

Understanding Migraines and Treatment Options

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Simplified Diagnosis of Migraine

Any person with a stable pattern of intermittent severe headache that causes at least some disability, with no worsening over time, is migraine until proven otherwise.

Migraine Prevalence American Migraine Study II

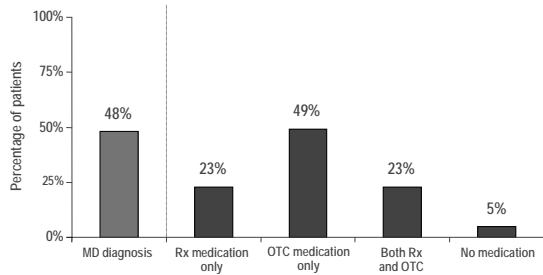
- 28 million migraine sufferers
 - 21 million females
 - 6 million males

One in 4 households has at least one migraine sufferer
Migraine prevalence peaks in the 25-55 age range

Lipton et al. Headache 2000;41:638-657

- 30% of migraineurs suffer their first attack before the age 10 and the problem is most common among adolescents and young adults, but can even strike in infancy.
- Over \$20 billion dollars a year is spent by sufferers desperate for relief.
- It is the second most common reason for loss of work for employers.

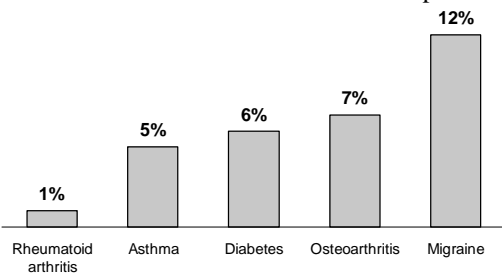
Migraine Remains Underdiagnosed and Undertreated



Adapted from Lipton et al. *Neurology*, 2002;58:885-894.

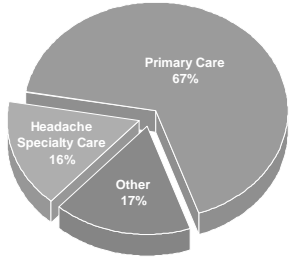
Migraine is More Common than Asthma & Diabetes Combined

Disease Prevalence in the US Population



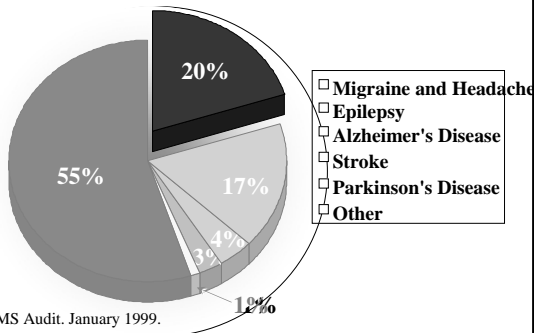
Data from the Centers for Disease Control and Prevention, US Census Bureau, and the

WHERE DO MIGRAINE SUFFERERS SEEK MEDICAL CARE?



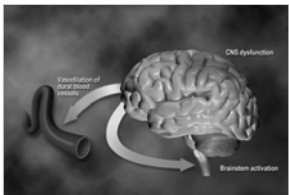
Lipton RB et al. *Headache*. 1998.

HEADACHE IS AN IMPORTANT PROBLEM FOR NEUROLOGISTS



IMS Audit. January 1999.

What Causes Migraine?



- Most experts believe migraines are caused by an imbalance of a naturally occurring chemical in the brain called serotonin
- This imbalance is believed to cause the blood vessels on the surface of the brain to expand
- Nerve endings around the blood vessels become irritated and can lead to the pain and other symptoms associated with migraines

Pathways of Migraine



- Migraine pain
- Can be felt on one or both sides of the head
- The same nerves that carry impulses to the eyes can be felt during a migraine
- The nerves that cause stuffy or runny nose and watery eyes can be activated during a migraine
- The nerves that cause neck pain can be activated during a migraine

Why Migraines Are Often Mistaken for Menstrual Headaches



- Migraines become more common (prevalent) in women than men after the onset of puberty¹
- Hormonal fluctuations associated with the menstrual cycle can trigger migraines²
- Migraines sometimes go away temporarily during pregnancy and after menopause³

1. Stewart WF et al. *JAMA*. 1992;267:64-69.
2. Somerville BW. *Neurology*. 1972;22:355-365.
3. Silberstein SD et al. *J of Pain and Symptom Management*. 1993;8:98-114.

