

ANALYSIS OF CURRENT MIGRAINE TREATMENTS: INTERSECTIONS OF
PHARMACOLOGIC AND NON-PHARMACOLOGIC, ACUTE AND
PREVENTATIVE METHODS OF CARE

by
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Migraine affects 23.6 million people in the United States alone. Treatment options can be sub-typed as abortive and preventative, as well as pharmacologic and non-pharmacologic. Due to the debilitating nature of migraine, patients and physicians often rely heavily on abortive treatments. A review of the literature, along with a series of personal interviews suggests that preventative measures, used alone or with abortive treatment, increase the patient's control over the migraines. Additionally, non-pharmacologic interventions such as relaxation training, biofeedback, and dietary modification may offer migraine relief while improving the patient's quality of life. The integration of several treatment avenues represents a growing change in western culture toward prospective medicine, and will aid in maximizing treatment efficacy for migraine.

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Chapter 1: Introduction

Humans have suffered from migraine for at least two-thousand years, and it remains one of the most elusive conditions of our time (Sacks 1992). A debilitating headache disorder, it is widely believed that migraine results from a combination of genetic and environmental factors, sometimes confounded by psychological conditions. As a migraine sufferer for the past eleven years, I have tried various medications with little to no alleviation. A few years ago I stumbled across diet modification as a preventative tool for migraine and found that this approach offered more relief than I had found with any medication. In this project I set out to determine whether all migraineurs can benefit from a non-pharmacologic approach to migraine treatment and to examine the barriers that prevent migraineurs and physicians from utilizing a comprehensive treatment plan.

Due to the incapacitating and overwhelming nature of migraine attacks, patients and physicians often seek abortive treatment for relief. However with migraine pathophysiology yet to be fully understood, abortive treatment only affects the symptoms of an unknown underlying mechanism. Alternatively, preventative medications can help patients exert control over their migraines especially when *comorbidities* exist, but also hold the potential for adverse side effects. Non-*pharmacologic* treatment lacks the level of comparable research of pharmacologic options; however, treatments such as behavioral interventions may prevent migraines while also improving *migraineurs'* overall quality of life. Given the limited efficacy of each treatment option and the wide range of factors contributing to migraine, migraineurs maximize control of their

migraines by eliminating migraine triggers, aggressively utilizing non-pharmacologic therapy, and relying only minimally on abortive treatments.

In 1989, a group of researchers determined the prevalence, socioeconomic profile and burden of migraine in the United States. They sent out a self-administered questionnaire to 20,000 households in the United States, asking each individual over 12 years of age to respond to questions regarding symptoms, frequency, and severity of their headaches and related disability. The results showed that approximately 18% of women and 6% of men suffer from migraine, and that 23% of households contained at least one migraineur. These results were replicated by an identical study ten years later. In the 1999 study, it was found that an estimated 23.6 million Americans suffer from migraine (Lipton et al, 2001). However Dr. David Mundall, a Eugene neurologist, suggests that these numbers may underestimate the actual number of migraineurs in the United States, as many patients fail to report their symptoms (Dr. John Mundall, interview, 5 April 2006). Migraine is a difficult condition to diagnose and treat because 1) no diagnostic test exists to define, ensure or differentiate *idiopathic* headache disorders 2) it is considered a functional disease, in which the migraineur often continues work, play and social activities despite the reduction in overall quality of life and episodes of disability (May 2005).

Migraine is more than a descriptive term for a bad headache (Dr. John Mundall, interview, 5 April 2006). While permanent anatomical and psychological effects are not well understood, the disability associated with migraine results in a great burden for patients, families and employers. It is estimated that 70% of migraineurs have impaired interpersonal relationships, and regular activities are limited during 78% of their attacks.

Not only do migraine patients have to deal with the pain, but also the burden of lost productivity, absence of control of the headache, and fear of the next attack (Solomon, 1993). In a personal interview, one migraineur explained, “My mom and I joke and call it the ‘M’ word, in fear if we talk or think about having one, we will actually trigger a migraine” (Personal interviews, March/ April 2006). The quality of life of these patients is impaired even between attacks. Migraine patients show more symptoms of emotional distress, as well as disturbed contentment, vitality and sleep than those without any headache disorders (Dahlof and Dimenas, 1995).

The economic burden of migraine is substantial, in both the amount of money spent by patients and insurance companies for treatment, as well as the amount of corporate costs for absenteeism and “*presenteeism*.” Burton et al estimated the direct and indirect corporate cost of migraine totaled between \$21.5 million and \$24.4 million, suggesting the need for a corporate response to migraineur employees (Burton et al, 2002).

Families of migraineurs also bear a portion of the migraine burden. Smith’s study in 1998 examined the impact of migraine on the family, finding that 61% of migraineurs reported their disorder had a significant effect on their families in terms of domestic and social activities, as well as interpersonal relationships. Twenty-five percent of the migraine sufferers questioned reported that their headaches had a negative influence on their relationships with their spouse/partner (Smith, 1998). In a collection of clinical vignettes, Rueveni wrote that headache sufferers “frequently experience a sense of isolation and guilt toward their spouses and children...family members can experience confusion, anger and frustration in their attempts to help...(and) often wonder whether

sufferers fake or exaggerate their headache pain or use the pain as a 'tool' to control others in the family" (Rueveni, 1992). It becomes clear that migraine affects more than just the 23.6 million people that experience the actual pain.

Given the pain and resultant burden of migraine, why is it that over 60% of migraineurs in the U.S. have never sought, or have discontinued, medical care (Goadsby and Oleson, 1997)? In a 1992 survey, only 29% of men and 41% of women with migraine reported ever receiving diagnosis for migraine (Lipton et al, 1992). As a functional condition, migraine sufferers may not feel the need to seek medical assistance unless attack frequency and severity increase drastically. Patients list speed of onset, improved safety, affordable price, freedom from recurrence, consistent relief from every headache as the most important factors in treatment (Goadsby and Oleson, 1997). Unfortunately, providing relief in all of these areas without completely understanding the physiology behind migraine proves to be a difficult task, leaving both patients and physicians frustrated and disillusioned. Treatment failure can occur for a number of reasons including patient noncompliance, inadequate medications or trial duration, medication overuse (causing rebound phenomenon) and incorrect original diagnosis (Loder and Biondi, 2005). As a result, some migraineurs simply accept their migraines as an integral part of their life. One 82-year-old migraineur elucidated, "If I don't have a headache, something must be wrong," reflecting the sentiments of some migraineurs with frequent headaches.

Migraine treatment can be partitioned into pharmacologic and non-pharmacologic groups. Within the pharmacologic group, physicians can prescribe abortive medications which are taken at the onset of an attack; and/or preventative medications that are taken

every day. Non-pharmacologic treatment includes the elimination of potential triggers as well as behavioral interventions. Each treatment option can be employed alone, or in conjunction with one or more of the other options.

As the underlying mechanism and intersection of triggers that cause migraine remain poorly understood, correct use of abortive medication allows the migraineur to lead a functional life while suffering minimally from their migraines. Avoiding some of the precipitating factors may not always be plausible, thus abortive medications provide a legitimate option for many migraineurs. Unfortunately the vast majority of abortive medications carry the potential for adverse side effects and overuse, the latter of which can lead to rebound, or transformed migraine headache.

