

AdChoices 

Migraine

By Mayo Clinic staff

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Definition

A migraine headache can cause intense throbbing or pulsing in one area of the head and is commonly accompanied by nausea, vomiting, and extreme sensitivity to light and sound. Migraine attacks can cause significant pain for hours to days and be so severe that all you can think about is finding a dark, quiet place to lie down.

Some migraines are preceded or accompanied by sensory warning symptoms (aura), such as flashes of light, blind spots or tingling in your arm or leg.

Medications can help reduce the frequency and severity of migraines. If treatment hasn't worked for you in the past, talk to your doctor about trying a different migraine headache medication. The right medicines, combined with self-help remedies and lifestyle changes, may make a tremendous difference.

Symptoms

Migraine headaches often begin in childhood, adolescence or early adulthood. Migraines may progress through four stages — prodrome, aura, attack and postdrome — though you may not experience all the stages.

Prodrome

One or two days before a migraine, you may notice subtle changes that may signify an oncoming migraine, including:

- Constipation
- Depression
- Diarrhea

- Food cravings
- Hyperactivity
- Irritability
- Neck stiffness

Aura

Most people experience migraine headaches without aura. Auras are usually visual but can also be sensory, motor or verbal disturbances. Each of these symptoms typically begins gradually, builds up over several minutes, then commonly lasts for 10 to 30 minutes. Examples of aura include:

- Visual phenomena, such as seeing various shapes, bright spots or flashes of light
- Vision loss
- Pins and needles sensations in an arm or leg
- Speech or language problems

Less commonly, an aura may be associated with aphasia or limb weakness (hemiplegic migraine).

Attack

When untreated, a migraine typically lasts from four to 72 hours, but the frequency with which headaches occur varies from person to person. You may have migraines several times a month or much less frequently. During a migraine, you may experience some of the following symptoms:

- Pain on one side of your head
- Pain that has a pulsating, throbbing quality
- Sensitivity to light, sounds and sometimes smells
- Nausea and vomiting
- Blurred vision
- Diarrhea
- Lightheadedness, sometimes followed by fainting

Postdrome

The final phase — known as postdrome — occurs after a migraine attack, when you may feel drained and washed out, though some people report feeling mildly

euphoric.

When to see a doctor

Migraine headaches are often undiagnosed and untreated. If you regularly experience signs and symptoms of migraine attacks, keep a record of your attacks and how you treated them. Then make an appointment with your doctor to discuss your headaches and decide on a treatment plan.

Even if you have a history of headaches, see your doctor if the pattern changes or your headaches suddenly feel different.

See your doctor immediately or go to the emergency room if you have any of the following signs and symptoms, which may indicate other, more serious medical problems:

- An abrupt, severe headache like a thunderclap
- Headache with fever, stiff neck, rash, mental confusion, seizures, double vision, weakness, numbness or trouble speaking
- Headache after a head injury, especially if the headache gets worse
- A chronic headache that is worse after coughing, exertion, straining or a sudden movement
- New headache pain if you're older than 50

Causes

Although much about the cause of migraines isn't understood, genetics and environmental factors seem to both play a role.

Migraines may be caused by changes in the brainstem and its interactions with the trigeminal nerve, a major pain pathway. Imbalances in brain chemicals, including serotonin — which helps regulate pain in your nervous system — also may be involved.

Serotonin levels drop during migraine attacks. This may trigger your trigeminal system to release substances called neuropeptides, which travel to your brain's outer covering (meninges). The result is headache pain.

Migraine headache triggers

Whatever the exact mechanism of the headaches, a number of things may trigger them. Common migraine triggers include:

- **Hormonal changes in women.** Fluctuations in estrogen seem to trigger

headaches in many women with known migraines. Women with a history of migraines often report headaches immediately before or during their periods, when they have a major drop in estrogen. Others have an increased tendency to develop migraines during pregnancy or menopause. Hormonal medications — such as oral contraceptives and hormone replacement therapy — also may worsen migraines, though some women find it's beneficial to take them.

- **Foods.** Some migraines appear to be triggered by certain foods. Common offenders include alcohol, especially beer and red wine; aged cheeses; chocolate; aspartame; overuse of caffeine; monosodium glutamate — a key ingredient in some Asian foods; salty foods; and processed foods. Skipping meals or fasting also can trigger migraine attacks.
- **Stress.** Stress at work or home can instigate migraines.
- **Sensory stimuli.** Bright lights and sun glare can induce migraines, as can loud sounds. Unusual smells — including pleasant scents, such as perfume, and unpleasant odors, such as paint thinner and secondhand smoke — can also trigger migraines.
- **Changes in wake-sleep pattern.** Either missing sleep or getting too much sleep may serve as a trigger for migraines in some individuals, as can jet lag.
- **Physical factors.** Intense physical exertion, including sexual activity, may provoke migraines.
- **Changes in the environment.** A change of weather or barometric pressure can prompt a migraine.
- **Medications.** Certain medications can aggravate migraines, especially oral contraceptives and vasodilators, such as nitroglycerin.

Risk factors

Several factors make you more prone to having migraines.

