

**Subject:** Migraine Headaches (Petition to Add Debilitating Medical Condition)  
**From:** [REDACTED]  
**To:** [REDACTED]  
**Date:** Thursday, July 25, 2013 1:44 PM

Hello AZDHS  
(and Dr. Christ)  
Please don't toss in  
the garbage since I'm  
sending an exact duplicate  
of this material to  
Dr. Doug Campos-Outcalt,  
Enid Zuckerman

Dear Arizona Medical Marijuana Program and  
School of Public Health

Enclosed please find my PETITION TO ADD MIGRAINES to the list  
of Medical Conditions Approved by the Arizona Medical  
Marijuana Act.

COVER SHEET

COVER SHEET

(Submittal of Medical Condition)

Submitter: [REDACTED]

MAIL ADDRESS:

[REDACTED]

NAME/TELEPHONE NUMBER/EMAIL ADDRESS (Contact Information)

[REDACTED]

NAME OF MEDICAL CONDITION TO BE ADDED: Migraines  
Medical Condition that is on the registry in the State of  
California as a qualifying condition.

Description of patient symptoms: Migraines are chronic  
headaches that can cause significant pain for hours or even  
days. Some patient migraines are preceded or accompanied by  
sensory symptoms or signs known as "auras". These include  
flashes of light, blind spots or tingling in the arms or

legs. Patients that are already suffering from other chronic diseases (glaucoma) will have heightened symptoms often times triggering a series of light sensory flashes making the patient extremely photosensitive (sunlight makes migraines worse). Migraines are often accompanied by nausea, vomiting and extreme sensitivity to light and sound. Symptoms can be so severe that many migraine sufferers need to find a dark, quiet place to lie down.

#### Severe Symptoms:

Painful throbbing at the temple (usually the right temple for patient suffering from migraines).

Blind spots or tingling

Extreme photo sensitivity

Nausea or even vomiting if a severe migraine

Triggered often by eating sweets or drinking red wine (that contains sulfites)

In women tied very closely to menstruation cycle (especially day 1 of menses).

Any sunlight or loud noises can exacerbate the migraine.

Does a patient suffering from this condition have his ability impaired to accomplish activities of daily living?

Yes often times a migraine headache is one of the main reasons for so many sick days in America by female workers.

Women are by far the vulnerable population that suffers the most from migraine headaches because of hormonal imbalances, electrolyte difficulties, glaucoma, heart disease, diabetes, cancer and even TMJ (temporal-mandible joint). I know that in July 2012 migraine headaches were submitted by a petitioner but the 7 doctor panel all agreed this should be added to the list of medical conditions but for some reason the Department turned down the recommendation. Hopefully a year later and more information and enlightenment (female patients suffer much greater numbers in having migraine headaches).

What are the conventional treatments:

Pharmaceutical drugs ranging from OTC (aspirin, Ibuprofen,

acetaminophen), Prescription Drugs (in the CSA schedule) including Imitrex and NSAIDs. The NSAIDs (like Aleve and Excedrin 3) are helpful but ultimately do not provide much palliative or therapeutic relief for a migraine headache that can last for days. In fact NSAIDs and OTC medications are very hard on the gastrointestinal system causing many upset stomachs, diarrhea and even liver damage if taken in too large of a dosage. There are 200 aspirin overdoses leading to death in the United States today and bleeding ulcers, kidney damage and liver damage are the major concerns for patients that have to use prescription (or over the counter) medicines to treat a migraine headache.

Is Cannabis an excepted treatment for Migraine Headaches?

Absolutely and in cases where people are having negative reactions to opiate or synthetic medications (aspirin is synthetic), Cannabis in it's dried flower form (buds) provides palliative and therapeutic relief when light auras are flashing, your temple is throbbing, your head feels like the hammer has come down and you're locked in a vise.

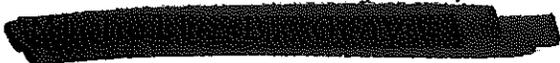
Cannabis is a known to promote blood flow and reduce inflammation and pressure behind the eyes when smoked via vaporization for patients that are looking for a non-smoking alternative that does not involve prescription pharmaceuticals. Many patients (especially baby boomer females) that are in their 50s (like myself) that do not use any alcohol, tobacco or even synthetic pharmaceuticals are the perfect patients to have a MMJ state green card to use cannabis in safer formats.

Journal article enclosed (scholarly and authoritative):

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

Pain 76(1998) pages 3-8

Submitted: July 25, 2013

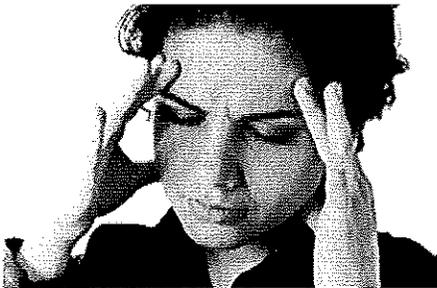


Thank you for having this process available.

## Migraine Headaches

Many patients have found that medical cannabis provides a safe and effective way to prevent and treat their migraine headaches...

Migraines are chronic headaches that can cause significant pain for hours or even days. Some migraines are preceded or accompanied by sensory symptoms or signs known as "auras." These include flashes of light, blind spots or tingling in the arms or legs. Migraines are often accompanied by nausea, vomiting, and extreme sensitivity to light and sound. Symptoms can be so severe that many migraine sufferers need to find a dark, quiet place to lie down.



Migraine headaches are fairly common. They affect around 18% of women and 6% of men. The exact cause of migraines is unclear. Some researchers feel that migraines are due to constriction followed by dilation of blood vessels in the brain. Others feel that it may be due to mechanical or chemical disturbances in the brain itself. Research has also shown that serotonin levels drop during migraines, which may result in headache pain.

Genetics and environmental factors also seem to play a role. Whatever the exact mechanism of migraines may be, a number of things may trigger them. Common triggers include hormonal changes in women, certain foods and alcohol, stress, changes in sleep pattern, changes in environment and certain medications.

Once diagnosed, a variety of drugs have been specifically designed to treat migraines. Some drugs are taken to abort or treat the acute pain of migraines. Others are taken regularly to reduce the severity or frequency of migraines.

Pain-relieving drugs commonly used to treat migraines include nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergot compounds, anti-nausea medications, sedatives and even opiates.

Medications commonly used to prevent migraines include cardiovascular drugs such as beta-blockers or calcium channel blockers, antidepressants and anti-seizure drugs.

The sheer number of different types of medications used to treat migraines is an indicator that none of them is altogether successful. Many of these prescription drugs are also associated with serious adverse reactions and side effects.

So you may be wondering how cannabis may be an effective treatment alternative for migraines. First, it's safe. The most commonly reported side effects are dry mouth, tiredness and appetite stimulation. The side effect profile of medical cannabis compares very favorably against the list of prescription drug categories that I just mentioned. And, there has never been a death due to an overdose of cannabis.

Secondly, it's effective. History shows that cannabis has been used for hundreds, if not thousands, of years for the treatment of migraines. Today, tinctures are available that are absorbed under the tongue and work in minutes.

Inhalation of vaporized cannabis, as a preferable alternative to smoking, can produce relief more rapidly.

The cannabis plant contains over 100 unique chemical compounds, known as cannabinoids, that work together to help relieve migraine symptoms. Cannabis has anti-inflammatory, pain relieving and anti-nausea properties. It also affects blood vessels; it relieves muscle cramps that can accompany migraines; and it lessens anxiety which can worsen the symptoms of migraines in some patients.

Medical cannabis works best when combined with a migraine prevention program and the use of natural relief strategies when an attack occurs – such as restricting light and sound.

A number of alternative treatment modalities may also be helpful if you have chronic headache pain. These include: acupuncture, massage, biofeedback, herbs, vitamins and minerals. Some supplements that may be helpful to prevent migraines include: feverfew, butterbur, riboflavin (vitamin B-2), coenzyme Q10, and possibly oral magnesium. You shouldn't use feverfew or butterbur if you're pregnant.

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AdChoices



# Migraine

By Mayo Clinic staff

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**Original Article:** <http://www.mayoclinic.com/health/migraine-headache/DS00120>

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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 N. migrans are expensive. Toxic have many side effects, and DO NOT work as effectively as narcotics does. Thanks!*

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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June 4, 2011

DS00120

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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?

May 26, 2004

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](mailto: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<sub>1A</sub> and inhibits 5-HT<sub>2A</sub> 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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# Migraine

<b>Migraine</b>	
<i>Classification and external resources</i>	
	
The pain of a migraine headache can be debilitating.	
<b>ICD-10</b>	G43 <sup>[1]</sup>
<b>ICD-9</b>	346 <sup>[2]</sup>
<b>OMIM</b>	157300 <sup>[3]</sup>
<b>DiseasesDB</b>	8207 <sup>[4]</sup> (Migraine) 31876 <sup>[5]</sup> (Basilar) 4693 <sup>[6]</sup> (FHM)
<b>MedlinePlus</b>	000709 <sup>[7]</sup>
<b>eMedicine</b>	neuro/218 <sup>[8]</sup> neuro/517 <sup>[9]</sup> emerg/230 <sup>[10]</sup> neuro/529 <sup>[11]</sup>
<b>MeSH</b>	D008881 <sup>[12]</sup>

**Migraine** is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. The word derives from the Greek *ἡμικρανία* (*hemikrania*), "pain on one side of the head", <sup>[13]</sup> from *ἡμι-* (*hemi-*), "half", and *κράνιον* (*kranion*), "skull". <sup>[14]</sup>

Typically the headache is unilateral (affecting one half of the head) and pulsating in nature, lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, photophobia (increased sensitivity to light), phonophobia (increased sensitivity to sound) and the pain is generally aggravated by physical activity. <sup>[15]</sup> Up to one-third of people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur. <sup>[15]</sup> Occasionally an aura can occur with little or no headache following it.

Migraines are believed to be due to a mixture of environmental and genetic factors. <sup>[1]</sup> About two-thirds of cases run in families. <sup>[1]</sup> Fluctuating hormone levels may also play a role: migraine affects slightly more boys than girls before puberty, but about two to three times more women than men. <sup>[11]</sup> Propensity for migraines usually decreases during pregnancy. <sup>[1]</sup> The exact mechanisms of migraine are not known. It is, however, believed to be a neurovascular disorder. <sup>[1]</sup> The primary theory is related to increased excitability of the cerebral cortex and abnormal control of pain neurons in the trigeminal nucleus of the brainstem. <sup>[16]</sup>

Initial recommended management is with simple analgesics such as ibuprofen and paracetamol (also known as acetaminophen) for the headache, an antiemetic for the nausea, and the avoidance of triggers. Specific agents such as triptans or ergotamines may be used by those for whom simple analgesics are not effective. Globally, approximately 15% of the population is affected by migraines at some point in life.

