Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • **Website:** www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: CT	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]	

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Fibromyalgia

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

See attached

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

See attached

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

See attached

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

See attached

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

See attached

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

See attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

See attached

Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

See attached

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Signature	Date Signed:
[redacted]	10/7/16.

Section A: Petitioner's Information

See attached form

Section B: Medical Condition, Medical Treatment or Disease

Fibromyalgia

Section C: Background

See attached:

Fibromyalgia is a chronic medical condition that includes widespread pain and tenderness among other symptoms. Fibromyalgia like arthritis can cause significant pain and fatigue that can interfere with the activities of daily living and negatively impact the quality of an individual's life. Other symptoms of Fibromyalgia include cognitive/memory problems; sleep disturbances, stiffness, headaches, irritable bowel syndrome, painful menstrual periods, numbness or tingling of the extremities, restless leg syndrome, and sensitivity to temperature, loud noises or bright lights.

Section D: Negative Effects of Current Treatment

See Attached:

There are only three medications that have been approved by the FDA for the treatment of fibromyalgia, duloxetine (Cymbalta), milnacipran (Savella) and pregabalin (Lyrica). The limited number of approved drugs makes it difficult to treat individuals who do not tolerate these medications and who cannot live with the side effects.

Section E: Negative Effects of Condition or Treatment

See Attached: PDFs of the PubMed Health information on these medications and their side effects

The side affects of the three FDA approved medication for fibromyalgia are as follows:

Duloxetine:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Blistering, peeling, red skin rash

Confusion, weakness, muscle twitching

Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes

Decrease in how much or how often you urinate

Eye pain, vision changes, seeing halos around lights

Feeling more energetic than usual

Lightheadedness, dizziness, or fainting

Restlessness, fever, fast heartbeat, sweating, muscle spasms, diarrhea, seeing or hearing things that are not there

Unusual moods or behaviors, worsening depression, thoughts about hurting yourself, trouble sleeping

Unusual bleeding or bruising
Decrease in appetite or weight
Dry mouth, constipation, mild nausea
Unusual drowsiness or tiredness

Milnacipran

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Blistering, peeling, red skin rash

Confusion, weakness, and muscle twitching

Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes

Eye pain, vision changes, seeing halos around lights

Fast, pounding, or uneven heartbeat or pulse

Increased energy, racing thoughts, reckless behavior, talking more than usual

Seizures or tremors

Unusual behavior or thoughts about hurting yourself or others

Unusual bleeding or bruising

Constipation, nausea, vomiting

Increased sweating

Mild headache, dizziness, trouble sleeping

Problems with urination or sex

Warmth or redness in your face, neck, arms, or upper chest

Pregabalin

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Blistering, peeling, red skin rash

Blurry or double vision

Fever, chills, cough, sore throat, and body aches

Muscle pain, tenderness, or weakness, fever, or general ill feeling

Rapid weight gain, swelling in your hands, ankles, or feet

Severe dizziness or drowsiness

Sudden mood changes, unusual thoughts or behavior such as extreme happiness or depression

Suicidal thoughts

Swelling in your throat, head, or neck

Uneven heartbeat

Unusual bleeding, bruising, or weakness

Confusion, trouble concentrating

Constipation

Dry mouth

Section F: Conventional Therapies

See Attached: Pub Med Health Reports and Questions and Answers on Fibromyalgia

As there are only three medications to help control the symptoms of fibromyalgia and they can all cause nausea and adverse side effects it is difficult to manage the pain, depression and anxiety associate with fibromyalgia enough to incorporate the other therapies that can be beneficial to individuals diagnosed with fibromyalgia. These include exercise, improving sleep, and physical therapy. Also in some cases NSAID pain relievers can be helpful but only for the pain relief aspect not the anti-inflammatory properties. NSAIDs have been shown to have adverse side effects and can be contraindicated in many situations.

Section G: General Evidence of Support for Medical Marijuana Treatment

See Attached: 25 Legal Medical Marijuana States.

Medical marijuana is helpful in reliving chronic pain, anxiety and depression as well as helping with appetite and nausea all of which would be beneficial to individuals either as an individual treatment or in combination with the traditionally accepted medications and treatments of fibromyalgia. Also marijuana has been shown to increase relaxation, which can help with muscle pain, and sleep, which will increase overall health and promote well-being.

Of the states that have legalized medical marijuana use 7 of 25, list chronic or severe pain as qualifying medical conditions for the use of medical marijuana. These states include; Alaska, Arizona, California, Maryland, Michigan, Montana, New Mexico,

Of the states that have legalized medical marijuana use 2 of 25, list fibromyalgia specifically. Illinois and Ohio have both already recognized the benefits of medical marijuana for the treatment of fibromyalgia.

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

See Attached:

Section I: Section J: Good Cause for Missing Sections

I have spoken to multiple doctors about medical marijuana as an option for treatment for fibromyalgia in conjunction with anxiety and depression however none of them had an experience with this as none of those conditions are on the list of legally approved conditions in the state of Connecticut. While my rheumatologist encouraged me to reach out and try to find a doctor with information on marijuana and fibromyalgia it has been very difficult if not impossible in Connecticut as it is not legal for patients to use marijuana for fibromyalgia. None of the medical professionals I spoke with could write letters or provide supporting evidence as none of them have encountered this particular situation and I am limited to the area I live in as far as medical professionals. I believe that the situation and the question of legality is a major roadblock in getting a medical

professional to write supporting something as many will not write supporting something they do not personally have evidence of.

Diseases and Conditions

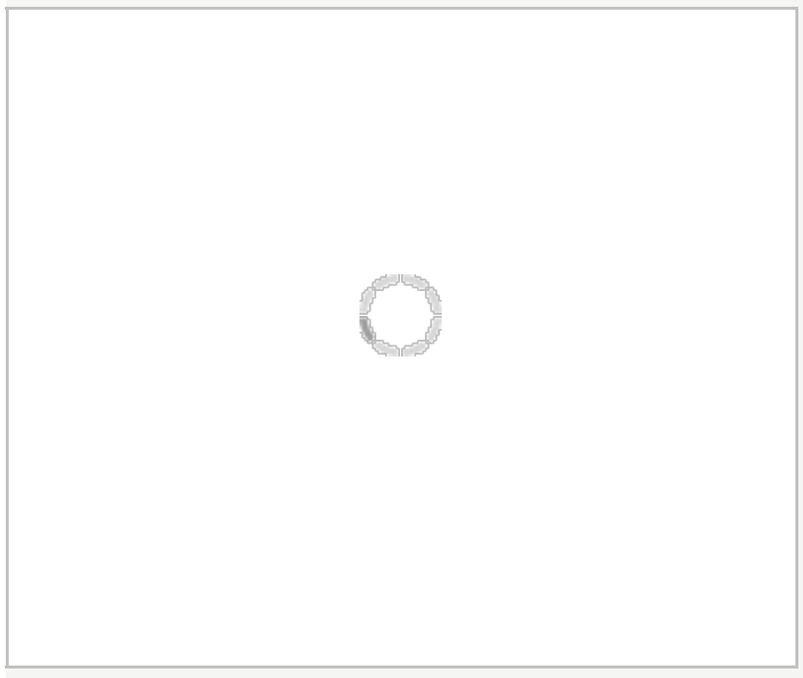
Fibromyalgia

Definition

By Mayo Clinic Staff

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. Researchers believe that fibromyalgia amplifies painful sensations by affecting the way your brain processes pain signals.

Symptoms sometimes begin after a physical trauma, surgery, infection or significant psychological stress. In other cases, symptoms gradually accumulate over time with no single triggering event.



Women are much more likely to develop fibromyalgia than are men. Many people who have fibromyalgia also have tension

headaches, temporomandibular joint (TMJ) disorders, irritable bowel syndrome, anxiety and depression.

While there is no cure for fibromyalgia, a variety of medications can help control symptoms. Exercise, relaxation and stress-reduction measures also may help.

Symptoms

Sept. 08, 2016

References

See also

Acupuncture

Antidepressant withdrawal: Is there such a thing?

Antidepressants and alcohol

Antidepressants and weight gain: What causes it?

Antidepressants: Can they stop working?

Antidepressants: Side effects

Antidepressants: Selecting one

Show more

Other Topics in Patient Care & Health Info

- Healthy Lifestyle
- Symptoms A-Z
- Diseases and Conditions A-Z
- Tests and Procedures A-Z
- Drugs and Supplements A-Z
- Appointments
- Patient and Visitor Guide
- Billing and Insurance
- Patient Online Services

We want to hear from you

Questions and Answers about Fibromyalgia

July 2014

This publication contains general information about fibromyalgia. It describes what fibromyalgia is, who gets it, and what causes it. It also explains how fibromyalgia is diagnosed and treated. At the end is a list of key words to help you understand the terms used in this publication. If you have further questions after reading this publication, you may wish to discuss them with your doctor.

What Is Fibromyalgia?

Fibromyalgia syndrome is a common and chronic disorder characterized by widespread pain, diffuse tenderness, and a number of other symptoms. The word “fibromyalgia” comes from the Latin term for fibrous tissue (*fibro*) and the Greek ones for muscle (*myo*) and pain (*algia*).

Although fibromyalgia is often considered an arthritis-related condition, it is not truly a form of arthritis (a disease of the joints) because it does not cause inflammation or damage to the joints, muscles, or other tissues. Like arthritis, however, fibromyalgia can cause significant pain and fatigue, and it can interfere with a person’s ability to carry on daily activities. Also like arthritis, fibromyalgia is considered a rheumatic condition, a medical condition that impairs the joints and/or soft tissues and causes chronic pain.

Information Box

In addition to pain and fatigue, people who have fibromyalgia may experience a variety of other symptoms including:

- cognitive and memory problems (sometimes referred to as “fibro fog”)
- sleep disturbances
- morning stiffness
- headaches
- irritable bowel syndrome
- painful menstrual periods
- numbness or tingling of the extremities
- restless legs syndrome
- temperature sensitivity
- sensitivity to loud noises or bright lights.

A person may have two or more coexisting chronic pain conditions. Such conditions can include chronic fatigue syndrome, endometriosis, fibromyalgia, inflammatory bowel disease, interstitial cystitis, temporomandibular joint dysfunction, and vulvodynia. It is not known whether these disorders share a common cause.

Who Gets Fibromyalgia?

Scientists estimate that fibromyalgia affects 5 million Americans age 18 or older.[1] For unknown reasons, between 80 and 90 percent of those diagnosed with fibromyalgia are women; however, men and children also can be affected. Most people are diagnosed during middle age, although the symptoms often become present earlier in life.

---

[1]Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National

Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008 Jan;58(1):26-35.

People with certain rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus (commonly called lupus), or ankylosing spondylitis (spinal arthritis) may be more likely to have fibromyalgia, too.

Several studies indicate that women who have a family member with fibromyalgia are more likely to have fibromyalgia themselves, but the exact reason for this—whether it is heredity, shared environmental factors, or both—is unknown. Researchers are trying to determine whether variations in certain genes cause some people to be more sensitive to stimuli, which lead to pain syndromes. (See "What Research Is Being Conducted on Fibromyalgia?")

What Causes Fibromyalgia?

The causes of fibromyalgia are unknown, but there are probably a number of factors involved. Many people associate the development of fibromyalgia with a physically or emotionally stressful or traumatic event, such as an automobile accident. Some connect it to repetitive injuries. Others link it to an illness. For others, fibromyalgia seems to occur spontaneously.

Many researchers are examining other causes, including problems with how the central nervous system (the brain and spinal cord) processes pain.

Some scientists speculate that a person's genes may regulate the way his or her body processes painful stimuli. According to this theory, people with fibromyalgia may have a gene or genes that cause them to react strongly to stimuli that most people would not perceive as painful. There have already been several genes identified that occur more commonly in fibromyalgia patients, and NIAMS-supported researchers are currently looking at other possibilities.

How Is Fibromyalgia Diagnosed?

Research shows that people with fibromyalgia typically see many doctors before receiving the diagnosis. One reason for this may be that pain and fatigue, the

main symptoms of fibromyalgia, overlap with those of many other conditions. Therefore, doctors often have to rule out other potential causes of these symptoms before making a diagnosis of fibromyalgia. Another reason is that there are currently no diagnostic laboratory tests for fibromyalgia; standard laboratory tests fail to reveal a physiologic reason for pain. Because there is no generally accepted, objective test for fibromyalgia, some doctors unfortunately may conclude a patient's pain is not real, or they may tell the patient there is little they can do.

A doctor familiar with fibromyalgia, however, can make a diagnosis based on criteria established by the American College of Rheumatology (ACR): a history of widespread pain lasting more than 3 months, and other general physical symptoms including fatigue, waking unrefreshed, and cognitive (memory or thought) problems. In making the diagnosis, doctors consider the number of areas throughout the body in which the patient has had pain in the past week.

How Is Fibromyalgia Treated?

Fibromyalgia can be difficult to treat. Not all doctors are familiar with fibromyalgia and its treatment, so it is important to find a doctor who is. Many family physicians, general internists, or rheumatologists (doctors who specialize in arthritis and other conditions that affect the joints or soft tissues) can treat fibromyalgia.

Fibromyalgia treatment often requires a team approach, with your doctor, a physical therapist, possibly other health professionals, and most importantly, yourself, all playing an active role. It can be hard to assemble this team, and you may struggle to find the right professionals to treat you. When you do, however, the combined expertise of these various professionals can help you improve your quality of life.

You may find several members of the treatment team you need at a clinic. There are pain clinics that specialize in pain and rheumatology clinics that specialize in arthritis and other rheumatic diseases, including fibromyalgia.

Only three medications, duloxetine,

milnacipran, and pregabalin are approved by the U.S. Food and Drug Administration (FDA) for the treatment of fibromyalgia.[2] Duloxetine was originally developed for and is still used to treat depression. Milnacipran is similar to a drug used to treat depression but is FDA approved only for fibromyalgia. Pregaballin is a medication developed to treat neuropathic pain (chronic pain caused by damage to the nervous system).

Doctors also treat fibromyalgia with a variety of other medications developed and approved for other purposes.

---

[2]All medicines can have side effects. Some medicines and side effects are mentioned in this publication. Some side effects may be more severe than others. You should review the package insert that comes with your medicine and ask your health care provider or pharmacist if you have any questions about the possible side effects.

