronic
Location	Localized	Unilateral	Unilateral	Global unilateral
Associated symptoms	N,V, focal neurologic symptoms	N,V, photophobia, phonophobia	Rhinorrhea, lacrimation of side	Multisomatic complaints
Pain characteristics	Throbbing	Throbbing	Sharp, stabbing	Ache
Duration	Brief	Prolonged	30 min-2 hrs	Daily
Prior history	(+)	(+)	(+)	(+)
Diagnostic tests	CT scan to rule out bleeding	-	-	-
Physical examination	Papilledema, decreased venous pulsations, decreased LOC, cerebrovascular changes	N,V, photophobia, phonophobia	Unilateral rhinorrhea, lacrimation, partial Horner's syndrome	(-)

Schick et al, 1999: Accentuated Virchow-Robin spaces (pia-lined extensions of the subarachnoid space which surround penetrating arteries as they enter the brain on its surface) on high-resolution MRI were found in 61% of the children with migrainous HA's and in 22% of children of those with tension HA's.

TYPES OF HEADACHES IN THE EMERGENCY DEPARTMENT

Final Diagnosis	Percentage
Infection - Other than Intracranial	39.3
Tension Headache	19.3
Miscellaneous	14.9
Post-Traumatic	9.3
Hypertension Related	4.8
Vascular (Migraine Type)	4.5
No Diagnosis	6.0
Subarachnoid hemorrhage	0.9
Meningitis	0.6
Migraine and tension	0.5

HEADACHE CLASSIFICATION

User-friendly IHS classification

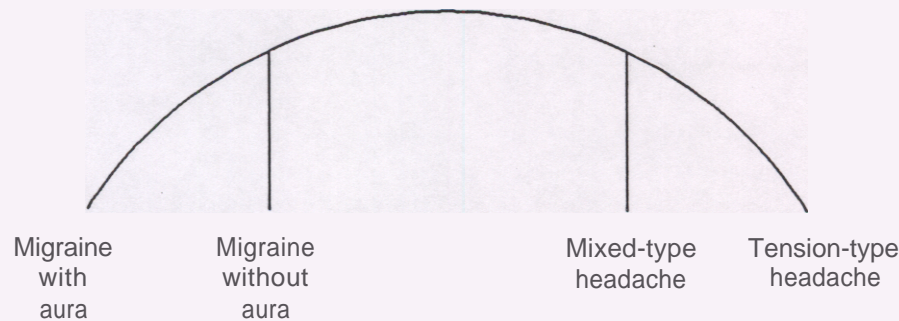
Divide the 13 general headings into 2 major categories

- Primary headaches (benign headache disorders)
 - Migraine (with or without aura)
 - Tension-type headache (episodic or chronic)
 - Cluster headache
 - Other benign headaches
 - Chronic paroxysmal hemicrania
 - Benign exertional headache
 - Headache associated with sexual activity
 - Post traumatic headache
 - Drug rebound headache
- Secondary headaches (headaches that are symptoms of organic disease)

Migraine and other headaches

There has been speculation for years that migraine and tension-type headache result from the same disordered mechanism. Two well-defined headaches, migraine with aura and chronic daily headache, would be at the opposite ends of the spectrum.

Spectrum of headache



Spectrum of Acute Primary Headache.

Adapted from Raskin NH. *Headache*, 2nd ed. New York, Churchill-Livingston, 1988.

- The symptoms of migraine and tension-type headache frequently overlap
- Migraine patients often have mixed headaches or interval headaches
- Migraine frequently evolves into chronic daily headache.
- Both conditions respond to similar treatments.

Criteria for diagnosis of episodic tension-type headache

- A. Headache pain accompanied by two of the following symptoms:
 - Pressing/tightening (nonpulsating) quality
 - Bilateral location
 - Not aggravated by routine physical activity
- B. Headache pain accompanied by both of the following symptoms:
 - No nausea or vomiting
 - Photophobia and phonophobia absent or only one present
- C. Fewer than 15 days per month with headache
- D. No evidence of organic disease

Criteria for diagnosis of cluster headache

- A. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes
 - frequency of 1 to 3 per day
- B. At least one of the following on the headache side:

<ul style="list-style-type: none"> • Conjunctival injection • Lacrimation • Nasal congestion • Rhinorrhea 	<ul style="list-style-type: none"> • Facial sweating • Miosis • Ptosis • Eyelid edema
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C. No evidence of organic disease

Men afflicted 5 to 6 times more often than women. The age of onset is typically 20 to 40 years. Infants as young as 1 year have been reported with cluster-type headaches,

- Rare - affects 0.4% of men and 0.08% of women
- Predominantly affects men: Type A personality, taller than average, tobacco, hazel colored eyes (60%)
- Periodicity is the main feature; seem to occur more frequently in spring and autumn
 - triggered by sleep
- Cluster period last on average 2 to 3 months; occur every year or two.
- The average period of remission is about 2 years; could be as short as 2 months or as long as 20 years
- Pain usually felt in the territory of the trigeminal nerve (80% of patients); is excruciating, penetrating, and usually nonthrobbing. Maximum pain is usually felt behind the eye and in the region of the supraorbital nerve and the temples.
- Tend to be nocturnal in more than 50% of patients

Treatment:

Oxygen: 5 to 8 liters/min effective in aborting cluster headaches in 70% adult patients; relieves pain almost immediately

Ergotamine: apart from oxygen, it is the most effective medication for acute headache; inhalation is the quickest way to achieve therapeutic blood levels; orally administered is too slow .

DHE: Effective when administered IV or IM; effective 2 to 11 minutes after IV administration
 - nasal DHE trials underway

Sumatriptan, 5-HT₁ agonist is effective and well-tolerated; after 6 mg SQ, 50% pain free within 10 minutes and approximately 80% within 15 minutes.

Corticosteroids: may be helpful in acute attacks; a large dose such as 8 mg dexamethasone may provide relief for several days.

Local anesthetics: intranasal 4% lidocaine has been reported to be successful in a few patients.

Characteristics of rebound headache

- Diffuse, bilateral headache every day or nearly every day, aggravated by mild physical or mental exertion
- Waking with early morning headache
- Restlessness, nausea, forgetfulness, asthenia, depression
- Medication withdrawal symptoms when ergotamine, a barbiturate, or codeine is involved
- Tolerance to acute/abortive migraine medication
- No response to preventive migraine medication

MIGRAINE HEADACHE

It is the commonest headache condition, first described in the Mesopotamian era, about 3,000 years BC. It is not a single clinical entity - it has two major variants.

It is a complex, multifactorial headache condition whose mechanism is still poorly understood. Therefore, treatment depends greatly on trial and error.

Prevalence

- Studies plagued by inconsistencies in clinical definition and biased sample selection; estimated in adults over the age of 16 years: 7.7% to 18.7%
 - 3 times more prevalent in women
 - predominantly affects young adults; first migraine may occur at any age but the peak incidence is between the ages of 25 and 34 years
 - migraine without aura: 80% (once called “common migraine”)
 - migraine with aura: 15-18% (once called “classical migraine”)
 - basilar migraine: uncommon
- Prevalence increases to about 40 years and decreases thereafter
- Estimated that 18 million women and 5.6 million men suffer severe migraines
- Prevalence higher in groups with low household income; if income less than \$10,000/year, prevalence 60% greater than in households with income greater than \$30,000. May be due to:
 - inadequate medical care
 - etiologic factors such as stress and diet
 - downward drift
- Diagnosed migraine: The tip of the iceberg
- Diagnosed/Undiagnosed: Females 41%/59% Males 29%/71%
 - Inadequate use of the health care system
 - Failure of the health care system
- More than 80% of undiagnosed sufferers experience migraine-related disability. Those most likely to be undiagnosed:
 - males; people living in low-income households; those who do not experience aura vomiting, and disability
- Highest risk: females aged. 30 to 49 years from lower income households

Medication use by migraine sufferers

- 28.3% of males and 40.1% of females use prescription drugs
- 3 or more disabling migraine attacks each month are considered candidates for preventive medication (34% females, 43% males eligible for prophylactic treatment not receiving it)
- Symptomatic or acute abortive treatment with prescription medication is warranted in migraineurs who experience moderate or severe disability fewer than 3 times/month (47% females, 61% males are not receiving optimum treatment)
- Rate of prescription medication use is higher than the overall rate in migraine sufferers who experience vomiting (females, 52%; males, 38%), visual aura (females, 48%; males, 30%), and very frequent attacks (2 to 6 (females, 48%; males, 39%) per week)

Migraine Pathogenesis

I. Vascular

Headache pain phase of migraine is caused by extracranial vasodilation and the neurologic symptoms are produced by intracranial vasoconstriction.