In addition to abortive drugs, physicians sometimes prescribe preventative, or *prophylactic*, drugs if a patient experiences a high frequency (more than once a week) or unusually severe migraine attacks. Researchers have found that the use of preventative medicines as an adjuvant to abortive medicines often improves the patient's response to the abortive medicine (Ramadan et al, 1997). These medications often help with comorbidities such as depression, anxiety, and asthma. However like the abortive drugs, many prophylactics carry a significant potential for adverse side effects.

Another mode of treatment, not often suggested by physicians until migraine frequency and severity increases dramatically, is non-pharmacological treatment in the form of biofeedback therapy, cognitive behavioral therapy and strict avoidance of triggers. Since these treatments appear to be less effective than pharmacological measures, physicians prescribe such treatment less often. Several precipitating factors of migraine have been identified through research, but more often through collective

observations of patients' testimonies. These triggers include dietary factors such as caffeine, monosodium glutamate (MSG) and cocoa; environmental factors including bright lights and changes in barometric pressure, as well as personal factors such as stress and/or stress letdown and physical exertion (Buchholz 2002). Although only limited research has provided insight into the role sleep and foods play in migraine pathogenesis, it has been suggested that sleep disturbance and food represent potentially modifiable triggers of migraine (Millichap 2003, Kelman 2005). Lifestyle modification generally presents a challenge that may seem to be a greater burden than the migraine itself. As Wolff states, "one must appreciate that elimination of the headache may demand more in personal adjustment than the patient is willing to give. It is the role of the physician to bring clearly into focus the cost to the patient of his manner of life. The subject must then decide whether he prefers to keep his headache or attempt to get rid of it" (Wolff 1963). Personal adjustment, as Wolff uses it here, includes stress reduction, sleep modification and other potentially avoidable triggers.

Regrettably, non-pharmacologic treatment appears underutilized in primary care. In a 1999 review of clinical psychological interventions, McGrath states that the low availability of psychological services on health care plans and lack of an "organized marketing arm" to inform physicians of the behavioral treatments prevents their use (McGrath 1999). Additionally patients may also be hesitant to utilize psychological treatment, as not to inflate the stereotype of the mythical "migraine personality." Another barrier to non-pharmacological strategies results from the lack of research done with primary care patients. Most of the studies on non-pharmacological treatments involve patients in headache clinics, who have already surpassed the limits of primary

care and experience *refractory* migraines. It is possible that non-pharmacological treatment may provide more benefits if employed earlier in a patient's therapy regimen.

In order to understand the benefits and disadvantages of various lines of treatment for migraine it is important to possess a basic understanding of the pathophysiology of migraine, as described in the next section.

Chapter 2: Background

Pathophysiology of Migraine

Even after 25 twenty-five years of well-aimed research, we still know relatively little about the pathophysiology of migraine. It is now widely accepted that migraine falls within a continuum of headache disorders also containing chronic daily headache and cluster headache. In 1988 the International Headache Society published a guide to classification and diagnosis of headache disorders, cranial neuralgias and facial pain that is used to distinguish between various headache disorders and administer the appropriate treatment (this classification system was updated in 2002, however the migraine criteria remained relatively unchanged). As most headache patients suffer from multiple types of headaches, the I.H.S. states that it is ideal to classify the most important one or two types and direct a treatment plan based on that assessment. The I.H.S. describes migraine as an “idiopathic, recurring headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of headache consist of one or more of the following: unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photo- and phonophobia (Headache Classification Subcommittee of the I.H.S., 2004).

Migraine is typically diagnosed as “with aura” or “without aura.” The term “aura” describes the neurological effects that some patients experience when cerebral blood flow decreases. The aura usually precedes the headache, but may occur simultaneously with the headache or after the headache begins. Some patients experience aura without headache, nausea, photophobia or phonophobia (Headache Classification Subcommittee of the I.H.S., 2004). Aura occurs in approximately 15% of the migraine

population (Russell and Oleson, 1996), creating a different visual effect for each migraineur as described in Box 1.

Box 1.—Descriptions of aura occurring with migraine

“It starts out with wavy lines and black spots that block out half of the words (when reading) in one eye, then I usually lose my peripheral vision on either one or both sides. This happens about 30 minutes before the pain starts

--Julie, 30-year-old female

“The aura would obscure my vision starting with the periphery and move towards the center of my field of view. It lasted for a period of time ranging from 1-3 hours, but always stopped before vision was completely obscured. Migraine pain followed the resolution of normal vision by not more than a half hour.

-- Taylor, 21-year-old male

“I begin to see bright spots and lose my vision. This is the major indicator that a migraine is coming and usually lasts for 30 minutes. I also get numbness to my fingers and tongue.

-- Maria, 23-year-old female

Source: Personal interviews, March/April 2006 (names have been changed to protect identity).

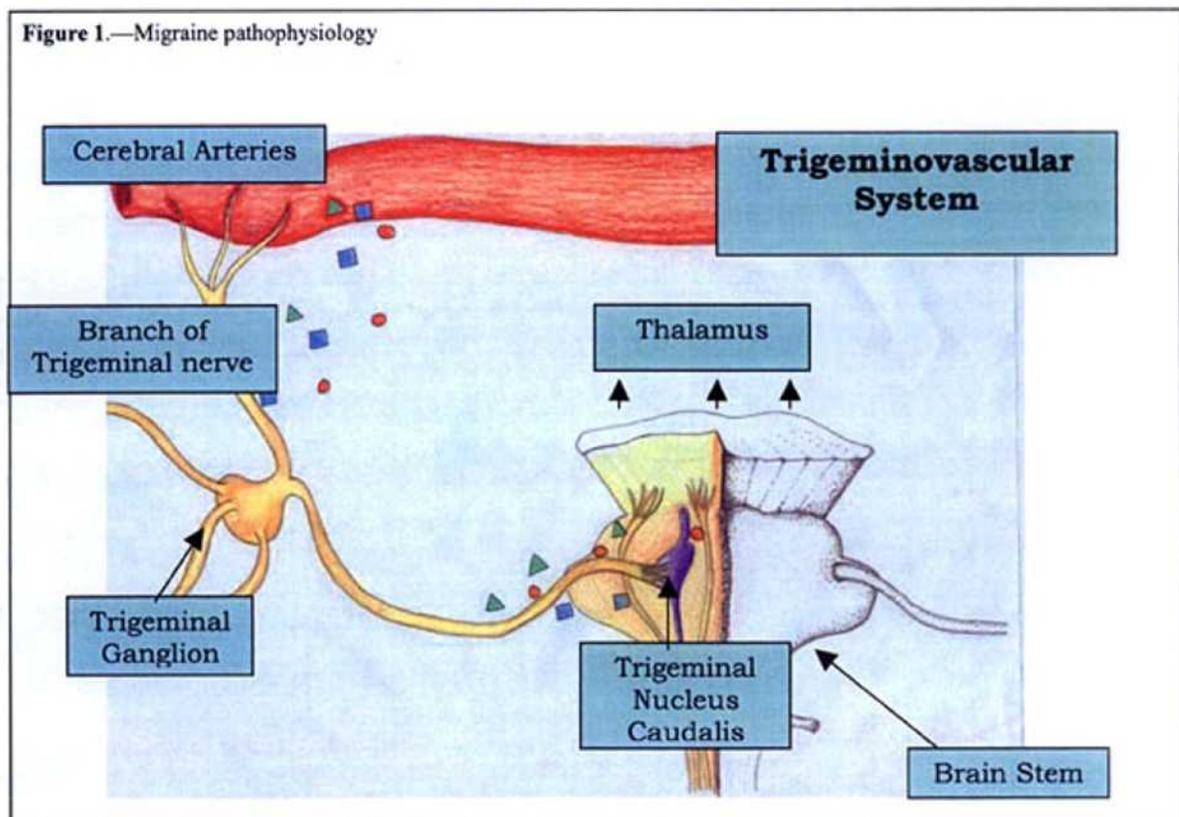
Migraine stems from environmental and genetic factors. While the exact genetics of migraine are not fully understood, a pattern for maternal transmission has long been recognized (Gardner 1999). Currently researchers have made significant progress in determining the genetic basis for a rare form of migraine known as familial hemiplegic migraine. These studies have laid the foundation for finding the genetic basis for other types of headaches (Ferrari 2003). However due to the difficulty in determining a dominant or recessive pattern to inheritance, and other factors such as migraine on both sides of the family and reliance on history for diagnosis, migraine is believed to be genetically complex (Gardner 1999).