Analgesics

Analgesics are painkillers. They range from over-the-counter products to prescription medicines. For a subset of people with fibromyalgia, narcotic medications are prescribed for severe muscle pain. However, there is no solid evidence showing that for most people narcotics actually work to treat the chronic pain of fibromyalgia, and most doctors hesitate to prescribe them for long-term use because of the potential that the person taking them will become physically or psychologically dependent on them.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

As their name implies, nonsteroidal anti-inflammatory drugs, including aspirin, ibuprofen, and naproxen sodium, are used to treat inflammation.[3] Although inflammation is not a symptom of fibromyalgia, NSAIDs also relieve pain. The drugs work by inhibiting substances in the body called prostaglandins, which play a role in pain and inflammation. These medications, some of which are available without a prescription, may help ease the muscle aches of fibromyalgia. They may also relieve menstrual cramps and the headaches often associated with fibromyalgia.

---

[3] Warning: Side effects of NSAIDs include stomach problems; skin rashes; high blood pressure; fluid retention; and liver, kidney, and heart problems. The longer a person uses NSAIDs, the more likely he or she is to have side effects, ranging from mild to serious. Many other drugs cannot be taken when a patient is being treated with NSAIDs, because NSAIDs alter the way the body uses or eliminates these other drugs. Check with your health care provider or pharmacist before you take NSAIDs. NSAIDs should only be used at the lowest dose possible for the shortest time needed.

Complementary and Alternative Therapies

Many people with fibromyalgia also report varying degrees of success with complementary and alternative therapies, including massage, movement therapies (such as Pilates and the Feldenkrais method), chiropractic treatments, acupuncture, and various herbs and dietary supplements for different fibromyalgia symptoms. (For more information on complementary and alternative therapies, contact the National Center for Complementary and Alternative Medicine. See “Where Can People Find More Information About Fibromyalgia?”)

Although some of these supplements are being studied for fibromyalgia, there is little, if any, scientific proof yet that they help. FDA does not regulate the sale of dietary supplements, so information about side effects, proper dosage, and the amount of a preparation’s active ingredients may not be well known. If you are using or would like to try a complementary or alternative therapy, you should first speak with your doctor, who may know more about the therapy’s effectiveness, as well as whether it is safe to try in combination with your medications.

Will Fibromyalgia Get Better With Time?

Fibromyalgia is a chronic condition, meaning it lasts a long time—possibly a lifetime. However, it may be comforting to know that fibromyalgia is not a progressive disease. It is never fatal, and it will not cause damage to the joints, muscles, or internal organs. In many people, the condition does improve over time.

What Can I Do to Try to Feel Better?

Besides taking medicine prescribed by your doctor, there are many things you can do to minimize the impact of fibromyalgia on your life. These include:

- **Getting enough sleep.** Getting enough sleep and the right kind of sleep can help ease the pain and fatigue of fibromyalgia (see "Tips for Good Sleep"). Even so, many people with fibromyalgia have problems such as pain, restless legs syndrome, or brainwave irregularities that interfere with restful sleep. It is important to discuss any sleep problems with your doctor, who can prescribe or recommend treatment for them.
- **Exercising.** Although pain and fatigue may make exercise and daily activities difficult, it is crucial to be as physically active as possible. Research has repeatedly shown that regular exercise is one of the most effective treatments for fibromyalgia. People who have too much pain or fatigue to do vigorous exercise should begin with walking or other gentle exercise and build their endurance and intensity slowly.
- **Making changes at work.** Most people with fibromyalgia continue to work, but they may have to make big changes to do so. For example, some people cut down the number of hours they work, switch to a less demanding job, or adapt a current job. If you face obstacles at work, such as an uncomfortable desk chair that leaves your back aching or difficulty lifting heavy boxes or files, your employer may make adaptations that will enable you to keep your job. An occupational therapist can help you design a more comfortable workstation or find more efficient and less painful ways to lift.
- **Eating well.** Although some people with fibromyalgia report feeling better when they eat or avoid certain foods, no specific diet has been proven to influence fibromyalgia. Of course, it is important to have a healthy, balanced diet. Not only will proper nutrition give you more energy and make you

generally feel better, it will also help you avoid other health problems.

Tips for Good Sleep

- Keep regular sleep habits. Try to get to bed at the same time and get up at the same time every day—even on weekends and vacations.
- Avoid caffeine and alcohol in the late afternoon and evening. If consumed too close to bedtime, the caffeine in coffee, soft drinks, chocolate, and some medications can keep you from sleeping or sleeping soundly. Even though it can make you feel sleepy, drinking alcohol around bedtime also can disturb sleep.
- Time your exercise. Regular daytime exercise can improve nighttime sleep. But avoid exercising within 3 hours of bedtime, which actually can be stimulating, keeping you awake.
- Avoid daytime naps. Sleeping in the afternoon can interfere with nighttime sleep. If you feel you cannot get by without a nap, set an alarm for 1 hour. When it goes off, get up and start moving.
- Reserve your bed for sleeping. Watching the late news, reading a suspense novel, or working on your laptop in bed can stimulate you, making it hard to sleep.
- Keep your bedroom dark, quiet, and cool.
- Avoid liquids and spicy meals before bed. Heartburn and late-night trips to the bathroom are not conducive to good

sleep.

- Wind down before bed. Avoid working right up to bedtime. Do relaxing activities, such as listening to soft music or taking a warm bath, that get you ready to sleep. (A warm bath also may soothe aching muscles.)

What Research Is Being Conducted on Fibromyalgia?

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) sponsors research that will improve scientists' understanding of the specific problems that cause or accompany fibromyalgia, in turn helping them develop better ways to diagnose, treat, and prevent this syndrome.

The research on fibromyalgia supported by the NIAMS covers a broad spectrum, ranging from basic laboratory research to studies of medications and interventions designed to encourage behaviors that reduce pain and change behaviors that worsen or perpetuate pain.

Following are descriptions of some of the promising research now being conducted:

Understanding pain. Research suggests that fibromyalgia is caused by a problem in how the body processes pain, or more precisely, a hypersensitivity to stimuli that normally are not painful. Therefore, several National Institutes of Health (NIH)-supported researchers are focusing on ways the body processes pain to better understand why people with fibromyalgia have increased pain sensitivity. These studies include:

- The establishment of a tissue bank of brain and spinal cord tissue to study fibromyalgia and to determine the extent to which chronic pain in fibromyalgia patients is associated with the activation of cells in the nervous system and the production of chemical messengers, called cytokines, that regulate immune cell function.

- The use of imaging methods to evaluate the status of central nervous system responses in patients diagnosed with fibromyalgia compared with those diagnosed with another chronic pain disorder and pain-free controls.
- An investigation to understand how the activation of immune cells from peripheral and central nervous system sources trigger a cascade of events leading to the activation of nerve cells, chronic pain, and the dysregulation of the effects of analgesic drugs against pain.
- An intensive evaluation of twins in which one of the pair has chronic widespread pain and the other does not, along with twins in which neither of the pair has chronic pain, to help researchers assess physiological similarities and differences in those with and without chronic pain and whether those differences are caused by genetics or environment.
- A study examining the use of cognitive behavioral therapy in pain patients, which researchers hope will advance their knowledge of the role of psychological factors in chronic pain as well as a new treatment option for fibromyalgia.
- The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative. The PROMIS initiative is researching and developing new ways to measure patient-reported outcomes (PROs), such as pain, fatigue, physical functioning, emotional distress, and social role participation that have a major impact on quality of life across a variety of chronic diseases. The goal of this initiative is to improve the reporting and quantification of changes in PROs. The NIAMS supports an effort to develop PROMIS specifically for use in patients with fibromyalgia.

Improving Symptoms. A better understanding of fibromyalgia and the mechanisms involved in chronic pain are enabling researchers to find effective treatments for it. Some of the most promising

lines of research in this area include the following:

- **Increasing exercise.** Although fibromyalgia is often associated with fatigue that makes exercise difficult, regular exercise has been shown to be one of the most beneficial treatments for the condition. Researchers are trying to determine whether increasing lifestyle physical activity (that is, adding more exercise such as walking up stairs instead of taking the elevator) throughout the day produces similar benefits to exercise for fibromyalgia, improving symptoms such as pain, fatigue, and tenderness. Scientists are also examining the potential mechanisms by which lifestyle physical activity might influence symptoms. Other research supported by the NIAMS is examining the effectiveness of a simplified form of Tai Chi on pain and other measures such as sleep quality, fatigue, anxiety, and depression.

  NIAMS-supported research is also examining ways to help people maintain helpful exercise programs. Because many people with fibromyalgia associate increased exercise with increased pain, doctors and therapists often have a difficult time getting patients to stick with their exercise program. The new research is examining patients' fears that cause them to avoid exercise as well as behavioral therapies to reduce fears and help them maintain exercise.

- **Improving sleep.** Researchers supported by the NIAMS are investigating ways to improve sleep for people with fibromyalgia whose sleep problems persist despite treatment with medications. One team has observed that fibromyalgia patients with persistent sleep problems share characteristics with people who have sleep-disordered breathing—a group of disorders, the most common of which is the obstructive sleep apnea, characterized by pauses in breathing during sleep. These researchers are studying whether continuous positive

airway pressure (CPAP, a therapy administered by a machine that increases air pressure in the throat to hold it open during sleep) might improve the symptoms of fibromyalgia.

Other groups of researchers are examining the link between sleep disturbance and chronic pain in fibromyalgia and are studying whether behavioral therapy for insomnia might improve fibromyalgia symptoms.

More information on research is available from the following resources:

- **National Institutes of Health (NIH) Clinical Research Trials and You** was designed to help people learn more about clinical trials, why they matter, and how to participate. Visitors to the website will find information about the basics of participating in a clinical trial, first-hand stories from clinical trial volunteers, explanations from researchers, and links on how to search for a trial or enroll in a research-matching program.
- **ClinicalTrials.gov** offers up-to-date information for locating federally and privately supported clinical trials for a wide range of diseases and conditions.
- **NIH RePORTER** is an electronic tool that allows users to search a repository of both intramural and extramural NIH-funded research projects from the past 25 years and access publications (since 1985) and patents resulting from NIH funding.
- **PubMed** is a free service of the U.S. National Library of Medicine that lets you search millions of journal citations and abstracts in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Where Can People Find More Information About Fibromyalgia?

National Institute of Arthritis and Musculoskeletal and Skin Diseases

(NIAMS)
Information Clearinghouse
National Institutes of Health

1 AMS Circle
Bethesda, MD 20892-3675
Phone: 301-495-4484
Toll free: 877-22-NIAMS (877-226-4267)
TTY: 301-565-2966
Fax: 301-718-6366
Email: NIAMSinfo@mail.nih.gov
Website: https://www.niams.nih.gov

If you need more information about available resources in your language or another language, please visit our website or contact the NIAMS Information Clearinghouse at NIAMSinfo@mail.nih.gov.

Other Resources

National Center for Complementary and Integrative Health
National Institutes of Health

Website: https://nccih.nih.gov/

American College of Rheumatology

Website: http://www.rheumatology.org

Advocates for Fibromyalgia Funding, Treatment, Education, and Research

Website: http://www.affter.org

Fibromyalgia Network

Website: http://www.fmnetnews.com

National Fibromyalgia Association

Website: http://www.fmaware.org

National Fibromyalgia Partnership, Inc.

Website: http://www.fmpartnership.org

Arthritis Foundation

Website: http://www.arthritis.org

Key Words

Adrenal glands. A pair of endocrine glands located on the surface of the kidneys. The adrenal glands produce corticosteroid hormones such as cortisol, aldosterone, and the reproductive hormones.

Analgesic. A medication or treatment that relieves pain.

Arthritis. Literally means joint inflammation but is often used to indicate a group of more than 100 rheumatic diseases. These diseases affect not only the joints but also other connective tissues of the body, including important supporting structures such as muscles, tendons, and ligaments, as well as the protective covering of internal organs.

Chronic disease. An illness that lasts for a long time, often a lifetime.

Connective tissue. The supporting framework of the body and its internal organs.

Cortisol. A hormone produced by the adrenal cortex, important for normal carbohydrate metabolism and for a healthy response to stress.

Fibromyalgia. A chronic syndrome that includes a history of widespread pain lasting more than 3 months and other general physical symptoms including fatigue, waking unrefreshed, and cognitive (memory or thought) problems.

Fibrous capsule. A tough wrapping of tendons and ligaments that surrounds the joint.

Inflammation. A characteristic reaction of tissues to injury or disease. It is marked by four signs: swelling, redness, heat, and pain. Inflammation is not a symptom of fibromyalgia.

Joint. A junction where two bones meet. Most joints are composed of cartilage, joint space, fibrous capsule, synovium, and ligaments.

Ligaments. Bands of cordlike tissue that connect bone to bone.

Muscle. A structure composed of bundles of specialized cells that, when stimulated by nerve impulses, contract and produce movement.

Nonsteroidal anti-inflammatory drugs (NSAIDs). A group of drugs, such as aspirin and aspirin-like drugs, used to reduce inflammation that causes joint pain, stiffness, and swelling.

Pituitary gland. A pea-sized gland attached beneath the hypothalamus at the base of the

skull that secretes many hormones essential to bodily functioning. The secretion of pituitary hormones is regulated by chemicals produced in the hypothalamus.

Sleep disorder. A disorder in which a person has difficulty achieving restful, restorative sleep. In addition to other symptoms, people with fibromyalgia usually have a sleep disorder.

Tendons. Fibrous cords that connect muscle to bone.

Acknowledgments

The NIAMS gratefully acknowledges the assistance of the following individuals in the preparation and review of the original version of this publication: Deborah Ader, Ph.D., formerly with NIAMS/NIH; Karen Amour and Lynne Matallana, National Fibromyalgia Association, Anaheim, CA; Michele L. Boutaugh, M.P.H., Arthritis Foundation, Atlanta, GA; Daniel Clauw, M.D., University of Michigan, Ann Arbor, MI; and Leslie Crofford, M.D., University of Kentucky College of Medicine, Lexington, KY; and Tamara Liller, National Fibromyalgia Partnership, Linden, VA.

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the U.S. Department of Health and Human Services' National Institutes of Health (NIH), is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases. The NIAMS Information Clearinghouse is a public service sponsored by the NIAMS that provides health information and information sources. Additional information can be found on the NIAMS website at www.niams.nih.gov.

For Your Information

This publication contains information about medications used to treat the health condition discussed here. When this publication was developed, we included the most up-to-date (accurate) information available. Occasionally, new information on medication is released.

For updates and for any questions about any medications you are taking, please contact

U.S. Food and Drug Administration

Toll free: 888-INFO-FDA (888-463-6332)
Website: http://www.fda.gov

For additional information on specific medications, visit Drugs@FDA at http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Drugs@FDA is a searchable catalog of FDA-approved drug products.