- Intracerebral vasoconstriction is responsible for the aura of migraine
- Headache pain results from the dilation and distention of extracranial vessels
- Pain is enhanced by vasoactive polypeptides which lower the pain threshold
- Evidence:
 - incr'd pulsation of the superficial temporal arteries during migraine
 - relief of headache pain by physical compression of temporal arteries
 - exacerbation of headache pain by vasodilating drugs
 - vasoactive drugs provide effective therapy
 - decrease in blood velocity in the mid. cerebral arteries during migraine

II. Neural hypothesis

- The primary cause of migraine is neuronal dysfunction.
- The primary disorder involves a low cerebral threshold to migraine attack.
- When precipitating factors individually or collectively exceed this threshold, an attack occurs.
- Vascular changes may be important in the production of certain symptoms, notably pain, but are secondary to the neural mechanism.
- **Evidence**
 - diverse prodromal (premonitory) symptoms of migraine
 - visual and sensory symptoms of the migraine aura
 - often unilateral location of migraine headache
 - cephalic vasodilation often occurs without head pain
 - ability of dietary, hormonal, and sensory, and psychological factors to precipitate an attack

Disturbed 5-HT neurotransmission

- During a migraine attack, blood levels of 5-HT decrease, while urinary concentrations of 5-hydroxyindoleacetic acid increase.
- Drugs that deplete 5-HT (e.g. reserpine) may trigger a migraine attack
- Intravenously administered 5-HT relieves migraine
- Some drugs effective against migraine have high affinity for 5-HT receptors
- Neurons containing 5-HT are present in the gut
- 5-HT receptors decline in number with age
- Serotonergic dorsal raphe nerve cells cease firing during sleep
- Electrodes placed near the dorsal raphe nuclei of the brain stem can cause migraine like symptoms

Potential triggers of migraine

- Hormones: before or during menstruation, relief in pregnancy
- Chronologic changes: regularity in schedules helps some migraneurs
- Carbon monoxide
- Sensory stimuli: bright or flickering lights, strong odors

- Foods and beverages (**vasoactive** substances)
 - tyramine: broad beans, other legumes, hard cheeses, organ meats, pickled herring, cultured dairy products (e.g., yogurt and sour cream), beer, and red wine
 - chocolate: phenylethylamine
 - octopamine: 'false neurotransmitter' found in citrus and other fruits
 - nitrites: cured meats, e.g., ham and bacon
 - monosodium glutamate
 - ethyl alcohol: vasodilator
- Drugs
 - caffeine, nitroglycerin, reserpine, oral contraceptives, hormone replacement products
- Emotional stress
 - "letdown" after "excitement"

Classification of 5-HT Receptors

Receptor	Effects mediated
5-HT _{1A,1B,1C,1D}	Neuronal inhibition of central nervous system (CNS) neurons; smooth muscle relaxation; contraction of some vascular smooth muscle
5-HT ₂	Neuronal depolarization; vasoconstriction of most blood vessels; bronchoconstriction; contraction of gastrointestinal smooth muscle; platelet aggregation
5-HT ₃	Neuronal depolarization leading to activation of autonomic reflexes; neuronal excitation in the CNS
5-HT ₄	Gastrokinetic action (cholinergically mediated ileal contraction); myocardial stimulation ; esophageal relaxation (in animal studies)

- **5-HT₁** receptor agonists (e.g., ergotamine, sumatriptan succinate) abort migraine **attacks and** relieve acute symptoms; some **5-HT₂** receptor antagonists (e.g., tricyclic antidepressants, methysergide) are useful in preventing migraine attacks.

Pathogenesis

The true pathophysiology remains a mystery. There appears to be a strong genetic influence that results in a disturbance of normal homeostatic functions of the blood vessels and/or the brain.

Traditional theory for aura: Symptoms of aura are due to vasoconstriction in the cranial vessels. Headache is the result of subsequent painful dilatation. Focal blood flow in specific brain regions reduces at the onset of aura.

Does blood flow reduction reach ischemic levels resulting in the classical **neurologic** symptoms?

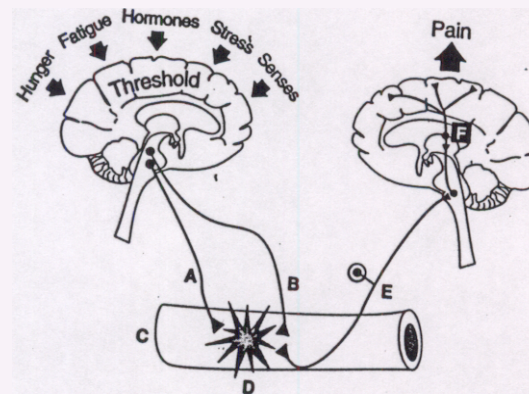
Answer: Debatable

Alternatively, reduction of blood flow in the aura is 2nd phenomenon due to reduced **neuronal** activity which spreads in a wave across the cortex. Reason?

Answer: Unknown

Theory for *headache*: The fact that headache commonly begins while blood flow is reduced seems to contradict vasodilatory theory. However, some intracranial arteries (particularly those of the dura mater) do become dilated and inflamed during migraine headache. If this happens, this is likely to trigger a complex sequence of events leading to vascular head pain.

III. Unified or Neurovascular Hypothesis



Adapted from Fozard JR The pharmacologic basis of migraine treatment. In: Blau JN, ed. *Migraine: Clinical and Research Aspects*. Baltimore, MD: The Johns Hopkins University Press; 1987:165-184.

- This scheme for migraine pathogenesis is based on ideas of several leading headache researches.
- One or more external trigger factors exceed a threshold and activate both **5-HT** and norepinephrine-containing neurons (A and B, respectively) in the locus ceruleus and dorsal **raphe** nuclei of the brain stem. This activation alters the physiology of neurons, glia, and blood vessels (C) in such a way that pain-provoking and neuroinflammatory mediators are generated within the cerebral cortex and supporting tissues.

- These mediators activate nociceptors on trigeminovascular afferent terminals ^(E) within the meninges, which in turn stimulate neurons in the brain stem, thalamus, and cerebral cortex **(F)** to create the awareness of pain.
- Activation of sensory perivascular terminals releases into the vessel wall substance I', **neurokinin A**, and calcitonin gene-related **peptide** to cause a sterile inflammatory process **(D)**, which sensitizes nerve endings, causes hyperalgesia, and sustains the **pain** long after the initial trigger has disappeared.
- Vasodilation is an epiphenomenon to sensory nerve activation, *rather than the cause of it*.

Mirza M, et al: June 1998: SPECT images revealed clear interhemispheric asymmetry in the upper frontal and occipital parts of the brain in migraineurs. It is suggested that an impaired regional cerebral vascular autoregulation may exist even during headache-free intervals.