- **Family history.** Up to 90 percent of people with migraines have a family history of migraine attacks. If one or both of your parents have migraines, there's a good chance you will, too.
- **Age.** Migraine can begin at any age, though most people experience their first migraine during adolescence. By age 40, most people with migraine have had their first attack.

- **Gender.** Women are three times more likely to have migraines. Headaches tend to affect boys more than girls during childhood, but by the time of puberty, more girls are affected.
- **Hormonal changes.** If you're a woman who has migraines, you may find that your headaches begin just before or shortly after onset of menstruation. They may also change during pregnancy or menopause. Some women report that their migraine attacks got worse during the first trimester of a pregnancy, though for many, the attacks improved during later stages in the pregnancy.

Complications

Sometimes your efforts to control your pain cause problems.

- **Abdominal problems.** Certain pain relievers, such as ibuprofen (Advil, Motrin, others), may cause abdominal pain, bleeding and ulcers — especially if taken in large doses or for a long period of time.
- **Rebound headaches.** In addition, if you take over-the-counter or prescription headache medications more than nine days per month or in high doses, you may be setting yourself up for a serious complication known as rebound headaches. Rebound headaches occur when medications not only stop relieving pain, but actually begin to cause headaches. You then use more pain medication, which traps you in a vicious cycle.
- **Serotonin syndrome.** This potentially life-threatening drug interaction can occur if you take migraine medicines called triptans, such as sumatriptan (Imitrex) or zolmitriptan (Zomig), along with antidepressants known as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Some common SSRIs include Zoloft, Prozac and Paxil. SNRIs include Cymbalta and Effexor. Fortunately, serotonin syndrome is rare.

Preparing for your appointment

You're likely to start by seeing your primary care provider, but you may be referred to a physician who specializes in headache (neurologist).

Because appointments can be brief, and because there's often a lot of ground to cover, it's a good idea to be well-prepared for your appointment. Here's some information to help you get ready for your appointment, and what to expect from your doctor.

What you can do

- **Write down symptoms you're experiencing**, even if they seem unrelated to your migraines.
- **Write down key personal information**, including any major stresses or recent life changes.
- **Make a list of all medications**, vitamins or supplements you're taking. It is particularly important to list all medications that you have used to treat your headaches. Include the dosages of the medications.
- **Take a family member or friend along**, if possible. Sometimes it can be difficult to soak up all the information provided to you during an appointment. Someone who accompanies you may remember something that you missed or forgot.
- **Write down questions to ask your doctor.**

Your time with your doctor is limited, so preparing a list of questions will help you make the most of your time together. List your questions from most important to least important, in case time runs out. For migraine headaches, some basic questions to ask your doctor include:

- What is likely triggering my migraine headaches?
- Are there other possible causes for my symptoms?
- What kinds of tests do I need?
- Is my condition likely temporary or chronic?
- What is the best course of action?
- What are the alternatives to the primary approach that you're suggesting?
- What changes to my lifestyle or diet do you suggest I make?
- I have these other health conditions. How can I best manage them together?
- Is there a generic alternative to the medicine you're prescribing for me?
- Are there any brochures or other printed material that I can take home with me? What websites do you recommend?

In addition to the questions that you've prepared to ask your doctor, don't hesitate to ask questions during your appointment.

What to expect from your doctor

Your doctor is likely to ask you a number of questions. Being ready to answer them may reserve time to go over any points you want to spend more time on. Your doctor may ask:

- When did you first begin experiencing symptoms?
- Have your symptoms been continuous or occasional?
- How severe are your symptoms?
- What, if anything, seems to improve your symptoms?
- What, if anything, appears to worsen your symptoms?

What you can do in the meantime

- **Keep a headache diary.** A diary can help you and your doctor determine what triggers your migraines. Note when your headaches start, how long they last and what, if anything, provides relief. Be sure to record your response to any headache medications you take. Also note the foods you ate in the 24 hours preceding attacks, any unusual stress, and how you feel and what you're doing when headaches strike.
- **Reduce stress.** Because stress triggers migraines for many people, try to avoid overly stressful situations, or use stress-reduction techniques like meditation.
- **Get enough sleep but don't oversleep.** Aim for six to eight hours of sleep a night.

Tests and diagnosis

If you have typical migraines or a family history of migraine headaches, your doctor will likely diagnose the condition on the basis of your medical history and a physical exam. But if your headaches are unusual, severe or sudden, your doctor may recommend a variety of tests to rule out other possible causes for your pain.

- **Computerized tomography (CT).** This imaging procedure uses a series of computer-directed X-rays that provides a cross-sectional view of your brain. This helps doctors diagnose tumors, infections and other possible medical problems that may be causing your headaches.
- **Magnetic resonance imaging (MRI).** MRIs use radio waves and a powerful magnet to produce very detailed cross-sectional views of your brain. MRI scans

help doctors diagnose tumors, strokes, aneurysms, neurological diseases and other brain abnormalities. An MRI can also be used to examine the blood vessels that supply the brain.