For updates and questions about statistics, please contact

Centers for Disease Control and Prevention, National Center for Health Statistics

Website: http://www.cdc.gov/nchs

Additional copies of this publication are available from:

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Information Clearinghouse
National Institutes of Health

1 AMS Circle
Bethesda, MD 20892-3675
Phone: 301-495-4484
Toll free: 877-22-NIAMS (877-226-4267)
TTY: 301-565-2966
Fax: 301-718-6366
Email: NIAMSinfo@mail.nih.gov
Website: https://www.niams.nih.gov

NIH Publication No. 14–5326

Micromedex Consumer Medication Information.

Published: October 1, 2016

Duloxetine (By mouth)

doo-LOX-e-teen

Treats depression, anxiety, diabetic peripheral neuropathy, fibromyalgia, and chronic muscle or bone pain. This medicine is an SSNRI.

Uses

Uses of This Medicine

Duloxetine is used to treat depression and anxiety. It is also used for pain caused by nerve damage associated with diabetes (diabetic peripheral neuropathy).

Duloxetine is also used to treat fibromyalgia (muscle pain and stiffness) and chronic (long-lasting) pain that is related to muscles and bones.

Duloxetine belongs to a group of medicines known as selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). These medicines are thought to work by increasing the activity of chemicals called serotonin and norepinephrine in the brain.

This medicine is available only with your doctor's prescription.

Other uses (PubMed Health)

How To Use

Capsule, Delayed Release Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Delayed-release capsule: Swallow the capsule whole. Do not crush, chew, break, or open it.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not take duloxetine if you have used an MAO inhibitor (MAOI) within the past 14 days. Do not start taking an MAO inhibitor within 5 days of stopping duloxetine.

Some medicines can affect how duloxetine works. Tell your doctor if you are using any of the following:

- Buspirone, fentanyl, lithium, St John's wort, tramadol, tryptophan, or warfarin
- Diuretic (water pill)
- Medicine for heart rhythm problems (including flecainide, propafenone, quinidine)

Contents

What works?

Learn more about the effects of these drugs. The most reliable research is summed up for you in our featured article.

Featured article »

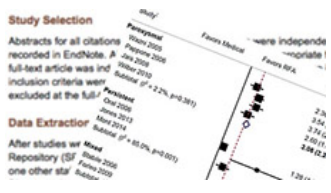
Things you need to know

Approved drug uses

More information about a drug

Tips about using medicines

PubMed Health Blog...



New Research Methods Resources - Plus a PubMed Filter

If you're interested in the scientific methods behind systematic reviews, we've now made it easier for you to...

read all...

- Triptan medicine to treat migraine headaches
- NSAID pain or arthritis medicine (including aspirin, celecoxib, diclofenac, ibuprofen, naproxen)
- Other medicine to treat depression or mood disorders (including desipramine, fluoxetine, paroxetine)
- Phenothiazine medicine (including chlorpromazine, perphenazine, prochlorperazine, promethazine, thioridazine)

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

When Not To Use

This medicine is not right for everyone. Do not use it if you had an allergic reaction to duloxetine.

Warnings

Tell your doctor if you are pregnant or breastfeeding, or if you have kidney disease, liver disease, diabetes, digestion problems, glaucoma, heart disease, high or low blood pressure, or problems with urination. Tell your doctor if you have a history of seizures, or drug or alcohol addiction.

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of bipolar disorder or suicide attempts.

This medicine may cause the following problems:

- Serious liver problems
- A serious drug reaction called serotonin syndrome (more likely when used with certain other medicines)
- Increased risk of bleeding problems
- Serious skin reactions
- Low sodium levels in the blood

This medicine can cause changes in your blood pressure. This may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you. Stand up slowly to avoid falls.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible side effects

Summary More details

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Blistering, peeling, red skin rash

Confusion, weakness, muscle twitching

Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes

Decrease in how much or how often you urinate

Eye pain, vision changes, seeing halos around lights

Feeling more energetic than usual

Lightheadedness, dizziness, or fainting

Restlessness, fever, fast heartbeat, sweating, muscle spasms, diarrhea, seeing or hearing things that are not there

Unusual moods or behaviors, worsening depression, thoughts about hurting yourself, trouble sleeping

Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Decrease in appetite or weight

Dry mouth, constipation, mild nausea

Unusual drowsiness or tiredness

If you notice other side effects that you think are caused by this medicine, tell your doctor.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

More side effects of this drug

Brand names include

Cymbalta, Irenka

There may be other brand names for this medicine.

More detailed version of this drug page

URL of this page: https://medlineplus.gov/druginfo/meds/a604030.html

Duloxetine

pronounced as (doo lox' e teen)

IMPORTANT WARNING:

A small number of children, teenagers, and young adults (up to 24 years of age) who took antidepressants ("mood elevators") such as duloxetine during clinical studies became suicidal (thinking about harming or killing oneself or planning or trying to do so). Children, teenagers, and young adults who take antidepressants to treat depression or other mental illnesses may be more likely to become suicidal than children, teenagers, and young adults who do not take antidepressants to treat these conditions. However, experts are not sure about how great this risk is and how much it should be considered in deciding whether a child or teenager should take an antidepressant. Children younger than 18 years of age should not normally take duloxetine, but in some cases, a doctor may decide that duloxetine is the best medication to treat a child's condition.

You should know that your mental health may change in unexpected ways when you take duloxetine or other antidepressants even if you are an adult over 24 years of age. These changes may occur even if you do not have a mental illness and you are taking duloxetine to treat a different type of condition. You may become suicidal, especially at the beginning of your treatment and any time that your dose is increased or decreased. You, your family, or caregiver should call your doctor right away if you experience any of the following symptoms: new or worsening depression; thinking about harming or killing yourself, or planning or trying to do so; extreme worry; agitation; panic attacks; difficulty falling asleep or staying asleep; aggressive or hostile behavior; irritability; acting without thinking; severe restlessness; frenzied abnormal excitement; or any other unusual changes in behavior. Be sure that your family or caregiver checks on you daily and knows which symptoms may be serious so they can call the doctor if you are unable to seek treatment on your own.

Your healthcare provider will want to see you often while you are taking duloxetine, especially at the beginning of your treatment. Be sure to keep all appointments for office visits with your doctor.

The doctor or pharmacist will give you the manufacturer's patient information sheet (Medication Guide) when you begin treatment with duloxetine. Read the information carefully and ask your doctor or pharmacist if you have any questions. You also can obtain the Medication Guide from the FDA website: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273 [http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273] .

No matter your age, before you take an antidepressant, you, your parent, or your caregiver should talk to your doctor about the risks and benefits of treating your condition with an antidepressant or with other treatments. You should also talk about the risks and benefits of not treating your condition. You should know that having depression or another mental illness greatly increases the risk that you will become suicidal. This risk is higher if you or anyone in your family has or has ever had bipolar disorder (mood that changes from depressed to abnormally excited) or mania (frenzied, abnormally excited mood), depression, or has thought about or attempted suicide. Talk to your doctor about your condition, symptoms, and personal and family medical history. You and your doctor will decide what type of treatment is right for you.

Why is this medication prescribed?

Duloxetine is used to treat depression and generalized anxiety disorder (GAD; excessive worry and tension that disrupts daily life and lasts for 6 months or longer). Duloxetine is also used to treat pain and tingling caused by diabetic neuropathy (damage to nerves that can develop in people who have diabetes) and fibromyalgia (a long-lasting condition that may cause pain, muscle stiffness and tenderness, tiredness, and difficulty falling asleep or staying asleep). Duloxetine is also used to treat ongoing bone or muscle pain such as lower back pain or osteoarthritis (joint pain or stiffness that may worsen over time). Duloxetine is in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). It works by increasing the amounts of serotonin and norepinephrine, natural substances in the brain that help maintain mental balance and stop the movement of pain signals in the brain.

How should this medicine be used?

Duloxetine comes as a delayed-release (releases the medication in the intestine to prevent break-down of the medication by stomach acids) capsule to take by mouth. When duloxetine is used to treat depression, it is usually taken once or twice a day with or without food. When duloxetine is used to treat generalized anxiety disorder, the pain of diabetic neuropathy, fibromyalgia, or ongoing bone or muscle pain, it is usually taken once a day with or without food. Take duloxetine at around the same time(s) every day. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not

understand. Take duloxetine exactly as directed. Do not take more or less of it, take it more often, or take it for a longer time than prescribed by your doctor.

Swallow the delayed-release capsules whole; do not split, chew, or crush them. Do not open the delayed-release capsules and mix the contents with liquids or sprinkle the contents on food.

Your doctor may start you on a low dose of medication and increase your dose after one week.

Duloxetine may help control your symptoms but will not cure your condition. It may take 1 to 4 weeks or longer before you feel the full benefit of duloxetine. Continue to take duloxetine even if you feel well. Do not stop taking duloxetine without talking to your doctor. Your doctor will probably decrease your dose gradually. If you suddenly stop taking duloxetine, you may experience withdrawal symptoms such as nausea; vomiting; diarrhea; anxiety; dizziness; tiredness; headache; pain, burning, numbness, or tingling in the hands or feet; irritability; difficulty falling asleep or staying asleep; sweating; and nightmares. Tell your doctor if you experience any of these symptoms when your dose of duloxetine is decreased.

Other uses for this medicine

Duloxetine is also sometimes used to treat stress urinary incontinence (leakage of urine during physical activity such as coughing, sneezing, laughing, and exercise) in women. Talk to your doctor about using this medication to treat your condition.

This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

What special precautions should I follow?

Before taking duloxetine,

- tell your doctor and pharmacist if you are allergic to duloxetine, any other medications, or any of the ingredients in duloxetine delayed-release capsules. Ask your doctor or pharmacist for a list of the ingredients.
- tell your doctor if you are taking thioridazine or a monoamine oxidase (MAO) inhibitor, such as isocarboxazid (Marplan), linezolid (Zyvox); methylene blue; phenelzine (Nardil), selegiline (Eldepryl, Emsam, Zelapar), and tranylcypromine (Parnate), or if you have stopped taking an MAO inhibitor within the past 14 days. Your doctor will probably tell you not to take duloxetine. If you stop taking duloxetine, you should wait at least 5 days before you start to take an MAO inhibitor.
- tell your doctor and pharmacist what other prescription and nonprescription medications and vitamins you are taking or plan to take. Be sure to mention any of the following: anticoagulants ('blood thinners') such as warfarin (Coumadin, Jantoven); antidepressants

such as amitriptyline (Elavil), amoxapine (Asendin), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Adapin, Sinequan), imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil); antihistamines; aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn); buspirone; cimetidine (Tagamet); diuretics ('water pills'); fentanyl (Abstral, Actiq, Fentora, Onsolis, others); medications for irregular heartbeat such as amiodarone (Cordarone), flecainide (Tambocor), moricizine (Ethmozine), propafenone (Rythmol), and quinidine (Quinidex); medications for anxiety, high blood pressure, mental illness, pain, and nausea; propranolol (Inderal); medications for migraine headaches such as almotriptan (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), and zolmitriptan (Zomig); lithium (Eskalith, Lithobid); proton pump inhibitors such as lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex); quinolone antibiotics such as ciprofloxacin (Cipro) and enoxacin (Penetrex); sedatives; certain selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox) and paroxetine (Paxil); sibutramine (Meridia); sleeping pills; theophylline (Theochron, Theolair); tramadol (Ultram); and tranquilizers. Many other medications may interact with duloxetine, so be sure to tell your doctor about all the medications you are taking, even those that do not appear on this list. Your doctor may need to change the doses of your medications or monitor you carefully for side effects.

- tell your doctor what nutritional supplements and herbal products you are taking, especially products containing St. John's wort or tryptophan.
- tell your doctor if you drink or have ever drunk large amounts of alcohol or if you use or have ever used street drugs or have ever overused prescription medications. Also tell your doctor if you have or have ever had a heart attack; high blood pressure; seizures; coronary artery disease (blockage or narrowing of the blood vessels that lead to the heart); or heart, liver, or kidney disease. If you have diabetes, be sure to talk to your doctor about how serious your condition is so your doctor can decide if duloxetine is right for you.
- tell your doctor if you are pregnant, especially if you are in the last few months of your pregnancy, or if you plan to become pregnant or are breast-feeding. If you become pregnant while taking duloxetine, call your doctor. Duloxetine may cause problems in newborns following delivery if it is taken during the last months of pregnancy.
- if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking duloxetine.
- you should know that duloxetine may make you drowsy, dizzy, or may affect your judgment, thinking or coordination. Do not drive a car or operate machinery until you know how this medication affects you.
- ask your doctor about the safe use of alcoholic beverages while you are taking duloxetine. Alcohol can increase the risk of serious side effects from duloxetine.
- you should know that duloxetine may cause dizziness, lightheadedness, and fainting when you get up too quickly from a lying position. This is more common when you first start taking duloxetine or with an increase in dose. To avoid this problem, get out of bed slowly, resting your feet on the floor for a few minutes before standing up.

- you should know that duloxetine may cause high blood pressure. You should have your blood pressure checked before starting treatment and regularly while you are taking this medication.
- you should know that duloxetine may cause angle-closure glaucoma (a condition where the fluid is suddenly blocked and unable to flow out of the eye causing a quick, severe increase in eye pressure which may lead to a loss of vision). Talk to your doctor about having an eye examination before you start taking this medication. If you have nausea, eye pain, changes in vision, such as seeing colored rings around lights, and swelling or redness in or around the eye, call your doctor or get emergency medical treatment right away.

What special dietary instructions should I follow?

Unless your doctor tells you otherwise, continue your normal diet.

What should I do if I forget a dose?

Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

What side effects can this medication cause?

Duloxetine may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- nausea
- vomiting
- constipation
- diarrhea
- heartburn
- stomach pain
- decreased appetite
- dry mouth
- increased urination
- difficulty urinating
- sweating or night sweats
- dizziness
- headache

- tiredness
- weakness
- drowsiness
- muscle pain or cramps
- changes in sexual desire or ability
- uncontrollable shaking of a part of the body

Some side effects can be serious. If you experience any of the following side effects, or those mentioned in the IMPORTANT WARNING or SPECIAL PRECAUTIONs section, call your doctor immediately or get emergency medical treatment:

- unusual bruising or bleeding
- pain in the upper right part of the stomach
- swelling of the abdomen
- itching
- yellowing of the skin or eyes
- dark colored urine
- loss of appetite
- extreme tiredness or weakness
- confusion
- flu-like symptoms
- fever, sweating, confusion, fast or irregular heartbeat, and severe muscle stiffness
- fever
- blisters or peeling skin
- rash
- hives
- difficulty breathing or swallowing
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness

Duloxetine may cause other side effects. Call your doctor if you have any unusual problems

while taking this medication.