Criteria for diagnosis of migraine without aura

A. Migraines lasting 4 to 72 hours (untreated or unsuccessfully treated)

B. Two of the following

- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by routine physical activity

C. During migraine at least one of the following occurs:

- Nausea and/or vomiting
- Photophobia and phonophobia

D. Both of the following:

- Similar pain **in the** past
- No evidence of organic disease

Criteria for diagnosis of migraine with aura

A. Headache pain is preceded by at least one of the following **neurologic** symptoms:

• Visual

- Scintillating scotoma
- Fortification spectra
- Photopsia

• Sensory

- Paresthesia
- Numbness
- Unilateral weakness
- Speech disturbance (aphasia)

B. No evidence of organic disease

Clinical Features

Paroxysmal, separated by intervals of freedom from headache

Phase One: The Prodrome

- present in up to 50%; develop insidiously and slowly over 24° preceding overt attack.
- heightened or dulled perception, irritability or withdrawal, cravings for particular foods (esp. sweet foods), excessive yawning, or speech difficulties.

Phase Two: The Aura

- visual disturbances most common.
- flashing lights (photopsia), shimmering zig-zag lines around area of lost vision from one or both eyes (scintillating scotoma)
- sensory symptoms: pins and needles, numbness in hands, dysphagia
- usually precedes headache by 60 minutes or less, and may last between 5 and 60 minutes.

Phase Three: The Headache

- most consistent and debilitating symptom, pulsatile quality
- usually unilateral
- accompanied by nausea, vomiting, photophobia, phonophobia
- aggravated by movement
- lasts 2 to 72 hours

Phase Four: The Postdrome

- drained, washed-out; some patients euphoric

Screening for migraine:

Gervil M et al Aug 1988: 5360 Danish twins; (1) Have you ever had a migraine? (2) Have you ever had a severe headache accompanied by nausea? (3) Have you ever had a severe headache accompanied by hypersensitivity to sound and light? (4) Have you **ever had** a visual disturbance lasting 5-60 minutes followed by headache?

- Sensitivity: 85%
- Combination of #1 and #4: Extracted 93% of twins with migraine with aura; 74% of twins with migraine without aura

Diagnosis in Children by History:

Gherpelli et al, July 1998: Compared to IHS, 'Prensky' criteria more sensitive. Sensitivity > 70%: pain of moderate/severe intensity, duration 2 and 48°, isolated photophobia, and aggravation with physical activity. Specificity > 70%: nausea, vomiting, phonophobia and photophobia, isolated photophobia, aggravation with physical activity, and isolated phonophobia

HEADACHE MANAGEMENT PRINCIPLES

ED Headache: Rule out Malignant Causes

- Screening history and exam
- CT scan (large bleed, mass, toxo)
- LP: meningitis, warning bleed, measure pressure after 12 hours of symptoms
- Hypertension
- Temporal arteritis (ESR)

The Repeat “Customer” / Sometimes Patient

- A small number of patients contribute up to 50% of headache visits
- Consume staff time and morale
- Usually making visits elsewhere: inquire; contact other hospitals and private MD
- Physician should be in control: **beware** manipulative behavior (Complementary, seductive, friends of CEO, etc)
- Set strict treatment guidelines and tracking of visits

Many patients presenting to the emergency department with migraine are treated with a narcotic, usually meperidine, rather than receiving primary care in the form of IV or IM dihydroergotamine (D.H.E.) or SQ Imitrex®(Sumatriptan). Narcotics have sedative and antianxiety effects, but they also have complications:

- excessive sedation
- risk of abuse and addiction
- respiratory depression

“Treatment with a benign headache is primarily aimed at relieving the acute pain, with the ultimate goal of getting the person into appropriate out-patient follow-up care.”

Callahan M, Raskin NH 1992

The overall management of headaches can be divided into several categories:

1. Self-diagnosis and self-medication: using non-prescription analgesics

2. Avoidance strategies: loud noise, strong smells, flashing lights, missing or delaying meals, stress and certain foods such as cheese, chocolate, citrus fruits and alcohol

3. Acute attack-aborting medications: simple analgesics (aspirin, acetaminophen), Nasal's, ergotamine

- May benefit from the co-administration of metoclopramide or other anti-emetic agents. Metoclopramide appears to improve absorption of other drugs.
- Drawbacks: rarely consistently effective in all patients and attacks. Some have disturbing side-effect profiles.

4. Symptomatic: relieve pain, nausea, or vomiting during an established attack

5. Prophylaxis: indicated when patient has 2 to 3 or more attacks per month that do not respond adequately to acute medication; taken on a daily basis; side effects and breakthrough attacks common

- *Beta-blockers:* Propanolol, Nadolol, Atenolol, Metoprolol
- *Calcium antagonists:* Verapamil, Diltiazem
- Side effects: nonmigrainous headache, edema, fatigue, dizziness, nausea, flushing
- *Antiserotonin drugs:* Methysergide, Cyproheptadine
- Methysergide maleate (Sansert®): semisynthetic alkaloid, potent prophylactic,
 - rare side effects: fibrosis of pleura and lungs, pericardium, and cardiac valves when taken more than 4 months at a time
 - short-term side effects: nausea, vomiting, gastric disturbance, dizziness, anxiety, depression, joint stiffness, insomnia, and vivid dreams

- Cyproheptadine (Periactin®): side effects: drowsiness, nausea, leg edema and pain, diarrhea, and weight gain

- *Tricyclic antidepressants:* Amitriptyline, Nortriptyline, Doxepin
- *Monoamine oxidase inhibitors:* Phenelzine sulfate, Isocarboxazid
-Side effects: deactivate the enzymes necessary to metabolize tyramine, therefore, can be used only with stringent dietary and drug restriction

SYMPTOMATIC MEDICATIONS USED IN THE TREATMENT OF HEADACHES & MIGRAINE HEADACHES

- **Aspirin or acetaminophen:** can cause rebound headaches when taken every day or almost every day
- **Proprietary analgesic-barbiturate and analgesic-codeine combinations:** for the symptomatic treatment of moderately severe to severe attacks. They are habit forming and may cause intractable rebound headache when they are taken more than 2 days a week.
- **Proprietary isomethene-acetaminophen-dichloralphenazone combination:** vasoconstrictor

OPIOIDS and SIMILAR DRUGS

- Widely used; esp. IM meperidine plus antihistamine or a phenothiazine to control nausea and vomiting.
- Should avoid in headache for 3 reasons: (1) narcotics are generally less effective than other, more specific headache medications (2) they are very sedating and occasionally may cause respiratory depression (3) have abuse potential
- If to be used, use in an adequate dose (50 mg to 100 mg or approx. 1 mg/kg)
- Deal only with pain aspects, therefore treating only a symptom
- Most effective when they put a patient to sleep; sleep is important in terminating the attack.
- They may be useful for women with intractable menstrual migraine, elderly patients unable to tolerate ergots, and selected pregnant patients

Summary: Meperidine (Demerol®)

- 3 RCTS - Am J Emerg Med 1995, Harden Headache 1996, Klapper Headache 1993
- Dose 75 mg IM + 25 mg promethazine
- 68% response
- 50 mg IM no different than placebo in 1 study
- Inferior to DHE

CORTICOSTEROIDS

- Can be used abortively and for protracted migraines; usually used when other medications have failed or are contraindicated.
- These are effective when the headache has persisted for a few days and when perivascular inflammation is thought to be the etiology of the persistent pain.

- Take 4 to 8 mg of dexamethasone orally stat, with F/U dose 1 to 3 hours later of the same strength or less if needed; decadron 4 -10 mg **IM** as adjunctive therapy also reported.
- Must be used conservatively, no more than 2 to 3 days per month

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Found to be as effective as aspirin or acetaminophen in the relief of migraine headache, but they are much more expensive. They DO NOT cause rebound headache.

- With different doses and dosing frequencies, NSAIDs can be used as acute/abortive or prophylactic migraine treatments.
- Side effects: GI irritation and bleeding, nausea, vomiting

Ketorolac: approved in PO, IM in U.S., IV in Europe, soon in the U.S.