According to Goadsby, migraine “is in essence a disorder of sensory dysmodulation, in which normal *afferent* activity is misperceived as being excessive due

to dysfunction in brainstem regions that normally control and gate sensory neuronal traffic. The result is excess throughput in the sensory *thalamus* that patients report as pain, and sensitivity to light (photophobia), sound (phonophobia), or head movement” (Goadsby 2005). This does not imply hyperexcitability of neurons, but actually that the migrainous brain does not *habituate* to stimuli in a normal way, leading to changes in cortical synchronization (Goadsby 2005). Typically sensory neurons habituate, or in a sense become accustomed to, sensory stimuli and decrease the frequency at which signals are sent to higher brain centers. With migraine the sensory neurons do not habituate, producing an effect similar to, but mechanistically different from hyperexcitation.

It is well understood that blood flow to the cranial and cerebral blood vessels increases during migraine, creating pain. Blood flow remains elevated in the brainstem even after relief from the headache (Weiller et al 1995). The development of 5-HT receptor agonists (the triptans) has lent insight into the exact pathophysiology of migraine. While the exact cause remains unknown, we do know that for some reason the cranial blood vessels become dilated, potentially due to *neurogenic inflammation*, which initiates a cascade of events in the brain (See Figure 1 on page 11) (Nozaki et al, 1992). The dilation activates afferent nerve fibers stemming from the trigeminal ganglion, which sends the signal to the trigeminal nucleus caudalis in the brainstem. These nerve fibers also release *substance P*, calcium gene-related peptide and neurokinin A (proteins that cause *vasodilation*) upon stimulation, which perpetuates the vicious cycle of vasodilation (Edvinsson et al, 1998). Substance P causes weak vasodilation, but is not implicated in sensitizing nerve fibers in the trigeminovascular system. Instead substance P conditions the nerve response to other inflammatory mediators as one of the first steps in migraine

pathogenesis (Limroth et al, 1996). Activation of neurokinin A receptors initiates the release of nitric oxide, which is a powerful vasodilator implicated in the induction and maintenance of migraine attacks (Jansen-Oleson et al, 2005). CGRP, another potent vasodilator, is the most abundant peptide within the trigeminovascular system. In addition to causing vasodilation CGRP may block substance P degradation, perpetuating the first step in the migraine chain reaction (Limroth et al, 1996). In the brainstem, as the pain is transmitted to higher brain centers, the release of more neuropeptides activates other ascending neural pathways, which may be the cause of symptoms related to migraine such as nausea and vomiting (Weiller et al 1995).



Several possible candidate regions have been identified for migraine initiation, including the *ventrolateral periaqueductal grey* (PAG) and *locus coeruleus* (LC) (Goadsby 2005). The PAG is known to inhibit pain receptors in the *trigeminovascular system* and it has also been suggested that activation of the PAG is associated with an animal becoming quiet and not engaging with its environment, similar to the behavior that many humans adopt when suffering from a migraine attack (Knight and Goadsby, 2001, Knight et al, 2003, Bandler and Keay, 1996). The LC also seems to be a plausible nucleus because its widespread projections influence pain receptor and *pan-sensory* processing (Goadsby and Duckworth, 1989; Goadsby et al, 1982).

Numerous psychological, physical and environmental factors have been identified as precipitating triggers to this mechanism; however the research to determine how the wide range of precipitating factors initiates the cascade of events during a migraine remains to be seen.

Triggers

Two main factors exist in the occurrence of migraine: genetic predisposition and environmental factors, or triggers. Some triggers are difficult to control or avoid, such as weather/barometric changes, hormonal fluctuations, sensory stimuli (bright light, perfumes, etc.), physical exertion, irregular sleep and stress. According to Fragoso et al, both migraine and tension-type headache patients report prolonged anxiety and stressful situations as the most important triggering factors, both of which almost always lead to an attack in migraineurs. Crying and menstrual cycles for women also rated high as triggers (Fragoso et al, 2003)

Controllable triggers include dietary factors, caffeine intake and to a certain extent sleep and stress. While occasional intake of caffeine is not considered a trigger (caffeine acts as a *vasoconstrictor*, thereby actually providing relief to some migraineurs) frequent intake can cause rebound headache similar to that caused by certain medications. Table 1 outlines some common dietary items believed to precipitate migraine, and the chemical culprits involved.

Offending Food Item	Chemical Trigger
Cheese	Tyramine
Chocolate	Pheylethylamine, theobromine
Citrus Fruits	Phenolic amines, octopamine
Hot dogs, ham, cured meats	Nitrites, nitric oxide
Dairy products, yogurt	Allergenic proteins (casein, etc.)
Fatty and fried foods	Linoleic and oleic fatty acids
Asian, frozen, snack foods	Monosodium glutamate
Coffee, tea, cola	Caffeine, caffeine withdrawal
Food dyes, additives	Tartrazine, sulfites
Artificial sweetener	Aspartame
Wine, beer	Histamine, tyramine, sulfites
Fasting	Stress hormone release, hypoglycemia
*Ice cream headache is probably a cold-induced vasoconstrictor reflex response.	

Source: Millichap and Yee, 2005.

Unfortunately, the broad range of triggers prevents researchers from finding a common underlying factor in all precipitating factors. As such, in his book *Heal Your Headache*, Dr. David Buchholz highlights the fact that avoiding all triggers can be overwhelming for the patient (Buchholz 2002). Each patient must find a balance between exposing themselves to certain triggers and controlling their headaches. The complexity of precipitating factors can be perplexing to patients presented with a generalized plan of

trigger avoidance. Box 2 illustrates the different triggers for several migraineurs elucidated from personal interviews (Migraineur interviews, 2006).