If you experience a serious side effect, you or your doctor may send a report to the Food and Drug Administration's (FDA) MedWatch Adverse Event Reporting program online (http://www.fda.gov/Safety/MedWatch [http://www.fda.gov/Safety/MedWatch]) or by phone (1-800-332-1088).

What should I know about storage and disposal of this medication?

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom).

Unneeded medications should be disposed of in special ways to ensure that pets, children, and other people cannot consume them. However, you should not flush this medication down the toilet. Instead, the best way to dispose of your medication is through a medicine take-back program. Talk to your pharmacist or contact your local garbage/recycling department to learn about take-back programs in your community. See the FDA's Safe Disposal of Medicines website (http://goo.gl/c4Rm4p [http://goo.gl/c4Rm4p]) for more information if you do not have access to a take-back program.

In case of emergency/overdose

In case of overdose, call your local poison control center at 1-800-222-1222. If the victim has collapsed or is not breathing, call local emergency services at 911.

Symptoms of overdose may include the following:

- agitation
- hallucinating (seeing things or hearing voices that do not exist)
- fast heartbeat
- fever
- loss of coordination
- nausea
- vomiting
- diarrhea
- drowsiness
- seizures
- dizziness

- lightheadedness
- fainting
- unresponsiveness

What other information should I know?

Keep all appointments with your doctor.

Do not let anyone else take your medication. Ask your pharmacist any questions you have about refilling your prescription.

It is important for you to keep a written list of all of the prescription and nonprescription (over-the-counter) medicines you are taking, as well as any products such as vitamins, minerals, or other dietary supplements. You should bring this list with you each time you visit a doctor or if you are admitted to a hospital. It is also important information to carry with you in case of emergencies.

Brand names

- Cymbalta ®

Last Revised - 05/15/2016

Fibromyalgia

Treatments and drugs

By Mayo Clinic Staff

In general, treatments for fibromyalgia include both medication and self-care. The emphasis is on minimizing symptoms and improving general health. No one treatment works for all symptoms.

Medications

Medications can help reduce the pain of fibromyalgia and improve sleep. Common choices include:

- **Pain relievers.** Over-the-counter pain relievers such as acetaminophen (Tylenol, others), ibuprofen (Advil, Motrin IB, others) or naproxen sodium (Aleve, others) may be helpful.

Your doctor might suggest a prescription pain reliever such as tramadol (Ultram, Conzip). Narcotics are not advised, because they can lead to dependence and may even worsen the pain over time.

- **Antidepressants.** Duloxetine (Cymbalta) and milnacipran (Savella) may help ease the pain and fatigue associated with fibromyalgia. Your doctor may prescribe amitriptyline at night to help promote sleep.
- **Anti-seizure drugs.** Medications designed to treat epilepsy are often useful in reducing certain types of pain. Gabapentin (Neurontin, Gralise) is sometimes helpful in reducing fibromyalgia symptoms, while pregabalin (Lyrica) was the first drug approved by the Food and Drug Administration to treat fibromyalgia.

Therapy

Talking with a counselor can help strengthen your belief in your abilities and teach you strategies for dealing with stressful situations.

← Tests and diagnosis

Lifestyle and home remedies →

Share Tweet

Sept. 08, 2016

References

See also

Antidepressant withdrawal: Is there such a thing?

Antidepressants and alcohol

Antidepressants and weight gain: What causes it?

Antidepressants: Can they stop working?

Antidepressants: Side effects

Antidepressants: Selecting one

Atypical antidepressants

Show more

Other Topics in Patient Care & Health Info

Healthy Lifestyle

Symptoms A-Z

Diseases and Conditions A-Z

Tests and Procedures A-Z

Drugs and Supplements A-Z

Appointments

Patient and Visitor Guide

Billing and Insurance

Patient Online Services

Micromedex Consumer Medication Information.

Published: October 1, 2016

Milnacipran (By mouth)

mil-NA-si-pran

Treats fibromyalgia. This medicine is an SSNRI.

Drug classes

Central Nervous System Agent (About this - PubMed Health)

Uses

Uses of This Medicine

Milnacipran is used to treat a condition called fibromyalgia, which causes muscle pain and stiffness.

Milnacipran belongs to a group of medicines known as selective serotonin and norepinephrine reuptake inhibitors (SNRIs). These medicines work by increasing the activity of certain chemicals in the brain called serotonin and norepinephrine.

This medicine is available only with your doctor's prescription.

Other uses (PubMed Health)

How To Use

Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Missed dose: If you miss a dose, skip the missed dose and take your next dose at your regularly scheduled time.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine if you have used an MAO inhibitor (MAOI) within the past 14 days. Do not take an MAOI for at least 5 days after stopping this medicine.

Tell your doctor if you are using any of the following:

- Buspirone, clomipramine, clonidine, digoxin, epinephrine, fentanyl, lithium, norepinephrine, St John's wort, tramadol
- Blood thinner (including warfarin)
- Diuretic (water pill)
- Triptans (medicine used to treat migraine headaches)
- NSAID pain or arthritis medicine (including aspirin, celecoxib, ibuprofen, naproxen)
- Tricyclic antidepressants or other medicine to treat depression
- Tryptophan supplements

.

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

When Not To Use

This medicine is generally considered safe for most people. Talk to your doctor if you have concerns.

Warnings

Tell your doctor if you are pregnant or breastfeeding, or if you have kidney disease, liver disease, heart disease, heart rhythm problems, high blood pressure, glaucoma, an enlarged prostate, or a history of painful or difficult urination. Also tell your doctor if you have a history of seizures, or if you drink alcohol.

This medicine may cause the following problems:

- Serotonin syndrome (more likely when used with certain other medicines)
- High blood pressure
- Liver problems
- Hyponatremia (low sodium levels)
- Higher risk of bleeding problems (especially if used with a blood thinner or NSAID medicine)

For some children, teenagers, and young adults, this medicine may increase mental or emotional problems. This may lead to thoughts of suicide and violence. Talk with your doctor right away if you have any thoughts or behavior changes that concern you. Tell your doctor if you or anyone in your family has a history of bipolar disorder or suicide attempts.

This medicine may make you drowsy or less alert. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments. Your blood pressure and heart rate will also be monitored while you use this medicine.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible side effects

Summary More details

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there

Blistering, peeling, red skin rash

Confusion, weakness, and muscle twitching

Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes

Eye pain, vision changes, seeing halos around lights

Fast, pounding, or uneven heartbeat or pulse

Increased energy, racing thoughts, reckless behavior, talking more than usual

Seizures or tremors

Unusual behavior or thoughts about hurting yourself or others

Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Constipation, nausea, vomiting

Increased sweating

Mild headache, dizziness, trouble sleeping

Problems with urination or sex

Warmth or redness in your face, neck, arms, or upper chest

If you notice other side effects that you think are caused by this medicine, tell your doctor.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

More side effects of this drug

Brand names include

Savella, Savella Titration Pack

There may be other brand names for this medicine.

More detailed version of this drug page

MEDICATION GUIDE

LYRICA (LEER-i-kah)
(pregabalin)
Capsules, CV

LYRICA (LEER-i-kah)
(pregabalin)
Oral Solution, CV

Read this Medication Guide before you start taking LYRICA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about LYRICA, ask your healthcare provider or pharmacist.

What is the most important information I should know about LYRICA?

LYRICA may cause serious side effects including:

- **Serious, even life-threatening, allergic reactions**
- **Suicidal thoughts or actions**
- **Swelling of your hands, legs and feet**
- **Dizziness and sleepiness**

These serious side effects are described below:

1. **Serious, even life-threatening, allergic reactions.**

   Stop taking LYRICA and call your healthcare provider right away if you have any of these signs of a serious allergic reaction:
   - swelling of your face, mouth, lips, gums, tongue, throat or neck
   - trouble breathing
   - rash, hives (raised bumps) or blisters

2. **Like other antiepileptic drugs, LYRICA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

   If you have suicidal thoughts or actions, do not stop LYRICA without first talking to a healthcare

provider.

- Stopping LYRICA suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

3. **Swelling of your hands, legs and feet**. This swelling can be a serious problem for people with heart problems.

4. **Dizziness and sleepiness.**

   Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects you. Ask your healthcare provider about when it will be okay to do these activities.

What is LYRICA?

LYRICA is a prescription medicine used in adults, 18 years and older, to treat:

- pain from damaged nerves (neuropathic pain) that happens with diabetes
- pain from damaged nerves (neuropathic pain) that follows healing of shingles
- partial seizures when taken together with other seizure medicines
- fibromyalgia (pain all over your body)
- pain from damaged nerves (neuropathic pain) that follows spinal cord injury

LYRICA has not been studied in children under 18 years of age.

Who should not take LYRICA?

Do not take LYRICA if you are allergic to pregabalin or any of the ingredients in LYRICA.

See "What is the most important information I should know about LYRICA?" for the signs of an allergic reaction.

See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my healthcare provider before taking LYRICA?

Before taking LYRICA, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems or get kidney dialysis
- have heart problems including heart failure
- have a bleeding problem or a low blood platelet count
- have abused prescription medicines, street drugs, or alcohol in the past
- have ever had swelling of your face, mouth, tongue, lips, gums, neck, or throat (angioedema)
- plan to father a child. Animal studies have shown that pregabalin, the active ingredient in LYRICA, made male animals less fertile and caused sperm to change. Also, in animal studies, birth defects were seen in the offspring (babies) of male animals treated with pregabalin. It is not known if these problems can happen in people who take LYRICA.
- **are pregnant or plan to become pregnant. It is not known if LYRICA will harm your unborn baby.** You and your healthcare provider will decide if you should take LYRICA while you are pregnant.

- If you become pregnant while taking LYRICA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy. Information about the registry can also be found at the website, http://www.aedpregnancyregistry.org/.
- **are breastfeeding or plan to breastfeed. LYRICA passes into your breast milk. It is not known if Lyrica can harm your baby.** Talk to your healthcare provider about the best way to feed your baby if you take LYRICA. Breastfeeding is not recommended while taking LYRICA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- angiotensin converting enzyme (ACE) inhibitors, which are used to treat many conditions, including high blood pressure. You may have a higher chance for swelling and hives if these medicines are taken with LYRICA. See "What is the most important information I should know about LYRICA?"
- Avandia (rosiglitazone), Avandamet (contains rosiglitazone and metformin), or Actos (pioglitazone) for diabetes. You may have a higher chance of weight gain or swelling of your hands or feet if these medicines are taken with LYRICA. See "What are the possible side effects of LYRICA?"
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA.
- any medicines that make you sleepy

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your healthcare provider will tell you how much LYRICA to take and when to take it. Take LYRICA at the same times each day.
- LYRICA may be taken with or without food.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Do not stop taking LYRICA without talking to your healthcare provider. If you stop taking LYRICA suddenly you may have headaches, nausea, diarrhea, trouble sleeping, increased sweating, or you may feel anxious. If you have epilepsy and you stop taking LYRICA suddenly, you may have seizures more often. Talk with your healthcare provider about how to stop LYRICA slowly.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. Do not take two doses at the same time.
- If you take too much LYRICA, call your healthcare provider or poison control center, or go to the nearest emergency room right away.

What should I avoid while taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects you.**
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness.

What are the possible side effects of LYRICA?

LYRICA may cause serious side effects, including:

- See "What is the most important information I should know about LYRICA?"
- **muscle problems, muscle pain, soreness, or weakness**. If you have these symptoms, especially if you feel

sick and have a fever, tell your healthcare provider right away.
- **problems with your eyesight, including blurry vision.** Call your healthcare provider if you have any changes in your eyesight.
- **weight gain.** If you have diabetes, weight gain may affect the management of your diabetes. Weight gain can also be a serious problem for people with heart problems.
- **feeling "high"**

The most common side effects of LYRICA are:
- dizziness
- blurry vision
- weight gain
- sleepiness
- trouble concentrating
- swelling of hands and feet
- dry mouth

LYRICA caused skin sores in animal studies. Skin sores did not happen in studies in people. If you have diabetes, you should pay attention to your skin while taking LYRICA and tell your healthcare provider about any sores or skin problems.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of LYRICA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LYRICA?
- Store LYRICA capsules and oral solution at room temperature, 68°F to 77°F (20°C to 25°C) in its original package.
- Safely throw away any LYRICA that is out of date or no longer needed.
- **Keep LYRICA and all medicines out of the reach of children.**

General information about LYRICA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LYRICA for a condition for which it was not prescribed. Do not give LYRICA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about LYRICA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LYRICA that is written for health professionals.

You can also visit the LYRICA website at www.LYRICA.com or call 1-866-459-7422 (1-866-4LYRICA).

What are the ingredients in LYRICA?

Active ingredient: pregabalin

Inactive ingredients:

LYRICA capsules: lactose monohydrate, cornstarch, talc

Capsule shell: gelatin and titanium dioxide; Orange capsule shell: red iron oxide; White capsule shell: sodium lauryl sulfate, colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells.

Imprinting ink: shellac, black iron oxide, propylene glycol, potassium hydroxide.

LYRICA oral solution: methylparaben, propylparaben, monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545 and purified water.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by

Parke-Davis

Division of Pfizer Inc, NY, NY 10017

LAB-0299-13.0

March 2016

Fibromyalgia

Complications

By Mayo Clinic Staff

The pain and lack of sleep associated with fibromyalgia can interfere with your ability to function at home or on the job. The frustration of dealing with an often-misunderstood condition also can result in depression and health-related anxiety.

Risk factors

Preparing for your appointment

Sept. 08, 2016

References

See also

Depression and anxiety
Endometriosis: Risk factor for ovarian cancer?
Fibromyalgia and acupuncture

Subscribe to Housecall

Our general interest e-newsletter keeps you up to date on a wide variety of health topics.

Sign up now

Mayo Clinic Store

Check out these best-sellers and special offers on books and newsletters from Mayo Clinic.

The Essential Diabetes Book

The Menopause Solution — NEW!

Guide to Stress-Free Living

Mayo Clinic on Healthy Aging

The Mayo Clinic Diet Online

Other Topics in Patient Care & Health Info

- Healthy Lifestyle
- Symptoms A-Z
- Diseases and Conditions A-Z
- Tests and Procedures A-Z
- Drugs and Supplements A-Z
- Appointments
- Patient and Visitor Guide
- Billing and Insurance
- Patient Online Services

CON-20019243

the Terms and Conditions and Privacy Policy linked below.