Single-dose comparative studies in post-operative pain models with 30 or 90 milligrams of ketorolac administered intramuscularly give pain relief comparable to 100 mg of meperidine or 12 mg of morphine. The duration of action was longer with ketorolac.

IM Ketorolac in headache management:

Harden's study 1991: suggests a possible role for use in headache.

Duarte et al: Ketorolac is as effective as meperidine and hydroxyzine for the treatment of acute migraine headache. 60% relief from 60 mg **IM** ketorolac group and 56% from meperidine (100 **mg**) and hydroxyzine had "a great deal of complete relief".

Larkin and Prescott's Study 1992: IM ketorolac tromethamine is less effective than meperidine in the ED treatment of severe migraine. Sustained headache relief experienced by 44% of meperidine group compared to 13% of patients treated with ketorolac.

Yealy(Editorial)1992: Ketorolac should be used primarily when a NSAID is optimal or of clear benefit. IM ketorolac should be reserved for those cases when oral or IV opiates cannot be delivered easily or safely.

Summary: 7 RCTs: Shrestha, *Arch Int Med* 1996, Davis *Am J Emerg Med* 1995, Klapper *Headache* 1991, Lakin *Ann Emerg Med* 1992, Duarte *Ann Emerg Med* 1992, Harden *Headache* 1996, Seim *Acad Emerg Med* 1997 4:426.

- Dose 30 mg to 60 mg **IM**
- 83% decrease in pain in 2 hours 1 study, 55% good response another, but only 22% felt they could return to work, 73% required rescue meds with 30 mg IM, 52% with 30 mg IV
- When compared to other agents, always inferior to:
 - meperidine, DHE, and prochlorperazine
 - 60 mg no different than placebo in 1 study.
- 48% adverse effects in 1 study

SYMPATHOMIMETIC AGENTS

Isometheptane, acetaminophen, dichloralphenazone: po; 2 capsules, may repeat in 1 hr; limit, 3 times per week.

ANTIEMETICS

- e.g.: phenothiazines: Chlorpromazine and prochlorperazine have been the best studied in the treatment of migraine. Nausea and vomiting more distressing than headache in some migraine sufferers. Both compounds possess antiemetic properties, and both have demonstrated some effectiveness in terminating headaches when given IV.
- Can be used alone or as antiemetics in conjunction with other agents.
- Pharmacologic basis for their efficacy in migraine is unknown and they are not licensed for this indication
- Complex receptor interactions: antagonist adrenergic receptors; weak peripheral anticholinergic activity; antihistaminic and antiserotonergic effects.
- Dose-limiting side-effects of phenothiazines are orthostatic hypotension and sedation;
 - can produce extrapyramidal effects, neuroleptic malignant syndrome
- Some think antidopaminergic effects are responsible, especially metoclopramide

Chlorpromazine (Thorazine)

- IV administration: (1) Dilute 30 mg chlorpromazine into approximately 50 ml of saline. (2) Drip in at rate of 10 mg every 20 minutes. (3) Pt can become pain-free or asleep after 1 to 3 of the 10 mg doses.
- In uncontrolled, unblinded studies, IV chlorpromazine at a dosage of 6.25 mg to 12 mg provided relief in 73% of patients and partial relief in 21%; IM administration of 1 mg/kg produced successful resolution in 96%.
- Randomized, controlled trial demonstrated lower efficacy rates, 47% achieving relief sufficient to return to daily activities; some degree of relief in 84%.
- Unblinded study of chlorpromazine IV at 12.5 mg to 37.5 mg; complete relief in 33%.

It can be administered by slow IV push but this is associated with considerable orthostatic hypotension. Some physicians avoid this by following slow IV push with IV fluid challenge.

- Lane et al, 1989: Two of the 24 in the chlorpromazine compared with 11 of the 22 in the meperidine with dimenhydrinate group experienced inadequate relief and required other medication.
- Bell et al, 1990: Reduction in mean headache intensity was significantly better among those treated with chlorpromazine ($P < .005$). Persistent headache relief was experienced by 16 of the chlorpromazine-treated patients (88%) contacted at 12 to 24 hours follow-up compared with ten of the D.H.E.-treated patients (52.6%) and five of the lidocaine-treated group (29.4%).

Summary: 6 RCTs - McEwen *Ann Emerg Med* 1987, Lane *Ann Emerg Med* 1989, Bell *Ann Emerg Med* 1990, Camerom *Acad Emerg Med* 1995, Arch *Int Med* 1996 156:1725-8.

- Dose: 1 mg/kg IM; IV 0.1 mg/kg (with 5 cc/kg NS); 500 NS + 12.5 mg IV, or 25 mg IV
- Very effective (47% return to work at 1 hour, 92% adequate relief, 80% decrease in pain)
- 89% no recurrence at 24 hours
- Frequent sedation (to 45%)
- 20-50% have orthostatic hypotension in most studies

- Equivalent to metoclopramide in 1 study

Prochlorperazine (Compazine®)

- Prochlorperazine: certain advantages compared to chlorpromazine.
 - less sedating, easier to administer intravenously, can be mixed with DHE so they can be given in a single venipuncture
 - highest risk of dystonic reactions
- In one single controlled study, 10 mg IV provided complete relief of migraine in 74% at one hour, some relief in 88%
- IV administration: 10 mg by slow IV injection over 1 to 2 minutes. About 30 to 45 minutes after a single dose, some patients will be headache-free. However, in many EDs, the antiemetic is given 10 to 20 minutes before ergotamine tartrate or dihydroergotamine to prevent the nausea and/or vomiting that often result from their use.
- Rectal Compazine®: Jones *Ann Emerg Med* 1994;24:237-41; Thomas *Ann Emerg Med* 1994
 - RCT: Rectal prochlorperazine 25 mg
 - all patients had at least a 50% pain reduction, vs. 50% of placebo at 2 hours
 - No adverse reactions
 - 6 times more pain @ 60 minutes rectal vs. IV, 26% vs. 9% required rescue meds

Summary: 7 RCTs - Jones *JAMA* 1989, *Ann Emerg Med* 1995, Jones *Am J Emerg Med* 1996, Coppola *Ann Emerg Med* 1995, Cameron *Acad Emerg Med* 1996, Thomas *Ann Emerg Med* 1994, Seim *Acad Emerg Med* 1997, 4:426

- Dose - 10 mg IV or IM (IM, 50% needed additional meds at 1 hour)
- 74% complete relief, improves nausea more than others
- Orthostatic hypotension rare or nonexistent
- No returns to ED
- Much better than sumatriptan or ketorolac; somewhat better than Reglan

Metoclopramide (Reglan®)

- Central and peripheral benzamide dopamine D2 receptor antagonist; also sensitizes tissues to the action of acetylcholine; 5-HT₃ receptor antagonist and a 5-HT₄ agonist
- Another antiemetic agent; good alternative to phenothiazines in controlling nausea and vomiting; NOT as effective as other agents in relieving the headache component of migraine (Raskin).
- Interaction with 5-HT receptors not documented; mechanism of action not known: its use for abortive therapy of migraine grew out of anecdotal reports
- Contraindicated in patients with epilepsy and cases of hypersensitivity; use with caution in pts. with hypertension and depression.
- Adverse effects: drowsiness, fatigue, and restlessness and occur in 10% of treated patients
- Extrapyrimal reactions including dystonia, Parkinsonism, and tardive dyskinesia reported in 0.2%; extrapyramidal reactions associated with repetitive or long-term use
- Tek et al, 1990: 67% of subjects compared with 19% of controls had effective pain relief within one hour. No significant side effects were observed. 10 mg IV

- metoclopramide as a single agent is effective and safe therapy for migraine in the ED.
- Ellis et al, 1993: Efficacy demonstrated in randomized, double-blind, placebo-controlled study. Metoclopramide (10 mg IV) vs. placebo plus ibuprofen(600 mg po) vs. placebo given then pain and nausea rated. The Metoclopramide groups had significantly better relief of pain and nausea.
 - Domperidone, a dopamine D2 receptor antagonist that does not cross the BBB, is free of the CNS liability of metoclopramide.
 - Cisapride, a benzamide 5HT₄ receptor agonist GI prokinetic drug, lacks dopamine antagonist activity

Summary: *Ellis Ann Emerg Med* 1993, *Cameron Acad Emerg Med* 1995, *Coppola Ann Emerg Med* 1995

- 5-10 mg or 0.1 mg/kg IV (IM not very effective, just like IM Compazine)
- 41% relief at 30 min and 88% at 60 min with metoclopramide (equivalent to chlorpromazine in 1 study, inferior to Compazine in another)
- Much better relief of nausea; only 10% needed rescue meds
- No significant side effects (but 30-50% overall)

IM Compazine® vs. Reglan®: Jones *Am J Emerg Med* 1996;14:262-4.