Box 2.—Examples of migraine triggers in a small sample of women

Elizabeth, 22: oversleeping, diet (bologna, sauces, chocolate, cheese and caffeine)—although moderation of these items does not present a problem, stress letdown

Maria, 23: stress, hormones, diet (too much dairy or caffeine), dehydration, bright light

Joanne, 49: staying up late and getting up early, stress, hormones, being in a hot stuffy room

Alecia, 53: hormones, diet (MSG, artificial sweeteners, chocolate), bright light for a prolonged period of time, excessive physical exertion, crying, sleeping with face partially under the covers (reduced oxygen intake).

Source: Personal interviews, March/April 2006 (names have been changed to protect identity).

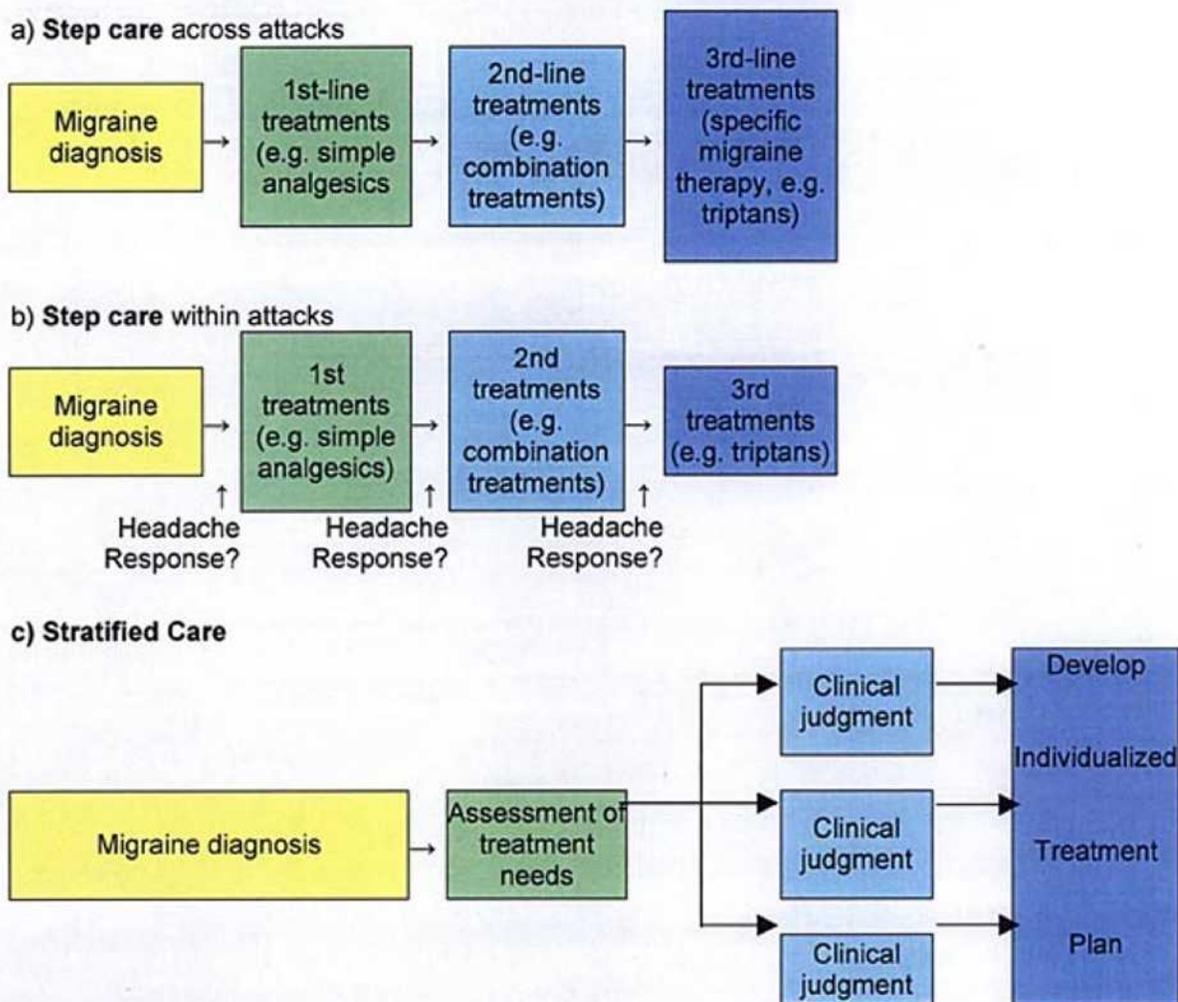
Although some triggers such as hormones and diet appear common, it is the combination of various triggers along with varying levels of predisposition that necessitate individualized treatment plans for migraineurs. In addition, some triggers may affect a greater response in certain patients while only minimally affecting others.

Chapter 3: Types of Treatment

Pharmacologic Acute Treatment

The evolution of migraine treatment has progressed significantly in the past twenty years. Some physicians still use conventional step care methods in which simple *analgesics* are prescribed after the initial migraine diagnosis, and the level and type of medication is adjusted based on the patient's success with the analgesic. The treatment becomes more specific as the previous line of treatment fails to help. This can be implemented within the duration of a single headache, or over the course of several attacks (Figure 1a and 1b). In 2001 Lipton and Silberstein proposed a more effective system of stratified care, in which treatment is individualized to each patient based on their presenting level of headache. Stratified care involves a more thorough assessment of treatment needs and the physician and patient work together to create an individualized treatment plan (Figure 1c). Lipton and Silberstein reported that stratified care ultimately resulted in a greater headache response rate when compared with the step-care method (Lipton and Silberstein, 2001).

Figure 2.--Step care vs. Stratified Care for the Choice of Acute Migraine Treatments



Source: Lipton and Silberstein, 2001

In stratified care, physicians recognize that patients presenting with migraine at different stages of progression may require different medications. Recent research has increased the options for *acute* migraine treatment. Table 2 (pg. 17) outlines the most common abortive medications used in the United States, compiled from U.S. Headache

Consortium guidelines (described below) as well as specific studies directly related to each treatment option.

In 1998, a multi-disciplinary panel of representatives from several medical professional organizations convened to create a set of clinical practice guidelines for headache, including the efficacy and evidence ratings of medications listed in Table 2. They accomplished this by analyzing all relevant controlled trials for headache treatment between 1966 and 1996. They generated four separate sets of guidelines, each dedicated to a separate type of management decisions. The four groups consisted of diagnostic testing, pharmacological management of acute attacks, migraine-preventative drugs and behavioral and physical treatments for migraine. After evaluating the pertinent studies the panel assigned each type of treatment within the four groups a letter grade of A, B or C based on the strength of evidence supporting the study. They also analyzed the clinical efficacy of each drug (Box 3) (McCrory et al 1998).