Terms and Conditions
Privacy Policy
Notice of Privacy Practices

We comply with the HONcode standard for trustworthy health information: verify here.

Diseases and Conditions

Fibromyalgia

Symptoms

By Mayo Clinic Staff

Symptoms of fibromyalgia include:

- **Widespread pain.** The pain associated with fibromyalgia often is described as a constant dull ache that has lasted for at least three months. To be considered widespread, the pain must occur on both sides of your body and above and below your waist.
- **Fatigue.** People with fibromyalgia often awaken tired, even though they report sleeping for long periods of time. Sleep is often disrupted by pain, and many patients with fibromyalgia have other sleep disorders, such as restless legs syndrome and sleep apnea.
- **Cognitive difficulties.** A symptom commonly referred to as "fibro fog" impairs the ability to focus, pay attention and concentrate on mental tasks.
- **Other problems.** Many people who have fibromyalgia also may experience depression, headaches, and pain or cramping in the lower abdomen.

Subscribe to Housecall

Our general interest e-newsletter keeps you up to date on a wide variety of health topics.

Sign up now

← Definition

Causes →

Share Tweet

Sept. 08, 2016

Advertising & Sponsorship

Policy | Opportunities

References

See also

Depression: Diagnosis is key

Fatigue

Fibromyalgia or not?

Headache

Male depression

Nervous breakdown

Pain and depression: Is there a link?

Other Topics in Patient Care & Health Info

Healthy Lifestyle

Symptoms A-Z

Diseases and Conditions A-Z

Tests and Procedures A-Z

Drugs and Supplements A-Z

Appointments

Patient and Visitor Guide

Billing and Insurance

Patient Online Services

Last updated on: 6/28/2016 10:44:25 AM PST

25 Legal Medical Marijuana States and DC

Laws, Fees, and Possession Limits

Medical Marijuana Home

Featured Resources

1. Should Marijuana Be a Medical Option?
2. Top 10 Pros and Cons
3. Did You Know?
4. Historical Timeline
5. Comments

+Pros & Cons by Category

Projects

6. 25 Legal Medical Marijuana States and DC
7. Three States Considering Medical Marijuana Legalization
8. 16 States with Laws Specifically about Legal Cannabidiol (CBD)
9. Deaths from Marijuana v. 17 FDA-Approved Drugs
10. 60 Peer-Reviewed Studies on Medical Marijuana
11. Number of Legal Medical Marijuana Patients
12. Teen Marijuana Use
13. 10 Pharmaceutical Drugs Based on Cannabis
14. Opinion Polls/Surveys
15. Ranking 20 Drugs and Alcohol by Overall Harm
16. 11 US Surgeons General and Their Views on Medical Marijuana, 1961-Present
17. 2016 Presidential Candidates' Positions on Medical Marijuana

Learn More

18. Source Biographies
19. Glossary
20. Notices Archive
21. Site Map

+ Additional Resources

I. Summary Chart | II. Details by State | III. Sources

I. Summary Chart: 25 states and DC have enacted laws to legalize medical marijuana

State	Year Passed	How Passed (Yes Vote)	Possession Limit
1. Alaska	1998	Ballot Measure 8 (58%)	1 oz usable; 6 plants (3 mature, 3 immature)
2. Arizona	2010	Proposition 203 (50.13%)	2.5 oz usable; 12 plants
3. California	1996	Proposition 215 (56%)	8 oz usable; 6 mature or 12 immature plants
4. Colorado	2000	Ballot Amendment 20 (54%)	2 oz usable; 6 plants (3 mature, 3 immature)
5. Connecticut	2012	House Bill 5389 (96-51 H, 21-13 S)	2.5 oz usable
DC	2010	Amendment Act B18-622 (13-0 vote)	2 oz dried; limits on other forms to be determined
6. Delaware	2011	Senate Bill 17 (27-14 H, 17-4 S)	6 oz usable
7. Hawaii	2000	Senate Bill 862 (32-18 H; 13-12 S)	4 oz usable; 7 plants
8. Illinois	2013	House Bill 1 (61-57 H; 35-21 S)	2.5 ounces of usable cannabis during a period of 14 days
9. Maine	1999	Ballot Question 2 (61%)	2.5 oz usable; 6 plants
10. Maryland	2014	House Bill 881 (125-11 H; 44-2 S)	30-day supply, amount to be determined
11. Massachusetts	2012	Ballot Question 3 (63%)	60-day supply for personal medical use (10 oz)
12. Michigan	2008	Proposal 1 (63%)	2.5 oz usable; 12 plants
13. Minnesota	2014	Senate Bill 2470 (46-16 S; 89-40 H)	30-day supply of non-smokable marijuana
14. Montana	2004	Initiative 148 (62%)	1 oz usable; 4 plants (mature); 12 seedlings
15. Nevada	2000	Ballot Question 9 (65%)	2.5 oz usable; 12 plants
16. New Hampshire	2013	House Bill 573 (284-66 H; 18-6 S)	Two ounces of usable cannabis during a 10-day period
17. New Jersey	2010	Senate Bill 119 (48-14 H; 25-13 S)	2 oz usable
18. New Mexico	2007	Senate Bill 523 (36-31 H; 32-3 S)	6 oz usable; 16 plants (4 mature, 12 immature)
19. New York	2014	Assembly Bill 6357 (117-13 A; 49-10 S)	30-day supply non-smokable marijuana
20. Ohio	2016	House Bill 523 (71-26 H; 18-15 S)	Maximum of a 90-day supply, amount to be determined
21. Oregon	1998	Ballot Measure 67 (55%)	24 oz usable; 24 plants (6 mature, 18 immature)
22. Pennsylvania	2016	Senate Bill 3 (149-46 H; 42-7 S)	30-day supply
23. Rhode Island	2006	Senate Bill 0710 (52-10 H; 33-1 S)	2.5 oz usable; 12 plants
24. Vermont	2004	Senate Bill 76 (22-7) HB 645 (82-59)	2 oz usable; 9 plants (2 mature, 7 immature)
25. Washington	1998	Initiative 692 (59%)	24 oz usable; 15 plants

Why are some states not on this list? Our list includes states that have legalized use of the marijuana plant for medical purposes. States that limit use to the nonpsychoactive marijuana extract called cannabidiol (CBD) are not included on this list, although we do keep track of those legal CBD states in our resource States with Laws Specifically about Legal Cannabidiol (CBD). Also not included are states whose legalization laws require physicians to "prescribe" marijuana (an illegal act under federal law) vs. "recommend" marijuana (considered protected free speech between doctor and patient), as well as states that have passed "affirmative defense" laws in which arrested marijuana users are allowed to mention medical use in their defense.

Notes: (click to expand)

1. Residency Requirement

II. Details by State: 25 states and DC that have enacted laws to legalize medical marijuana	
State and Relevant Medical Marijuana Laws	**Contact and Program Details**
1. Alaska **Ballot Measure 8** -- Approved Nov. 3, 1998 by 58% of voters **Effective:** Mar. 4, 1999 Removed state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess written documentation from their physician advising that they "might benefit from the medical use of marijuana." **Approved Conditions:** Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV or AIDS, multiple sclerosis and other disorders characterized by muscle spasticity, and nausea. Other conditions are subject to approval by the Alaska Department of Health and Social Services. **Possession/Cultivation:** Patients (or their primary caregivers) may legally possess no more than one ounce of usable marijuana, and may cultivate no more than six marijuana plants, of which no more than three may be mature. The law establishes a confidential state-run patient registry that issues identification cards to qualifying patients. **Amended**: **Senate Bill 94** **Effective:** June 2, 1999 Mandates all patients seeking legal protection under this act to enroll in the state patient registry and possess a valid identification card. Patients not enrolled in the registry will no longer be able to argue the "affirmative defense of medical necessity" if they are arrested on marijuana charges. **Update:** Alaska Statute Title 17 Chapter 37 Creates a confidential statewide registry of medical marijuana patients and caregivers and establishes identification card.	**Alaska Bureau of Vital Statistics** Marijuana Registry P.O. Box 110699 Juneau, AK 99811-0699 Phone: 907-465-5423 BVSSpecialServices@health.state.ak.us **Website:** AK Marijuana Registry Online **Information provided by the state on sources for medical marijuana:** No information is provided **Patient Registry Fee:** $25 new application/$20 renewal **Accepts other states' registry ID cards?** No **Registration:** Mandatory
2. Arizona **Ballot Proposition 203** "Arizona Medical Marijuana Act" -- Approved Nov. 2, 2010 by 50.13% of voters Allows registered qualifying patients (who must have a physician's written certification that they have been diagnosed with a debilitating condition and that they would likely receive benefit from marijuana) to obtain marijuana from a registered nonprofit dispensary, and to possess and use medical marijuana to treat the condition. Requires the Arizona Department of Health Services to establish a registration and renewal application system for patients and nonprofit dispensaries. Requires a web-based verification system for law enforcement and dispensaries to verify registry identification cards. Allows certification of a number of dispensaries not to exceed 10% of the number of pharmacies in the state (which would cap the number of dispensaries around 124). Specifies that a registered patient's use of medical marijuana is to be considered equivalent to the use of any other medication under the direction of a physician and does not disqualify a patient from medical care, including organ transplants.	**Arizona Department of Health Services (ADHS)** Medical Marijuana Program 150 North 18th Avenue Phoenix, Arizona 85007 Phone: 602-542-1025 **Website:** Arizona Medical Marijuana Program **Information provided by the state on sources for medical marijuana:** "Qualifying patients can obtain medical marijuana from a dispensary, the qualifying patient's designated caregiver, another qualifying patient, or, if authorized to cultivate, from home cultivation. When a qualifying patient obtains or renews a registry identification card, the Department will provide a list of all operating dispensaries to the qualifying patient." ADHS, "Qualifying Patients FAQs," Mar. 25, 2010 **Patient Registry Fee:** $150 / $75 for Supplemental Nutrition Assistance Program participants **Accepts other states' registry ID cards?** Yes, but does not permit visiting patients to obtain marijuana

Specifies that employers may not discriminate against registered patients unless that employer would lose money or licensing under federal law. Employers also may not penalize registered patients solely for testing positive for marijuana in drug tests, although the law does not authorize patients to use, possess, or be impaired by marijuana on the employment premises or during the hours of employment.

Approved Conditions: Cancer, glaucoma, HIV/AIDS, Hepatitis C, ALS, Crohn's disease, Alzheimer's disease, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms (including multiple sclerosis). Starting Jan.1, 2015, PTSD was added to the list.

Possession/Cultivation: Qualified patients or their registered designated caregivers may obtain up to 2.5 ounces of marijuana in a 14-day period from a registered nonprofit medical marijuana dispensary. If the patient lives more than 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.

Amended: Senate Bill 1443
Effective: Signed by Governor Jan Brewer on May 7, 2013
"Specifies the prohibition to possess or use marijuana on a postsecondary educational institution campus does not apply to medical research projects involving marijuana that are conducted on the campus, as authorized by applicable federal approvals and on approval of the applicable university institutional review board."

[**Editor's Note:** On Apr. 11, 2012, the Arizona Department of Health Services (ADHS) announced the revised rules for regulating medical marijuana and set the application dates for May 14 through May 25.

On Nov. 15, 2012, the first dispensary was awarded "approval to operate." ADHS Director Will Humble stated on his blog that, "[W]e'll be declining new 'requests to cultivate' among new cardholders in most of the metro area… because self-grow (12 plants) is only allowed when the patient lives more than 25 miles from the nearest dispensary. The vast majority of the Valley is within 25 miles of this new dispensary."

On Dec. 6, 2012, the state's first dispensary, Arizona Organix, opened in Glendale.]

from an Arizona dispensary

Registration:
Mandatory

3. California

Ballot Proposition 215 -- Approved Nov. 5, 1996 by 56% of voters
Effective: Nov. 6, 1996

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess a "written or oral recommendation" from their physician that he or she "would benefit from medical marijuana." Patients diagnosed with any debilitating illness where the medical use of marijuana has been "deemed appropriate and has been recommended by a physician" are afforded legal protection under this act.

Approved Conditions: AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms, including spasms associated with multiple sclerosis, seizures, including seizures associated with epilepsy, severe nausea; Other chronic or persistent medical symptoms.

Amended: Senate Bill 420
Effective: Jan. 1, 2004

Imposes statewide guidelines outlining how much medicinal marijuana patients may grow and possess.

Possession/Cultivation: Qualified patients and their primary caregivers may possess no more than eight ounces of dried marijuana and/or six mature (or 12 immature) marijuana plants. However, S.B. 420 allows patients to possess larger amounts of marijuana when recommended by a physician. The legislation also allows counties and municipalities to approve and/or maintain local ordinances permitting patients to possess larger quantities of medicinal pot than allowed under the new state guidelines.

California Department of Public Health
Public Health Policy and Research Branch
Attention: Medical Marijuana Program Unit
MS 5202
P.O. Box 997377
Sacramento, CA 95899-7377
Phone: 916-552-8600
Fax: 916-440-5591

mmpinfo@cdph.ca.gov

Website:
CA Medical Marijuana Program

Guidelines for the Security and Non-diversion of Marijuana Grown for Medical Use

Information provided by the state on sources for medical marijuana:
"The MMP is not authorized to provide information on acquiring marijuana or other related products."
"Medical Marijuana Program Frequently Asked Questions," cdph.ca.gov (accessed Mar. 1, 2016)

"The California Department of Public Health's MMP does not have jurisdiction over medical marijuana cooperatives, dispensaries, or collectives. For questions related to these areas, please contact your local city or county business licensing office."
"Medical Marijuana Identification Card Program," cdph.ca.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$66 non Medi-Cal / $33 Medi-Cal, plus additional county fees (varies by location)

Accepts other states' registry ID cards?

S.B. 420 also grants implied legal protection to the state's medicinal marijuana dispensaries, stating, "Qualified patients, persons with valid identification cards, and the designated primary caregivers of qualified patients ... who associate within the state of California in order collectively or cooperatively to cultivate marijuana for medical purposes, shall not solely on the basis of that fact be subject to state criminal sanctions."

Challenge to Possession Limits: On Jan. 21, 2010, the California Supreme Court affirmed (S164830) the May 22, 2008 Second District Court of Appeals ruling in the Kelly Case that the possession limits set by SB 420 violate the California constitution because the voter-approved Prop. 215 can only be amended by the voters.