Why Migraines Are Often Mistaken for Sinus Headaches



- Migraine pain can be felt on the face, around the eyes, or in the sinuses¹
- Migraines can include symptoms such as stuffy or runny nose and watery eyes¹
- Weather changes and “allergies” can be triggers for migraines^{1,2}

1. Schreiber CP et al. Poster presented at: The 55th Annual Meeting of the American Academy of Neurology, March 29 - April 5, 2003; Honolulu, HI.
2. Scharf L et al. *Headache*. 1995; 35:397-403.

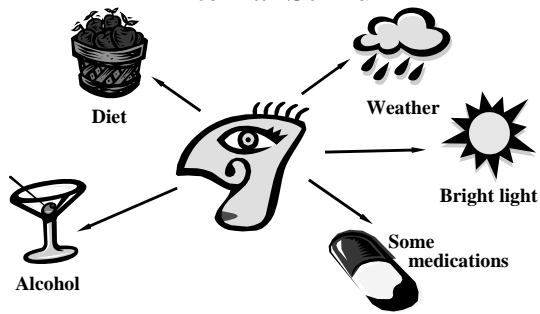
Why Migraines Are Often Mistaken for Tension Headaches



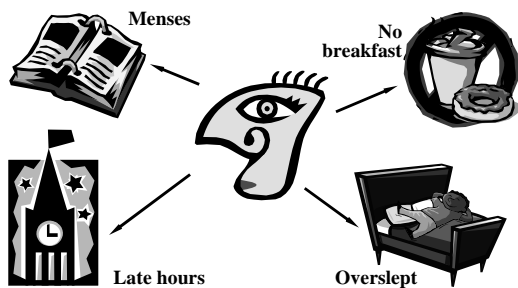
- Migraine pain can be felt in the back of the neck¹
- Migraine pain can be felt on one or both sides of the head²
- Stress and tension are common triggers for migraines³
- In a recent study, 3 out of 4 migraine patients reported neck pain with their migraine attack¹

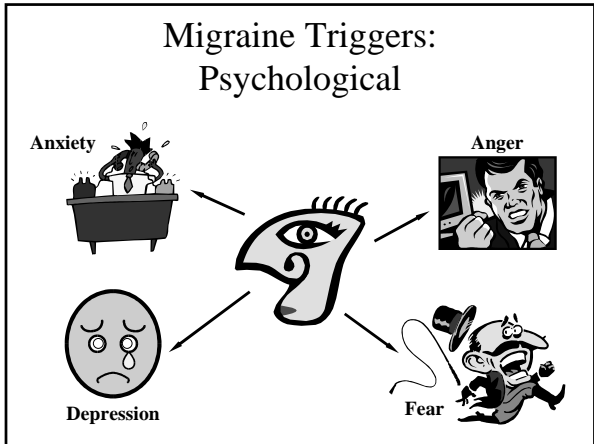
1. Kaniecki RG. *Neurology*. 2002;58 (suppl 6):S15-S20.
2. Lipton RB et al. *Headache*. 2001;41:646-657.
3. Scharff L et al. *Headache*. 1995;35:397-403.

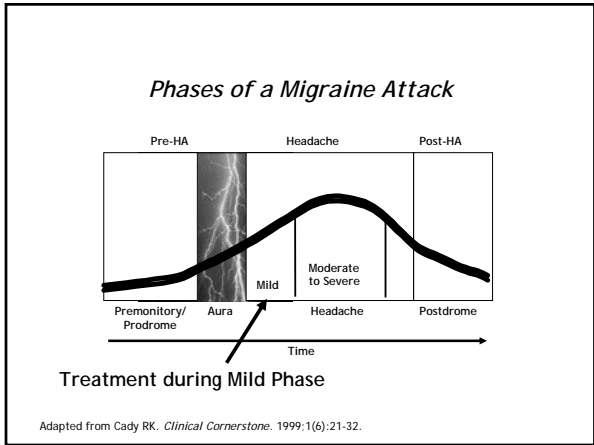
Migraine Triggers: External Stimuli



Migraine Triggers: Physiological







Prodrome

- This can occur hours to days before a migraine.
- About 40% of patients will experience prodromes
- 20-60% of patients report irritability, depression, hunger, thirst or drowsiness.
- Griffin et al demonstrated that up to 72% of patients with premonitory symptoms can accurately predict a migraine attack