Box 3.—U.S. Headache Consortium Scales for Strength of Evidence and Clinical Effect for Acute Migraine Treatments

Strength of Evidence

- A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.
- B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group for the recommendation.
- C. The U.S. Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized trials

Clinical Effect

- 0 Ineffective: most people get no improvement
- + Somewhat effective: few people get clinically significant improvement
- ++ Effective: some people get clinically significant improvement
- +++ Very effective: most people get clinically significant improvement

This information, along with details concerning side effects and contraindications are included in Table 2 in order to effectively compare various abortive migraine treatment strategies. Acute medications allow for fine tuning in individualized treatment plans, increasing options for patients with certain comorbidities and preferences (Ashkenzi and Silberstein, 2003). While several abortive medications are readily available, the triptans remain the only migraine-specific medication available today.

According to Goadsby, serotonin receptor agonists developed in the early 1990s, also known as triptans, represent “the most important advance in migraine therapeutics in the four millennia that the condition has been recognized” (Goadsby 2005). The triptans work as 5-HT_{1b/1d} receptor agonists, mimicking the effects of serotonin on 5-HT_{1b/1d} receptors (Goadsby 1997). Triptan molecules bind to these receptors on the cranial vessels, inhibiting the release of the *vasoactive* peptides, allowing the vessels to constrict to normal diameter (Longmore et al, 1997). The 5-HT_{1d} receptors are also located throughout the trigeminal nerve fibers, more specifically on the trigeminal ganglion and trigeminal nucleus caudalis. When bound by triptan molecules, these receptors prevent the transmission of pain signals to higher brain centers (Rebeck et al 1994; Kaube et al 1993).

Table 2.--Abortive drugs for migraine and potential effects

Line of Treatment	Efficacy	Evidence Grade	Advantages	Disadvantages				
				Contraindication	Cardiovascular AE	Neurological AE	Gastrointestinal AE	Other
Simple analgesics, NSAID's	2+	A		ulcer disease, renal disease		headache, dizziness, lightheadedness, somnolence	GI pain, nausea, constipation, diarrhea	Other
	1+	B						
	2+	A						
Combination analgesics	2+	A	can reduce risk of side effects—lower doses of each med. is used.		caffeine—increased heart rate			overuse can lead to rebound
	2+	A						
Triptans	3+	A		ischemic heart disease, Prinzmetal's angina, history of myocardial infarction, uncontrolled hypertension, cerebrovascular disease	also binds to serotonin receptors in coronary arteries, can cause coronary adverse effects	dizziness, fatigue, somnolence	nausea	
	3+	A	Onset: 10 min sublingual, 15 min nasal spray					
	*	C						
	3+	A						
	2+	A						
Barbituate hypnotics	3+	C	can reduce risk of side effects—lower doses of each med. is used.			sedation	GI pain, nausea, constipation, diarrhea	same side effects as NSAID's
	3+	B						
Ergot alkaloids	2+	B	Onset: Nasal spray—30min	ergotamine: renal and hepatic disease, coronary artery disease, peripheral vascular disease, hypertension, increased side effects when used with anti-emetic		paresthesia, anxiety	nausea, vomiting	leg cramps, overuse can cause habituation and ergotism
	3+	A						
Opiate analgesics	3+	B				nervousness, taste perversion, blurred vision, drowsiness, vertigo, fatigue	nausea, vomiting	greater risk of medication overuse
	2+	A						
	2+	B						
	2+	B						
	2+	B						
Corticosteroids	2+	C						acne, increased hair growth, irregular or absent menstrual periods, intranasal irritation (lidocaine)
	2+	C						
	2+	B						
2+	B							

Source: Data compiled from Tfelt-Hansen et al, 1998; Goldstein et al, 1998; Kramer et al, 1998; National Library of Medicine, accessed 4/3/2006; Gallagher 1996; Silberstein et al, 2000; Matchar et al 1998.

AE=Adverse Effects

*treatment not available for U.S. Headache Consortium analysis

All triptans work by the same basic mechanism of binding to serotonin receptors within the brain and periphery. Differences between the triptans include time of onset, *bioavailability*, *selectivity*, and interactions with other drugs (Ferrari 1997; Goadsby and Hargreaves, 2000). The presence of identical serotonin receptors in the *coronary* arteries presents a potential setback for the triptans, as binding to the coronary receptors can lead to adverse coronary events. The Imitrex (sumatriptan) drug information pamphlet lists coronary artery vasospasm, *transient ischemia*, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, various cerebrovascular events and death as possible side effects to the drug (Imitrex package insert). However since the concentration of 5-HT_{1B/1D} receptors is much higher in the cranial vessels, and the primary receptor for coronary constriction is of a different 5-HT class, the triptans are considered safe for migraine treatment (Longmore et al, 1997).

All abortive medications have the potential to cause rebound, or transformed migraine headache, if overused. Classic rebound headache is classified by the I.H.S. as headache induced by or due to substance withdrawal ((Headache Classification Subcommittee of the I.H.S., 2004). This can quickly worsen to chronic daily headache (CDH), often recognized as the presence of headaches for more than 15 days per month, lasting longer than 4 hours and presence for at least one year (Konno et al 1999). Patients with CDH may be the most difficult headache patients to treat, as they often develop physical, emotional and drug dependencies and reduced coping skills. Drug-induced rebound headache is the most common cause of CDH in patients attending specialty clinics in the United States (Silberstein and Lipton, 1997; Siniatchkin et al 1999).

None of the abortive medicines specifically target early processes in the migraine mechanism, with the exception of the triptans and caffeine containing analgesics. Instead they work as general pain-killers (e.g. analgesics) or vasoconstrictors (e.g. ergotamine) and may or may not directly affect the migraine mechanism. Even the mode in which triptans inhibit migraines remains limited, as increasing evidence has suggested to leading neurologists that migraine is primarily a neurological problem (Goadsby et al 2002). As listed in Table 2, triptans have the potential to induce serious adverse effects. Simple analgesics and NSAIDs can cause gastrointestinal disturbances if taken too frequently and also are a major culprit in rebound headache (Rapoport et al 1996). Barbituate hypnotics, although effective, contain butalbital—a chemical implicated in poor migraine control, disability, drug induced headaches and withdrawal symptoms (Wenzel and Sarvis, 2002). Ergot alkaloids can complicate several comorbidities in migraineurs, and like opiate analgesics and corticosteroids can cause serious side effects as well as early dependence.

With advances in migraine research, physicians may soon be able to phase out prescriptions of harsh, non-specific migraine medications. In 2005 Goadsby compiled a list of potential neuro-active drugs and potential targets for both preventative and acute migraine treatment. For migraine prevention, inhibition of *cortical spreading depression* and voltage-gated calcium channels appear to hold major promise. Many more targets exist for acute treatment, including serotonin receptors (different that the receptors that triptans target), glutamate receptors, nociceptin opioid receptor-like 1 (ORL) receptors, vanilloid receptors, cannabinoid receptors and orexin receptor modulators (Goadsby 2005).

vanilloid receptors, cannabinoid receptors and orexin receptor modulators (Goadsby 2005).

The development of neurally acting drugs could increase treatment efficacy and reduce side effects for migraineurs choosing abortive medication, as the new medications would ideally inhibit the migraine earlier in the causative process.