ProCon.org contacted the California Medical Marijuana Program (MMP) on Dec. 6, 2010 to ask 1) how the ruling affected the implementation of the program, and 2) what instructions are given to patients regarding possession limits. A California Department of Public Health (CDPH) Office of Public Affairs representative wrote the following in a Dec. 7, 2010 email to ProCon.org: "The role of MMP under Senate Bill 420 is to implement the State Medical Marijuana ID Card Program in all California counties. CDPH does not oversee the amounts that a patient may possess or grow. When asked what a patient can possess, patients are referred to www.courtinfo.ca.gov, case S164830 which is the Kelly case, changing the amounts a patient can possess from 8 oz, 6 mature plants or 12 immature plants to 'the amount needed for a patient's personal use.' MMP can only cite what the law says."

According to a Jan. 21, 2010 article titled "California Supreme Court Further Clarifies Medical Marijuana Laws," by Aaron Smith, California Policy Director at the Marijuana Policy Project, the impact of the ruling is that people growing more than 6 mature or 12 immature plants are still subject to arrest and prosecution, but they will be allowed to use a medical necessity defense in court.]

Attorney General's Guidelines:
On Aug. 25, 2008, California Attorney General Jerry Brown issued guidelines for law enforcement and medical marijuana patients to clarify the state's laws. Read more about the guidelines here.

On Oct. 9, 2015, Gov. Jerry Brown signed three bills to regulate California's medical marijuana industry: AB 243, AB 266, and SB 643. The bills cover licensing requirements for cultivation, transportation, distribution, and more.

No

Registration:
Voluntary

4. Colorado

Ballot Amendment 20 -- Approved Nov. 7, 2000 by 54% of voters
Effective: June 1, 2001

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess written documentation from their physician affirming that he or she suffers from a debilitating condition and advising that they "might benefit from the medical use of marijuana." (Patients must possess this documentation prior to an arrest.)

Approved Conditions: Cancer, glaucoma, HIV/AIDS positive, cachexia; severe pain; severe nausea; seizures, including those that are characteristic of epilepsy; or persistent muscle spasms, including those that are characteristic of multiple sclerosis. Other conditions are subject to approval by the Colorado Board of Health.

Possession/Cultivation: A patient or a primary caregiver who has been issued a Medical Marijuana Registry identification card may possess no more than two ounces of a usable form of marijuana and not more than six marijuana plants, with three or fewer being mature, flowering plants that are producing a usable form of marijuana.

Patients who do not join the registry or possess greater amounts of marijuana than allowed by law may argue the "affirmative defense of medical necessity" if they are arrested on marijuana charges.

Amended: House Bill 1284 and Senate Bill 109
Effective: June 7, 2010

Medical Marijuana Registry
Colorado Department of Public Health and Environment
HSV-8608
4300 Cherry Creek Drive South
Denver, CO 80246-1530
Phone: 303-692-2184

medical.marijuana@state.co.us

Website:
CO Medical Marijuana Registry

Information provided by the state on sources for medical marijuana:
The Marijuana Enforcement Division (MED) website provides a list of licensed Medical Marijuana Centers, which are retail operations "from which Medical Marijuana Registry patients purchase Medical Marijuana and Medical Marijuana infused products." MED "is responsible for the regulation of both the Medical and Retail Marijuana industries, each of which have separate and distinct statute and rules under which they operate."
"Medical Marijuana Licensing Information," colorado.gov/revenue/med (accessed Feb. 26, 2014)
"Licensing Information," colorado.gov/revenue/med (accessed Feb. 26, 2014)

Patient Registry Fee:
$15

Accepts other states' registry ID cards?
No

Registration:
Mandatory

Colorado Governor Bill Ritter signed the bills into law and stated the following in a June 7, 2010 press release:

"House Bill 1284 provides a regulatory framework for dispensaries, including giving local communities the ability to ban or place sensible and much-needed controls on the operation, location and ownership of these establishments.

Senate Bill 109 will help prevent fraud and abuse, ensuring that physicians who authorize medical marijuana for their patients actually perform a physical exam, do not have a DEA flag on their medical license and do not have a financial relationship with a dispensary."

5. Connecticut

HB 5389 -- Signed into law by Gov. Dannel P. Malloy (D) on May 31, 2012
Approved: By House 96-51, by Senate 21-13
Effective: Some sections from passage (May 4, 2012), other sections on Oct. 1, 2012

"A qualifying patient shall register with the Department of Consumer Protection... prior to engaging in the palliative use of marijuana. A qualifying patient who has a valid registration certificate... shall not be subject to arrest or prosecution, penalized in any manner,... or denied any right or privilege."

Patients must be Connecticut residents at least 18 years of age. "Prison inmates, or others under the supervision of the Department of Corrections, would not qualify, regardless of their medical condition."

Approved Conditions: "Cancer, glaucoma, positive status for human immunodeficiency virus or acquired immune deficiency syndrome [HIV/AIDS], Parkinson's disease, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, wasting syndrome, Crohn's disease, posttraumatic stress disorder, or... any medical condition, medical treatment or disease approved by the Department of Consumer Protection..."

On Mar. 14, 2016, the Connecticut Department of Consumer Protection announced six new qualifying conditions: sickle cell disease, post laminectomy syndrome with chronic radiculopathy, severe psoriasis and psoriatic arthritis, amyotrophic lateral sclerosis, ulcerative colitis, and complex regional pain syndrome.

Possession/Cultivation: "The maximum allowable monthly amount is 2.5 ounces unless your physician indicates a lesser amount is appropriate."

Updates: The Connecticut Medical Marijuana Program website posted an update on Sep. 23, 2012 with instructions on how to register for the program starting on Oct. 1, 2012. "Patients who are currently receiving medical treatment for a debilitating medical conditions set out in the law may qualify for a temporary registration certificate beginning October 1, 2012. To qualify, a patient must also be at least 18 years of age and a Connecticut resident."

Draft Regulations on Medical Marijuana were posted on Jan. 16, 2013.

On Apr. 3, 2014, the Connecticut Department of Consumer Protection announced the names and locations of the first six dispensary facilities that will be authorized by the state. The first dispensary opened on Aug. 20, 2014.

Medical Marijuana Program
Department of Consumer Protection (DCP)
165 Capitol Avenue, Room 145
Hartford, CT 06106
Phone: 860-713-6066
Toll-Free: 800-842-2649

dcp.mmp@ct.gov

Website:
CT Medical Marijuana Program

Information provided by the state on sources for medical marijuana:
Connecticut's Medical Marijuana Program website has a list of six dispensary facilities.

Patient Registry Fee:
$100

Accepts other states' registry ID cards?
No

Registration:
Mandatory

DC (District of Columbia)

Amendment Act B18-622 "Legalization of Marijuana for Medical Treatment Amendment Act of 2010" -- Approved 13-0 by the Council of the District of Columbia on May 4, 2010; signed by the Mayor on May 21, 2010|

Effective: July 27, 2010 [After being signed by the Mayor, the law underwent a 30-day Congessional review period. Neither the Senate nor the House acted to stop the law, so it became effective when the review period ended.]

Health Regulation and Licensing Administration
899 N. Capitol Street, NE
2nd Floor
Washington, DC 20002
Phone: 202-442-5955

doh.mmp@dc.gov

Website:
Medical Marijuana Program

Information provided by the state on sources for medical

Approved Conditions: HIV, AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms, such as multiple sclerosis; patients undergoing chemotherapy or radiotherapy, or using azidothymidine or protease inhibitors.

Possession/Cultivation: "Patients are permitted to purchase up to two (2) ounces of dried medical marijuana per month or the equivalent of two ounces of dried medical marijuana when sold in any other form." ("Patient FAQ," doh.dc.gov, Mar. 1, 2016)

Updates: On Apr. 14, 2011, Mayor Vincent C. Gray announced the adoption of an emergency amendment to title 22 of the District of Columbia Municipal Regulations (DCMR), which added a new subtitle C entitled "Medical Marijuana." The emergency amendment "will set forth the process and procedure" for patients, caregivers, physicians, and dispensaries, and "implement the provisions of the Act that must be addressed at the onset to enable the Department to administer the program." The final rulemaking was posted online on Jan. 3, 2012.

On Feb. 14, 2012, the DC Department of Health's Health Regulation and Licensing Administration posted a revised timeline for the dispensary application process, which listed June 8, 2012 as the date by which the Department intends to announce dispensary applicants available for registration.

The first dispensary, Capital City Care, was licensed in Apr. 2013.

marijuana:
"A dispensary is a facility operated by an organization or business registered with the Department of Health... Patients are required to choose a single dispensary to register with...

Dispensaries and cultivation centers may dispense or distribute medical marijuana in any form deemed safe which allows patients to eat, inhale, or otherwise use medical marijuana for medical purposes. Medical marijuana will be subject to testing for quality assurance and safety purposes."
"Medical Marijuana Program Frequently Asked Questions," doh.dc.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$100 initial or renewal fee / $25 for low income patients

Accepts other states' registry ID cards?
No

Registration:
Mandatory

6. Delaware

Senate Bill 17 -- Signed into law by Gov. Jack Markell (D) on May 13, 2011
Approved: By House 27-14, by Senate 17-4
Effective: July 1, 2011

Under this law, a patient is only protected from arrest if his or her physician certifies, in writing, that the patient has a specified debilitating medical condition and that the patient would receive therapeutic benefit from medical marijuana. The patient must send a copy of the written certification to the state Department of Health and Social Services, and the Department will issue an ID card after verifying the information. As long as the patient is in compliance with the law, there will be no arrest.

The law does not allow patients or caregivers to grow marijuana at home, but it does allow for the state-regulated, non-profit distribution of medical marijuana by compassion centers.

Approved Conditions:
Approved for treatment of debilitating medical conditions, defined as cancer, HIV/AIDS, decompensated cirrhosis (Hepatitis C), ALS, Alzheimer's disease. Also approved for "a chronic or debilitating disease or medical condition or its treatment that produces 1 or more of the following: cachexia or wasting syndrome; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than 3 months or for which other treatment options produced serious side effects; intractable nausea; seizures; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis."

"Post-traumatic stress disorder (PTSD) can qualify as a debilitating medical condition when it manifests itself in severe physical suffering, such as severe or chronic pain or severe nausea and vomiting, or otherwise severely impairs the patient's physical ability to carry on the activities of daily living."
("Medical Marijuana Questions & Answers," dhss.delaware.gov (accessed Mar. 1, 2016))

Possession/Cultivation: Patients 18 and older with certain debilitating conditions may possess up to six ounces of marijuana with a doctor's written recommendation. A registered compassion center may not dispense more than 3 ounces of marijuana to a registered qualifying patient in any fourteen-day period, and a patient may register with only one compassion center. Home cultivation is not allowed. Senate Bill 17 contains a provision that allows for an affirmative defense for individuals "in possession of no more than six ounces of usable marijuana."

Updates: On Feb. 12, 2012, Gov. Markell released the following statement (presented in its entirety), available on delaware.gov,

Delaware Department of Health and Social Services
Division of Public Health
Phone: 302-744-4749
Fax: 302-739-3071

MedicalMarijuanaDPH@state.de.us

Website:
DE Medical Marijuana Program

Information provided by the state on sources for medical marijuana:
"The State currently recognizes properly permitted compassion centers as the only legal way to obtain marijuana."
"Medical Marijuana Questions & Answers," dhss.delaware.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$125 (a sliding scale fee is available based on income)

Accepts other states' registry ID cards?
No

Registration:
Mandatory

in response to a letter from US District Attorney Charles Oberly:

"I am very disappointed by the change in policy at the federal department of justice, as it requires us to stop implementation of the compassion centers. To do otherwise would put our state employees in legal jeopardy and I will not do that. Unfortunately, this shift in the federal position will stand in the way of people in pain receiving help. Our law sought to provide that in a manner that was both highly regulated and safe."

On Aug. 15, 2013, Gov. Markell announced in a letter to Delaware lawmakers his intention to relaunch the state's medical marijuana program, despite his previous decision to stop implementation. Markell wrote that the Department of Health and Social Services "will proceed to issue a request for proposal for a pilot compassion center to open in Delaware next year."

On June 23, 2015, Gov. Markell signed Rylie's Law, SB 90, which allows the use of non-smoked cannabis oil that is no more than 7% THC for minors with intractable epilepsy or dystonia.

On June 26, 2015, the state's first medical marijuana dispensary opened near Wilmington, Delaware.

7. Hawaii

Senate Bill 862 -- Signed into law by Gov. Ben Cayetano on June 14, 2000
Approved: By House 32-18, by Senate 13-12
Effective: Dec. 28, 2000

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess a signed statement from their physician affirming that he or she suffers from a debilitating condition and that the "potential benefits of medical use of marijuana would likely outweigh the health risks." The law establishes a mandatory, confidential state-run patient registry that issues identification cards to qualifying patients.

Approved conditions: Cancer, glaucoma, positive status for HIV/AIDS; A chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe pain, severe nausea, seizures, including those characteristic of epilepsy, or severe and persistent muscle spasms, including those characteristic of multiple sclerosis or Crohn's disease. PTSD added July 2015. Other conditions are subject to approval by the Hawaii Department of Health.

Possession/Cultivation: The amount of marijuana that may be possessed jointly between the qualifying patient and the primary caregiver is an "adequate supply," not to exceed seven plants and no more than four ounces of usable marijuana jointly between a registered patient and caregiver.

Amended: HB 668
Effective: June 25, 2013

Establishes a medical marijuana registry special fund to pay for the program and transfers the medical marijuana program from the Department of Public Safety to the Department of Public Health by no later than Jan. 1, 2015.

Amended: SB 642
Effective: Jan. 2, 2015

Redefines "adequate supply" as seven marijuana plants, whether immature or mature, and four ounces of usable marijuana at any given time; stipulates that physician recommendations will have to be made by the qualifying patient's primary care physician.

Amended: Act 241
Signed: July 14, 2015

Created "a regulated statewide dispensary system for medical marijuana" and added PTSD to list of conditions.

"The department shall issue eight dispensary licenses statewide... A dispensary licensee may establish up to two retail dispensing locations...

Department of Health
Medical Marijuana Program
4348 Waialae Avenue #648
Honolulu, Hawaii 96816
Phone: 808-733-2177

medicalmarijuana@doh.hawaii.gov

Website:
HI Medical Marijuana Registry Program

Information provided by the state on sources for medical marijuana:
"[A]s a registered program participant, and assuming that you indicated your intent to grow your own supply of medical marijuana on your application, you are allowed to grow an 'adequate supply' of medical marijuana, not to exceed seven (7) plants and posses no more than 4oz of usable marijuana jointly between a registered patient and caregiver...