- RCT of 86 patients - 10 mg prochlorperazine vs. 10 mg metoclopramide IM; no other analgesics
- 67% decreased pain with Compazine vs. 34% Reglan vs. 16% placebo
- Neither sufficient as a single agent

IV prochlorperazine vs. IV ketorolac: Seim *Acad Emerg Med* 1998

- Prochlorperazine IV had a statistically significant greater decrease in their pain scores than those receiving ketorolac IV.

When treating nausea, prochlorperazine has the greatest risk for dystonic reactions. However, its advantage is that it alone can abort a migraine attack. The safest drugs to use for nausea are metoclopramide 10 mg PO or IV or promethazine 25 to 50 mg PO or IM.

ACUTE ABORTIVE THERAPY FOR MIGRAINE

Serotonin: Its role in the treatment of migraine

Migraine develops as a consequence of activity within the trigeminovascular system and reflects events occurring 'within the vessel wall, the vessel lumen, and the brain.

- 5-HT₁ receptors are located on peptide-containing trigeminovascular axons within the dura mater; they are not present on extracranial vascular tissue innervated by the trigeminal nerve.
- The binding of anti-migraine drugs to specific receptor populations on cephalic vessels (and not on peripheral tissues) may explain why migraine, but not other painful conditions, is relieved by such agents. 5-HT₁ agonists selectively block the development of neurogenic inflammation within the dura mater following trigeminal antidromic stimulation.

- Headaches can be treated with serotonin agonists that couple to 5-HT₁ presynaptic receptors to block activity in the trigeminovascular system. Such agents, by inhibiting neuropeptidase release, block the development of neurogenic inflammation within the coverings of the brain, especially the dura mater
- Unfortunately, their post-junctional 5-HT activity (vasoconstriction) renders them unsuitable for patients with ischemic heart disease, peripheral vascular disease, raised intracranial pressure, vasospasm

ERGOTAMINE TARTRATE

Effectively aborts attacks; but its use in North America is declining due to undesirable side effects that can result from both its short-term and long-term use.

- Side effects: nausea, vomiting, vasospasm, muscular aches and cramps, tingling of the extremities, tremor, and rarely- as a result of overdose-gangrene of the limbs (*ergotism*).
- When used more than 3 days a week, ergotamine can cause rebound headaches that resemble migraines. These headaches occur every day and are refractory to further treatment with ergotamine or any other pharmacologic therapy.

Ergotamine tartrate, sometimes in combination with caffeine: given as 2-mg oral dose stat, followed one hour later by 1 to 2 mg.

- daily dose should not exceed 4 mg.
- strict rule of ergots 2 days in 7 only except during menses
- rectal absorption of ergots > than that by oral routes so lower dose (0.5 to 1.0 mg)

DIHYDROERGOTAMINE

Dihydroergotamine (D.H.E.) vs. other Ergot Agents:

- Offers primary therapy, not simply pain relief
- Has minimal to no arterial vasoconstrictor effects (but should be avoided in patients with CASHD or peripheral vascular disease); it is a venoconstrictor.
- Has minimal side effects, produces less nausea
- Does not result in physical dependence
- Is non-narcotic
- Not associated with rebound headache
- Considered to be the first line of therapy for acute, severe headache.
- Pharmacologic profiles differ
- Mechanism of action differs
- Safety margins not alike
- D.H.E. is unlikely to raise blood pressure (however, ergotamine causes only modest and transient elevations in blood pressure). Therefore, mildly elevated blood pressure during a painful attack is not a contraindication for DHE.
- cost \$7-10.

Adverse Effects of D.H.E.

- Weaker arterial constrictor but more potent venous constrictor: therefore less likely to cause vascular reactions
- However, should take same general precautions
 - with risk factors of obesity, age over 60 years, diabetes or hypertension, an initial ECG is recommended (per pharmaceutical manufacturer)
- side effects: nausea, chest tightness, leg cramps, vomiting, elevated BP (? How much of this is due to pain?)

Contraindications

- Hypersensitivity to the drug, sepsis, active thrombophlebitis, pregnancy, and/or untreated major organ failure
- Use with caution: peripheral vascular disease, coronary heart disease, other vasoconstrictor disorders, diastolic BP >100 mm Hg

Mechanism of action: It has an ability to bind agonistically to specific serotonin receptors in the brain.

Administration: can be given subcutaneously(X), IM, IV.

- IM blood levels 50% higher than SC, IV several-fold higher.
- Peak blood levels: SC-45 min, IM-30 min, IV-11 min
- Active metabolites have an elimination half-life of about 20 hours and its efficacy persists from hours to days.
- Nausea: DHE has antiemetic effects by nature of its effect of treating underlying mechanisms of migraine. However, it is emetic when given IV; but not with either SC or IM routes.
- IV preferred in ED: more reliable and provides more rapid relief

Nasal DHE: available in several European countries; bioavailability 40% compared with IV route

- 6 cross-over placebo-controlled studies studying efficacy of nasal route:

Dose 2 mg; 34%-52% responded compared to 20-43% placebo; efficacy same within 2 hours of onset or during aura

DHE plus Prochlorperazine:

Effectiveness established in several studies.

1. e.g. Callahan and Raskin: (prospective, double-blind, crossover trial); Patients received 5 mg IV prochlorperazine plus placebo or 0.75 mg IV D.H.E. 85% of patients receiving both D.H.E. and prochlorperazine required no narcotics compared to 45% of migraine patients not enrolled in the study. Only 11% had significant pain relief with prochlorperazine treatment alone.

Comparative studies

2. Belgrade et al (1989) treated vascular headaches with D.H.E., meperidine, or butorphanol. Posttreatment pain scores were lowest in the D.H.E. group.
3. Klapper & Stanton (1993): (randomized, double blind prospective trial). DHE 1 mg and metocloperamide 10 mg IV (Grp A) vs. meperidine 75 mg and hydroxyzine 75 mg IM (Grp B); mild or no headache after treatment in Grp A (13/14) significantly greater than Grp B (3/14).

4. Carleton et al (1998): Double-blind, multi-center ED study.
 - 100-mm visual analogue scale.

DHE (1 mg)	53.5% reduction	23.5% CNS adverse effects
MEP (1.5 mg /kg)	55.7% reduction	37.6% CNS adverse effects

Parenteral Administration of DHE

Method I

1. Pretreatment patient with:
 - 10 mg IV/IM **prochlorperazine** (Compazine®) over 2 min
 - or 25 - 50 mg IM promethazine (Phenergan®)
 - or 8 to 10 mg chlorpromazine (Thorazine) in 100 cm³ of saline over 30 minutes (good when sleep is desired)

then 2. 5 to 10 minutes later, administer
 0.75-1.0 mg **IV DHE** via 2-min slow IV push

Method II

1. Draw up 1 mL (1.0 mg) **DHE** and 2 ml (10 mg) **prochlorperazine** in single 3-mL syringe
2. Administer through single venopuncture via 2-min slow IV push.
 - IM: 1 mg (1 mL) into **gluteal** muscle
 - **Study: Saadah** HA 1992: 71% complete response rate at 12 hours; side effects - sedation (25%), nausea(24%), transient HA worsening (15%)
 - If unsatisfactory relief after 1 hour, give second **0.75-mg** dose of DHE.
- Headache still present after second dose of DHE: use narcotic or sleep inducing agent (IV chlorpromazine)

Subcutaneous DHE at Home

Headache 1997;36:144-148.