Pharmacologic Preventative Treatment

Several reasons exist for early implementation of preventative therapy in the treatment of migraine. It has been long recognized that episodic migraine can evolve into a chronic headache disorder that is more difficult to treat. The progression of this type of disorder may be redirected with early implementation of preventative therapy (Loder and Biondi, 2005). Several studies have shown that migraine patients tend to suffer lower quality of life during, and also between, migraine attacks. Part of the explanation for this effect is that patients are often forced to rely on unsatisfactory acute treatments for attacks of varying severity and unpredictable onset (Dahlof and Dimenas, 1995). For these patients, preventative therapy offers a better chance at predicting the onset of an attack because patients retain better control of their migraines. Box 4 summarizes indications for migraine prevention.

Box 4.—Commonly Accepted Indications for Migraine Prophylaxis

- Headache—related disability occurs three or more days per month
- Migraine duration is greater than 48 hours
- Acute migraine medications are ineffective, contraindicated, or likely to be overused
- Attacks produce profound disability, prolonged aura, or true migrainous infarction
- Attacks occur more than two to four times per month, even with adequate acute care treatment
- Patient preference for preventative therapy

Source: Loder, 2005.

Preventative treatment does more than protect migraineurs from episodic pain. Recent research suggests that migraines may have permanent anatomical effects on certain regions of the brain. More specifically, Welch et al found that migraineurs were more likely to have non-heme iron deposits in areas of the brainstem corresponding to the periaqueductal gray matter in the brain, an area important in the regulation of ascending pain signals (also a potential control center for migraine). It is possible that chronic activation of these structures, along with the resultant *hyperemia*, may lead to free radical formation, neuronal injury, and the observed iron deposition (Welch et al, 2001). The use of preventative medication can help to avert these unwanted anatomical changes.

Unfortunately, similar to the abortive medicines, no preventative medicine exists solely for migraine prevention. However several medications, including topiramate, divalproex sodium, propranolol and timolol have garnered FDA approval for migraine *prophylaxis*. A summary of prophylactic medications prescribed in the United States is summarized in Table 3 on page 25. The evidence for topiramate and botulinum toxin became available after the U.S. Headache Consortium convened, thus efficacy and evidence ratings were not available for analysis. The U.S. Headache Consortium used the same criteria for efficacy and evidence ratings with abortive and preventative medications. Preventative drugs are not prescribed in a specific line of treatment like the abortive medications. Instead, physicians examine any existing comorbidities and pick a medication that will treat both conditions with minimal side effects. For example, a patient presenting with both migraine and depression could potentially benefit from an anti-depressant medication. The medication treats both conditions by separate

mechanisms (John Mundall, interview, 5 April 2006). If no comorbidities exist, the patient and physician work to find a medication that produces the fewest side effects.

To date, topiramate has been the most studied drug for migraine prophylaxis (Brandes and Lewis, 2005). It seems likely that anti-epileptic drugs, also called neuromodulators for their modulatory effect on neural and cortical hyperexcitability, are more effective in preventing not only the underlying mechanism of migraine but also the neuralplasticity and progressive CNS injury mentioned above (Loder and Biondi, 2005). Nevertheless, the efficacy of all migraine prophylactic drugs remains limited until more is understood regarding the pathophysiology of migraine.

The use of botulinum toxin type A (BOTOX) has recently been indicated as a potential prophylactic treatment for patients with refractory migraine. This was discovered anecdotally by patients receiving BOTOX injections for facial wrinkle-reduction, who then realized that the injections appeared to decrease their headache frequency. The treatment involves injection of BOTOX every 3-6 months into a fixed fronto-temporal site. Although a few double-blind, placebo-controlled studies have been performed on highly selected groups of patients suffering from chronic refractory headaches, more studies in the future with primary care migraineurs will indicate whether BOTOX demonstrates effective migraine prevention (Dodick et al, 2005).

The use of medications with vascular effects, such as beta-blockers and calcium channel-blockers, is limited by several contraindications and adverse side effects. Additionally, the emerging understanding of migraine as a neurological disease, as opposed to a vascular disease, will potentially reduce the use of these medications for migraine prophylaxis.

Table 3.--Preventative drugs for migraine and potential effects

	Efficacy	Evidence Grade	Advantages	Disadvantages				
				Contraindication	Cardiovascular AE	Gastrointestinal AE	Neurological AE	Other
Analgesical/NSAID's	1+ 1+ 1+ 2+ 2+ 3+	B B C B B A	can help with arthritis	ulcer disease, renal disease		GI pain, nausea, constipation, diarrhea	headache, dizziness, lightheadedness, somnolence	irritius, fluid retention
Anti-depressants	3+ 1+ 3+ 3+	A C C C	can help with depression, anxiety	glaucoma, urinary retention, hypotension, cardiac dysrhythmia, bowel obstruction		weight gain, constipation, dietary restrictions required for phenelzine	mania, anti-cholinergic adverse effects, crowtiness	urinary retention, dry mouth, decreased libido, delayed orgasm
Anti-epileptics	3+ 3+ 2+	A A C	can help with mania, epilepsy, anxiety topiramate can cause weight loss, onset within first month	divalproex sodium: liver disease, bleeding disorders		weight loss, systemic metabolic perturbations, nausea	paresthesia, tremor, memory difficulty, language problems, impaired concentration, depression, somnolence	taste perversion, kidney stones, acute myopia, angle-closure glaucoma, oligohidrosis, hyperthermia, birth defects, hair loss, hemorrhagic pancreatitis, liver toxicity, polycystic ovary syndrome
Beta-blockers	2+ 3+ 3+ 3+ 2+	B B B A A	can help with hypertension, anxiety	congestive heart failure, diabetes, asthma, Raynaud's disease, basilar migraine, PVD, Wolff-Parkinson-White syndrome	decreased exercise tolerance	weight gain	nightmares, depression, drowsiness, insomnia, memory disturbances	impotence
Botulinum Toxin Type A--BOTOX	*	*	onset--1 month	neuromuscular disease			headache, dizziness	patient can form blocking antibodies which leads to nonresponse, blepharoptosis, diplopia, injection site weakness, shoulder pain, neck rigidity or pain
Calcium channel blockers	0 1+ 1+	C B B	can help with asthma, stroke, prolonged or atypical migraine aura	congestive heart failure, heart block, hypotension, sick sinus syndrome, atrial flutter or fibrillation	hypotension, atrioventricular block, heart failure, edema	constipation, nausea, weight gain, abdominal pain	headache, sedation	
Ergot alkaloids	1+ 3+	C A	may have distinct antihemioceptive action (inhibits release of glutamate, substance P, CGRP), inhibits central sensitization of trigeminovascular neurons	possible drug interactions with triptans		GI pain		early onset of physical dependence

Source: Data adapted and compiled from Schulman and Silberstein 1992; National Library of Medicine, accessed 4/9/2006; Brandeis 2005; Klein 2001; Brin et al, 2000; Dodick et al, 2005; Brandis et al, 2004; D'Amico et al, 2005; Frediani 2004; Ramadan et al 1998.