## Signs and symptoms

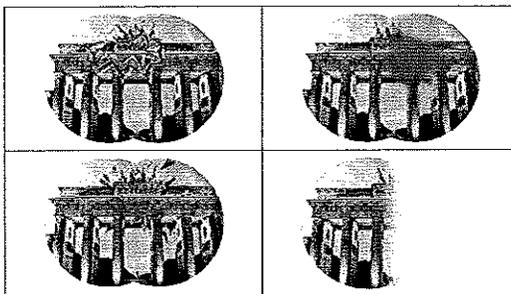
Migraines typically present with self-limited, recurrent severe headache associated with autonomic symptoms.<sup>[1]</sup> About 15-30% of people with migraines experience migraines with an aura<sup>[17]</sup> and those who have migraines with aura also frequently have migraines without aura.<sup>[18]</sup> The severity of the pain, duration of the headache, and frequency of attacks is variable.<sup>[1]</sup> A migraine lasting longer than 72 hours is termed status migrainosus.<sup>[19]</sup> There are four possible phases to a migraine, although not all the phases are necessarily experienced:<sup>[15]</sup>

1. The prodrome, which occurs hours or days before the headache
2. The aura, which immediately precedes the headache
3. The pain phase, also known as headache phase
4. The postdrome, the effects experienced following the end of a migraine attack

### Prodrome phase

Prodromal or premonitory symptoms occur in ~60% of those with migraines<sup>[1]</sup> with an onset of two hours to two days before the start of pain or the aura.<sup>[1]</sup> These symptoms may include a wide variety of phenomena<sup>[20]</sup> including: altered mood, irritability, depression or euphoria, fatigue, craving for certain food, stiff muscles (especially in the neck), constipation or diarrhea, and sensitivity to smells or noise.<sup>[1]</sup> This may occur in those with either migraine with aura or migraine without aura.<sup>[1]</sup>

### Aura phase



An aura is a transient focal neurological phenomenon that occurs before or during the headache.<sup>[1]</sup> They appear gradually over a number of minutes and generally last fewer than 60 minutes.<sup>[1]</sup> Symptoms can be visual, sensory or motor in nature and many people experience more than one.<sup>[21]</sup> Visual effects occur most frequently; they occur in up to 99% of cases and in more than 50% of cases are not accompanied by sensory or motor effects.<sup>[21]</sup> Vision disturbances often consist of a scintillating scotoma (an area of partial alteration in the field of vision which flickers and may interfere with a person's ability to read or drive.)<sup>[1]</sup> These typically start near the center of vision and then spread out to the sides with zigzagging lines which have been described as looking like fortifications or walls of a castle.<sup>[21]</sup> Usually the lines are in black and white but some people also see colored lines.<sup>[21]</sup> Some people lose part of their field of vision known as hemianopsia while others experience blurring.<sup>[21]</sup>

Sensory auras are the second most common type; they occur in 30–40% of people with auras.<sup>[21]</sup> Often a feeling of pins-and-needles begins on one side in the hand and arm and spreads to the nose-mouth area on the same side.<sup>[21]</sup> Numbness usually occurs after the tingling has passed with a loss of position sense.<sup>[21]</sup> Other symptoms of the aura phase can include: speech or language disturbances, world spinning, and less commonly motor problems.<sup>[21]</sup> Motor

symptoms indicate that this is a hemiplegic migraine, and weakness often lasts longer than one hour unlike other auras.<sup>[21]</sup>

An aura rarely occurs without a subsequent headache,<sup>[21]</sup> known as a silent migraine. However, it is difficult to assess the frequency of such cases, because patients who do not experience symptoms severe enough to drive them to seek treatment, may not realise that anything special is happening to them, and pass it off without reporting anything.

## Pain phase

Classically the headache is unilateral, throbbing, and moderate to severe in intensity.<sup>[1]</sup> It usually comes on gradually<sup>[1]</sup> and is aggravated by physical activity.<sup>[15]</sup> In more than 40% of cases however the pain may be bilateral, and neck pain is commonly associated.<sup>[22]</sup> Bilateral pain is particularly common in those who have migraines without an aura.<sup>[1]</sup> Less commonly pain may occur primarily in the back or top of the head.<sup>[1]</sup> The pain usually lasts 4 to 72 hours in adults<sup>[1]</sup> however in young children frequently lasts less than 1 hour.<sup>[1]</sup> The frequency of attacks is variable, from a few in a lifetime to several a week, with the average being about one a month.<sup>[23][24]</sup>

The pain is frequently accompanied by nausea, vomiting, sensitivity to light, sensitivity to sound, sensitivity to smells, fatigue and irritability.<sup>[1]</sup> In a basilar migraine, a migraine with neurological symptoms related to the brain stem or with neurological symptoms on both sides of the body,<sup>[1]</sup> common effects include: a sense of the world spinning, light-headedness, and confusion.<sup>[1]</sup> Nausea occurs in almost 90% of people, and vomiting occurs in about one-third.<sup>[1]</sup> Many thus seek a dark and quiet room.<sup>[1]</sup> Other symptoms may include: blurred vision, nasal stuffiness, diarrhea, frequent urination, pallor, or sweating.<sup>[1]</sup> Swelling or tenderness of the scalp may occur as can neck stiffness.<sup>[1]</sup> Associated symptoms are less common in the elderly.<sup>[1]</sup>

## Postdrome

The effects of migraine may persist for some days after the main headache has ended; this is called the migraine postdrome. Many report a sore feeling in the area where the migraine was, and some report impaired thinking for a few days after the headache has passed. The patient may feel tired or "hung over" and have head pain, cognitive difficulties, gastrointestinal symptoms, mood changes, and weakness.<sup>[1]</sup> According to one summary, "Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise."<sup>[25]</sup>

## Cause

The underlying causes of migraines are unknown.<sup>[1]</sup> However, they are believed to be related to a mix of environmental and genetic factors.<sup>[1]</sup> They run in families in about two-thirds of cases<sup>[1]</sup> and rarely occur due to a single gene defect.<sup>[1]</sup> A number of psychological conditions are associated including: depression, anxiety, and bipolar disorder<sup>[26]</sup> as are many biological events or triggers.

## Genetics

Studies of twins indicate a 34 to 51% genetic influence of likelihood to develop migraine headaches.<sup>[1]</sup> This genetic relationship is stronger for migraines with aura than for migraines without aura.<sup>[18]</sup> A number of specific variants of genes increase the risk by a small to moderate amount.<sup>[1]</sup>

Single gene disorders that result in migraines are rare.<sup>[1]</sup> One of these is known as familial hemiplegic migraine, a type of migraine with aura, which is inherited in an autosomal dominant fashion.<sup>[27][28]</sup> Four genes have been shown to be involved in familial hemiplegic migraine.<sup>[1]</sup> Three of these genes are involved in ion transport.<sup>[1]</sup> The fourth is an axonal protein associated with the exocytosis complex.<sup>[1]</sup> Another genetic disorder associated with migraine is CADASIL syndrome or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.<sup>[1]</sup>

## Triggers

Migraines may be induced by triggers, with some reporting it as an influence in a minority of cases<sup>[1]</sup> and others the majority.<sup>[1]</sup> Many things have been labeled as triggers, however the strength and significance of these relationships are uncertain.<sup>[1][29]</sup> A trigger may be encountered up to 24 hours prior to the onset of symptoms.<sup>[1]</sup>

### Physiological aspects

Common triggers quoted are stress, hunger, and fatigue (these equally contribute to tension headaches).<sup>[1]</sup> Migraines are more likely to occur around menstruation.<sup>[30]</sup> Other hormonal influences, such as menarche, oral contraceptive use, pregnancy, perimenopause, and menopause, also play a role.<sup>[31]</sup> These hormonal influences seem to play a greater role in migraine without aura.<sup>[32]</sup> Migraines typically do not occur during the second and third trimesters or following menopause.<sup>[1]</sup>

### Dietary aspects

Reviews of dietary triggers have found that evidence mostly relies on self-reports and is not rigorous enough to prove or disprove any particular triggers.<sup>[33][1]</sup> Regarding specific agents there does not appear to be evidence for an effect of tyramine on migraine<sup>[1]</sup> and while monosodium glutamate (MSG) is frequently reported as a dietary trigger,<sup>[34]</sup> evidence does not consistently support this.<sup>[35]</sup>

### Environmental aspects

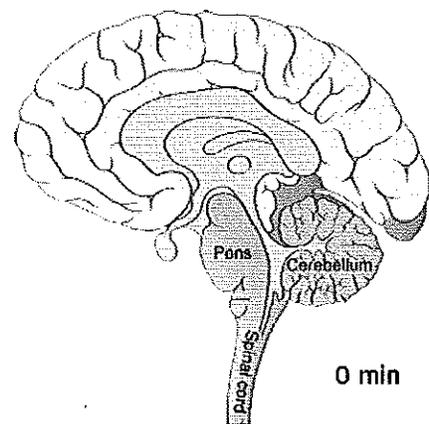
A review on potential triggers in the indoor and outdoor environment concluded the overall evidence was of poor quality, but nevertheless suggested people with migraines take some preventive measures related to indoor air quality and lighting.<sup>[36]</sup> While migraines were once believed to be more common in those of high intelligence, this does not appear to be true.<sup>[32]</sup>

## Pathophysiology

Migraines are believed to be a neurovascular disorder<sup>[1]</sup> with evidence supporting its mechanisms starting within the brain and then spreading to the blood vessels.<sup>[37]</sup> Some researchers feel neuronal mechanisms play a greater role,<sup>[38]</sup> while others feel blood vessels play the key role.<sup>[39]</sup> Others feel both are likely important.<sup>[40]</sup> High levels of the neurotransmitter serotonin, also known as 5-hydroxytryptamine, are believed to be involved.<sup>[37]</sup>

### Aura

Cortical spreading depression or spreading depression of Leão is bursts of neuronal activity followed by a period of inactivity, which is seen in those with migraines with an aura.<sup>[41]</sup> There are a number of explanations for its occurrence including activation of NMDA receptors leading to calcium entering the cell.<sup>[41]</sup> After the burst of activity the blood flow to the cerebral cortex in the area affected is decreased for two to six hours.<sup>[41]</sup> It is believed that when depolarization travels down the underside of the brain, nerves that sense pain in the head and neck are triggered.<sup>[41]</sup>



Animation of cortical spreading depression

## Pain

The exact mechanism of the head pain which occurs during a migraine is unknown.<sup>[1]</sup> Some evidence supports a primary role for central nervous system structures (such as the brainstem and diencephalon)<sup>[42]</sup> while other data support the role peripheral activation (such as via the sensory nerves that surround blood vessels of the head and neck).<sup>[1]</sup> The potential candidates vessels include: dural arteries, pial arteries and extracranial arteries such as those of the scalp.<sup>[1]</sup> The role of vasodilatation of the extracranial arteries, in particular, is believed to be significant.<sup>[43]</sup>

## Diagnosis

The diagnosis of a migraine is based on signs and symptoms.<sup>[1]</sup> Imaging tests are occasionally performed to exclude other causes of headaches.<sup>[1]</sup> It is believed that a substantial number of people with the condition have not been diagnosed.<sup>[1]</sup>

The diagnosis of migraine without aura, according to the International Headache Society, can be made according to the following criteria, the "5, 4, 3, 2, 1 criteria":<sup>[15]</sup>

- Five or more attacks—for migraine *with* aura, two attacks are sufficient for diagnosis.
- Four hours to three days in duration
- Two or more of the following:
  - Unilateral (affecting half the head);
  - Pulsating;
  - "Moderate or severe pain intensity";
  - "Aggravation by or causing avoidance of routine physical activity"
- One or more of the following:
  - Nausea and/or vomiting;
  - Sensitivity to both light (photophobia) and sound (phonophobia)

If someone experiences two of the following: photophobia, nausea, or inability to work / study for a day the diagnosis is more likely.<sup>[44]</sup> In those with four out of five of the following: pulsating headache, duration of 4–72 hours, pain on one side of the head, nausea, or symptoms that interfere with the person's life, the probability that this is a migraine is 92%.<sup>[1]</sup> In those with less than three of these symptoms the probability is 17%.<sup>[1]</sup>

## Classification

Migraines were first comprehensively classified in 1988.<sup>[18]</sup> The International Headache Society most recently updated their classification of headaches in 2004.<sup>[15]</sup> According to this classification migraines are primary headaches along with tension-type headaches and cluster headaches, among others.<sup>[45]</sup>

Migraines are divided into seven subclasses (some of which include further subdivisions):

- Migraine without aura, or "common migraine", involves migraine headaches that are not accompanied by an aura
- Migraine with aura, or "classic migraine", usually involves migraine headaches accompanied by an aura. Less commonly, an aura can occur without a headache, or with a nonmigraine headache. Two other varieties are familial hemiplegic migraine and sporadic hemiplegic migraine, in which a person has migraines with aura and with accompanying motor weakness. If a close relative has had the same condition, it is called "familial", otherwise it is called "sporadic". Another variety is basilar-type migraine, where a headache and aura are accompanied by difficulty speaking, world spinning, ringing in ears, or a number of other brainstem-related symptoms, but not motor weakness. This type was initially believed to be due to spasms of the basilar artery, the artery that supplies the brainstem.<sup>[1]</sup>
- Childhood periodic syndromes that are commonly precursors of migraine include cyclical vomiting (occasional intense periods of vomiting), abdominal migraine (abdominal pain, usually accompanied by nausea), and benign paroxysmal vertigo of childhood (occasional attacks of vertigo).