- **Spinal tap (lumbar puncture).** If your doctor suspects an underlying condition, such as meningitis — an inflammation of the membranes (meninges) and cerebrospinal fluid surrounding your brain and spinal cord — he or she may recommend a spinal tap (lumbar puncture). In this procedure, a thin needle is inserted between two vertebrae in your lower back to extract a sample of cerebrospinal fluid (CSF) for laboratory analysis.

Treatments and drugs

A variety of drugs have been specifically designed to treat migraines. In addition, some drugs commonly used to treat other conditions also may help relieve or prevent migraines. Medications used to combat migraines fall into two broad categories:

- **Pain-relieving medications.** Also known as acute or abortive treatment, these types of drugs are taken during migraine attacks and are designed to stop symptoms that have already begun.
- **Preventive medications.** These types of drugs are taken regularly, often on a daily basis, to reduce the severity or frequency of migraines.

Choosing a strategy to manage your migraines depends on the frequency and severity of your headaches, the degree of disability your headaches cause, and your other medical conditions.

Some medications aren't recommended if you're pregnant or breast-feeding. Some aren't used for children. Your doctor can help find the right medication for you.

Pain-relieving medications

For best results, take pain-relieving drugs as soon as you experience signs or symptoms of a migraine. It may help if you rest or sleep in a dark room after taking them:

- **Pain relievers.** These medications, such as ibuprofen (Advil, Motrin, others) or acetaminophen (Tylenol, others) may help relieve mild migraines. Drugs marketed specifically for migraines, such as the combination of acetaminophen, aspirin and caffeine (Excedrin Migraine), also may ease moderate migraine pain but aren't effective alone for severe migraines. If taken too often or for long periods of time, these medications can lead to ulcers,

gastrointestinal bleeding and rebound headaches. The prescription pain reliever indomethacin may help thwart a migraine headache and is available in suppository form, which may be helpful if you're nauseous.

- **Triptans.** For many people with migraine attacks, triptans are the drug of choice. They are effective in relieving the pain, nausea, and sensitivity to light and sound that are associated with migraines. Medications include sumatriptan (Imitrex), rizatriptan (Maxalt), almotriptan (Axert), naratriptan (Amerge), zolmitriptan (Zomig), frovatriptan (Frova) and eletriptan (Relpax). Side effects of triptans include nausea, dizziness and muscle weakness. They aren't recommended for people at risk for strokes and heart attacks. A single-tablet combination of sumatriptan and naproxen sodium (Treximet) has proved more effective in relieving migraine symptoms than either medication on its own.
- **Ergot.** Ergotamine and caffeine combination drugs (Migergot, Cafergot) are much less expensive, but also less effective, than triptans. They seem most effective in those whose pain lasts for more than 48 hours. Dihydroergotamine (D.H.E. 45, Migranal) is an ergot derivative that is more effective and has fewer side effects than ergotamine. It's also available as a nasal spray and in injection form.
- **Anti-nausea medications.** Because migraines are often accompanied by nausea, with or without vomiting, medication for nausea is appropriate and is usually combined with other medications. Frequently prescribed medications are metoclopramide (Reglan) or prochlorperazine (Compro).
- **Opiates.** Medications containing narcotics, particularly codeine, are sometimes used to treat migraine headache pain when people can't take triptans or ergot. Narcotics are habit-forming and are usually used only as a last resort.
- **Dexamethasone.** This corticosteroid may be used in conjunction with other medication to improve pain relief. Because of the risk of steroid toxicity, dexamethasone should not be used frequently.

Preventive medications

You may be a candidate for preventive therapy if you have two or more debilitating attacks a month, if pain-relieving medications aren't helping, or if your migraine signs and symptoms include a prolonged aura or numbness and weakness.

- Preventive medications can reduce the frequency, severity and length of migraines and may increase the effectiveness of symptom-relieving medicines used during migraine attacks. Your doctor may recommend that you take preventive medications

Medications for migraines are expensive and DO NOT have many side effects, and DO NOT work as effectively as Cannabis does! Grants!

daily, or only when a predictable trigger, such as menstruation, is approaching.

In most cases, preventive medications don't eliminate headaches completely, and some cause serious side effects. If you have had good results from preventive medicine and have been migraine-free for six months to a year, your doctor may recommend tapering off the medication to see if your migraines return without it.

For best results, take these medications as your doctor recommends:

- **Cardiovascular drugs.** Beta blockers — commonly used to treat high blood pressure and coronary artery disease — can reduce the frequency and severity of migraines. The beta blocker propranolol (Inderal La, Innopran XL, others) has proved effective for preventing migraines. Calcium channel blockers, another class of cardiovascular drugs, especially verapamil (Calan, Verelan, others), also may be helpful in preventing migraines and relieving symptoms from aura. In addition, the antihypertensive medication lisinopril (Zestril) has been found useful in reducing the length and severity of migraines. Researchers don't understand exactly why these cardiovascular drugs prevent migraine attacks. Side effects can include dizziness, drowsiness or lightheadedness.
- **Antidepressants.** Certain antidepressants are good at helping to prevent some types of headaches, including migraines. Tricyclic antidepressants, such as amitriptyline, nortriptyline (Pamelor) and protriptyline (Vivactil) are often prescribed for migraine prevention. Tricyclic antidepressants may reduce migraine headaches by affecting the level of serotonin and other brain chemicals, though amitriptyline is the only one proved to be effective for migraine headaches. You don't have to have depression to benefit from these drugs. Other classes of antidepressants called selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) haven't been proved as effective for migraine headache prevention. However, preliminary research suggests that one SNRI, venlafaxine (Effexor, Venlafaxine HCL), may be helpful in preventing migraines.
- **Anti-seizure drugs.** Some anti-seizure drugs, such as valproate (Depacon), topiramate (Topamax) and gabapentin (Neurontin), seem to reduce the frequency of migraines. Lamotrigine (Lamictal) may be helpful if you have migraines with aura. In high doses, however, these anti-seizure drugs may cause side effects, such as nausea and vomiting, diarrhea, cramps, hair loss, and dizziness.