Aura

It occurs minutes before a migraine attack, or during and attack
About 20% of people with migraines experience aura.

Migraine Characteristics

- Usually Unilateral
- Pulsing or throbbing
- Moderate or intense pain affecting daily activities
- Nausea and Vomiting
- Sensitivity to light or sound
- Attacks last 4-72 hours or longer
- Exertion makes headache worse

Symptoms of Migraine

Dizziness
Frequent urination
Diarrhea
Sweating
Cold Hands and Feet
Sensitivity to Light, Sound or Odors
Numbness and Tingling

RESOLUTION PHASE

- Tiredness or unusual feeling of euphoria
- Irritability and mood changes
- Impaired concentration
- Scalp tenderness

Types of Headaches

- Migraine with and without Aura
- Tension-Type Headache (Chronic & Episodic)
- Cluster Headache
- Exertional Headaches
- Medication overuse Headaches (MOH)
- Sex Headaches
- Hemicrania Continua
- Chronic Daily Headache
- Post Traumatic Headache

2004 International Headache Society (IHS) Criteria for Migraine (TTHA)

1.1 Migraine without Aura/ 2.1 Episodic TTHA

- At least 5 (10) attacks lasting 4-72 hours with
- At least 2 of the following 4:
 - Unilateral (Bilateral)
 - Pulsating (Not pulsating)
 - Moderate to severe intensity, inhibits or prohibits activities (Mild to moderate): Migraine, not TTH has impact!
 - Physical activity aggravates (Does not aggravate): Migraine, not TTH has impact!
- At least 1 of the following:
 - Nausea and/or vomiting (No nausea or vomiting)
 - Photo and phonophobia (One or neither)
- Normal history, exam, or imaging test

1.6 Probable Migraine (Migrainous)

- Missing one of the above criteria

ID Migraine

ID Migraine

During the last 3 months, did you have the following with your headaches:

1. You felt **nauseated**
Yes No
2. **Light bothered you**(a lot more than when you don't have headaches)
Yes No
3. Your headaches **limited your ability** to work, study, or do what you needed to do for at least 1 day
Yes No

Lipton et al. *Neurology* 2003;61:375382.

Treatment Options

Education Management
Stress Management
Medication Management

Education Management

- Identify early symptoms
 - prodrome
 - aura
- Avoidance of triggers
 - foods
 - medications
 - activities
 - stress
- Rebound Education

Stress Management

- Individual or Group Psychotherapy
- Headache Support Groups
- Self-Help or Stress Management Books
- Improved Self-Care/Personal Exercise Program

Stress Management cont...

- Relaxation Techniques
 - Abdominal Breathing
 - Meditation
 - Yoga
 - Tai Chi
- Biofeedback
 - Autogenic Relaxation
 - Progressive Muscle Relaxation
 - Guided Imagery

Acute Management or Abortive Therapy

Goals for Successful Treatment of Acute Attacks of Migraine

- Treat attacks rapidly and consistently without headache recurrence
- Restore patient's ability to function
- Minimize the use of back-up and rescue medications
- Optimize self-care and reduce subsequent use of resources
- Be cost-effective for overall management, and
- Have minimal and no adverse events

US Headache Consortium

Benefits of Early Intervention

- Early pain-free response
- Reduced recurrence rate
- Limits attack and associated symptoms
- Reduction in disability
- Less use of medication, including rescue meds
- Improved absorption of medication
- More cost effective
- ★ May prevent chronic daily headache – transformed migraine

Medication Management

- Identify the severity of the headache
- Use a pain scale of 1-10.
 - 1-3 = mild pain
 - 4-6 = moderate pain
 - 7-10 = severe pain
- Treatment will depend on the level of pain.