- Retinal migraine involves migraine headaches accompanied by visual disturbances or even temporary blindness in one eye.
- Complications of migraine describe migraine headaches and/or auras that are unusually long or unusually frequent, or associated with a seizure or brain lesion.
- Probable migraine describes conditions that have some characteristics of migraines, but where there is not enough evidence to diagnose it as a migraine with certainty (in the presence of concurrent medication overuse).
- Chronic migraine is a complication of migraines, and is a headache that fulfills diagnostic criteria for *migraine headache* and occurs for a greater time interval. Specifically, greater or equal to 15 days/month for longer than 3 months.<sup>[46]</sup>

## Abdominal migraine

The diagnosis of abdominal migraines is controversial.<sup>[1]</sup> Some evidence indicates that recurrent episodes of abdominal pain in the absence of a headache may be a type of migraine<sup>[47]</sup> or are at least a precursor to migraines.<sup>[18]</sup> These episodes of pain may or may not follow a migraine like prodrome and typically last minutes to hours.<sup>[1]</sup> They often occur in those with either a personal or family history of typical migraines.<sup>[1]</sup> Other syndromes that are believed to be precursors include: cyclical vomiting syndrome and benign paroxysmal vertigo of childhood.<sup>[18]</sup>

## Differential diagnosis

Other conditions that can cause similar symptoms to a migraine headache include: temporal arteritis, cluster headaches, acute glaucoma, meningitis and subarachnoid hemorrhage.<sup>[1]</sup> Temporal arteritis typically occurs in people over 50 years old and presents with tenderness over the temple, cluster headaches presents with one-sided nose stuffiness, tears and severe pain around the orbits, acute glaucoma is associated with vision problems, meningitis with fevers, and subarachnoid hemorrhage with a very fast onset.<sup>[1]</sup> Tension headaches typically occur on both sides, are not pounding, and are less disabling.<sup>[1]</sup>

## Prevention

Preventive treatments of migraines include: medications, nutritional supplements, lifestyle alterations, and surgery. Prevention is recommended in those who have headaches more than two days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not easily controlled.<sup>[1]</sup>

The goal is to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy.<sup>[1]</sup> Another reason for prevention is to avoid medication overuse headache. This is a common problem and can result in chronic daily headache.<sup>[1][48]</sup>

## Medication

Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%.<sup>[1]</sup> Guidelines are fairly consistent in rating topiramate, divalproex/sodium valproate, propranolol, and metoprolol as having the highest level of evidence for first-line use.<sup>[1]</sup> Recommendations regarding effectiveness varied however for gabapentin.<sup>[1]</sup> Timolol is also effective for migraine prevention and in reducing migraine attack frequency and severity, while frovatriptan is effective for prevention of menstrual migraine.<sup>[1]</sup> Amitriptyline and venlafaxine are probably also effective.<sup>[49]</sup> Botox has been found to be useful in those with chronic migraines but not those with episodic ones.<sup>[50]</sup>

## Alternative therapies

While acupuncture may be effective, "true" acupuncture is not more efficient than sham acupuncture, a practice where needles are placed randomly.<sup>[1]</sup> Both have a possibility of being more effective than routine care, with fewer adverse effects than preventative medications.<sup>[1]</sup> Chiropractic manipulation, physiotherapy, massage and relaxation might be as effective as propranolol or topiramate in the prevention of migraine headaches; however, the research had some problems with methodology.<sup>[52]</sup> The evidence to support spinal manipulation is poor and insufficient to support its use.<sup>[53]</sup> There is some tentative evidence of benefit for magnesium,<sup>[1]</sup> coenzyme Q(10),<sup>[1]</sup> riboflavin,<sup>[1]</sup> vitamin B(12),<sup>[54]</sup> and feverfew, although data is limited and better quality trials must be conducted to reach more definitive conclusions.<sup>[55]</sup> Of the alternative medicines, butterbur has the best evidence for its use.<sup>[56]</sup>



*Petasites hybridus* (butterbur) root extract has proven effective for migraine prevention.<sup>[51]</sup>

## Devices and surgery

Medical devices, such as biofeedback and neurostimulators, have some advantages in migraine prevention, mainly when common anti-migraine medications are contraindicated or in case of medication overuse. Biofeedback helps people be conscious of some physiological parameters so as to control them and try to relax and may be efficient for migraine treatment.<sup>[57][58]</sup> Neurostimulation uses implantable neurostimulators similar to pacemakers for the treatment of intractable chronic migraines with encouraging results for severe cases.<sup>[59][60]</sup> Migraine surgery, which involves decompression of certain nerves around the head and neck, may be an option in certain people who do not improve with medications.<sup>[1]</sup>

## Management

There are three main aspects of treatment: trigger avoidance, acute symptomatic control, and pharmacological prevention.<sup>[1]</sup> Medications are more effective if used earlier in an attack.<sup>[1]</sup> The frequent use of medications may result in medication overuse headache, in which the headaches become more severe and more frequent.<sup>[15]</sup> This may occur with triptans, ergotamines, and analgesics, especially narcotic analgesics.<sup>[15]</sup>

## Analgesics

Recommended initial treatment for those with mild to moderate symptoms are simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) or the combination of paracetamol, acetylsalicylic acid, and caffeine.<sup>[1]</sup> A number of NSAIDs have evidence to support their use. Ibuprofen has been found to provide effective pain relief in about half of people<sup>[61]</sup> and diclofenac has been found effective.<sup>[62]</sup>

Aspirin can relieve moderate to severe migraine pain, with an effectiveness similar to sumatriptan.<sup>[63]</sup> Ketorolac is available in an intravenous formulation.<sup>[1]</sup> Paracetamol (also known as acetaminophen), either alone or in combination with metoclopramide, is another effective treatment with a low risk of adverse effects.<sup>[64]</sup> In pregnancy, paracetamol and metoclopramide are deemed safe as are NSAIDs until the third trimester.<sup>[1]</sup>

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## Triptans

Triptans such as sumatriptan are effective for both pain and nausea in up to 75% of people.<sup>[65]</sup> They are the initially recommended treatments for those with moderate to severe pain or those with milder symptoms who do not respond to simple analgesics.<sup>[1]</sup> The different forms available include oral, injectable, nasal spray, and oral dissolving tablets.<sup>[1]</sup> In general, all the triptans appear equally effective, with similar side effects. However, individuals may respond better to specific ones.<sup>[1]</sup> Most side effects are mild, such as flushing; however, rare cases of myocardial ischemia have occurred.<sup>[1]</sup> They are thus not recommended for people with cardiovascular disease.<sup>[1]</sup> While historically not recommended in those with basilar migraines there is no specific evidence of harm from their use in this population to support this caution.<sup>[1]</sup> They are not addictive, but may cause medication overuse headaches if used more than 10 days per month.<sup>[66]</sup>

## Ergotamines

Ergotamine and dihydroergotamine are older medications still prescribed for migraines, the latter in nasal spray and injectable forms.<sup>[1]</sup> They appear equally effective to the triptans,<sup>[1]</sup> are less expensive,<sup>[67]</sup> and experience adverse effects that typically are benign.<sup>[1]</sup> In the most debilitating cases, such as those with status migrainosus, they appear to be the most effective treatment option.<sup>[1]</sup>

## Other

Intravenous metoclopramide or intranasal lidocaine are other potential options.<sup>[1]</sup> Metoclopramide is the recommended treatment for those who present to the emergency department.<sup>[1]</sup> A single dose of intravenous dexamethasone, when added to standard treatment of a migraine attack, is associated with a 26% decrease in headache recurrence in the following 72 hours.<sup>[68]</sup> Spinal manipulation for treating an ongoing migraine headache is not supported by evidence.<sup>[69]</sup> It is recommended that opioids and barbiturates not be used.<sup>[1]</sup>

## Prognosis

Long term prognosis in people with migraines is variable.<sup>[1]</sup> Most people with migraines have periods of lost productivity due to their disease<sup>[1]</sup> however typically the condition is fairly benign<sup>[1]</sup> and is not associated with an increased risk of death.<sup>[1]</sup> There are four main patterns to the disease: symptoms can resolve completely, symptoms can continue but become gradually less with time, symptoms may continue at the same frequency and severity, or attacks may become worse and more frequent.<sup>[1]</sup>

Migraines with aura appear to be a risk factor for ischemic stroke<sup>[1]</sup> doubling the risk.<sup>[70]</sup> Being a young adult, being female, using hormonal contraception, and smoking further increases this risk.<sup>[1]</sup> There also appears to be an association with cervical artery dissection.<sup>[71]</sup> Migraines without aura do not appear to be a factor.<sup>[1]</sup> The relationship with heart problems is inconclusive with a single study supporting an association.<sup>[1]</sup> Overall however migraines do not appear to increase the risk of death from stroke or heart disease.<sup>[1]</sup> Preventative therapy of migraines in those with migraines with auras may prevent associated strokes.<sup>[72]</sup>

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## Epidemiology

Worldwide, migraines affect nearly 15% or approximately one billion people.<sup>[1]</sup> It is more common in women at 19% than men at 11%.<sup>[1]</sup> In the United States, about 6% of men and 18% of women get a migraine in a given year, with a lifetime risk of about 18% and 43% respectively.<sup>[1]</sup> In Europe, migraines affect 12–28% of people at some point in their lives with about 6–15% of adult men and 14–35% of adult women getting at least one yearly.<sup>[1]</sup> Rates of migraines are slightly lower in Asia and Africa than in Western countries.<sup>[32][1]</sup> Chronic migraines occur in approximately 1.4 to 2.2% of the population.<sup>[73]</sup>

These figures vary substantially with age: migraines most commonly start between 15 and 24 years of age and occur most frequently in those 35 to 45 years of age.<sup>[1]</sup> In children, about 1.7% of 7 year olds and 3.9% of those between 7 and 15 years have migraines, with the condition being slightly more common in boys before puberty.<sup>[1]</sup> During adolescence migraines becomes more common among women<sup>[1]</sup> and this persists for the rest of the lifespan, being two times more common among elderly females than males.<sup>[1]</sup> In women migraines without aura is more common than migraines with aura, however in men the two types occur with similar frequency.<sup>[32]</sup>

During perimenopause symptoms often get worse before decreasing in severity.<sup>[1]</sup> While symptoms resolve in about two thirds of the elderly, in between 3 and 10% they persist.<sup>[1]</sup>

## History

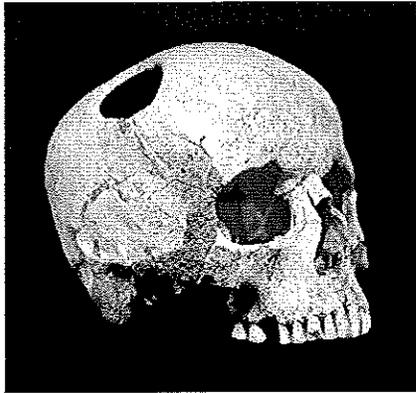
An early description consistent with migraines is contained in the Ebers papyrus, written around 1500 BCE in ancient Egypt.<sup>[1]</sup> In 200 BCE, writings from the Hippocratic school of medicine described the visual aura that can precede the headache and a partial relief occurring through vomiting.<sup>[1]</sup>



Disability-adjusted life year for migraines per 100,000 inhabitants in 2002



*The Head Ache*, George Cruikshank (1819)



A trepanated skull, from the iron age. The perimeter of the hole in the skull is rounded off by ingrowth of new bony tissue, indicating that the person survived the operation.