- **Cyproheptadine.** This antihistamine specifically affects serotonin activity. Doctors sometimes give it to children as a preventive measure.
- **Botulinum toxin type A (Botox).** The FDA has approved botulinum toxin type A for treatment of chronic migraine headaches in adults. During this procedure, injections are made in muscles of the forehead and neck. When this is effective, the treatment typically needs to be repeated every 12 weeks.

Lifestyle and home remedies

Self-care measures can help ease the pain of a migraine headache.

- **Try muscle relaxation exercises.** Progressive muscle relaxation, meditation and yoga don't require any equipment. You can learn them in classes or at home using books or tapes. Or spend at least a half-hour each day doing something you find relaxing — listening to music, gardening, taking a hot bath or reading.
- **Get enough sleep, but don't oversleep.** The average adult needs six to eight hours of sleep a night. It's best to go to bed and wake up at regular times, as well.
- **Rest and relax.** If possible, rest in a dark, quiet room when you feel a headache coming on. Place an ice pack wrapped in a cloth on the back of your neck and apply gentle pressure to painful areas on your scalp.
- **Keep a headache diary.** Continue keeping your headache diary even after you see your doctor. It will help you learn more about what triggers your migraines and what treatment is most effective.

Alternative medicine

Nontraditional therapies may be helpful if you have chronic migraine pain:

- **Acupuncture.** In this treatment, a practitioner inserts many thin, disposable needles into several areas of your skin at defined points. Clinical trials have found that acupuncture may be helpful for headache pain.
- **Biofeedback.** Biofeedback appears to be especially effective in relieving migraine pain. This relaxation technique uses special equipment to teach you how to monitor and control certain physical responses related to stress, such as muscle tension.

- **Manual therapy.** Massage and chiropractic treatments may help reduce the frequency of migraines. And it can improve the quality of your sleep, which can, in turn, help prevent migraine attacks.
- **Herbs, vitamins and minerals.** There is some evidence that the herbs feverfew and butterbur may prevent migraines or reduce their severity. A high dose of riboflavin (vitamin B-2) also may prevent migraines by correcting tiny deficiencies in the brain cells. Coenzyme Q10 supplements may decrease the frequency of migraines, but they have little effect on the severity of the headache. Due to low magnesium levels in some people with migraines, magnesium supplements have been used, but with mixed results. Ask your doctor if these treatments are right for you. Don't use feverfew or butterbur if you're pregnant.

Prevention

Whether or not you take preventive medications, you may benefit from lifestyle changes that can help reduce the number and severity of migraines. One or more of these suggestions may be helpful for you:

- **Avoid triggers.** If certain foods seem to have triggered your migraines in the past, avoid those foods. If certain scents are a problem, try to avoid them. In general, establish a daily routine with regular sleep patterns and regular meals. In addition, try to control stress.
- **Exercise regularly.** Regular aerobic exercise reduces tension and can help prevent migraines. If your doctor agrees, choose any aerobic exercise you enjoy, including walking, swimming and cycling. Warm up slowly, however, because sudden, intense exercise can cause headaches. Obesity is also thought to be a factor in migraine headaches, and regular exercise can help you keep your weight down.
- **Reduce the effects of estrogen.** If you're a woman who has migraines and estrogen seems to trigger or make your headaches worse, you may want to avoid or reduce the medications you take that contain estrogen. These medications include birth control pills and hormone replacement therapy. Talk with your doctor about the best alternatives or dosages for you.

References

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Abstract: Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?

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Neuroendocrinol Lett. 2004 Feb-Apr;25(1/2):31-39. Russo EB. Senior Medical Advisor, GW Pharmaceuticals, 2235 Wylie Avenue, Missoula, MT 59802, USA. erusso@montanadsl.net OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis. METHODS: Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources. RESULTS: Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT_{1A} and inhibits 5-HT_{2A} receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging. CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines. PMID: 15159679 [PubMed - as supplied by publisher]

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Review Article

Cannabis for migraine treatment: the once and future prescription?
An historical and scientific review

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Abstract

Cannabis, or marijuana, has been used for centuries for both symptomatic and prophylactic treatment of migraine. It was highly esteemed as a headache remedy by the most prominent physicians of the age between 1874 and 1942, remaining part of the Western pharmacopoeia for this indication even into the mid-twentieth century. Current ethnobotanical and anecdotal references continue to refer to its efficacy for this malady, while biochemical studies of THC and anandamide have provided a scientific basis for such treatment. The author believes that controlled clinical trials of *Cannabis* in acute migraine treatment are warranted. © 1998 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Migraine; Headache; *Cannabis*; Marijuana; Dronabinol; Ethnobotany

1. Introduction

One of the basic tenets of medical history is that remedies fall in and out of favor. Once supplanted, most pharmaceuticals fail to re-attain a position of prominence. Very few are popular for many decades.