AE=Adverse effects

*treatment not available for U.S. Headache Consortium analysis

Non-pharmacologic Preventative Therapy

All migraineurs, regardless of contraindications or severity of migraine, retain the ability to make lifestyle changes to prevent the frequency and severity of attacks. Non-pharmacological options also include behavioral interventions such as biofeedback and relaxation training. Several barriers exist to the use of preventative therapy, both pharmacological and non-pharmacological, in migraine treatment. First, many patients do not receive the correct diagnosis of migraine. Second, physicians may not be familiar with effective preventative agents and/or simply do not view migraine as a chronic serious illness that causes disability in otherwise healthy patients. Lastly, poor patient compliance often complicates effective treatment, as sometimes patients do not understand why they have to take a medication or practice daily lifestyle changes for a problem that occurs sporadically (Loder and Biondi, 2005).

Though not widely studied, the use of non-pharmacologic preventative therapy as an adjuvant to abortive therapy may provide significant relief from migraine attacks, while also giving the migraineur significant control over their condition. McGrath states, "The use of psychological interventions to enhance compliance to treatment or treatment effects is an underutilized resource. Psychological measurement is also critical in development and understanding of quality of life scales and the examination of decision-making by patients in taking medication" (McGrath 1999). According to the U.S. Headache Consortium, the indications for behavioral and physical treatments are as follows (Campbell et al, available at <http://www.aan.com>, accessed 4 April 2006):

- a) patient preference for nonpharmacological interventions;
- b) poor tolerance for specific pharmacological treatments;
- c) medical contraindications for specific pharmacological treatments;
- d) insufficient or no response to pharmacological treatment;

- e) pregnancy, planned pregnancy, or nursing;
- f) history of long-term, frequent, or excessive use of analgesic or acute medications that can aggravate headache problems (or lead to decreased responsiveness to other pharmacotherapies); and
- g) significant stress or deficient stress-coping skills

While all the indications listed represent excellent reasons to initiate preventative therapy, an analysis of studies indicating that migraineurs experience psychological abnormalities during the headache phase suggests that behavioral interventions may provide a greater benefit to the patient than treatment purely medicinal treatment (Brandt et al 1990; McGrath 1999). As Sacks pointed out, “It would be cruel and pointless to deny any medication to an acutely suffering patient, but it is another matter altogether to tout any form of drug therapy as the sole treatment of severe, frequently-recurring migraines” (Sacks 1992). Physicians and patients must find a balance between acutely treating migraine attacks while aggressively working to prevent their occurrence.

The most commonly used behavioral interventions are biofeedback, relaxation therapy and cognitive therapy. These therapies not only work to reduce migraine symptoms but also improve patients’ quality of life. In a study of migraine patients at the Gothenburg Headache Clinic in Sweden, Dahlof and Dimenas found that migraineurs perceived greater emotional distress, a lesser sense of well-being, as well as disturbed contentment, vitality and sleep even between migraine attacks (Dahlof and Dimenas, 1995). As behavioral interventions emphasize the learning of self-control and self-maintenance strategies to be used outside of treatment, the implementation of these strategies may maximize patients’ control of their migraine and also improve their quality of life (McGrath 1999). A summary of behavioral interventions is provided in Table 4 below.

Table 4.--Behavioral Interventions for Migraine		
Biofeedback		
<i>Finger temperature biofeedback</i>	<i>Cephalic artery biofeedback</i>	<i>Muscle tension biofeedback</i>
<ul style="list-style-type: none"> •patient is encouraged to use imagery, suggestion and relaxation to warm the hands. Change is signaled by auditory or visual signal 	<ul style="list-style-type: none"> •Uses a device that measures blood flux in the cephalic artery, rarely used clinically due to cost and difficulty obtaining a clean signal 	<ul style="list-style-type: none"> •possible with migraine, but used more often with tension-type headache
Relaxation Therapy		
<i>Relaxation with tension</i>	<i>Relaxation using imagery and suggestion</i>	<i>Relaxation induced by breathing exercises</i>
<ul style="list-style-type: none"> •different muscle groups are tensed and relaxed in turn, provides sharp contrast between tension and relaxation so patient learns relaxation 	<ul style="list-style-type: none"> •suggestions of heaviness and warmth in specific muscle groups and visualizing pleasant images used to induce muscle relaxation 	<ul style="list-style-type: none"> •based on eastern meditation, slow, deep breaths are used to induce muscle relaxation
Cognitive Therapy		
<ul style="list-style-type: none"> •patient is taught to become aware of their thoughts in stressful situations and to challenge non-productive patterns of thinking, irrational self-statements and erroneous beliefs are contested 		

Source: Mcgrath, 1999

In addition to behavioral interventions, many patients eliminate potential triggers in an effort to prevent migraine attacks. The most common elimination occurs with dietary triggers. The eradication of dietary triggers can be delicate though, as physicians must ensure that patients avoid diets resulting in B₁₂ or other vitamin deficiencies (Holroyd and Mauskop, 2003). Patients eliminate all potential dietary triggers and then reintroduce the products one by one in order to identify potential triggers. Bic et al concluded that a low-fat diet may decrease the frequency, duration and severity of migraine headaches (Bic et al, 1999). This conclusion was reached based on reviewing

literature suggesting that a) overall levels of free fatty acids rose by more than 10% during a migraine attack, b) fatty foods are also often high in linoleic acid, which is a prostaglandin (a vasodilator) precursor and c) high dietary fat intake increases blood platelet aggregation, which in turn releases serotonin, reducing the amount available for normal brain function (Anthony 1978; Horrobin 1977, Bic et al 1999).

In addition to diet, it may be beneficial to examine a migraineurs sleep pattern when assessing treatment modalities. Paiva et al found that 55% of patients awakening with headache reflected a sleep disturbance. Each patient was treated for the sleep disorder, and 100% reported improvement of headache symptoms while 65% reported complete resolution (Paiva et al 1997).

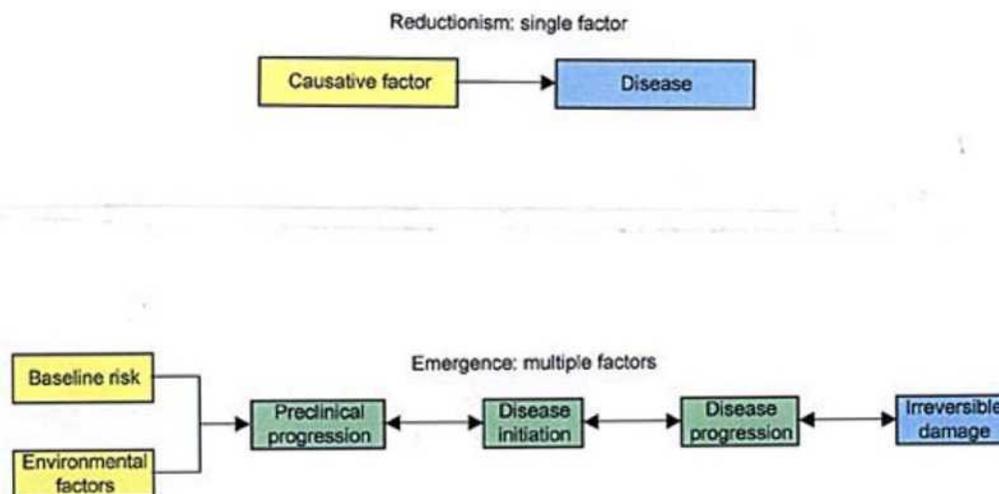
Non-pharmacological treatment proves to be beneficial by allowing the patient more control over their migraines. Rebound headache has proven to be one of the biggest problems with abortive medications. Patients experiencing frequent migraines requiring abortive medication more than twice a week often take abortive medication more frequently than the recommended allowance, finding that they need to take a greater amount each time the headache comes back. In essence as the medication wears off, the migraine returns stronger than before. Thus the patient takes more medicine, and becomes dependent on the drug. The only way to cure rebound headache is by quitting the medication “cold turkey” style and suffer from debilitating headache(s) until the rebound phenomenon wears off (Dr. John Mundall, interview, 5 April 2006). This problem can be at least ameliorated, if not completely avoided, by non-pharmacological treatment plans.