A second-century description by Aretaeus of Cappadocia divided headaches into three types: cephalalgia, cephalea, and heterocrania.<sup>[1]</sup> Galen of Pergamon used the term hemicrania (half-head), from which the word migraine was eventually derived.<sup>[2]</sup> He also proposed that the pain arose from the meninges and blood vessels of the head.<sup>[3]</sup> Migraines were first divided into the two now used types - migraine with aura (*migraine ophthalmique*) and migraine without aura (*migraine vulgaire*) in 1887 by Louis Hyacinthe Thomas, a French Librarian.<sup>[4]</sup>

Trepanation, the deliberate drilling of holes into a skull, was practiced as early as 7,000 BCE.<sup>[5]</sup> While sometimes people survived, many would have died from the procedure due to infection.<sup>[74]</sup> It was believed to work via "letting evil spirits escape".<sup>[75]</sup> William Harvey recommended trepanation as a treatment for migraines in the 17th century.<sup>[76]</sup>

While many treatments for migraines have been attempted, it was not until 1868 that use of a substance which eventually turned out to be effective began.<sup>[7]</sup> This substance was the fungus ergot from which ergotamine was isolated in 1918.<sup>[8]</sup> Methysergide was developed in 1959 and the first triptan, sumatriptan, was developed in 1988.<sup>[9]</sup> During the 20th century with better study design effective preventative measures were found and confirmed.<sup>[10]</sup>

## Society and culture

Migraines are a significant source of both medical costs and lost productivity. It has been estimated that they are the most costly neurological disorder in the European Community, costing more than €27 billion per year.<sup>[11]</sup> In the United States direct costs have been estimated at 17 billion USD.<sup>[12]</sup> Nearly a tenth of this cost is due to the cost of triptans.<sup>[13]</sup> Indirect costs are around 15 Billion USD, of which missed work is the greatest component.<sup>[14]</sup> In those who do attend work with a migraine effectiveness is decreased by around a third.<sup>[15]</sup> Negative impacts also frequently occur for a person's family.<sup>[16]</sup>

## Research

Calcitonin gene related peptides (CGRPs) have been found to play a role in the pathogenesis of the pain associated with migraine.<sup>[17]</sup> CGRP receptor antagonists, such as olcegepant and telcagepant, have been investigated both *in vitro* and in clinical studies for the treatment of migraine.<sup>[18]</sup> In 2011, Merck stopped phase III clinical trials for their investigational drug telcagepant.<sup>[19]</sup> Transcranial magnetic stimulation also shows promise.<sup>[20]</sup>

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## Notes

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## External links

- Migraine ([http://www.dmoz.org/Health/Conditions\\_and\\_Diseases/Neurological\\_Disorders/Headaches/Migraine/](http://www.dmoz.org/Health/Conditions_and_Diseases/Neurological_Disorders/Headaches/Migraine/)) at the Open Directory Project

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# Medical Marijuana for the Treatment of Migraine Headaches: An Evidence Review

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## **Introduction**

### **Purpose of the Evidence Review**

This review evaluates evidence on cannabis use in adults for the treatment of migraine headaches. The Arizona Department of Health Services (ADHS) funded this report to assist in assessing migraines as a condition to add to those that qualify for the use of medical marijuana in Arizona.

### **Background**

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS “shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012”. After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not.

## **Scope of the Evidence Review**

### **List of Key Questions**

Benefits and harms of cannabis therapy for migraine headaches

1. What are the benefits (short and long-term benefits) of cannabis use for treatment or prevention of migraine headaches?
2. What are the harms (short and long-term harms) of cannabis use for the treatment or prevention of migraine headaches?

### **Conflicts of Interest**

The reviewer had no conflicts of interest to disclose.

## **Methods**

### **Literature Search and Strategy**

The topics of cannabis use and migraine headaches were searched in the following databases: The Cochrane Library, Ovid MEDLINE®, Web of Science, Dynamed, Google Scholar, National Center for Complimentary and Alternative Medicine, and PsycINFO. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

### **Inclusion and Exclusion Criteria**

Studies that met all of the following criteria were included:

1. Evaluated adults ( $\geq 18$  years old) with migraine or cluster headaches
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

### **Quality Assessment**

Types of studies available to assess are listed and described in Appendix 2. Observational studies were assessed using the main domains described in tools commonly used ( Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, et al. Evaluating non-randomized intervention studies. *Health Technology Assessment* 2003;7(27) ). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. *Methods Guide for Comparative Effectiveness Reviews*. Rockville, MD. Available at: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60>.)

### **Studies Submitted by the Public**

The scientific literature submitted by the public in support of including migraine headaches was also assessed using the same methodology.

## **Results**

The search resulted in 20 articles, 14 of these did not meet the inclusion criteria. Each included article is summarized in table 1. Articles that were listed in the search but that did not meet the inclusion criteria are listed in table 2. Only one article was submitted by the public and it was in the list uncovered by the search and is indicated by an \* in table 1.

There were a total of 6 articles that met the inclusion criteria and 3 were by the same author. Four articles were case reports. Among them there were a total of 4 patients with migraine headaches (although it is unclear in 2 if these were actually migraine type headaches) who reported relief of migraines with marijuana or dronabinol. Three individuals reported on set of migraines upon stopping marijuana use and one reported on set of possible migraine with joint use of marijuana and ecstasy. There were two articles reporting a cross sectional study. One appears to be a subset of the other but this is not clear. Neither directly addresses the clinical question of effectiveness and both studies are of extremely low quality.

**Table 1**  
**Articles Included in the Review**

Article and Citation	Description and Design of Study	Findings	Quality
1. Noyes R, Baram D. Cannabis Analgesia. <i>Comprehensive Psychiatry</i> 1974;15(6):531-535.	Case reports. 1 patient with migraine headaches and 2 patients with headaches that might have been migraines, in the USA.	All 3 reported pain relief with the use of marijuana. One reported a decreased frequency of headaches with regular marijuana use.	Very low. Case reports.
2. Robbins MS, Tarshish T, Soloman S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. <i>Headache</i> 2009; June:914-916 *	Case report of a single patient in the USA.	His cluster headaches were responsive to cannabis and then also to dronabinol.	Very low. Case report.
3. El-Mallakh RS, Kansler HR, Kamanitz JR. Headaches and psychoactive substance use. <i>Headache</i> 1991;31:584-587.	Cross sectional study asking about headaches. 236 patients admitted to substance abuse ward in the U.S., 80 with history of migraines.	Mean age of onset of migraines was 2 years before mean age of onset of substance abuse. Substances abused not described. Unknown how many were marijuana users. No data on effect of abused drugs on headaches.	Very low Biased sample, subject to recall bias. Poor quality of the data collected.
4. El-Mallakh RS. Marijuana and migraine. <i>Headache</i> 1987;27:442-443.	3 case reports of long term marijuana users in the U.S..	All 3 on cessation of marijuana use developed migraine headaches. One was also a cocaine user. Very little clinical or demographic information on any of the patients.	Very low
5. El-Mallakh RS. Migraine headaches and drug abuse. <i>Southern Medical Journal</i> 1989;82:805.	Cross sectional study of 54 patients admitted to an inpatient drug and alcohol abuse program at one center in Connecticut. It is not clear but this population appears to be the same as citation 3.	Those with migraine headaches were more likely to be using marijuana and cocaine than those with other headache types. (30% vs 54%)	Very low. Letter to the editor with very little information. Biased sample. High non response rate (46%)
6. Trittbach P, Frueh BE, Goldblum D. Bilateral angle-closure glaucoma after combined consumption of ecstasy and marijuana. <i>American Journal of Emergency Medicine</i> 2005;23:813-814.	Case study of woman in Switzerland who had also been in Africa.	Ophthalmological migraine and angle closure glaucoma occurred on several occasions after using ecstasy and marijuana together and resolved after she stopped.	Very low.

**Table 2**

**Articles Not Included**

Author, title, citation	Content	Reason not used
7. Bagshaw SM. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. <i>Journal of Palliative Care</i> 2002;18:111-122.	A review of the literature but not a systematic review of the quality of the literature. References on migraine treatment were checked to see if there were any not found in the library search.	Does not contain any new information. It is a summary of already existing studies.
8. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. <i>Pain</i> 1998;76:3-8.	A historical review of the use of cannabis for treatment of migraines. References on were checked to see if there were any not found in the library search.	A very interesting historical article with no useable scientific data.
9. Taylor FR. Nutraceuticals and headache: the biological basis. <i>Headache</i> 2011;51:484-501.	A review of the basic science of migraine mechanisms and research on proposed mechanism of action of magnesium, riboflavin, coenzyme Q10, petasites, feverfew, marijuana and oxygen/hyperbaric oxygen.	A review of possible CNS receptor sites and mechanisms of action of cannabis and various forms of cannabis. No clinical data provided. References were checked to see if any relevant ones included.
10. Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. <i>International Journal of Clinical Pharmacology Research</i> 1985;4:243-246.	Biochemical study on blood from 7 patients.	Not a clinical trial. Very preliminary data on a small number of subjects. Clinical relevance uncertain.
11. Juhasz G. et al. Variations in the cannabinoid receptor 1 gene predispose to migraine. <i>Neuroscience Letters</i> 2009;461:116-120.	Gene association study of cannabinoid receptor 1 (CB1) gene with migraine as diagnosed by 3 of the most predictive symptoms.	Very preliminary study of a potential pathophysiological mechanism. The odds ratios and likelihood ratios are not very impressive.
12. Napchan U, Buse DC, Loder W. The use of marijuana or synthetic cannabinoids for the treatment of headache. <i>Headache</i> 2011; 51:502-505.	Commentary on two articles published previously; citation #2 above and a cross sectional study published in German with 6.6% of cannabis users reporting they used it for migraines.	Commentary.
13. Evans RW, Ramadan NM. Are cannabis based chemicals helpful in headache? <i>Headache</i> 2004;44:726-727.	Case report.	Headache not due to migraine
14. Cupini LM, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. <i>Neurobiology of disease</i> 2008;30: 186-189.	Study of biochemical pathophysiological pathways.	Does not address the key questions.
15. Rossi C, Pini LA, Cupini ML, Calabresi P. Endocannabinoids in platelets of chronic migraine patients and medication overuse headache patients: relation with serotonin levels. <i>European Journal of Clinical Pharmacology</i> 2008;64:1-8.	Study of biochemical pathophysiological pathways.	Does not address the key questions.
16. Russo EB. Clinical endocannabinoid deficiency: can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment resistant conditions? <i>Neuroendocrinology letters</i> 2004;25:31-39.	Review of pathophysiology.	Does not address the key questions.
17. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. <i>California Medical Association Journal</i> 2008;178(13):1669-78.	Review of published articles on adverse effects.	Does not address migraine specifically.
18. Cupini LM, Bari M, Argiro G, et al.	Study of potential pathophysiology pathways.	Does not address the key question

Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. Cephalalgia 2005;26:277-281.		
19. Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology 2007;32:1384-1390.	Study of potential pathophysiology mechanisms.	Does not address the key question.
20. Robson B. Therapeutic aspects of cannabis and cannabinoids. British Journal of Psychiatry 2001;178:107-115.	1996 review of medical use and evidence behind it.	No mention of migraines.

## Conclusions

We could not find any research that directly addressed the key questions. The most relevant literature was of very low quality and no conclusions can be drawn about the benefits or harms of marijuana use for the treatment of migraines.

## Current Treatment Guidelines for Migraines

A search of the guideline clearinghouse resulted in one clinical guideline on the treatment of migraine headaches, from the European Federation of Neurological Societies. (Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS, European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. European Journal of Neurology 2009 Sep;16(9):968-81.) It is included as an attachment.

# Appendix 1

## Search Terms

"Migraine Disorders"[Mesh]

Covers these Entry Terms:

- \* Disorder, Migraine
- \* Disorders, Migraine
- \* Migraine Disorder
- \* Migraine
- \* Migraines
- \* Migraine Headache
- \* Headache, Migraine
- \* Headaches, Migraine
- \* Migraine Headaches
- \* Acute Confusional Migraine
- \* Acute Confusional Migraines
- \* Migraine, Acute Confusional
- \* Migraines, Acute Confusional
- \* Status Migrainosus
- \* Hemicrania Migraine
- \* Hemicrania Migraines
- \* Migraine, Hemicrania
- \* Migraines, Hemicrania
- \* Migraine Variant
- \* Migraine Variants
- \* Variant, Migraine
- \* Variants, Migraine
- \* Sick Headache
- \* Headache, Sick
- \* Headaches, Sick
- \* Sick Headaches
- \* Abdominal Migraine
- \* Abdominal Migraines
- \* Migraine, Abdominal
- \* Migraines, Abdominal
- \* Cervical Migraine Syndrome
- \* Cervical Migraine Syndromes
- \* Migraine Syndrome, Cervical
- \* Migraine Syndromes, Cervical
- \* Migraine with Aura
- \* Migraine without Aura
- \* Ophthalmoplegic Migraine

ANDED with:

((("Marijuana Abuse"[Mesh]) OR "Cannabis"[Mesh]) OR Tetrahydrocannabinol"[Mesh])\cannabinoids

## Appendix 2

### Description of Study Types

#### **BOX 1** Taxonomy of study designs to assess the effectiveness of an intervention

##### **Experimental designs**

A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

**1. Randomised controlled trial**

Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.