Not many physicians today are aware of the prominence that *Cannabis* drugs once held in medical practice. Problems with quality control and an association with perceived dangerous effects sounded the death knell for *Cannabis* as a recognized Western therapy. Other medicines that are far more potentially damaging than *Cannabis* remain in our pharmacopeias because of recognized medical indications: opiates for pain control, amphetamines for narcolepsy and attention deficit hyperactivity disorder, etc. Thalidomide, which was banned due to its role in birth defects, may be effecting a therapeutic revival. Even the lowly leech is once again the object of serious medical investigation.

This study will examine the history of *Cannabis* use for one indication, that of headache treatment, its scientific

rationale, and possible future as an alternative therapeutic agent.

2. Historical and ethnobotanical usage of *Cannabis* in migraine treatment

Headaches have likely afflicted man throughout history. Archeological records substantiate an ancient association between man and the plant genus *Cannabis*, plant family, Cannabaceae. Its botanical origin has been debated to be as far east as China, but most experts suspect it to be in Central Asia, possibly in the Pamir Plains (Camp, 1936). Some botanists have maintained *Cannabis* as monotypic genus, while others (Schultes et al., 1974) have provided convincing documentation of three *Cannabis* species: *sativa*, *indica*, and *ruderalis*. All contain the psychoactive chemical delta-9-tetrahydrocannabinol (THC) in varying degree.

Use of *Cannabis* fibers to make hemp has been documented as early as 4000 BC by Carbon-14 dating (Li, 1974), and that use has been maintained continuously up to the present day. Its seed grain was an ancient human foodstuff, which may have lead to an early recognition of its medicinal use. The first records of the latter seem to be in the *Pên-tsoo*

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Ching, a traditional herbal written down in the first two centuries AD, but said to be based on the oral traditions passed down from the Emperor Shên-nung in the third millennium BC. The text noted that the plant fruits 'if taken in excess will produce hallucinations' (literally 'seeing devils') (Li, 1974).

The *Zend-Avesta*, the holy book of Zoroastrianism, which survives only in fragments, dating from around 600 BC in Persia, alludes to the use of *Banga* in a medical context, and it is identified as hemp by the translator (Darmsteter, 1895).

The classical Greek literature also documents knowledge of the inebriating actions of *Cannabis*. Herodotus, circa 450 BC, described how the Scythians set up tents, heated stones and threw *Cannabis* seeds or flowering tops upon them to create a vapor, and 'the Scythians, delighted, shout for joy'. The Greek physicians Dioscorides and Galen expounded on medical indications, mainly gastrointestinal (Brunner, 1977).

The *Atharva Veda* of India, dated to between 1400 and 2000 BC referred to a sacred grass, *bhanga*, and medicinal references to *Cannabis* were cited by Susrata in the sixth to seventh centuries AD (Chopra and Chopra, 1957) and included indication for its use for headache (Dwarakanath, 1965).

O'Shaughnessy introduced the medical use of *Cannabis indica*, or 'Indian hemp', to the West in 1839 (Walton, 1938; Mikuriya, 1973). His treatise on the subject supported the utility of an extract in patients suffering from rabies, cholera, tetanus, and infantile convulsions.

Throughout the latter half of the nineteenth century, many prominent physicians in Europe and North America advocated the use of extracts of *Cannabis indica* for the symptomatic and preventive treatment of headache. Proponents included Weir Mitchell in 1874, E.J. Waring in 1874, Hobart Hare in 1887, Sir William Gowers in 1888, J.R. Reynolds in 1890, J.B. Mattison in 1891, and others (Walton, 1938; Mikuriya, 1973). *Cannabis* was included in the mainstream pharmacopeias in Britain and America for this indication.

As late as 1915, Sir William Osler, the acknowledged father of modern medicine, stated of migraine treatment (Osler and McCrae, 1915), '*Cannabis indica* is probably the most satisfactory remedy. Seguin recommends a prolonged course'. This statement supports its use for both acute and prophylactic treatment of migraine.

In 1916, in a quotation attributed to Dr. Dixon, Professor of Pharmacology, Kings' College, and the University of Cambridge (Ratnam, 1916), reference is specifically made to the therapeutic effects of smoked *Cannabis* for headache treatment. He stated, 'In cases where immediate effect is desired, the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, feelings of fatigue disappear and the subject is able to continue his work refreshed and soothed'.