Chapter 4: Conclusion

Epidemiological studies within the last twenty years suggest that migraine represents a remarkably common cause of disability in patients of all ages, races, genders and personalities (Lipton et al 2001; Lipton and Bigal, 2005; Lipton and Bigal, 2005). Research in both acute and preventative migraine therapies ideally will provide migraineurs with even more options for treatment, promote the use of individualized treatment plans, and lend greater insight to the pathophysiology of migraine. In addition, organizations like the World Headache Alliance and Lifting the Burden work to “increase awareness and understanding of headache as a public health concern with profound social and economic impact,” offering emotional and psychological support to migraineurs worldwide (World Headache Alliance, available at <http://www.i-h-s.org>, accessed 2 February 2006).

The use of preventative measures for migraine treatment represents a growing trend toward prospective care in all fields of medicine. Snyderman and Yoediono assert that “current approaches to health care are largely reductionist, based on the concept that a disease is due to a pathologic event initiated by a specific initiating factor and that if the defect is found, it can be reversed and fixed” (Snyderman and Yoediano, 2006). While this approach works with some diseases, the evolution of almost all diseases, including migraine, is comprised of more variables than the ‘find it and fix it’ concept implies (Snyderman and Yoediano, 2006) (Figure 2).

Figure 3.--Concepts of Disease



Source: Snyderman and Yoediono, 2006

With increasing research regarding migraine genomics, the model of disease emergence can be readily applied to migraine therapy in the form of personalized treatment plans. Loder and Biondi emphasizes this theory, concluding that “the future of migraine prevention will involve the development of evidence-based disease management approaches to prevent the evolution of disability, medication overuse, and psychosocial morbidity that now characterize a subset of migraine patients” (Loder and Biondi, 2005). It has been increasingly important to consider migraine as a process, reaction and experience simultaneously (Sacks 1992). In addition, it is imperative to avoid the false systems partitioning that suggests migraine results strictly from neurological or vascular origin. If migraine affects neural, vascular and psychological processes, why not create a treatment plan that addresses each affected area of the brain?

As the nervous and vascular systems are complexly intertwined, it may be counterproductive to look for a migraine origin in just one system—perhaps migraine originates from a synergic combination of several existing factors that alone would not induce an attack.

Not only is it essential to examine various physiological systems in treating migraine, but to also analyze the various physiological and psychological symptoms that each patient presents with to create a complete, individualized treatment plan. No two migraine patients are alike, and must be treated accordingly. This individualized, integrative treatment can be achieved by including behavioral interventions for prevention and consequent psychological effects, preventative medication as needed, and minimal use of abortive medication for breakthrough attacks. Ideally this comprehensive approach, incorporating pharmacologic and non-pharmacologic, acute and preventative treatments, will increase treatment efficacy and allow migraineurs to maximize control over their headaches.

Appendix A.—Glossary of Terms

5-HT receptors—serotonin receptors, 5-HT_{1b} and 5-HT_{1d} represent different subtypes

abortive— providing or concerned with short-term medical care

acute—see *acute*

afferent—conveying impulses toward the central nervous system

analgesic—an agent that alleviates pain

anti-cholinergic—inhibits acetylcholine receptors

anti-emetic—used or tending to prevent or check vomiting

aura—a subjective sensation (as of voices or colored lights or crawling and numbness) experienced before an attack of some nervous disorders (as epilepsy or migraine)

bioavailability—the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity

blepharoptosis—drooping or abnormal relaxation of the upper eyelid

comorbidity—a condition existing simultaneously with and usually independently of another medical condition

contraindication—something (as a symptom or condition) that makes a particular treatment or procedure inadvisable

coronary—of, relating to, affecting, or being the coronary arteries or veins of the heart

diplopia—a disorder of vision in which two images of a single object are seen (as from unequal action of the eye muscles)—double vision

dysrhythmia—an abnormal rhythm; *especially* : a disordered rhythm exhibited in a record of electrical activity of the brain or heart

glutamate—excitatory neurotransmitters

habituation— a: tolerance to the effects of a drug acquired through continued use
b: psychological dependence on a drug after a period of use

hepatic—of, relating to, affecting, or associated with the liver

hyperemia—excess of blood in a body part (as from an increased flow of blood due to vasodilation)

hyperthermia—exceptionally high fever especially when induced artificially for therapeutic purposes

ischemic—deficient supply of blood to a body part (as the heart or brain) that is due to obstruction of the inflow of arterial blood (as by narrowing of the arteries)

migraineur—an individual who experiences migraines

neurogenic inflammation—swelling of tissue induced, controlled, or modified by nervous factors

oligohidrosis—deficiency in perspiration

presenteeism—reduced work efficiency while still remaining at the work site

pan-sensory—involving a wide range of sensory nerves

paresthesia—a sensation of prickling, tingling or creeping on the skin having no objective cause and usually associated with injury or irritation of a sensory nerve or root

pharmacologic—a drug-based medical treatment

prophylactic—guarding from or preventing the spread or occurrence of disease or infection

refractory—resistant to treatment or cure

selectivity—the quality, state, or degree of being selective

sick sinus syndrome—a cardiac disorder typically characterized by alternating tachycardia and bradycardia

subcutaneous—under the skin

substance P—neuropeptide widely distributed in the brain, spinal cord and peripheral nervous system, and that acts across nerve synapses to produce prolonged synaptic transmission

thalamus—the largest subdivision of the diencephalon that mainly consists of a mass of nuclei that serve to relay impulses and especially sensory impulses to and from the cerebral cortex

trigeminovascular system—refers to the complex of the trigeminal nerves and offshoots with the vascular system of the brain

vasoactive—affecting the blood vessels especially in respect to the degree of their relaxation or contraction

vasoconstrictor—an agent (as a sympathetic nerve fiber or a drug) that induces or initiates vasoconstriction

vasodilation—widening of the lumen of blood vessels

Note: Information adapted from the National Library of Medicine and National Institutes of Health, available at [http:// www.nlm.nih.gov/medlineplus/mplusdictionary.html](http://www.nlm.nih.gov/medlineplus/mplusdictionary.html); and Merriam-Webster Dictionary, available at <http://www.m-w.com>.

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