Abortive Therapy

- Most effective when used at the first sign of headache
- helps to prevent the symptoms of migraine
 - pain
 - nausea
 - light and sound sensitivity

Mild to Moderate Pain

- **Nsaids**
 - Naproxen Sodium (Naproxen)
 - Diclofenac (Voltarin, Cataflam)
 - Celecoxib (Celebrex)
- **Anti-emetics**
 - Metoclopramide (Reglan)
 - Promethazine (Phenergan)
 - Prochlorperazine (Compazine)
- **Anti-Histamines**
 - Cyproheptadine (Periactin)

Moderate to Severe Pain

- **Triptans**
 - Sumatriptan (Imitrex)
 - Sumatriptan and naproxan sodium (Treximet)
 - Zolmitriptan (Zomig)
 - Naratriptan (Amerge)
 - Rizatriptan (Maxalt)
 - Almotriptan (Axert)
 - Frovatriptan (Frova)
 - Eletriptan (Relpax)
- DHE-45, Migranal

TRIPTANS: TREATMENT CHOICES

<input type="checkbox"/> Sumatriptan <ul style="list-style-type: none"> • Tablet (25, 50, 100 mg) • Injection (6 mg) <input type="checkbox"/> Zolmitriptan <ul style="list-style-type: none"> • Tablet (2.5, 5 mg) • Nasal spray (5 mg) <input type="checkbox"/> Naratriptan <ul style="list-style-type: none"> • Tablet (1, 2.5 mg) <input type="checkbox"/> Rizatriptan <ul style="list-style-type: none"> • Tablet (5, 10 mg) 	<input type="checkbox"/> Almotriptan <ul style="list-style-type: none"> • Tablet (6.25, 12.5 mg) <input type="checkbox"/> Frovatriptan <ul style="list-style-type: none"> • Tablet (2.5 mg) <input type="checkbox"/> Eletriptan <ul style="list-style-type: none"> • Tablet (20, 40 mg)
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Question and Answer

- Are there differences between the triptans?
- If one triptan fails, will another triptan work?