In the years that followed, *Cannabis* came to be perceived as a drug of abuse, smoked by certain classes of people as

'marijuana' or 'marihuana'. Nevertheless, it retained adherents for a variety of medical indications, throughout the early decades of the twentieth century. In 1938 Robert Walton published a comprehensive review of *Cannabis*, with botanical, historical, chemical and political discussions (Walton, 1938). After discussing the abuse issue, he stated his belief that the political action that had rendered marijuana illegal in the USA in 1937 (and which the American Medical Association vigorously opposed), should not serve to prohibit further medical use and scientific investigation of *Cannabis*' possible applications. Walton referred to 12 major authorities on its efficacy for migraine, and only one detractor.

In 1941, *Cannabis* preparations were dropped from the United States Pharmacopeia (U.S.P.), but the following year, the editor of the *Journal of the American Medical Association* still advocated oral preparations of *Cannabis* in treatment of menstrual (catamenial) migraine (Fishbein, 1942). This practitioner seemed to prefer *Cannabis* to ergotamine tartrate, which remains in the migraine armamentarium, some 55 years later.

Thus, *Cannabis* was touted in eight consecutive decades in the mainstream Western medical literature as a, or the, primary treatment for migraine.

As late as 1957, despite governmental controls in that country, *Cannabis* drugs retained a role in the indigenous medicine of India (Chopra and Chopra, 1957), and other countries.

In the 1960s marijuana moved to center stage of Western consciousness, and attained a degree of notoriety sufficient to render medical usage inconceivable to most. Medical research has resumed only recently, spurred on by anecdotal reports of patients who serendipitously discovered its benefits on their maladies.

3. Modern research developments on Cannabis

In 1974, the first of several studies appeared examining issues of pain relief with Cannabis (Noyes and Baram, 1974). This article examined five case studies of patients who volitionally experimented with the substance to treat painful conditions. Three had chronic headaches, and found relief by smoking *Cannabis* that was comparable, or superior to ergotamine tartrate and aspirin.

One subsequent study of *Cannabis* pertained to pain tolerance in an experimental protocol (Milstein et al., 1975). A statistically significant increase in pain threshold was observed after smoking *Cannabis* in both naive (8% increase) and experienced subjects (16% increase).

Another trial involved oral THC in cancer patients (Noyes et al., 1975a). They observed a trend toward pain relief with escalating doses significant to the $P < 0.001$ level. The peak effect occurred at three hours with doses of 10 and 15 mg, but not until 5 h after ingestion of 20 mg.

Subsequently, the analgesic effect of THC was compared to codeine (Noyes et al., 1975b). In essence, 10 mg of oral THC vs. 60 mg of codeine, and 20 mg of THC vs. 120 mg of codeine relieved the subjective pain burden of patients by similar decrements. The effects of 10 mg of THC were well tolerated, but at 20 mg, sedation and psychic disturbances bothered many of the elderly *Cannabis*-naive subjects.

In the 1980s more comprehensive data on pharmacological effects of *Cannabis* and its derivative, THC became available. In 1983, research with varying potencies of smoked *Cannabis* demonstrated some correlation between serum THC levels and subjective 'high' (Chiang and Barnett, 1984). Additionally, experimental subjects were able to distinguish the potency of the various samples with accuracy.

In a forensic review (Mason et al., 1985), the issue of marijuana's effect on driving was addressed, and it was indicated that isolated reports of adverse outcomes secondary to impairment by *Cannabis* as a sole inebriant were rare. The authors concluded that there was no suitable correlation between plasma or blood levels of THC and the degree of apparent impairment a human might exhibit.

In 1986 the journal *Pharmacological Reviews* devoted an entire issue to *Cannabis* and cannabinoids. In "Cellular Effects of Cannabinoids" (Martin, 1986), the author noted their analgesic properties, but reported that the mode of action was not blocked by naloxone, and seemed to work independently of opioid mechanisms.

Another article examined pharmacokinetics (Agurell et al., 1986). Many facets were presented, including their findings that smoking a standard marijuana cigarette destroyed 30% of available THC.

The final article of the issue was entitled "Health Aspects of Cannabis" (Hollister, 1986). Pertinent points made included dose delivery efficiency of THC by inhalation of 10% in marijuana-naive vs. 23% in experience smokers. Oral bioavailability for THC was only about 6%, and onset of effects was not seen for 30–120 min.

Smoking of massive *Cannabis* doses daily for a prolonged period produced lower intraocular pressure, serum testosterone levels, and airway narrowing, but no chromosomal aberrations, or impairment of immune responses were noted (Cohen, 1976).

Other 'marijuana myths' were unsupported by careful review of the literature. While aggravation of pre-existing psychotic conditions by marijuana use was documented, no cause and effect relationship was noted. Similarly, chronic use studies in Jamaica (Comitas, 1976), revealed no deficits in worker motivation or production. Two studies of brain computerized tomography (CT scan) refuted prior claims of heavy use producing cerebral atrophy (Co et al., 1977; Kuehnle et al., 1977).

With respect to behavior, Hollister refuted the tenet that depicted *Cannabis* as a contributor to violent and aggressive behavior. Concerning addiction, he noted minimal withdrawal symptoms of nausea, vomiting, diarrhea, and tremors in

some experimental subjects after very heavy chronic usage. Such effects were brief and self-limited.