- 51 patients taught home injection
- 35% excellent response, 18% good
- 35% discontinued (side effects): nausea, limb numbness or pain, chest or **thorax tightness**
- dramatically reduced ED visits in 65% of patients

Characteristics of Intractable Headache

- Illness began as intermittent, typical migraine
- Headaches transformed, over 7 to 14 years, into a daily pattern with pain in the neck and/or head
- Acute migrainous events were superimposed on the daily pattern
- Significant incidence of depression and overuse of analgesics and family history of the same
- 88% of patients had a family history of headache in a close relative, i.e., mother, father, or sibling

Treatment: Repetitive IV DHE; invaluable in breaking the cycle of overuse of simple analgesics, mixed analgesics, and ergotamine.

Most hospitalized patients can withdraw from analgesics and become headache free within 2 days of treatment (**Raskin** 1986). Regimen consists of IV DHE 0.5 to

0.6 mg every 8 hours (3 to 5 days) in conjunction with metoclopramide (discontinued after 24°).

Characteristics of rebound headache

- Diffuse, bilateral headache nearly every day, aggravated by mild physical or mental exertion
- Waking with early morning headache
- Restlessness, nausea, forgetfulness, asthenia, depression
- Medication withdrawal symptoms when ergotamine, a barbiturate, or codeine is involved
- Tolerance to acute/abortive migraine medication
- No response to preventive migraine medication

Management of rebound headache:

- Recognition and withdrawal of the offending agent, which may require inpatient detoxification
- Proper prescribing practices (e.g., Rx of no more than 20 doses of an acute/abortive agent with no refills)
- Administration of an appropriate preventive drug

TRIPTANS

Mechanism of action: cranial vasoconstriction and inhibition of trigeminovascular activation from both peripheral and central projections.

Tryptamine derivatives display partial agonist properties at 5-HT_{1B/D/F} receptors.

- 2nd generation have affinity for 5HT_{1F} binding sites and better oral pharmacokinetics than sumatriptan.

SUMATRIPTAN

- Serotonin receptor agonist but differs from DHE in 3 major respects
- (1) Does not require the concomitant use of an antiemetic agent; has antiemetic properties of its own
- (2) It is expected to be available in a SC auto-injectable format containing a fixed 6-mg dose
- (3) Sumatriptan has a relatively short half-life of about 2 hours.
- Other advantages
 - patient can be given an auto-injector to take home with them and administer sumatriptan if they have a recurrence.
 - painless, patient acceptance very high, nasal spray formulation being developed

NEJM 1991: randomized, double-blind, placebo-controlled, parallel-group; 639 patients with migraine attacks.

- SC injections of 6 mg or 8 mg of sumatriptan or placebo; effect on the severe headache and associated migraine symptoms assessed at 30, 60, and 120

minutes. Patients with pain after 60 minutes were given a second dose of their initial regimen.

- after 60 minutes, sumatriptan group: almost 50% no pain, 70% had either decreased severity of headache or no pain.
- after 120 minutes, after 1 6-mg dose sumatriptan: 60% had no pain; approx. 85% had either decreased severity of headache or no pain.
- after 120 minutes, 2 6-mg doses of sumatriptan: 70% had no pain, 90% showed improvement.
- after placebo doses: 1 dose: 20% relief, after 2 doses: 40% relief
- significantly more effective than placebo in relieving nausea, vomiting, photophobia, and phonophobia.
- 38% treated with 1 or 2 6-mg doses of sumatriptan, who initially had shown complete headache resolution, had a recurrence of headache within 24 hours. Half-life is short: the 'rebound phenomenon' is actually the drug wearing off after its half-life of 2 hours. Migraines can last 48-72 hours, so subsequent sumatriptan will be required.

Subcutaneous Sumatriptan in the ED

Ann Emerg Med 1995;25:464-9.

- Multicenter RCT of 136 patients - 6 mg sumatriptan vs. placebo, plus sumatriptan po on discharge
- 75% relief with sumatriptan vs. 35% placebo
- Sumatriptan discharged at 60 min vs. 96 for placebo
- 62% had recurrence and 65% relief from oral sumatriptan

DHE vs Sumatriptan

- Both are highly effective in aborting headache attacks in the ED
- Sumatriptan is associated with relatively high recurrence rate
- DHE IV can cause nausea and vomiting; countered with antiemetics
- Sumatriptan has antiemetic effects
- Sumatriptan side effects: flushing, feelings of heaviness or pressure in various parts of the body; transient and mild.
- Sumatriptan more convenient to administer than DHE but total patient time in the ED about the same due to subsequent monitoring of initial responses.
- Cost: approx \$35 per dose (2 doses frequently needed)

Oral Sumatriptan: The oral dosage is one 25 mg tablet.

Goadsby PJ. Lancet 1991; 100 mg po had 51% response rate compared to 10% of placebo. There were no clinically significant side-effects. Oral sumatriptan is an effective agent orally for some patients.

Comments on Sumatriptan

- It continues to be an effective drug for treating migraine and cluster headache attacks.
- It works rapidly and completely and has few acute side effects.
- The recurrence of headache within 24 hours after effective repression remains the major objection to its use. However, this recurrence could have a pharmacokinetic cause.
- Recurrence is treated with a subsequent dose of sumatriptan.

- It should not be administered during aura phase of an attack.
- IV formulation of sumatriptan carried an unacceptably high risk of chest pain. However, it has never been demonstrated to be with or without ECG changes. Therefore, it is not known whether or not the chest pain was due to GI source or ischemia. Nevertheless, this route has been abandoned.
- 2 deaths linked to this drug; very weak association. 1. Women with COPD was found dead in her car and sumatriptan injector was lying on the seat beside her. (2) Patient with CASHD had MI 6 days after using sumatriptan.
- Transient 20 minute discomfort in chest may be due to esophageal spasm.

However, it is expected that we are going to be hearing more about sumatriptan (Imitrex) causing heart problems. There was a report (*Lancet* 1993; 341:861) of a 47 yo woman who had a myocardial infarction after using Imitrex® injection for cluster headaches. She had no history of heart disease but reported having chest pains when using sumatriptan. Recovered without complications.

Sumatriptan causes coronary artery vasoconstriction and a vasopressor response in the systemic and pulmonary arterial circulation. In patients undergoing diagnostic coronary arteriography, sumatriptan (6 mg subcutaneously) causes a 16% reduction in coronary artery diameter at 10 minutes and a 17% reduction at 30 minutes. Hillis and MacIntyre reviewed the case reports of cardiac ischemia and the Glaxo database of 6124 patients with 28,648 migraine attacks, of whom 2150 had electrocardiograms within 4 hours of oral or SQ therapy and 5,388 had ECGs at some stage.

4.6% had chest pressure; 99% no ECG change; NSSTTW changes in 0.5%; and new changes of possible myocardial ischemia in 10 (0.2%), five of which were believed to be related to sumatriptan (0.1%).

It is now estimated that 5% of patients using sumatriptan get chest pain or tightness. Is this angina in all of them? Unlikely but patients with heart disease should not use the drug.