Medication Overuse Headache

A Vicious Cycle

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    graph TD
      A[Frequent attacks] --> B[Acute therapy]
      B --> C["'Rebound' headache"]
      C --> D[Acute therapy]
      D --> A
  
```

Medication Overuse Headache

- Caused by frequent and excessive use of certain medications
- Unless the medication overuse headache is eliminated, the original headache condition is unlikely to be adequately treated

Associated	Associated?	Not Associated
Butalbital	Acetaminophen	Dihydroergotamine
Caffeine	Aspirin	Neuroleptics
Ergotamine	Short acting	Long acting
Opioids	NSAIDs	NSAIDs
Triptans		



Take 2 tablets every 4 hours until you are addicted.

Preventative Therapy

- to treat frequent headaches >4/month
- for both tension and migraine headaches
- if significant disability despite acute treatment
- if failure of or contraindications to acute medications
- patient preference

GENERAL PRINCIPLES

- Start low and go slow
- Adequate therapeutic trial
- Avoid overuse of acute medications
- Re-evaluate
- Discuss potential risks on the fetus
- Take patient preference into account
- Consider co-morbid disease

Beta Blockers

- **Nadolol**
- **Inderal**
- **Lopressor**

- **Side effects:**
 - Depression
 - Nausea
 - Dizziness
 - Decreased exercise tolerance
 - Bradycardia and hypotension

- **Contraindications (nonselective):**
 - Asthma
 - Diabetes
 - CHF

Calcium Channel Blockers

- **Verapamil-(Calan)**
- **Diltiazem-(Cardizem)**
- **Amlodipine-(Norvasc)**

- **Side effects:**
 - Transient increase in headache
 - Dizziness
 - Depression
 - Vasomotor changes
 - Peripheral edema
 - Orthostatic hypotension and bradycardia
 - Constipation

Tricyclic Antidepressants

- **Amitriptyline-(Elavil)**
 - **Nortriptyline-(Pamelor)**
 - **Doxepin-(Sinequan)**
 - **Desipramine-(Norpramine)**
 - **Protriptyline-(Vivactil)**
- **Side Effects:**
 - Sedation
 - Anticholinergic side effects
 - Weight gain
 - May precipitate mania
 - Lower seizure threshold
 - Prolonged QT interval
 - **Wide variation in TCA metabolism**
 - Dose must be individualized

SSRIs

- **Fluoxetine-(Prozac)**
- **Sertraline-(Zoloft)**
- **Paroxetine-(Paxil)**
- **Citalopram-(Celexa)**
- **Escitalopram-(Lexapro)**

- Mixed data for use- may increase HA
- Better tolerated for depression
- May decrease anxiety
- Avoid combined use with MAOIs

SNRIs

- **Venlafaxine-(Effexor)**
- **Duloxetine-(Cymbalta)**

- May increase anxiety
- May be associated with hypertension
- More effective than SSRIs for headache

AEDs

- **Divalproex Sodium (FDA approved):**
 - Na Valproate:Valproic acid 1:1
 - Start with: 250 mg/d. Max. dose: 60mg/kg
 - SE: GI, tremor, alopecia, thrombocytopenia
 - Rare: pancreatitis and hepatitis
 - Hyperandrogenism
 - Teratogenic
 - Few cognitive side effects or sedation
 - Contraindications: liver, pancreatic or hematologic disease

AEDs

- Topiramate (FDA approved):
 - Effective dose: 50-200 mg/day
 - Responder rate: 36-54%
 - Reduced use of acute medications
 - SE: paresthesias, fatigue, weight loss, cognitive impairment
 - Rare: urolithiasis, glaucoma
 - >200 mg may decrease effectiveness of OCPs

AEDs

- Gabapentin:
 - 36% responder rate in one placebo controlled trial
 - Common SE: drowsiness and dizziness
 - Max dose 3600 mg
- Lamotrigine:
 - Migraine with aura
 - Slow titration: Rash

AEDs

- Zonisamide
 - Useful as adjunctive therapy in refractory migraine
 - 40-50% reduction headache severity and frequency
 - Also effective as monotherapy

Unresolved Migraines

- Trigger Point Injections
 - Magnesium
 - Local Anesthetics
 - Botox
- Infusion Therapy
 - Short term = 1 day quick abort
 - Long term = 3 day, detox or break headache cycle
- Subcutaneous DHE Infusion Pump
- Steroid Therapy

Still Unresolved

Chronic Pain Management Program
or
IMATCH Program

When should we see a neurologist ?

- More than 3 headaches per month
- Sudden onset of headache
- Progressive neurological symptoms
 - Change in behavior
 - Weakness
 - Numbness or other sensory change