The next year, an article entitled 'Marijuana and Migraine' (El-Mallakh, 1987), presented three cases in which abrupt cessation of frequent, prolonged, daily marijuana smoking were followed by migraine attacks. One patient noted subsequent remission of headaches with episodic marijuana use, while conventional drugs successfully treated the others. The author hypothesized that THC's peripheral vasoconstrictive actions in rats, or its action to minimize serotonin release from the platelets of human migraineurs (Vofse et al., 1985), might explain its actions.

In 1988 action was initiated through the DEA to reclassify marijuana to Schedule 2, potentially making it available for prescription to patients. The DEA administrative law judge, Francis Young, reviewed a tremendous amount of testimony from patients, scientists, and politicians in rendering his ruling (Young, 1988). Although a medical indication of marijuana for migraine was not considered, its use was approved as an anti-emetic, an anti-spasticity drug in multiple sclerosis and paraplegia, while its utilization in glaucoma was considered reasonable. He stated, 'By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care'.

In 1992, a study examined subjective preferences of experimental subjects smoking *Cannabis*, or ingesting oral THC (Chait and Zacny, 1992). Ten subjects in two trials preferred smoking active *Cannabis* over placebo, while 10 of 11 preferred oral THC to placebo. These results call into serious question the plausibility of true blinding with placebo preparations in prospective therapeutic drug studies of marijuana, especially when smoked.

A more profound understanding of *Cannabis*, THC, and their actions in the brain has occurred with the discovery of an endogenous cannabinoid in the human brain, arachidonylethanolamide, named anandamide, from the Sanskrit word *ananda*, or 'bliss' (Devane et al., 1992). This ligand inhibits cyclic AMP in its target cells, which are widespread throughout the brain, but demonstrate a predilection for areas involved with nociception (Herkenham, 1993). The exact physiological role of anandamide is unclear, but preliminary tests of its behavioral effects reveal actions similar to those of THC (Fride and Mechoulam, 1993).

Additional research sheds light on possible mechanisms of therapeutic action of the cannabinoids on migraine. An inhibitory effect of anandamide and other cannabinoid agonists on rat serotonin type 3 (5-HT₃) receptors was demonstrated (Fan, 1995). This receptor has been implicated as a mediator of emetic and pain responses. In 1996, a study in rats demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray matter (Lichtman et al., 1996). The PAG has been frequently cited as a likely anatomic area for migraine generation (Goadsby and Gundlach, 1991).

The understanding that *Cannabis* and THC effect their actions through natural cerebral biochemical processes has

intensified the public debate on medical benefits of marijuana. In 1993, a book entitled *Marihuana: The Forbidden Medicine* (Grinspoon and Bakalar, 1993) examined a variety of claims for ailments treated by marijuana, and included an entire section on migraine. One clinical vignette discussed at length the medical odyssey of a migraineur through failures with standard pharmaceuticals, and ultimate preference for small doses of smoked marijuana for symptom control.

The editor of the *British Medical Journal* (Smith, 1995) recently wrote an editorial espousing moderation in the drug war. The *Journal of the American Medical Association* published a supportive commentary in 1995 (Grinspoon and Bakalar, 1995). The author rated the respiratory risks potent medical marijuana as low, and pointed out the contradiction of the Schedule 2 status of synthetic THC, dronabinol, while its natural source, marijuana remained a Schedule 1 product, and thus unavailable for legal use to patients who might prefer its easier dose titration. Grinspoon raised as a theoretical possibility the synergistic effects of the whole plant and its components as compared to pure THC.

The *American Journal of Public Health* issued its plea (AJPH, 1996), to allow access to medical marijuana as an Investigational New Drug (IND).

The Australian government (Hall et al., 1995) recently compiled a recent exhaustive review of sequelae of *Cannabis* use. In the summary, it states the following acute effects:

- Anxiety, dysphoria, panic and paranoia, especially in naive users;
- Cognitive impairment, especially of attention and memory, for the duration of intoxication;
- Psychomotor impairment, and probably an increased risk of accident if an intoxicated person attempts to drive a motor vehicle, or operate machinery;
- An increased risk of experiencing psychotic symptoms among those who are vulnerable because of personal or family history of psychosis;
- An increased risk of low birth weight babies if cannabis is used during pregnancy.

In a current review of over 65 000 patient records in an HMO (Sidney et al., 1997), little effect of smoked *Cannabis* was seen on morbidity and mortality of non-AIDS patients.

Surely, not all in the medical establishment are convinced of the relative safety or benefit of *Cannabis* for medical usage. In a recent review (Voth and Schwartz, 1997) the authors concluded, 'The evidence does not support the reclassification of crude marijuana as a prescribable medicine'. However, their study was far from comprehensive, confining itself to the clinical issues of nausea, appetite stimulation, glaucoma, and spasticity. Methodologically, it was flawed in that only the medical literature from 1975 to 1996 was screened, an era during which it was quite difficult to initiate research seeking to support medical indications for *Cannabis*. These authors did not examine migraine as an indication for *Cannabis* usage, nor did they review the

extensive literature of the past. The debate on the subject of 'medical marijuana' has extended to the World Wide Web, and includes myriad postings with anecdotal attestations of efficacy for a variety of indications.