**2. Quasi-randomised trial**

Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)

**3. Non-randomised trial/quasi-experimental study**

The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

##### **Observational designs**

A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

**4. Controlled before-and-after study**

A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.

**5. Concurrent cohort study**

A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.

**6. Historical cohort study**

A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.

**7. Case-control study**

Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.

**8. Before-and-after study**

Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.

**9. Cross-sectional study**

Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.

**10. Case series**

Description of a number of cases of an intervention and outcome (no comparison with a control group).

### Appendix 3

#### GRADE Method to Assess Overall Quality of the Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or  +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious  Publication bias -1 Likely -2 Very likely	

## Appendix 4

### List of Articles Reviewed

1. Noyes R, Baram D. Cannabis Analgesia. *Comprehensive Psychiatry* 1974;15(6):531-535.
2. Robbins MS, Tarshish T, Solomon S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. *Headache* 2009; June:914-916
3. El-Mallakh RS, Kansler HR, Kamanitz JR. Headaches and psychoactive substance use. *Headache* 1991;31:584-587
4. El-Mallakh RS. Marijuana and migraine. *Headache* 1987;27:442-443.
5. El-Mallakh RS. Migraine headaches and drug abuse. *Southern Medical Journal* 1989;82:805.
6. Trittibach P, Frueh BE, Goldblum D. Bilateral angle-closure glaucoma after combined consumption of ecstasy and marijuana. *American Journal of Emergency Medicine* 2005;23:813-814.
7. Bagshaw SM. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. *Journal of Palliative Care* 2002;18:111-122.
8. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain* 1998;76:3-8.
9. Taylor FR. Nutraceuticals and headache: the biological basis. *Headache* 2011;51: 484-501.
10. Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *International Journal of Clinical Pharmacology Research* 1985;4:243-246.
11. Juhasz G, Lazary J, Chase D, Pegg E, et al. Variations in the cannabinoid receptor 1 gene predispose to migraine. *Neuroscience Letters* 2009;461:116-120.
12. Napchan U, Buse DC, Loder W. The use of marijuana or synthetic cannabinoids for the treatment of headache. *Headache* 2011; 51:502-505.
13. Evans RW, Ramadan NM. Are cannabis based chemicals helpful in headache? *Headache* 2004;44:726-727.
14. Cupini LM, Costa C, Sarchielli P, Mari M, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. *Neurobiology of disease* 2008;30: 186-189.
15. Rossi C, Pini LA, Cupini ML, Calabresi P. Endocannabinoids in platelets of chronic migraine patients and medication overuse headache patients: relation with serotonin levels. *European Journal of Clinical Pharmacology* 2008;64:1-8.
16. Russo EB. Clinical endocannabinoid deficiency: can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment resistant conditions? *Neuroendocrinology letters* 2004;25:31-39.
17. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *California Medical Association Journal* 2008;178(13):1669-78.
18. Cupini LM, Bari M, Argiro G, et al. Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. *Cephalalgia* 2005;26:277-281.
19. Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. *Neuropsychopharmacology* 2007;32:1384-1390.
20. Robson B. Therapeutic aspects of cannabis and cannabinoids. *British Journal of Psychiatry* 2001;178:107-115.

# EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force

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## Keywords:

evidence-based medicine, migraine, prophylaxis, triptans

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**Background:** Migraine is one of the most frequent disabling neurological conditions with a major impact on the patients' quality of life.

**Objectives:** To give evidence-based or expert recommendations for the different drug treatment procedures in the particular migraine syndromes based on a literature search and the consensus of an expert panel.

**Methods:** All available medical reference systems were screened for the range of clinical studies on migraine with and without aura and on migraine-like syndromes. The findings in these studies were evaluated according to the recommendations of the European Federation of Neurological Societies (EFNS) resulting in level A, B, or C recommendations and good practice points.

**Recommendations:** For the acute treatment of migraine attacks, oral non-steroidal antiinflammatory drug (NSAID) and triptans are recommended. The administration should follow the concept of stratified treatment. Before intake of NSAID and triptans, oral metoclopramide or domperidone is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice. Status migrainosus can be treated by corticosteroids, although this is not universally held to be helpful, or dihydroergotamine. For the prophylaxis of migraine, betablockers (propranolol and metoprolol) flunarizine, valproic acid, and topiramate are drugs of first choice. Drugs of second choice for migraine prophylaxis include amitriptyline, naproxen, petasites, and bisoprolol.

## Objectives

These guidelines aim to give evidence-based recommendations for the drug treatment of migraine attacks and of migraine prophylaxis. The non-drug management (e.g. behavioral therapy) will not be included. The definitions follow the diagnostic criteria of the International Headache Society (IHS).

## Background

The second edition of the classification of the IHS provided a new subclassification of different migraine

syndromes [1]. The basic criteria for migraine attacks remained nearly unchanged. The different migraine syndromes with specific aura features, however, were classified in a new system. The diagnostic criteria for all migraine syndromes have been published on the homepage of the IHS (<http://www.i-h-s.org>).

The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by the respective task force of the EFNS. The legal aspects of drug prescription and drug availability in the different European countries will not be considered. The definitions of the recommendation levels follow the EFNS criteria [2].

## Search strategy

A literature search was performed using the reference databases MedLine, Science Citation Index, and the Cochrane Library; the key words used were 'migraine' and 'aura' (last search in January 2009). All papers published in English, German, or French were

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This is a Continuing Medical Education article, and can be found with corresponding questions on the internet at <http://www.efns.org/content.php?pid=132>. Certificates for correctly answering the questions will be issued by the EFNS

considered when they described a controlled trial or a case series on the treatment of at least five patients. In addition, a review book [3] and the German treatment recommendations for migraine [4] were considered.

### Method for reaching consensus

All authors performed an independent literature search. The first draft of the manuscript was written by the chairman of the task force. All other members of the task force read the first draft and discussed changes by email. A second draft was then written by the chairman and again discussed by email. All recommendations had to be agreed to by all members of the task force unanimously.

### Drug treatment of migraine attacks

Several large randomized, placebo-controlled trials have been published on the acute management of migraine. In most of these trials, successful treatment of migraine attacks was defined by the following criteria [5]:

- pain free after 2 h
- improvement of headache from moderate or severe to mild or none after 2 h [6]
- consistent efficacy in two of three attacks
- no headache recurrence and no further drug intake within 24 h after successful treatment (so-called sustained pain relief or pain free).

### Analgesics

Drugs of first choice for mild or moderate migraine attacks are analgesics. Evidence of efficacy in migraine treatment in at least one placebo-controlled study has been obtained for acetylsalicylic acid (ASA) up to 1000 mg [7–10], ibuprofen 200–800 mg [8,10–12], diclofenac 50–100 mg [13–15], phenazon 1000 mg [16], metamizol 1000 mg [17], tolfenamic acid 200 mg [18], and paracetamol 1000 mg [19]. In addition, the fixed combination of ASA, paracetamol, and caffeine is effective in acute migraine treatment and is also more effective than the single substances or combinations without caffeine [20–22]. Intravenous ASA was more effective than subcutaneous ergotamine [23]; intravenous metamizol was superior to placebo in migraine without and with aura [24]. Lysine-ASA in combination with metoclopramide had comparable efficacy as sumatriptan [9]. Effervescent ASA 1000 mg is probably as effective as ibuprofen 400 mg and as sumatriptan 50 mg [10,25,26].

Also the selective COX-2 inhibitors have been investigated in clinical trials. Valdecoxib 20–40 mg and rofecoxib 25–50 mg, the latter one not available on the market any more, have shown efficacy in acute migraine

**Table 1** Analgesics with evidence of efficacy in at least one study on the acute treatment of migraine, the level of recommendation also considers side effects and consistency of the studies

Substance	Dose, mg	Level of recommendation	Comment
Acetylsalicylic acid (ASA)	1000 (oral)	A	Gastrointestinal side effects,
(ASA)	1000 (i.v.)	A	Risk of bleeding
Ibuprofen	200–800	A	Side effects as for ASA
Naproxen	500–1000	A	Side effects as for ASA
Diclofenac	50–100	A	Including diclofenac-K
Paracetamol	1000 (oral)	A	Caution in liver and kidney
	1000 (supp.)	A	Failure
ASA plus mol plus caffeine	250 (oral)	A	As for ASA and paraceta-
	200–250		paracetamol
	50		
Metamizol	1000 (oral)	B	Risk of agranulocytosis
	1000 (i.v.)	B	Risk of hypotension
Phenazon	1000 (oral)	B	See paracetamol
Tolfenamic acid	200 (oral)	B	Side effects as for ASA

treatment [27–30]. Table 1 presents an overview of analgesics with efficacy in acute migraine treatment.

In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days per month and the intake of combined analgesics to 10 days per month.

### Antiemetics

The use of antiemetics in acute migraine attacks is recommended to treat nausea and potential emesis and because it is assumed that these drugs improve the resorption of analgesics [31–33]. However, there are no prospective, placebo-controlled randomized trials to prove this assertion. Metoclopramide also has a genuine mild analgesic efficacy when given orally [34] and a higher efficacy when given intravenously [35]. There is no evidence that the fixed combination of an antiemetic with an analgesic is more effective than the analgesic alone. Metoclopramide 20 mg is recommended for adults and adolescents, in children domperidon 10 mg should be used because of the possible extrapyramidal side effects of metoclopramide. Table 2 presents the antiemetics recommended for the use in migraine attacks.

### Ergot alkaloids

There are only very few randomized, placebo-controlled trials on the efficacy of ergot alkaloids in the

**Table 2** Antiemetics recommended for the acute treatment of migraine attacks

Substances	Dose, mg	Level	Comment
Metoclopramide	10–20 (oral) 20 (suppository) 10 (intramuscular, intravenous, subcutaneous)	B	Side effect: dyskinesia; contraindicated in childhood and in pregnancy; also analgesic efficacy
Domperidon	20–30 (oral)	B	Side effects less severe than in metoclopramide; can be given to children

acute migraine treatment [36]. In comparative trials, triptans showed better efficacy than ergot alkaloids [37–40]. The advantage of ergot alkaloids is a lower recurrence rate in some patients. Therefore, these substances should be restricted to patients with very long migraine attacks or with regular recurrence. The only compounds with sufficient evidence of efficacy are ergotamine tartrate and dihydroergotamine 2 mg (oral and suppositories, respectively). Ergot alkaloids can induce drug overuse headache very fast and in very low doses [41]. Therefore, their use must be limited to 10 days per month. Major side effects are nausea, vomiting, paraesthesia, and ergotism. Contraindications are cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, and pregnancy and lactation.

### Triptans (5-HT<sub>1B/1D</sub>-agonists)

The 5-HT<sub>1B/1D</sub> receptor agonists sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan,

and frovatriptan (order in the year of marketing), so-called triptans, are migraine medications and should not be applied in other headache disorders except cluster headache. The different triptans for migraine therapy are presented in Table 3. The efficacy of all triptans has been proven in large placebo-controlled trials of which metaanalyses have been published [42,43]. For sumatriptan [9,44] and zolmitriptan [45] comparative studies with ASA and metoclopramide exist. In these comparative studies, the triptans were not or only a little more effective than ASA. In about 60% of nonresponders to NSAID, triptans are effective [46]. Sumatriptan 6 mg subcutaneously is more effective than intravenous ASA 1000 mg s.c. but has more side effects [47]. Triptans can be effective at any time during a migraine attack. However, there is evidence that the earlier triptans are taken the better their efficacy is [48–52]. It is still debated whether triptans are less efficacious or even may fail when taken after the onset of allodynia during a migraine attack [49,53], with randomized controlled trials not supporting a difference for allodynic patients [52,54]. A strategy of strictly early intake can, however, lead to frequent drug treatment in certain patients. The use of triptans is restricted to maximum 9 days per month by the IHS criteria; in epidemiological studies, the risk for chronification became significant at 12 days per month of triptan intake [55]. Otherwise, the induction of a drug overuse headache is possible for all triptans [41,56,57].