- Prolonged auras

Worrisome Headache Red Flags: 'SNOOP'
When in doubt, investigate the atypical!

- S**ystemic symptoms (fever, weight loss) or **S**econdary risk factors- underlying disease (HIV, systemic cancer)
- N**eurologic symptoms or abnormal signs (confusion, impaired alertness, or consciousness)
- O**nset: sudden, abrupt, or split-second (First, Worst)
- O**lder: new onset and progressive headache, especially in older-age >50 (giant cell arteritis)
- P**attern change: first headache or different, change from
- P**revious headache history: attack frequency, severity, or clinical features

Sadovsky D, Dodick DW. Am J Med 2005; 118, Suppl 1, 11S-17S.

What you can have patients do?

VERY IMPORTANT

- Keep a headache diary/calendar
 - rate severity of headaches
 - symptoms associated with headaches
 - menses (if female)
- keep list of medications you have tried
 - Successful
 - Failed
 - Length of time used

Conclusion

- Migraine is a frequent and disabling disorder
- Effective treatment options are available
- Patient education is important
- Goal: improve quality of life of migraineurs



TRIPTANS

TABLE 5-4 Triptan Medications

Generic	Brand	Formulations	Doses	Maximum Daily Dose	
Sumatriptan	Imitrex	Tablets	25 mg, 50 mg, 100 mg	200 mg (US)	
		Nasal spray	5 mg, 20 mg	40 mg	
		Subcutaneous injection	4 mg, 6 mg	12 mg	
		Suppositories (EU)	25 mg	50 mg	
Zolmitriptan	Zomig	Tablets	2.5 mg, 5.0 mg	10 mg	
		Zomig-ZMT	Orally disintegrating	2.5 mg, 5.0 mg	10 mg (US)
		Nasal spray	5.0 mg	10 mg (US)	
Rizatriptan	Maxalt	Tablets	5 mg, 10 mg	30 mg (US)	
		Maxalt-MLT	Orally disintegrating tablet	5 mg, 10 mg	30 mg (15 mg if on concomitant propranolol)
Naratriptan	Amerge	Tablets	1.0 mg, 2.5 mg	5 mg	
Almotriptan	Axert	Tablets	12.5 mg	25 mg	
Frovatriptan	Frova	Tablets	12.5 mg	25 mg	
Eletriptan	Relpax	Tablets	20 mg, 40 mg	80 mg	

US = United States; EU = European Union.

TABLE 5-5 Pharmacokinetics of the Triptans

Drug	T _{max} (h)	T _{1/2} (h)	Bioavailability (%)	Elimination Route/ Metabolism
Sumatriptan	2			Hepatic; MAO-A; 60% renal
50-mg tablet	2.5	2	14	
20-mg spray	1		17	
6-mg subcutaneous	0.2		97	
Zolmitriptan				Hepatic (1 active and 2 inactive metabolites; CYP/MAO-A)
2.5-mg tablet	2	2.5-3.0	40-48	
2.5-mg ZMT	3.3	2.5-3.0	40-48	
2.5-mg nasal				
Rizatriptan	1.2 (Tablet)	2.0-3.0	45	Hepatic; MAO-A; 30% excreted renally unchanged
	1.6-2.5 (MLT)	2.0-3.0		
Naratriptan	2.0-3.0	5.0-6.3	63 (men), 74 (women)	70% excreted renally unchanged; CYP; not MAO-A
Almotriptan	1.4-3.8	3.2-3.7	80	Hepatic; CYP/MAO-A; 15% active N-demethyl metabolite; 26%-35% excreted renally unchanged
Eletriptan	1.0-2.0	3.6-5.5	50	Hepatic; CYP2A4; 15% active N-demethyl metabolite; not MAO-A
Frovatriptan	2.0-4.0	25	24-30	Hepatic; CYP/MAO-A; 26%-35% excreted renally unchanged

T_{max} = time to peak plasma concentration; T_{1/2} = half-life; MAO-A = monoamine oxidase-A; CYP = cytochrome P450.
 Modified from Tepper SJ, Rapoport AM. The triptans: a summary. CNS Drugs 1999;12:403-417, with permission from Adis International.

TABLE 5-6 Clinical End Points for the Triptans From Selected Clinical Trials

Drug	Dose and Route	Therapeutic Gain at 2 Hours (%)	Recurrence Rate (%)
Sumatriptan	6-mg subcutaneous	51	34-38
	50-mg oral RT	25	26-28
	100-mg oral RT	30	28-30
	20-mg nasal spray		
Zolmitriptan	2.5-mg oral	34	30
	2.5-mg ODT	41	
	2.5-mg nasal spray	26	
	5.0-mg nasal spray	40	
Naratriptan	2.5-mg oral	22	17-28
Rizatriptan	10-mg oral	27-40	30-47
	10-mg ODT	19-46	
Almotriptan	12.5-mg oral	26-32	18
Eletriptan	40-mg oral	22-41	19-23
Frovatriptan	2.5-mg oral	16-19	7-25

RT = Formulated with RT Technology ODT = orally disintegrating tablet.

Data from Rapoport AM, Tepper SJ, Bigal ME, Sheffield JD. The triptan formulations: how to match patients and products. CNS Drugs 2003;17:483-487. Sheffield JD, Dahof CG, Brander JJ, et al. Two replicate randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a fast-disintegrating/orally-release formulation of sumatriptan tablets. Clin Ther 2005;27:407-417.