Sumatriptan (Imitrex®) Adverse Effects

- Injection site reactions 59%
- Muscle tightness
- Dizzy 12%, tingling 13%
- Hot feeling 11%
- Chest pressure or pain 6% (Coronary vasoconstriction averages 16%)

COMPARISON STUDIES

Following summary is one study representative of literature regarding efficacy

Efficacy of currently available treatments for severe migraines

Meperidine + hydroxyzine	22%
Metoclopramide (10 mg IV)	67%
Prochlorperazine (10 mg IV)	74%
Sumatriptan (8 mg SQ)	78%
Chlorpromazine (0.1 mg/kg IV)	92%
<u>DHE 1 mg IV + metoclopramide 10 mg IV</u>	<u>93%</u>

Klapper AJ, Stanton J, *Headache* 1993

Dihydroergotamine vs. Sumatriptan

Ricalder R et al 1994. An unpublished multicenter controlled trial compared a single subcutaneous injection of DHE with sumatriptan for abortive treatment of moderate to severe migraine in 295 patients.

Patient with Relief		
Time	DHE-45	Sumatriptan
2 hours	73%	85%
4 hours	85%	83%
24 hours	90%	77%
Recurrence at 24 hours	18%	45%

NARATRIPTAN (Amerge®)

- 1 mg and 2.5 mg tablets:
 - effective as early as 1- hour and 4-hour efficacy rates ranging from 60% to 68%
 - long duration of action
 - low rate of recurrence: 72% - 81% had no significant worsening over 24 hours
 - tolerability comparable to placebo
 - good or excellent in 61% of 7566 treated attacks (Bomhoff 1998)

ZOLMITRIPTAN (Zomig®; 311C90)

5-HT_{1B/D} receptor agonist that is selectively centrally and peripherally acting; comes in 2.5 mg and 5 mg tablets

- novel antimigraine drug enters the brain, and experimental evidence indicates that it has inhibitory effects at both central and peripheral trigeminal neurons.
- studies suggest that it is an effective acute migraine treatment within one hour at doses of 2.5 and 5 mg: continued treatment out to four hours;
- 2 hour response rate for moderate to severe: 81%; pain free 55% of all attacks
- Second dose of 5 mg, when required: 90% response rate
- highly effective in migraine relief with (1) rapid onset of action (2) consistent predictable efficacy and (3) well-defined dose-response curve

FUTURE TRIPTANS**Eletriptan**

- eletriptan slightly more lipophilic which may enhance absorption

Rizatriptan (MAXALT) (Merck)

- 10 mg PO is efficacious (77%) vs. placebo (37%); $p < 0.0011$ and generally well-tolerated.

TRIPTAN +

Krymchantowski 1999: Sumatriptan + tolfenamic acid reduces recurrence rate from 62.5% (sumatriptan alone) to 23.8%

OTHER TREATMENT OPTIONS

NONPRESCRIPTION ACETAMINOPHEN, ASPIRIN, & CAFFEINE: Significantly greater reductions in migraine headache intensity 1 to 6 hours after dose than in those taking placebo in three DB, randomized, parallel-group, single-dose, placebo-controlled studies.

- Pain intensity mild to none at 2 hours: 59.3% vs. 32.8% placebo controls
- Pain intensity mild to none at 6 hours: 79% vs. 52%
- No pain at 6 hours: 50.8% vs. 23.5%

LIDOCAINE: At some institutions, DHE is given IV. If the patient experiences partial relief or significant side effects, lidocaine 50 to 100 mg is titrated to physiologic effect. The headache subsides in approximately 90% of the patients. Sometimes, lidocaine is given first if there is severe nausea and then 0.5 to 1 mg DHE is given IV.

Maizels et al 1996: 0.4 cc of 4% intranasal lidocaine vs saline; 55% of intranasal lidocaine had 50% reduction in headache compared with 28% of controls. Nausea and photophobia were significantly reduced. Most of the effect was within 5 minutes. 42% of responders had relapse of headache to a moderate or severe intensity; 28% needed rescue meds.

BUTORPHANOL TARTRATE, STADOL®: synthetically derived opioid analgesic with mixed agonist and antagonist properties. It has been used primarily for pain control related to surgery and labor.

Has a sedative effect that promotes sleep, with a 43% incidence of somnolence which is in itself an aid to resolving migraine attacks.

- IM, IV, metered dose nasal spray
- 2 mg butorphanol = 10 mg MS
 - sig. relief with 2 mg and 3 mg dose
 - nasal dose 1.0 mg/spray
- Onset of analgesia: IV: few minutes; IM: 10-15 min ; Nasal: 15 minutes
- Peak analgesic effect : 30-60 minutes IM/IV; 1 to 2 hours after nasal spray
- Duration of analgesia: 3 to 4 hours IM/IV; 4 to 5 hours transnasal
- Abuse potential of transnasal butorphanol is lower than that of IM due to limits of absorption.
- *Am J Emerg Med* 1997; 15:57-61: 1 mg transnasal butorphanol, repeated in 45 min PRN
 - Pain decreased from 7.9 to 2.5 @ 90 minutes
 - 60% required no further treatment
 - 75% rated it good to excellent
 - 36% side effects, mostly mild
 - 21% needed rescue med, and 42% needed an antiemetic

*Cost of 2.5 mL nasal spray which provides 12 to 13 (2 mg)doses is \$60, approx \$5/treatment

CAPSAICIN

- A vanillyl alkaloid and powerful releaser of substance P, is pungent ingredient of various species of red peppers
- Topical application to nasal mucosa on side of cluster headache shown to be beneficial in 3 studies
- Acts on nociceptive type C sensory neurons, some of which release substance P and related tachikins
- Substance P and other neuropeptides have been shown to play a role in cluster headache
- Burning subsides after repeated applications for 5 consecutive days
- # of headaches decreased by 67% in 10 days
- Cost: 0.075% capsaicin cream: 1 oz - \$26; 20 g of 0.025% - \$10

BUTYROPHENONES

- Richman P, et al (unpub): 37 patients (84% female) received droperidol 12.5 mg IM.
 - t30: 30 (81%) symptomatic relief, 2 (5%) partial relief, 5 (14%) no relief
 - Onset 3 to 10 minutes
 - Side effects: drowsiness 14%, akathisia 88%
- Wang 1997: 32 of 35 patients (91%) had relief with 2.5 mg IV droperidol q 30 min up to 3 doses
- Fisher 1995: 6 of 6 patients relief with Haldol 5 mg IV.

MAGNETS

- Sherman RA, et al 1998: Two studies with 23 patients with chronic migraines were exposed to pulsing electromagnetic fields over the inner thigh.
 - * Study 1: Open, 11 patients: HA's/week decreased from 4.03 during baseline to 0.43 during the initial 2 -week f/u and to 0.14 during the extended f/u (avg 8 months)
 - * Study 2: 9 in double-blind crossover study: 3.32 /week to 0.58 / week

PERICRANIAL INJECTION

- Brofeldt *Acad Emerg Med* 1997;4:406.
- RCT of lido/bupivacaine injection (mostly semispinalis capitis; some temporalis) vs. 1 mg DHE + 10 mg Compazine IM
- Most DHE failures rescued by lidocaine, but not vice versa
- 48% decreased pain with DHE in 30 minutes, 83% injection; similar results for nausea
- 26% DHE headache returned to work 24 hours later; 15% injection

TOLFENAMIC ACID

- Comparable in efficacy to sumatriptan

Drug	Reduction in pain	Second attack relief	Adverse
Placebo	29%	39%	
Tolfenamic Acid	77%	70%	30%
Sumatriptan	79%	64%	41%

NITROUS OXIDE

- Barfield *Acad Emerg Med* 1997;4:406

- RCT of 22 patients, 20 min of N2O
- 44% **decr.** pain with nitrous, 18% with O2
- Only 20% of N2O pts. needed other meds, vs. 83% with O2
- Triner May 1999
 - nitrous oxide: pain decreased 69 to 21 mm, $P = .02$; 80%/60% did not require rescue medication immediately and at 20 minutes
 - oxygen: 78 to 72, $P = .09$; 17%/8% did not require rescue medication

STUDIES NEEDED

- Double-blinded RCT of acute HA in emergency setting
- DHE vs. sumatriptan vs. chlorpromazine (or other phenothiazine)
- Preferably non-parenteral administration; IM better than IV
- Careful monitoring of side effect, rescue meds, 24 hr. recurrence

SUMMARY OF TREATMENTS

Meperidine: opioid, not very effective, high incidence side effects, routinely abused

Ketorolac: one of the least effective, expensive

DHE: effective, moderate cost, no rebound, non-narcotic, can be given IM, but high incidence of side effects

Sumatriptan: much like DHE, relieves nausea / vomiting, can be self-administered, causes rare coronary vasoconstriction

Chlorpromazine: Cheap, effective, sedation, usually requires IV hydration

Prochlorperazine: Cheap, very effective for HA and nausea, safe, but requires IV

Metoclopramide: cheap, good but somewhat inferior to prochlorperazine

ADDITIONAL NOTES

Pregnant women: hormonally sensitive episodic headache disorder which may worsen during the first trimester, but usually improves during later pregnancy.