One typical problem of attack treatment in migraine is headache recurrence defined as a worsening of headache after pain free or mild pain has been achieved with a drug within 24 h [58]. About 15–40% (depending on the primary and the lasting efficacy of the drug) of the patients taking an oral triptan experience

Substance	Dose, mg	Level	Comment
Sumatriptan	25, 50, 100 (oral including rapid-release)	A	100 mg sumatriptan is reference to all triptans
	25 (suppository)	A	
	10, 20 (nasal spray)	A	
	6 (subcutaneous)	A	
Zolmitriptan	2.5, 5 (oral including disintegrating form)	A	
	2.5, 5 (nasal spray)	A	
Naratriptan	2.5 (oral)	A	Less but longer efficacy than sumatriptan
Rizatriptan	10 (oral including 5 mg when taking propranolol wafer form)	A	
Almotriptan	12.5 (oral)	A	Probably less side effects than sumatriptan
Eletriptan	20, 40 (oral)	A	80 mg allowed if 40 mg not effective
Frovatriptan	2.5 (oral)	A	Less but longer efficacy than sumatriptan

**Table 3** Different triptans for the treatment of acute migraine attacks (order in the time of marketing), not all doses or application forms are available in all European countries

General side effects for all triptans: chest symptoms, nausea, distal paraesthesia, fatigue.  
General contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular disease, Raynaud's disease, pregnancy and lactation, age under 18 (except sumatriptan nasal spray) and age above 65, severe liver or kidney failure.

recurrence. A second dose of the triptan is effective in most cases [59]. If the first dose of a triptan is not effective, a second dose is useless. Combining an NSAID with a triptan (naproxen with sumatriptan) reduces headache recurrence [60].

After application of sumatriptan, severe adverse events have been reported such as myocardial infarction, cardiac arrhythmias, and stroke. The incidence of these events was about 1 in 1 000 000 [61,62]. Reports on severe adverse events also exist for other triptans and for ergotamine tartrate. However, all of the reported patients had contraindications against triptans or the diagnosis of migraine was wrong. In population-based studies, no increased risk of vascular events could be detected for triptan users as compared with a healthy population [63,64]. Contraindications for the use of triptans are untreated arterial hypertension, coronary heart disease, Raynaud's disease, history of ischaemic stroke, pregnancy, lactation, and severe liver or renal failure.

Owing to safety aspects, triptans should not be taken during the aura although no specific severe adverse events have been reported. The best time for application is the very onset of headache. Furthermore, triptans are not efficacious when taken during the aura phase before headache has developed [65,66].

### Comparison of triptans

Some minor differences between triptans exist which will be discussed in order to give a guidance which triptan to use in an individual patient. A triptan can be efficacious even if another triptan was not [67,68].

Subcutaneous sumatriptan has the fastest onset of efficacy of about 10 min [69]. Oral rizatriptan and eletriptan need about 30 min, oral sumatriptan, almotriptan, and zolmitriptan need about 45–60 min [42], and naratriptan and frovatriptan need up to 4 h for the onset of efficacy [70,71]. Zolmitriptan nasal spray has a shorter duration until efficacy than oral zolmitriptan [72]. There is no evidence that different oral formulations such as rapidly dissolving tablets, wafer forms, or rapid release forms [73] act earlier than others.

Pain relief after 2 h as the most important efficacy parameter is best in subcutaneous sumatriptan with up to 80% responders [74]. Sumatriptan nasal spray has the same efficacy as oral sumatriptan 50 mg or 100 mg. 25 mg oral sumatriptan is less effective than the higher doses but has less side effects [42]. Sumatriptan suppositories are about as effective as oral sumatriptan 50 or 100 mg and should be given to patients with vomiting [75–77]. Naratriptan and frovatriptan (2.5 mg) are less effective than sumatriptan 50 or 100 mg but have less side effects. The duration until the onset of efficacy

is longer in these two triptans as compared with all others. Rizatriptan 10 mg is a little more effective than sumatriptan 100 mg. Oral zolmitriptan 2.5 or 5 mg, almotriptan 12.5 mg and eletriptan 40 mg show a similar efficacy and similar side effects [78–80]. Eletriptan 80 mg is the most effective oral triptan but also has the most side effects [42].

The highest recurrence rate is observed after subcutaneous sumatriptan. Naratriptan and frovatriptan show the lowest recurrence rates but have poor initial response rates. Frovatriptan has been compared with sumatriptan but the recurrence data has never been made public, which at least calls the assertion that it has a lower recurrence rate into question. It might be that triptans with a longer half-life time have a lower recurrence rate [81], although if frovatriptan does not have a lower recurrence rate this argument would no longer be tenable. Another problem in clinical practice is inconsistency of efficacy. Therefore, efficacy only in two of three attacks is regarded as good. Rizatriptan in combination with dexamethasone seems to be significantly more effective than rizatriptan alone, although this combination is associated with a higher rate of adverse events [82].

### Other drugs

There is some evidence that the intravenous application of valproic acid in a dose of 300–800 mg is efficacious also in the acute treatment of migraine attacks [83,84], and similarly an older study for intravenous flunarizine [85]. However, the evidence is weak. Tramadol in combination with paracetamol has also shown efficacy in acute migraine attacks [86]. However, opioids are of only minor efficacy, no modern controlled trials are available for these substances; opioids and tranquilizers should not be used in the acute treatment of migraine.

### Migraine prophylaxis

Prophylactic drugs for the treatment of migraine with good efficacy and tolerability and evidence of efficacy are betablockers, calcium channel blockers, anti-epileptic drugs, NSAID, antidepressants, and miscellaneous drugs. The use of all these drugs, however, is based on empirical data rather than on proven pathophysiological concepts. The decision to introduce a prophylactic treatment has to be discussed with the patient carefully. The efficacy of the drugs, their potential side effects, and their interactions with other drugs have to be considered in the individual patient. There is no commonly accepted indication for starting a prophylactic treatment. In the view of the Task Force,

prophylactic drug treatment of migraine should be considered and discussed with the patient when:

- the quality of life, business duties, or school attendance are severely impaired
- frequency of attacks per month is two or higher
- migraine attacks do not respond to acute drug treatment
- frequent, very long, or uncomfortable auras occur.

A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within 3 months. For therapy evaluation, a migraine diary is extremely useful. In the following paragraphs, the placebo-controlled trials in migraine prophylaxis are summarized. The recommended drugs of first choice, according to the consensus of the Task Force, are given in Table 4. Tables 5 and 6 present drugs recommended as second or third

**Table 4** Recommended substances (drugs of first choice) for the prophylactic drug treatment of migraine

Substances	Daily dose (mg)	Level
<b>Betablockers</b>		
Metoprolol	50–200	A
Propranolol	40–240	A
<b>Calcium channel blockers</b>		
Flunarizine	5–10	A
<b>Antiepileptic drugs</b>		
Valproic acid	500–1800	A
Topiramate	25–100	A

**Table 5** Drugs of second choice for migraine prophylaxis (evidence of efficacy, but less effective or more side effects than drugs of Table 6)

Substances	Daily dose (mg)	Level
Amitriptyline	50–150	B
Venlafaxine	75–150	B
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

**Table 6** Drugs of third choice for migraine prophylaxis (only probable efficacy)

Substances	Daily dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200–1600 mg	C
Magnesium	24 mmol	C
Tanacetum parthenium	3 × 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4–12 mg	C

choice when the drugs of Table 4 are not effective, contraindicated, or when comorbidity of the patients suggests the respective drug of second or third choice.

### Betablockers

Betablockers are clearly effective in migraine prophylaxis and very well studied in a lot of placebo-controlled, randomized trials. The best evidence has been obtained for metoprolol [87–91] and propranolol [87,88,92–98]. Also, bisoprolol [91,99], timolol [93,100], and atenolol [101] might be effective but evidence is less convincing compared with propranolol and metoprolol.

### Calcium channel blockers

The 'non-specific' calcium channel blocker flunarizine has been shown to be effective in migraine prophylaxis in several studies [90,98,102–111]. The dose is 5–10 mg, female patients seem to benefit from lower doses than male patients [112]. Another 'non-specific' calcium channel blocker, cyclandelate, has also been studied but with conflicting results [107,113–116]. As the better designed studies were negative, cyclandelate cannot be recommended.

### Antiepileptic drugs

Valproic acid in a dose of at least 600 mg [117–120] and topiramate in a dose between 25 and 100 mg [121–124] are the two antiepileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable to those of metoprolol, propranolol, and flunarizine. Topiramate is also efficacious in the prophylaxis of chronic migraine and may have some effect in migraine with medication overuse [125,126]. Other antiepileptic drugs studied in migraine prophylaxis are lamotrigine and gabapentin. Lamotrigine did not reduce the frequency of migraine attacks but may be effective in reducing the frequency of migraine auras [127,128]. Gabapentin showed efficacy in one placebo-controlled trial in doses between 1200 and 1600 mg using a non-intention-to-treat analysis [129]. Oxcarbazepine was without any efficacy in a very recent study [130].

### NSAID

In some comparative trials, ASA was equivalent to or worse than a comparator (with known efficacy in migraine) but never has achieved a better efficacy than placebo in direct comparison. In two large cohort trials, ASA 200–300 mg reduced the frequency of migraine attacks [131,132]. Naproxen 1000 mg was better than

placebo in three controlled trials [133–135]. Also tolfenamic acid showed efficacy in two placebo-controlled trials [136,137].

### Antidepressants

The only antidepressant with consistent efficacy in migraine prophylaxis is amitriptyline in doses between 10 and 150 mg. It has been studied in four older placebo-controlled trials, all with positive results [138–141]. Since the studies with amitriptyline were small and showed central side effects, this drug is recommended only with level B. For femoxetine, two small positive placebo-controlled trials have been published [142,143]. Fluoxetine in doses between 10 and 40 mg was effective in three [144–146] and not effective in one placebo-controlled trial [147]. Venlafaxine extended release (dose 75–150 mg) has shown efficacy in one placebo-controlled [148] and two open trials [149,150] and can therefore be recommended as a second choice antidepressant in migraine prophylaxis.

### Miscellaneous drugs

The antihypertensive drugs lisinopril [151] and candesartan [152] showed efficacy in migraine prophylaxis in one placebo-controlled trial each. However, these results have to be confirmed before the drugs can definitely be recommended. The same is true for high-dose riboflavin (400 mg) and coenzyme Q10 which have shown efficacy in one placebo-controlled trial each [153,154]. For oral magnesium, conflicting studies (one positive, one negative) have been published [155,156]. A herbal drug with evidence of efficacy is butterbur root extract (*Petasites hybridus*). This has been shown for a remedy with 75 mg in two placebo-controlled trials [157,158]. Another herbal remedy, feverfew (*Tanacetum parthenium*), has been studied in several placebo-controlled trials with conflicting results. Also, the two most recent and best designed studies showed a negative [159] and a positive [160] result; a Cochrane review resulted in a negative meta-analysis of all controlled studies on *tanacetum* [161].

In older studies, clonidine, pizotifen and methysergide have shown efficacy in migraine prophylaxis. The more recent and better designed studies on clonidine, however, did not confirm any efficacy (for review see 162). Methysergide, which is clearly effective, can be recommended for short-term use only (maximum 6 months per treatment period) because of potentially severe side effects [163]. Pizotifen is not generally recommended because the efficacy is not better than in the substances mentioned above and the side effects (dizziness, weight gain) are classified as very severe by the

task force and limit the use too much [164]. Some experts have found it useful in childhood migraine. Ergot alkaloids have also been used in migraine prophylaxis. The evidence for dihydroergotamine is weak since several studies reported both positive and negative results (for review see 162).

Botulinum toxin was studied so far in four published placebo-controlled trials [165–168]. Only one study showed an efficacy for the low-dose (but not the high-dose) treatment with botulinum toxin [165]. In another study, a *post hoc* analysis of a subgroup of chronic migraine patients without further prophylactic treatment showed benefit from botulinum toxin A [168]. This indication is currently evaluated in a trial program.