Various investigators have examined the roles of different smoke delivery systems (Gieringer, 1996). From these studies, it is clear that vaporization of marijuana makes it possible to deliver even high doses of THC to the lungs of a prospective patient far below the flash point of the *Cannabis* leaf, eliminating a fair amount of smoke, containing tar and other possible carcinogens. However, the marijuana joint was about as effective as any examined smoking device, including waterpipes, in providing a favorable ratio of THC to tar and other by-products of smoking. A standardized smoking procedure for use of *Cannabis* in medical research has been developed (Foltin et al., 1988).

Suppository preparations of *Cannabis* have been used to advantage in the past, and may be an acceptable form of administration for the migraineur, although dose titration would be less available.

4. Discussion

Despite the development of serotonin 1D-agonist medications, migraine remains a serious public health issue. An estimated 23 million Americans suffer severe migraine. Of these, 25% have four or more episodes per month, and 35% have one to three severe headaches each month (Stewart et al., 1992). In economic terms, the impact of migraine is enormous: an estimated 14% of females, and 8% of males missed a portion of, or an entire day of work or school in one month (Linet et al., 1989). Migraine has been estimated to account for an economic impact of US\$1.2 to \$17.2 billion annually in the USA in terms of lost productivity (Lipton and Stewart, 1993).

In 1990 studies were published outlining the biochemical basis of migraine treatment in serotonin receptor pharmacology (Peroutka, 1990). It was this research that led to the development of the first drugs active on serotonin receptor subtypes, sumatriptan, and ondansetron.

However, despite the justifiable success of sumatriptan in treating acute migraine, problems remain. Although rapidly active subcutaneously, its oral absorption is relatively slow, and often unreliable in the migraineur. Sumatriptan and its analogs are ineffective when administered in the 'aura phase' of classic migraine (Ferrari and Saxena, 1995). Additionally, headache recurrence after 'triptan' 5-HT_{1D} agonist agents is a not infrequent occurrence. Unfortunately, repetitive dosing, and development of agents with longer half-lives does not seem to avert the issue (Ferrari and Saxena, 1995).

Another curiosity in the development of sumatriptan is its relative inability to pass the blood-brain barrier. Once more, the development of newer agents with improved central nervous system penetration has not necessarily

improved efficacy, but does increase the likelihood of side effects, such as chest and throat tightness, numbness, tingling, anxiety, etc. (Ferrari and Saxena, 1995; Mathew, 1997). Ultimately disappointing, none of the triptan drugs seems to exert any benefit on the frequency of migraine incidence, unlike dihydroergotamine, which has degree of prophylactic benefit.

Thus, it is the author's contention that this group of agents, though impressive, may represent somewhat of a 'therapeutic dead end'. Especially considering the large percentages of migraineurs who either fail to respond to the triptans, or cannot tolerate them, there seems to be definite need for alternative treatment agents.

The author believes that the issue of medical marijuana, and its possible role in migraine treatment deserves proper scientific examination, both biochemically and clinically.

Results of controlled clinical trials may be valuable for migraineurs and professionals who treat them because there is a strong need for additional medications that will effectively this condition in its acute state. At this time, the best available medication, injected sumatriptan (Imitrex) has been ineffective in up to 30% of patients, or has produced undesirable side effects for up to 66% when administered subcutaneously (Mathew, 1997). The available evidence seems to suggest that smoked *Cannabis* would be a far safer alternative than butorphanol nasal spray (Stadol-NS), which, heretofore, has been an unscheduled drug approved in the USA for migraine treatment despite its addictive potential and unfavorable side effect profile (Fisher and Glass, 1997).

5. Conclusions

1. *Cannabis*, whether ingested or smoked, has a long history of reportedly safe and effective use in the treatment and prophylaxis of migraine.
2. *Cannabis* has a mild but definite analgesic effect in its own right.
3. *Cannabis* seems to affect nociceptive processes in the brain, and may interact with serotonergic and other pathways implicated in migraine.
4. *Cannabis* is reportedly an effective anti-emetic, a useful property in migraine treatment.
5. *Cannabis*, even when abused, has mild addiction potential, and seems to be safe in moderate doses, particularly under the supervision of a physician.
6. *Cannabis*' primary problem as a medicine lies in its possible pulmonary effects, which seem to be minimal in occasional, intermittent use.
7. *Cannabis*, when inhaled, is rapidly active, obviates the need for gastrointestinal absorption (impaired markedly in migraine), and may be titrated to the medical requirement of the patient for symptomatic relief.
8. *Cannabis* delivered by pyrolysis in the form a marijuana cigarette, or 'joint', presents the hypothetical potential

for quick, effective parenteral treatment of acute migraine.

In closing, a quotation seems pertinent (Schultes, 1973):

There can be no doubt that a plant that has been in partnership with man since the beginnings of agricultural efforts, that has served man in so many ways, and that, under the searchlight of modern chemical study, has yielded many new and interesting compounds will continue to be a part of man's economy. It would be a luxury that we could ill afford if we allowed prejudices, resulting from the abuse of *Cannabis*, to deter scientists from learning as much as possible about this ancient and mysterious plant.

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