Act 241 was signed into law on July 14, 2015... [tentatively on] July 15, 2016 – and not sooner, licensed dispensaries may begin dispensing from 8 AM – 8 PM and closed Sunday and state/federal holidays."
"Growing Medical Marijuana," health.hawaii.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$35

Accepts other states' registry ID cards?
No
(According to Act 241, beginning January 1, 2018: "qualifying patients from other states [will be accepted] provided that the patient is verified as a patient in their home state and registers with the department.")

Registration:
Mandatory

A qualifying patient or primary caregiver... shall be allowed to purchase no more than four ounces of marijuana within a consecutive period of fifteen days."

8. Illinois

House Bill 1
Approved: Apr. 17, 2013 by House, 61-57 and May 17, 2013 by Senate, 35-21
Signed into law by Gov. Pat Quinn on Aug. 1, 2013
Effective: Jan. 1, 2014

The Compassionate Use of Medical Cannabis Pilot Program Act establishes a patient registry program, protects registered qualifying patients and registered designated caregivers from "arrest, prosecution, or denial of any right or privilege," and allows for the registration of cultivation centers and dispensing organizations. Once the act goes into effect, "a tax is imposed upon the privilege of cultivating medical cannabis at a rate of 7% of the sales price per ounce."

Approved Conditions: "Debilitating medical conditions include 40 chronic diseases and conditions: cancer, glaucoma, positive status for human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, Rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and post concussion syndrome, Multiple Sclerosis, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Parkinson's Disease, Tourette Syndrome, Myoclonus, Dystonia, Reflex Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndrome Type II), Neurofibromatosis, Chronic inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's Syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome or residual limb pain; or the treatment of these conditions."
"Frequently Asked Questions," idph.state.il.us (accessed Apr. 23, 2014)

PTSD and terminal illness with a diagnosis of less than six months were added on July 1, 2016.

On July 20, 2014, Gov. Quinn signed Senate Bill 2636, which amended the Compassionate Use of Medical Cannabis Act to allow children under 18 to be treated with non-smokable forms of medical marijuana for the same conditions orginially approved for adults. An underage patient's parent or guardian must serve as caregiver, and signatures from two doctors are required. The bill, which becomes effective Jan. 1, 2015, also added seizures, including those related to epilepsy, to the list of approved conditions.

Possession/Cultivation: "Adequate supply" is defined as "2.5 ounces of usable cannabis during a period of 14 days and that is derived solely from an intrastate source." The law does not allow patients or caregivers to cultivate cannabis.

Updates: Governor Pat Quinn's Aug. 1, 2013 signing statement explains key points of the law and notes that it is a four-year pilot program.

On Jan. 21, 2014, the Department of Public Health released a draft of the proposed rules for public comments. The proposal included a fingerprint-based criminal history background check and an annual $150 application fee for qualifying patients. The rules also state that qualifying patients and caregivers "are not eligible for a Firearm Owners Identification Card or a Firearm Concealed Carry License."

On Apr. 18, 2014, the Department of Health released revised preliminary rules that removed from the previous versions the restrictions on gun owners applying for medical marijuana cards. The application fees were dropped to $100 ($50 for veterans and eligible patients on Social Security Insurance and Social Security Disability Insurance, and $25 for caregivers).

On July 1, 2016, Gov. Bruce Rauner (R) signed SB 10 into law, which extends the state's medical marijuana program through July 2020 and adds PTSD and terminal illness to the list

Illinois Department of Public Health
Division of Medical Cannabis
Illinois Department of Public Health
535 W. Jefferson Street
Springfield, IL 62761-0001
Attn: Rulemaking

DPH.MedicalCannabis@illinois.gov

Website:
Medical Cannabis Program

Information provided by the state on sources for medical marijuana:
"The first medical cannabis dispensary opened for business in Illinois on November 9, 2015. A total of twenty dispensaries were licensed in Illinois by December 31, 2015."
"Illinois Medical Cannabis Registry Pilot Program Mid-Year Report – January 2016," dph.illinois.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$100 / $50 for veterans or persons enrolled in federal Social Security Disability Income (SSDI) or Supplemental Security Income (SSI) disability programs

Accepts other states' registry ID cards?
No

Registration:
Mandatory

of approved conditions.

9. Maine

Ballot Question 2 -- Approved Nov. 2, 1999 by 61% of voters
Effective: Dec. 22, 1999

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess an oral or written "professional opinion" from their physician that he or she "might benefit from the medical use of marijuana." The law does not establish a state-run patient registry.

Approved diagnosis: Epilepsy and other disorders characterized by seizures; glaucoma; multiple sclerosis and other disorders characterized by muscle spasticity; nausea or vomiting as a result of AIDS or cancer chemotherapy; ant PTSD.

Possession/Cultivation: Patients (or their primary caregivers) may legally possess no more than one and one-quarter (1.25) ounces of usable marijuana, and may cultivate no more than six marijuana plants, of which no more than three may be mature. Those patients who possess greater amounts of marijuana than allowed by law are afforded a "simple defense" to a charge of marijuana possession.

Amended: Senate Bill 611
Effective: Signed into law on Apr. 2, 2002

Increases the amount of useable marijuana a person may possess from one and one-quarter (1.25) ounces to two and one-half (2.5) ounces.

Amended: Question 5 -- Approved Nov. 3, 2009 by 59% of voters

List of approved conditions changed to include cancer, glaucoma, HIV, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, Alzheimer's, nail-patella syndrome, chronic intractable pain, cachexia or wasting syndrome, severe nausea, seizures (epilepsy), severe and persistent muscle spasms, and multiple sclerosis.

Instructs the Department of Health and Human Services (DHHS) to establish a registry identification program for patients and caregivers. Stipulates provisions for the operation of nonprofit dispensaries.

[**Editor's Note:** An Aug. 19, 2010 email to ProCon.org from Catherine M. Cobb, Director of Maine's Division of Licensing and Regulatory Services, stated:

"We have just set up our interface to do background checks on caregivers and those who are associated with dispensaries. They may not have a disqualifying drug offense."]

Amended: LD 1062
Effective: Enacted without the governor's signature on June 26, 2013

Adds post-traumatic stress disorder (PTSD) to the list of approved conditions for medical marijuana use.

Maine Medical Use of Marijuana Program (MMMP)
Division of Licensing and Regulatory Services
Department of Health and Human Services
11 State House Station
Augusta, ME 04333
Phone: 207-287-4325

dhhs@maine.gov

Website:
Maine Medical Marijuana Program

Information provided by the state on sources for medical marijuana:
A list of dispensaries is available on the MMMP website. "The patient may either cultivate or designate a caregiver or dispensary to cultivate marijuana." ("Program Bulletin," Maine.gov, Sep. 28, 2011)

Patient Registry Fee:
$0
Caregivers pay $300/patient (limit of 5 patients; if not growing marijuana, there is no fee)

Accepts other states' registry ID cards?
Yes
"Law enforcement will accept appropriate authorization from a participating state, but that patient cannot purchase marijuana in Maine without registering here. That requires a Maine physician and a Maine driver license or other picture ID issued by the state of Maine. The letter from a physician in another state is only good for 30 days." (Aug. 19, 2010 email from Maine's Division of Licensing and Regulatory Services)

Registration:
Voluntary

"In addition to either a registry ID card or a physician certification form, all patients, including both non-registered and voluntarily registered patients, must also present their Maine driver license or other Maine-issued photo identification card to law enforcement, upon request." ("Program Bulletin," Maine.gov, Sep. 28, 2011)

10. Maryland

House Bill 881
Approved: Apr. 8, 2014 by House, 125-11 and by Senate, 44-2
Signed by Gov. Martin O'Malley on Apr. 14, 2014
Effective: June 1, 2014

The Natalie M. LaPrade Medical Marijuana Commission and the Maryland Department of Health and Mental Hygiene are tasked with developing regulations for patient registry and identification cards, dispensary licensing, setting fees and possession limits, and more. The Commission will issue yearly request for applications from academic medical centers to operate medical marijuana compassionate use programs.

Approved diagnosis: Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the Commission.

Maryland Department of Health and Mental Hygiene
201 West Preston Street
Baltimore, MD 21201
dhmh.medicalcannabis@maryland.gov

Website:
Natalie M. LaPrade Medical Marijuana Commission

Information provided by the state on sources for medical marijuana:
"A Maryland patient can only obtain legal medical cannabis from Maryland-licensed dispensaries. The dispensaries can only obtain their cannabis from Maryland-licensed growers, and their extracts from Maryland-licensed processors... The Commission anticipates that medical cannabis may first be available to patients in the second half of 2016."
"Frequently Asked Questions (FAQ's)," mmcc.maryland.gov, June 26, 2015

Patient Registry Fee:
To be determined by the Commission during the rulemaking

Possession/Cultivation: Patients are allowed to possess a 30-day supply (amount to be determined by the Commission). "Beginning June 1, 2016, the Commission may issue the number of [dispensary] licenses necessary to meet the demand for medical marijuana by qualifying patients and caregivers issued identification cards."

Learn more about medical marijuana laws in Maryland prior to legalization.

process

Accepts other states' registry ID cards?
No

Registration:
Mandatory

11. Massachusetts

Ballot Question 3 -- Approved Nov. 6, 2012 by 63% of voters
Effective: Jan. 1, 2013

"The citizens of Massachusetts intend that there should be no punishment under state law for qualifying patients, physicians and health care professionals, personal caregivers for patients, or medical marijuana treatment center agents for the medical use of marijuana...

In the first year after the effective date, the Department shall issue registrations for up to thirty-five non-profit medical marijuana treatment centers, provided that at least one treatment center shall be located in each county, and not more than five shall be located in any one county."

Approved diagnosis: "Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome (AIDS), hepatitis C, amyotrophic lateral sclerosis (ALS), Crohn's disease, Parkinson's disease, multiple sclerosis and other conditions as determined in writing by a qualifying patient's physician."

Possession/Cultivation: Patients may posses a sixty-day supply, defined as 10 ounces.

"The Department shall issue a cultivation registration to a qualifying patient whose access to a medical treatment center is limited by verified financial hardship, a physical incapacity to access reasonable transportation, or the lack of a treatment center within a reasonable distance of the patient's residence. The Department may deny a registration based on the provision of false information by the applicant. Such registration shall allow the patient or the patient's personal caregiver to cultivate a limited number of plants, sufficient to maintain a 60-day supply of marijuana, and shall require cultivation and storage only in an enclosed, locked facility."

Updates: The DPH website wrote on Oct. 8, 2014 that "the Medical Use of Marijuana Online System (MMJ Online System) is now available for qualifying patients to register to possess marijuana for medical purposes. You will need to register with the MMJ Online System by January 1, 2015 in order to possess marijuana for medical purposes, even if you already have a paper written certification from your physician. Paper written certifications will no longer be valid as of February 1st, 2015."

Department of Public Health of the Commonwealth of Massachusetts
One Ashburton Place
11th Floor
Boston, MA 02108
Phone: 617-624-5062

medicalmarijuana@state.ma.us

Website:
www.mass.gov/medicalmarijuana

Information provided by the state on sources for medical marijuana:
On February 12, 2016, Gov. Charlie Baker's Administration approved Patriot Care Corp. to begin retail sales of marijuana to registered qualifying patients and personal caregivers.

Patient Registry Fee:
$50

Accepts other states' registry ID cards?
Unknown

Registration:
Mandatory

12. Michigan

Proposal 1 "Michigan Medical Marihuana Act" -- Approved by 63% of voters on Nov. 4, 2008
Approved: Nov. 4, 2008
Effective: Dec. 4, 2008

Approved Conditions: Approved for treatment of debilitating medical conditions, defined as cancer, glaucoma, HIV, AIDS, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, nail patella, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, multiple sclerosis, and PTSD.

Possession/Cultivation: Patients may possess up to two and one-half (2.5) ounces of usable marijuana and twelve marijuana plants kept in an enclosed, locked facility. The twelve plants may be kept by the patient only if he or she has not specified a primary caregiver to cultivate the marijuana for him or her.

Amended: HB 4856
Effective: Dec. 31, 2012

Michigan Medical Marihuana Program
Department of Licensing and Regulatory Affairs
Bureau of Professional Licensing
Michigan Medical Marihuana Program
PO Box 30083
Lansing, MI 48909
Phone: 517-284-6400

BHP-MMMPINFO@michigan.gov

Website:
MI Medical Marihuana Program

Information provided by the state on sources for medical marijuana:
"This is not addressed in the MMMA, therefore; the MMP is not authorized to provide information regarding this issue... The MMMA provides for a system of designated caregivers... The MMP is not authorized to associate patients and caregivers nor release the names of registered caregivers." "Frequently Asked Questions," Michigan.gov (accessed Apr. 24, 2014)

Patient Registry Fee:
$60 new or renewal application

Makes it illegal to "transport or possess" usable marijuana by car unless the marijuana is "enclosed in a case that is carried in the trunk of the vehicle." Violation of the law is a misdemeanor "punishable by imprisonment for not more than 93 days or a fine of not more than $500.00, or both."

Amended: HB 4834
Effective: Apr. 1, 2013

Requires proof of Michigan residency when applying for a registry ID card (driver license, official state ID, or valid voter registration) and makes cards valid for two years instead of one.

Amended: HB 4851
Effective: Apr. 1, 2013

Requires a "bona fide physician-patient relationship," defined in part as one in which the physician "has created and maintained records of the patient's condition in accord with medically accepted standards" and "will provide follow-up care;" protects patient from arrest only with registry identification card and valid photo ID.

Amended: State of Michigan vs. McQueen
Decided: Feb. 8, 2013

The Michigan Supreme Court ruled 4-1 that dispensaries are illegal. As a result, medical marijuana patients in Michigan will have to grow their own marijuana or get it from a designated caregiver who is limited to five patients.

Accepts other states' registry ID cards?
Yes

The Office of Communications in the Department of Licensing and Regulatory Affairs told ProCon.org in an Oct.30, 2014 email: "The law says that cards from other states are recognized. However, the Michigan Medical Marihuana Program does not have any control over enforcement of that section of the statute."

Registration:
Mandatory

13. Minnesota

SF 2470 -- Signed into law by Gov. Mark Dayton on May 29, 2014
Approved: By Senate 46-16, by House 89-40
Effective: May 30, 2014

Approved Conditions: cancer (if the underlying condition or treatment produces severe or chronic pain, nausea or severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette's syndorme, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn's disease, terminal illness with a life expectancy of under one year.

Patients certified as having intractable pain become eligible to receive medical marijuana starting Aug. 2016.