No efficacy in migraine prophylaxis has been shown for homoeopathic remedies [169–171]; for montelukast [172]; for acetazolamide 500 mg per day [173]; and for lanepitant [174].

## Specific situations

### Emergency situation

Patients with a severe migraine attack in an emergency situation have often already tried oral medication without any success. Treatment of first choice in this situation is the intravenous application of 1000 mg ASA with or without metoclopramide [47]. Alternatively, 6 mg subcutaneous sumatriptan can be given. For the treatment of a status migrainosus, 50–100 mg prednisone or 10 mg dexamethasone is recommended by expert consensus. In placebo-controlled trials, however, no consistent efficacy of this procedure in the acute treatment of migraine attacks [175] or in the prevention of recurrence could be proven [176–179]. Also by expert consensus and supported by open label studies, dihydroergotamine 2 mg (nasal spray or suppositories) is recommended for severe migraine attacks [29]. The intravenous application of metamizol was significantly superior to placebo but can cause severe arterial hypotension and allergic reactions [24,180]. The intravenous application of paracetamol was not efficacious in a placebo-controlled trial in acute migraine attacks [181].

### Menstrual migraine

Different drug regimes have been studied to treat menstrual migraine. On the one hand, acute migraine treatment with triptans has been studied showing the same efficacy of triptans in menstrual migraine attacks as compared with non-menstrual migraine attacks. On the other hand, short-term prophylaxis of menstrual migraine has been studied.

Naproxen sodium (550 mg twice daily) has been shown to reduce pain including headache in the premenstrual syndrome [182]. Its specific effects on menstrual migraine (550 mg twice daily) have also been evaluated [183–185]. In one trial [183], patients reported fewer and less severe headaches during the week before menstruation than patients treated with placebo. In the other two placebo-controlled trials, naproxen sodium, given during 1 week before and 1 week after the start of menstruation, resulted in fewer perimenstrual headaches; in one study, severity was not reduced [185], but in the other both severity and analgesic requirements were decreased [184]. Even triptans have been used as short-term prophylaxis of menstrual migraine. For naratriptan ( $2 \times 1$  mg per day for 5 days starting 2 days prior to the expected onset of menses) and for frovatriptan ( $2 \times 2.5$  mg given for 6 days perimenstrually), superiority over placebo has been shown [186–188]; however, it can happen that the menstrual migraine attack is delayed into another time of the menstrual cycle [188].

Another prophylactic treatment regime of menstrual migraine is oestrogen replacement therapy. The best evidence, although not as effective as betablockers or other first line prophylactic drugs, has been achieved for transdermal estradiol (not  $< 100 \mu\text{g}$  given for 6 days perimenstrually as a gel or a patch) [189–192]. A recent study, however, did not show efficacy of hormone replacement with respect to attack frequency during the whole menstrual cycle [193].

### Migraine in pregnancy

There are no specific clinical trials evaluating drug treatment of migraine during pregnancy, most of the migraine drugs are contraindicated. If migraine occurs during pregnancy, only paracetamol is allowed during the whole period. NSAID can be given in the second trimester. These recommendations are based on the advices of the regulatory authorities in most European countries. There might be differences in some respect between different countries (in particular, NSAID might be allowed in the first trimester).

Triptans and ergot alkaloids are contraindicated. For sumatriptan, a large pregnancy register has been established with no reports of any adverse events or complications during pregnancy which might be attributed to sumatriptan [194–198]. Similar results have been published for rizatriptan [199]. Based on the published data, administration of triptans in the first trimester of pregnancy is recommended by expert consensus if the child is more at risk by severe attacks with vomiting than by the potential impact of the triptan. For migraine prophylaxis, only magnesium and meto-

prolol are recommended during pregnancy (level B recommendation) [200].

### Migraine in children and adolescents

The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen 10 mg per kg body weight and paracetamol 15 mg per kg body weight [201]. The only antiemetic licensed for the use in children up to 12 years is domperidon. Sumatriptan nasal spray 5–20 mg is the only triptan with positive placebo-controlled trials in the acute migraine treatment of children and adolescents [202–204], the recommended dose for adolescents from the age of 12 is 10 mg. Oral triptans did not show significant efficacy in the first placebo-controlled childhood and adolescents studies [205–207]. This was in particular because of high placebo responses of about 50% in this age group. In *post hoc* analyses, however, 2.5–5 mg zolmitriptan were effective in adolescents from the age of 12 to 17 [208,209]. In recent trials, oral zolmitriptan 2.5 mg [210], nasal zolmitriptan 5 mg [211], and oral rizatriptan 5–10 mg [212] have been superior to placebo in acute migraine treatment. Ergotamine should not be used in children and adolescents. Also children and adolescents can develop drug-induced headache due to analgesic, ergotamine, or triptan overuse.

For migraine prophylaxis, flunarizine 10 mg and propranolol 40–80 mg per day showed the best evidence of efficacy in children and adolescents [206,213]. Recently, topiramate in a dose between 15 and 200 mg showed efficacy in children and adolescents as well [214,215]. Other drugs have not been studied or did not show efficacy in appropriate studies.

### Need of update

These recommendations should be updated within 3 years and should be complemented by recommendations for the non-drug treatment of migraine.

### Conflicts of interest

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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 pharmacopoeias 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-tsao*

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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, *bhang*, 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*-naïve 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 (Aguirell 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-naïve 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; Kuehne 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 (Volfe 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-HT<sub>3</sub>) 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 (AJP, 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<sub>1D</sub> 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.

## Acknowledgements

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Medical Marijuana Home Page > Diseases / Conditions > Migraines >

## Is Marijuana an Effective Treatment for Migraines?

### General Reference (not clearly pro or con)

MedlinePlus, the National Library of Medicine's online Medical Encyclopedia (accessed June 26, 2006), wrote:

*"A **Migraine** is a type of primary headache that some people get repeatedly over time. Migraines are different from other headaches because they occur with symptoms such as nausea, vomiting, or sensitivity to light. In most people, a throbbing pain is felt only on one side of the head."*

June 26, 2006 - MedlinePlus ☆

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John Claude Krusz, PhD, MD, Medical Advisor on the Board of Directors of MAGNUM at the National Migraine Association, on Mar. 23, 2005 said in response to "Studies About the Effects of Marijuana on Migraine?" on "Ask the Clinician" on about.com:

*"The literature on the effect of marijuana on migraines is very poor, indeed. As you can imagine, it is not a topic the government will support readily. Most 'studies' are anecdotes and formal research is lacking. There is some theoretical information why cannabinoids may be useful in treating migraines and pain and there are also small published studies suggesting that marijuana can increase headaches."*

Mar. 23, 2005 - John Claude Krusz, MD, PhD ☆☆☆☆

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## Is Marijuana an Effective Treatment for Migraines?

### PRO (yes)

Philip Denney, MD, Co-founder of a medical cannabis evaluation practice, in the June 2, 2005 *Whittier Daily News* is quoted by Shirley Hsu in the article "Migraine Sufferer Finds Relief from Marijuana":

*"Cannabis is one of the best medicines for migraines. It's so effective - it works rapidly, and it has limited toxicity, although lung damage from smoking is a concern."*

June 2, 2005 - Philip Denney, MD ☆☆☆☆

### CON (no)

*Journal of Palliative Care* reported in a Summer 2002 article "Medical Efficacy of Cannabinoids and Marijuana: A Comprehensive Review of the Literature" by Sean M. Bagshaw and Neil A. Hagen:

*"To date, no randomized clinical trials in humans have established a role for either smoked or oral formulations of cannabinoids for use as acute or prophylactic therapy in patients suffering from migraine."*

Summer 2002 - Journal of Palliative Care ☆☆

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Jack Herer, author and pro-marijuana activist, wrote in his Nov. 2000 book *The Emperor Wears No Clothes*:

The Institute of Medicine published in its Mar. 1999

*"Because migraine headaches are the result of artery spasms combined with over-relaxation of veins, the vascular changes cannabis causes in the covering of the brain (the meninges) usually make migraines disappear."*

Nov. 2000 - Jack Herer ☆

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Ethan Russo, MD, Senior Medical Advisor at the Cannabinoid Research Institute, in a 2001 article "Hemp for Headache: An In-Depth Historical and Scientific Review of Cannabis in Migraine Treatment," published in the *Journal of Cannabis Therapeutics*, wrote:

*"In closing, a unique dance of medical science and politics is occurring that will soon decide whether herbal cannabis (a derivative, or synthetic analogue) will rise like the legendary phoenix to resume an ancient role as a remedy for migraine and neuropathic pain."*

2001 - Ethan Russo, MD ☆☆☆☆

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David L. Bearman, MD, physician and medical marijuana expert, in a letter printed in the Feb. 3, 2005 edition of *Los Angeles City Beat*, wrote:

*"Not only are there thousands of migraine patients who benefit from cannabis, but cannabis has been cited by such historical medical luminaries as Sir William Osler, M.D. (considered the father of modern medicine) and Dr. Morris Fishbein (long-time editor of JAMA) as the best treatment for migraines (back in the days before the Congress ignored the AMA and over the AMA's objection, passed the Marijuana Tax Act)."*

[Editor's Note: Dr. Bearman responded to the Con statements in a Jan. 11, 2011 email to ProCon.org:

*"A couple of the con statements on the use of cannabis to prevent and/or relieve the symptoms of migraine headaches correctly note that there have been no double blind studies done. This observation does not abrogate thousands of years of anecdotal evidence and over one hundred years of support by prominent figures in the medical establishment... While double blind studies are certainly important, in the*

report titled "Marijuana and Medicine: Assessing the Science Base":

*"Marijuana has been proposed numerous times as a treatment for migraine headaches, but there are almost no clinical data on the use of marijuana or cannabinoids for migraine.*

*Our search of the literature since 1975 yielded only one scientific publication on the subject. It presents three cases of cessation of daily marijuana smoking followed by migraine attacks -- not convincing evidence that marijuana relieves migraine headaches.*

*The same result could have been found if migraine headaches were a consequence of marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider all logical possibilities.*

*Various people have claimed that marijuana relieves their migraine headaches, but at this stage there are no conclusive clinical data or published surveys about the effect of cannabinoids on migraine."*

Mar. 1999 - Institute of Medicine ☆  
"Marijuana and Medicine: Assessing the Science Base" (988 KB)  ☆☆☆☆☆

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William Young, MD, Director of the In-Patient Program at the Jefferson Headache Center, and Mary Paolone, RN, wrote in the Summer 2003 *Headache*, the newsletter of the American Council for Headache Education:

*"As a physician treating headache patients for a number of years, I have seen no one who has reported a sustained headache benefit from using marijuana.*

*There have also been reports of marijuana being associated with increased headache. One study suggested that migraine sufferers usually develop tension-type headache after chronic use.*

*The potential intoxicating effect, possible long-term harm with frequent use, and the social stigma associated with this herb are likely to restrict its medicinal use for*

United States such studies have not been allowed...

*headache conditions."*

Summer 2003 - William Young, MD ☆☆☆☆

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Dr. Russo, a well respected neurologist, author, researcher and North American Consultant to GW Pharmaceuticals, tried for four years to get the federal government to approve just such a double blind research project. They refused...

Just as a historical note; when aspirin was first used for treating headaches no double blind studies were done, yet we still believe that aspirin treats headaches. Aspirin was based on centuries of use of willow bark by Native Americans. Aspirin was grand-mothered in by the 1938 Food, Cosmetics and Drug Act and to the best of my knowledge has never received modern FDA approval because it never had to. Many experts say that if aspirin had to undergo the contemporary FDA approval process it would be far from a shoe in to receive that approval."]

Feb. 3, 2005 - David L. Bearman, MD ☆☆☆☆

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**Cannabis in acute migraine treatment project:  
Response to National Institutes of Health Critique  
Ethan Russo, M.D.**

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*I recently received the "formal" critique of our team's proposal by the NIH Review Committee. Although I would admit to discouragement, and my doubts as to how to rectify deficiencies that may not in fact exist, my research partners and I intend to re-submit this proposal to NIH for the Spring cycle. The critique contained many instances calling for elements that the protocol in fact already contained. ...of 29 members of the review team... only eight were neurologists, and none appear to be headache specialists.*

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AS A NEUROLOGIST with research interests in migraine and ethnobotany, it was natural that I would be interested in the controversy concerning medical marijuana. Over the years, I have had numerous patients relate to me the efficacy of smoked Cannabis in allaying their migraine symptoms.