- Treatment should be conservative: rest, reassurance, ice packs
- If not responding and occasional attacks: acetaminophen alone or with codeine; other narcotics
- Severe acute attacks: hospitalize, IV fluids, ice packs, and narcotics; prednisone in preference to dexamethasone (which crosses placenta more readily)
- Aspirin should not be used
- Barbiturate and **benzodiazepine** use should be limited
- Ergotamine, dihydroergotamine (**DHE**) and sumatriptan should be avoided
- Nausea: **Emetrol®**, prochlorperazine suppositories, or doxylamine succinate and Vitamin B6 (**Bendectin®**)

Drug Labeling in Pregnancy: Key to FDA Ratings for Use in Pregnancy

Category A: Controlled studies show no risk

Category D: Positive evidence of risk

Category B: No evidence of risk in humans

Category X: Contraindicated in pregnancy

Category C: Risk cannot be ruled out

Drug	Fetal Risk	Breast Feeding	Drug	Fetal Risk	Breast Feeding
Analgesics			NSAID's		
Aspirin	C	Caution	Ibuprofen	B	Compatible
Acetaminophen	B	Compatible	Naproxen	B	Compatible
Butorphanol	B	Compatible	Barbiturates		
Codeine	C	Compatible	Phenobarbital	D	Caution
Hydromorphone	B	Compatible	Benzodiazepines		
Meperidine	B	Compatible	Diazepam	D	Concern
Methadone	B	Compatible	Lorazepam	D	Concern
Morphine	B	Compatible	Other		
Propoxyphene	C	Compatible	Emetrol	B	Compatible
Neuroleptics			Bendectin	B	NA
Chlorpromazine	C	Concern	Ergots		
Prochlorperazine	C	Compatible	Ergotamine	X	Contraindicated
Promethazine	C	NA	DHE	X	Contraindicated
Reglan	B	Concern	Sumatriptan	C	Caution

DRUGS FOR TREATMENT OF MIGRAINE

DRUG	DOSAGE	COST
Acetaminophen 325 mg- isometheptene 65 mg - dichloralphenazone 100 mg <i>Midrin</i>	2 caps, then 1 g 1h PRN (max 5 q 12)	\$1.85
Aspirin 325 mg - caffeine 40 mg - butalbital 50 mg <i>Fiorinal</i>	1 to 2 tablets or capsules q 4h (max 6 q 24h)	\$2.87
Butorphanol <i>Stadol NS</i>	One spray in one nostril; can be repeated once in 3 to 5 hours	\$7.66 to 14.36
Dihydroergotamine <i>D.H.E. 45</i>	1 mg IM; can be repeated twice at 1-hour intervals	\$10.46/ 1 mg
Ergotamine 1 mg - caffeine 100 mg <i>Cafergot</i>	2 tabs po, then 1 q30 min x 4 PRN (max. 6 mg/attack)	\$2.86
Ergotamine 2 mg caffeine 100 mg <i>Cafergot</i>	One rectal suppository: can be repeated once in one hour	\$7.86
Sumatriptan <i>Imitrex</i>	6 mg SC?; may be repeated at one hour or 25 mg -100 mg po; may be repeated in 2 hours up to 300 mg/day	\$35.34

FOLLOW-UP

- Patients need to be referred to a physician for follow-up care.
- More effective abortive agents and of the use of prophylactic antimigraine drugs needed
- Narcotic analgesics should be reserved for refractory migraines or for patients with contraindications to the other medications (for example, those with significant cardiovascular disease)
- Occasionally, patients need to be admitted into the hospital for fluid replacement and further antimigraine therapy.
- Many abortive agents , if taken frequently, can paradoxically increase the number of headache attacks. A significant number of patients with migraines refractory to therapy have rebound headaches that may require hospital admission.

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Web Sites

JAMA Migraine Peer-Reviewed Resources: <http://www.ama-assn-org/migraine>

* comparison studies

CASE DISCUSSIONS

CASE ONE

A 25 year old male requires immediate attention due to severe headache. He was disrupting the waiting area and triage area due to “ice pick” like pain on the left side of his face and in his left eye. He recalls approx 3 similar episodes in a 2 month period 1 year ago. Since they resolved, he never had follow-up. This pain developed suddenly approx 30 minutes ago.

Physical exam: alert, oriented, in sever pain. T: 99.4°F, P: 108 BP: 136/98
No trauma to head. Face remarkable for conjunctival injection, lacrimation, miosis, and ptosis on the left. No other neurologic abnormalities. No evidence of organic disease.

What is your diagnosis?

What are your treatment options?

What is the role of DHE or sumatriptan in these type of headaches?

CASE TWO

A 36 yo female presents with severe left-sided cephalgia of one day’s duration. It is throbbing and radiates from the front of her head to the back of her eye and the back of her head. She is nauseous and photophobic. She took her prescribed Fioricet without relief.

Her LNMP was 4 weeks ago and she is due soon. PMHx significant for migraines since her early 20’s. Cafergot had never worked in the past and DHE makes her nauseous.

Physical Exam: T:99.0°F P: 110 RR: 26 She is in severe distress but non-toxic. She has her face covered with a wet towel but removes it to acknowledge your presence at the bedside. She is photophobic. There are no focal neurologic deficits.

What is your diagnosis?

What are your treatment options?

How would you manage this case if she was pregnant?

CASE THREE

A 29 year old professional, who started a long-awaited vacation one day ago, presents with one of the worst headaches of his life. He noted the onset of a bilateral frontal headache while driving with his family many hours to his vacation destination earlier today. He said it is similar to previous migraines that he has suffered due to the presence of nausea, photophobia, and an onset after a stressful period at work has ended. He feels like his head is splitting down the middle and has had pain in the back of his head and neck as well since the drive.

Physical exam: T: 100.4°F; I? 118 RR: 24 BP: 120/86 He is alert but in severe painful distress. Neck is supple without meningismus. PERRL, EOMI. Neuro non-focal. Discs sharp on fundoscopic exam. Reflexes 2+ and brisk.

What is your working diagnosis?

How would you manage this case?

CASE 4

A 42 yo male presents with “severe migraine” for the last 36 hours. He claims that this headache is not the worst of his life but it is close. He has photophobia, throbbing sensation, and nausea. He was seen in another ED last night and given “Toradol” with moderate relief. Pain tonight is worse and refuses to even consider another shot of “that stuff”. He is also “allergic” to “DHE” because it makes his nausea worse. He is allergic to morphine but not Demerol.

Physical exam: T: 100.0°F; P: 96 RR: 24 BP: 146/76 Patient is alert, in moderate distress. Physical exam is normal except for photophobia.

How do you manage these “difficult” patients with multiple “allergies” and drug sensitivities?