In 1997, with benefit of some financial support from MAPS, I submitted an application to the National Institutes of Health (NIH) for a grant to study the use of smoked marijuana in the treatment of migraine. This application process has been mandated by the Federal government as necessary for the approval of any therapeutic clinical Cannabis studies. To date, the Short-term Effects of Cannabinoids in HIV Patients study of Dr. Donald Abrams and his team remains the only other application of this type to NIH. That study was recently approved, while the Cannabis in Acute Migraine Treatment Project was rejected.

I recently received the "formal" critique of our team's proposal by the NIH Review Committee. After examining it, I feel that virtually all points of that criticism can be adequately addressed. My team plans, with additional support from MAPS, to submit a revised grant application to NIH for its June 1, 1998 grant cycle. The following is a review of the points of the critique along with my initial inclinations as to how they might be addressed.

**Study design**

It is always a daunting task to defend one's work, particularly when the effort involved was as intense as for this one, and with so much at

stake. The entire protocol was written so as to incorporate systematically the approaches and procedures that were outlined by Dr. Robert Temple (Associate Director for Medical Policy, FDA Center for Drug Evaluation and Research) at the NIH Workshop on the Medical Utility of Marijuana in February 1997.

The study is designed to examine migraine sufferers who have either failed to respond to or tolerate subcutaneous sumatriptan injection, the current ne plus ultra in acute headache management. Patients selected for the study would then be initially treated with one of the following: smoked Cannabis with 4% THC content (the highest potency provided by NIDA), oral dronabinol 10 mg. (synthetic THC), placebo capsules, or an injected meperidine/hydroxyzine mixture (a common emergency room fallback approach).

### **Criticisms**

The criticisms leveled at the protocol by the NIH are multiple, and occasionally contradictory. One reviewer felt the protocol too ambitious, another not sufficiently rigorous. Finding middle ground acceptable to all was not the intent of this study. Rather, the guidelines from Dr. Temple did not call for either a preliminary "open label" study of therapeutic marijuana use or definitive "Phase 3" studies. They did call for comparison of smoked marijuana to oral dronabinol, as well as a control. We arrived at the figure of 30 study subjects through a sophisticated statistical analysis that indicated that this number would be sufficient to demonstrate clinically relevant differences between the four study drugs.

### **Precedent of anecdotal accounts**

Another criticism revolved around the inclusion in the protocol of multiple "anecdotal" accounts as evidence of the efficacy of Cannabis in headache treatment. It bears repeating that this agent has been used therapeutically and continuously for 4000 years or more, and was pre-eminent, or nearly so in migraine treatment for eight decades among American and European physicians (Grinspoon and Bakalar, 1997; Mikuriya, 1973; Russo, 1998). We might still be using it were it not for the government's prohibition of Cannabis on false pretenses in 1937. During that previous era, there were no controlled studies, nor were any needed for this agent. Doctors as prominent as Queen Victoria's personal physician, J. Russell Reynolds (Russell, 1890), Sir William Gowers (Gowers, 1888), and Sir William Osler, the father of modern medicine (Osler and McRae, 1915), preferred Cannabis for migraine patients because it worked effectively and safely. In more modern times, there have been no controlled studies of therapeutic use of Cannabis solely because they have been politically prohibited. This is precisely why studies such as ours should be allowed to proceed.

The proposal contained many scientific citations as to proposed mechanisms for Cannabis' analgesic effects and modulation of serotonergic mechanisms, but apparently these were not sufficiently compelling to the reviewers.

One critique suggested that marijuana might work on headaches due to its soporific effect, promotion of relaxation, or because of its anti-nausea properties. I find this unsupported by the facts. Most people who use Cannabis therapeutically do not fall asleep; rather, many use only enough to reduce symptoms so that they may return to their prior activities. Several of my patients use it in this manner. It is well known that relaxation techniques may modestly reduce migraine pain, but transiently, and incompletely. As to nausea, the 5-HT<sub>3</sub> antagonists ondansetron and granisetron are powerful agents in its control, but have no effect on migraine pain (Peroutka, 1990). These criticisms betray a basic lack of familiarity with migraine pathogenesis.

### **Elements overlooked by reviewers**

The critique contained many instances calling for elements that the protocol in fact already contained: use of visual analogue scales for symptom quantification, clear exclusions for pregnancy, drug abuse, etc. Perhaps the protocol was not carefully read, or the appendices that contained some of this material were not circulated. In any event, it is difficult to be criticized for omissions that did not, in fact, occur. A valid request would be tighter controls for women in childbearing years to ensure that pregnancy risks are minimized (i.e., contraception, spousal vasectomy, etc.).

One reviewer suggested that anyone who ever smoked marijuana be excluded from participation in the study. I have never seen this as a criterion for previous studies, and it seems totally unnecessary. We planned a mixture of experienced and Cannabis-naïve subjects to more closely test "real-world" clinical issues.

### **Objections to confidentiality procedure**

Objections were raised as to confidentiality procedures. We outlined every reasonable precaution for locked records, limited access, etc. I personally felt these were adequate. It is true to say they are not foolproof, but short of draconian police-state tactics, they would be the best that could be provided. The study would receive the usual intense monitoring by NIH personnel, and additionally the local Investigational Review Board, which happens to be located one floor below that where the study would be performed.

A stinging personal criticism was leveled at me, questioning my ability to carry out the study due to a perceived lack of experience in "human trials." This seems to be a variation of the old chestnut that

one has to have a job to get a job. In fact, I have been carrying out "human trials" for twenty years: it is called the practice of medicine, where every prescription is an experiment with its failures, side effects and pitfalls. To say that this study contains elements beyond my expertise is unfounded, unsubstantiated, and inaccurate. As a faculty member of two universities at an undergraduate, graduate, and professional level, and with personal recommendations from two distinguished chairmen of university departments of pharmacy for this study, I had hoped not to be disparaged in this manner.

One critic upbraided me for inclusion of an anecdote that suggested Cannabis was no better than standard pharmaceutical for one patient. Is that surprising? Nothing works for everyone. That is called clinical variation, and inclusion of such information is required in a critical review of the subject in order for it to retain the kind of scientific objectivity that I am not applying in this document written for readers of the MAPS Bulletin.

### **Inclusion criteria questioned**

One reviewer questioned selection criteria for patients. How would we know that they really had migraine, and not some more dire brain disease? It was even suggested that patients might require MRI scans before entry (each scan costs \$1,200). Actually, established criteria exist, provided by the IHS (International Headache Society) and were incorporated in our questionnaires (Headache, 1988). Each subject can be clinically examined prior to entry, and this has been sufficient for virtually all previous clinical headache protocols. Imaging studies for migraine patients are not always necessary.

Another questioned whether 30 study subjects could be recruited. I believe that I could find them solely from my patient clientele! Many headache patients are seeking better treatments and are very open to "new ideas," for better or worse, even ones that are currently illegal. Let us crunch a few numbers. Migraine afflicts 14% of females and 8% of males (Linnet et al., 1989), for a composite of 11%. One fourth of those are severe or 2.75% (Stewart et al., 1992). About 70% of people respond to subcutaneous administration of sumatriptan (Mathew, 1997). About 30% fail, or an even greater number have sufficient side effects that they prefer not to use it. Multiplying that by an estimated adult local population of 60,000, that would be:  $60,000 \times 0.0275 \times 0.30 = 495$  potential subjects. I feel that this is, in fact, a very conservative figure. Obviously, not all would wish to be part of a study in which they would smoke marijuana, but this is a university town, and many would not object; some may be doing so now. I am confident we can recruit sufficient subjects if only allowed to do so.

### **Question of placebo**

Another issue concerned use of placebo. One reviewer mistakenly thought that certain subjects would be stuck with placebo or other treatment for their entire course of ten treatments. I believe they failed to understand the randomization scheme as it was presented. Here I was caught in a bind. I would prefer not to use placebo: it is inhumane. It was my intention to eschew "dummy dope" that would require subjects to smoke an inert material with the attendant risks, but no benefits. It has previously been shown that even marijuana-naive subjects can detect when they are receiving placebo as compared to active Cannabis. The placebo was included in the protocol because it was considered essential by the NIH Committee on the Medical Utility of Marijuana. Moreover, no subject in our study would receive placebo more than once.

Another questioned our use of intramuscular meperidine. Once more, I included it because, for better or worse, it seems to be the drug of choice in treating migraine in emergency rooms across the United States. I personally never use it, and do not recommend it. However, it does provide a recognized point of comparison to a potential alternative treatment such as smoked Cannabis. Alternatives such as morphine increase nausea, while butorphanol (Stadol) has been associated with myriad dangers (Fisher and Glass, 1997).

One reviewer felt a two hour period of observation was insufficient, and suggested patients be kept overnight. This requirement alone would serve to more than triple the cost of the study (not that we the taxpayers should be concerned). Since migraine is primarily an outpatient disease, this stipulation represents extreme overkill, and would impair subject recruitment, perhaps prohibitively. One of the main aims of this study is to ascertain whether people can function better after migraine treatment with Cannabis. They can not do that wasting time and money in the hospital. What about that confidentiality anyway? In this small town, your nurse might be a friend of your cousin, and tell him you were in the hospital. We plan to treat patients up to ten times in a six month period. Another fear expressed was that patients might not have 10 headaches during business hours in the 6-month period of time that each patient will be enrolled in the study. I feel this is unlikely. Most headaches are generated in AM hours, and our selected study subjects will have sufficient frequency of attacks to ensure that many will reach this goal. Our statistical analysis did not require that all study subjects meet the ten-treatment goal.

### **Rigor of clinical measures**

A difficult issue revolved around whether our clinical measures would be adequate to answer the questions asked. In fact they are more rigorous than those employed in the studies that established the efficacy of sumatriptan in migraine treatment (Cady et al., 1991). Again, I am confident that useful results will be obtained if the study

is ultimately allowed to proceed.

One reviewer wondered how non-responders to sumatriptan might be characterized, and why they might be better treated with Cannabis. The initial issue has been studied (Visser et al., 1996). The answer is that sumatriptan non-responders may be obese, or take the medicine too early. Beyond that, the study found no features distinguishing responders from non-responders. I would add one other observation from my clinical experience: people with chronic daily headache (a difficult subset of migraine) respond poorly to subcutaneously sumatriptan. Because this proposal focuses on migraineurs with episodic attacks, CDH patients would not be accepted for inclusion.

### **Inadequacy of review process**

Finally, I would level criticism of my own at The National Institutes of Health. Not unexpectedly, none of the reviewers of my protocol were on the panel of the Workshop on the Medical Utility of Marijuana that proposed criteria for clinical Cannabis studies. What is surprising, and unacceptable is that this group was apparently not informed of NIH's own expressed suggestions for such studies into the medical use of marijuana. Unfortunately, government agencies have a longstanding tradition of ignoring their own commissions' recommendations. Additionally, of 29 members of the review team for the Division of Neurological Diseases and Stroke, only eight were neurologists, and none appear to be headache specialists. I do know this much: none are members of the American Association for the Study of Headache, the premier research organization devoted to the study of migraine. I am, and would have hoped for examination by a jury of my peers.

As if that were not enough, this proposal was initially assigned to the AIDS Division of the National Institute on Drug Abuse, although it pertained to neither HIV nor "abuse," and was not re-assigned until I pointed out the inherent contradiction. This indicates that the NIH bureaucracy has been operating as a "split-brain preparation." That is, the right hemisphere has no idea what the left hemisphere is doing.

In summary, I am extremely disappointed with the repudiation of this proposal. It has considerably greater merit and validity than the criticisms would allow. Although I would admit to discouragement, and my doubts as to how to rectify deficiencies that may not in fact exist, my research partners and I intend to re-submit this proposal to NIH for the spring cycle.

Contributions of interested parties to MAPS, earmarked for this purpose, will be most appreciated.

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