Possession/Cultivation: The Commissioner of Health will register two in-state manufacturers for the production of all medical cannabis within the state. Manufacturers are required to ensure that the medical cannabis distributed contains a maximum of a 30-day supply of the dosage determined for that patient.

"Medical cannabis" is defined as any species of the genus cannabis plant delivered in the form of (1) liquid, including, but not limited to, oil; (2) pill; (3) vaporized delivery method that does not require the use of dried leaves or plant form.

Smoking is not a method approved by the bill.

Minnesota Department of Health
Office of Medical Cannabis
651-201-5598
844-879-3381 (toll-free)

health.cannabis@state.mn.us

Website:
Medical Cannabis Program

Information provided by the state on sources for medical marijuana:
The cannabis program website has a list of three operating dispensaries and five more scheduled to open in Spring 2016.

Patient Registry Fee:
$200 annual fee / $50 for patients on Social Security disability, Supplemental Security Insurance, or enrolled in MinnesotaCare

Accepts other states' registry ID cards?
No

Registration:
Mandatory

14. Montana

Initiative 148 -- Approved by 62% of voters on Nov. 2, 2004
Effective: Nov. 2, 2004

Approved Conditions: Cancer, glaucoma, or positive status for HIV/AIDS, or the treatment of these conditions; a chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures, including seizures caused by epilepsy, or severe or persistent muscle spasms, including spasms caused by multiple sclerosis or Crohn's disease; admittance to hospice care; or any other medical condition or treatment for a medical condition adopted by the department by rule.

Possession/Cultivation: "Registered cardholders are limited to 12 seedlings (<12"), 4 mature flowering plants, and 1 ounce of usable marijuana. If a registered cardholder assigns a provider, they cannot grow for themselves."

Medical Marijuana Program
Montana Department of Health and Human Services
Licensure Bureau
2401 Colonial Drive, 2nd Floor
P.O. Box 202953
Helena, MT 59620-2953
Phone: 406-444-0596

jbuska@mt.gov

Website:
MT Medical Marijuana Program

Medical Marijuana Program FAQs

Information provided by the state on sources for medical marijuana:
"The department has no advice on obtaining marijuana."
"MMP FAQ," dphhs.mt.gov (accessed Mar. 1, 2016)

Patient Registry Fee:

Amended: SB 423 -- Passed on Apr. 28, 2011 and transmitted to the Governor on May 3, 2011
Effective: July 1, 2011

SB 423 changes the application process to require a Montana driver's license or state issued ID card. A second physician is required to confirm a chronic pain diagnosis.

"A provider or marijuana-infused products provider may assist a maximum of three registered cardholders..." and "may not accept anything of value, including monetary remuneration, for any services or products provided to a registered cardholder."

Approved Conditions: Cancer, glaucoma, or positive status for HIV/AIDS when the condition or disease results in symptoms that seriously and adversely affect the patient's health status; Cachexia or wasting syndrome; Severe, chronic pain that is persistent pain of severe intensity that significantly interferes with daily activities as documented by the patient's treating physician; Intractable nausea or vomiting; Epilepsy or intractable seizure disorder; Multiple sclerosis; Chron's Disease; Painful peripheral neuropathy; A central nervous system disorder resulting in chronic, painful spasticity or muscle spasms; Admittance into hospice care.

Possession/Cultivation: Amended to 12 seedlings (less than 12"), four mature flowering plants, and one ounce of usable marijuana.

On Nov. 6, 2012, Montana voters approved initiative referendum No. 124 by a vote of 56.5% to 43.5%, upholding SB 423.

$75 new application / $75 renewal

Accepts other states' registry ID cards?
No (reciprocity ended when SB 423 took effect)

Registration:
Mandatory

15. Nevada

Ballot Question 9 -- Approved Nov. 7, 2000 by 65% of voters
Effective: Oct. 1, 2001

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who have "written documentation" from their physician that marijuana may alleviate his or her condition.

Approved Conditions: AIDS; cancer; glaucoma; and any medical condition or treatment to a medical condition that produces cachexia, persistent muscle spasms or seizures, severe nausea or pain, and PTSD. Other conditions are subject to approval by the health division of the state Department of Human Resources.

Possession/Cultivation: Patients (or their primary caregivers) may legally possess no more than two and a half ounces of usable marijuana in a 14-day period and 12 plants.

Registry: The law establishes a confidential state-run patient registry that issues identification cards to qualifying patients. Patients who do not join the registry or possess greater amounts of marijuana than allowed by law may argue the "affirmative defense of medical necessity" if they are arrested on marijuana charges. Legislators added a preamble to the legislation stating, "[T]he state of Nevada as a sovereign state has the duty to carry out the will of the people of this state and regulate the health, medical practices and well-being of those people in a manner that respects their personal decisions concerning the relief of suffering through the medical use of marijuana." A separate provision requires the Nevada School of Medicine to "aggressively" seek federal permission to establish a state-run medical marijuana distribution program.

Amended: Assembly Bill 453
Effective: Oct. 1, 2001

Created a state registry for patients whose physicians recommend medical marijuana and tasked the Department of Motor Vehicles with issuing identification cards. No state money will be used for the program, which will be funded entirely by donations.

Amended: Senate Bill 374
Signed into law by Gov. Brian Sandoval on June 12, 2013

"Provides for the registration of medical marijuana establishments authorized to cultivate or dispense marijuana or manufacture edible marijuana products or marijuana-infused products for sale to persons authorized to engage in the

Nevada State Health Division
4150 Technology Way, Suite 106
Carson City, NV, 89706
Phone: 775-684-3487
Fax: 775-684-4156

medicalmarijuana@health.nv.gov

Website:
NV Medical Marijuana Program

Information provided by the state on sources for medical marijuana:
The medical marijuana program website has a list of 15 open dispensaries. Nevada law allows patients to home cultivate only in specific circumstances. "The Nevada MM Program is not a resource for the growing process and does not have information to give to patients. It is recommended that you talk to an attorney to learn about your rights and protections." "Medical Marijuana Patient Cardholder Registry - FAQs," health.nv.gov, Jan. 19, 2016

Patient Registry Fee:
$25 application fee, plus $75 for the card

Accepts other states' registry ID cards?
Yes, starting Apr. 1, 2014 with an affidavit

Registration:
Mandatory

medical use of marijuana...

From Apr. 1, 2014, through Mar. 31, 2016, a nonresident purchaser must sign an affidavit attesting to the fact that he or she is entitled to engage in the medical use of marijuana in his or her state or jurisdiction of residency. On and after Apr. 1, 2016, the requirement for such an affidavit is replaced by computer cross-checking between the State of Nevada and other jurisdictions." Patients who were growing before July 1, 2013 are allowed to continue home cultivation until Mar. 31, 2016.

Updates: The Department of Health and Human Services adopted regulations based on the previous amendment on Apr. 1, 2014.

16. New Hampshire

House Bill 573
Approved: May 23, 2013 by Senate, 18-6 and June 26, 2013 by House, 284-66
Signed into law by Gov. Maggie Hassan on July 23, 2013
Effective: Upon passage

The bill authorizes the use of therapeutic cannabis in New Hampshire, establishes a registry identification card system, allows for the registration of up to four non-profit alternative treatment centers in the state, and establishes an affirmative defense for qualified patients and designated caregivers with valid registry ID cards.

HB 573 also calls for the creation of a Therapeutic Use of Cannabis Advisory Council, which in five years will be required to "issue a formal opinion on whether the program should be continued or repealed."

A valid ID card from another medical marijuana state will be recognized as allowing the visiting patient to possess cannabis for therapeutic purposes, but the "visiting qualifying patient shall not cultivate or purchase cannabis in New Hampshire or obtain cannabis from alternative treatment centers..."

Approved Conditions: "(1) Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C currently receiving antiviral treatment, amyotrophic lateral sclerosis, muscular dystrophy, Crohn's disease, multiple sclerosis, chronic pancreatitis, spinal cord injury or disease, traumatic brain injury, epilepsy, lupus, Parkinson's disease, Alzheimer's disease, or one or more injuries that significantly interferes with daily activities as documented by the patient's provider; AND

(2) A severely debilitating or terminal medical condition or its treatment that has produced at least one of the following: elevated intraocular pressure, cachexia, chemotherapy-induced anorexia, wasting syndrome, agitation of Alzheimer's disease, severe pain that has not responded to previously prescribed medication or surgical measures or for which other treatment options produced serious side effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms."

Possession/Cultivation: "A qualifying patient shall not obtain more than 2 ounces of usable cannabis directly or through the qualifying patient's designated caregiver during a 10-day period." A patient may possess two ounces of usable cannabis at any one time.

Updates: On Apr. 3, 2014, the Department of Health and Human Services (DHHS) posted proposed Therapeutic Cannabis Program Registry Rules and began the formal rulemaking process.

DHHS began issuing Registry Identification Cards on Dec. 28, 2015 by mail to qualifying patients and designated caregivers whose applications had been approved. The cards cannot be used in New Hampshire until the Alternative Treatment Center (ATC) dispensaries open.

The state's first dispensary opened in Plymouth, New Hampshire, on May 1, 2016.

New Hampshire Department of Health and Human Services
Therapeutic Cannabis Program
129 Pleasant Street, Brown Building
Concord, NH 03301-3857
Phone: 603-271-9234

Email Contact Form

Website:
Therapeutic Use of Cannabis Program

Information provided by the state on sources for medical marijuana:
"There will be four Alternative Treatment Centers (ATCs) operating in New Hampshire. The ATCs will be located in Dover, Merrimack, Lebanon, and Plymouth. A Qualifying Patient may select any of the ATCs but may select only one at any given time. A Qualifying Patient will be allowed to purchase cannabis only from the ATC he or she has selected. No Alternative Treatment Center in New Hampshire is open for business at this time. It is expected that they will become operational in Spring 2016."
"Alternative Treatment Centers" dhhs.nh.gov (accessed Feb. 29, 2016)

Patient Registry Fee:
$50

Accepts other states' registry ID cards?
Yes

Registration:
Mandatory

Department of Health (DOH)

17. New Jersey

Senate Bill 119
Approved: Jan. 11, 2010 by House, 48-14; by Senate, 25-13
Signed into law by Gov. Jon Corzine on Jan. 18, 2010
Effective: Six months from enactment

Protects "patients who use marijuana to alleviate suffering from debilitating medical conditions, as well as their physicians, primary caregivers, and those who are authorized to produce marijuana for medical purposes" from "arrest, prosecution, property forfeiture, and criminal and other penalties."

Also provides for the creation of alternative treatment centers, "at least two each in the northern, central, and southern regions of the state. The first two centers issued a permit in each region shall be nonprofit entities, and centers subsequently issued permits may be nonprofit or for-profit entities."

Approved Conditions: Amyotrophic lateral sclerosis (Lou Gehrig's disease); multiple sclerosis; terminal cancer; muscular dystrophy; inflammatory bowel disease, including Crohn's disease; terminal illness, if the physician has determined a prognosis of less than 12 months of life.

The following conditions apply if conventional therapy is unsuccessful: Seizure disorder, including epilepsy; intractable skeletal muscular spasticity; glaucoma.

The following conditions, if severe or chronic pain, severe nausea or vomiting, cachexia, or wasting syndrome results from the condition or treatment: Positive status for HIV/AIDS; cancer.

Possession/Cultivation: Physicians determine how much marijuana a patient needs and give written instructions to be presented to an alternative treatment center. The maximum amount for a 30-day period is two ounces.

Amended: SB 2842
Signed into law by Gov. Chris Christie on Sep. 10, 2013 following legislative adoption of his conditional veto

Allows edible forms of marijuana only for qualifying minors, who must receive approval from a pediatrician and a psychiatrist.

Updates:
S119 was supposed to become effective six months after it was enacted on Jan. 18, 2010, but the legislature, DHHS, and New Jersey Governor Chris Christie had difficulty coming to agreement on the details of how the program would be run.

The New Jersey Department of Health and Senior Services released draft rules outlining the registration and application process on Oct. 6, 2010. A public hearing to discuss the proposed rules was held on Dec. 6, 2010 at the New Jersey Department of Health and Senior Services, according to the *New Jersey Register*.

On Dec. 20, 2011, Senator Nicholas Scutari (D), lead sponsor of the medical marijuana bill, submitted Senate Concurrent Resolution (SCR) 140 declaring that the "Board of Medical Examiners proposed medicinal marijuana program rules are inconsistent with legislative intent." The New Jersey Senate Health, Human Services and Senior Citizens committee held a public hearing to discuss SCR 140 and a similar bill, SCR 130, on Jan. 20, 2010.

On Feb. 3, 2011, the Department of Health proposed new rules that streamlined the permit process for cultivating and dispensing, prohibited home delivery by alternative treatment centers, and required that "conditions originally named in the Act be resistant to conventional medical therapy in order to qualify as debilitating medical conditions."

On Aug. 9, 2012, the New Jersey Medical Marijuana Program opened the patient registration system on its website. Patients must have a physician's recommendation, a government-issued ID, and proof of New Jersey residency to register. The first dispensary is expected to be licensed to open in September.

On Oct. 16, 2012, the Department of Health issued the first dispensary permit to Greenleaf Compassion Center, allowing it to operate as an Alternative Treatment Center and dispense marijuana. The center opened on Dec. 6, 2012, becoming New

P. O. Box 360
Trenton, NJ 08625-0360
Phone: 609-292-0424

Contact form

Website:
Medicinal Marijuana Program

Information provided by the state on sources for medical marijuana:
Patients are not allowed to grow their own marijuana. On Mar. 21, 2011, the New Jersey DOH announced the locations of six nonprofit alternative treatment centers (ATCs) from which medical marijuana may be obtained, five of which were operational as of Mar. 1, 2016.

Medical marijuana is not covered by Medicaid.

Patient Registry Fee:
$200 (valid for two years). Reduced fee of $20 for patients qualifying for state or federal assistance programs

Accepts other states' registry ID cards?
No

Registration:
Mandatory

Jersey's first dispensary.

18. New Mexico

Senate Bill 523 "The Lynn and Erin Compassionate Use Act"
Approved: Mar. 13, 2007 by House, 36-31; by Senate, 32-3
Effective: July 1, 2007

Removes state-level criminal penalties on the use and possession of marijuana by patients "in a regulated system for alleviating symptoms caused by debilitating medical conditions and their medical treatments." The New Mexico Department of Health is designated to administer the program and register patients, caregivers, and providers.

Approved Conditions: Amyotrophic Lateral Sclerosis (Lou Gehrig's disease); cancer; Crohn's disease; epilepsy; glaucoma; hepatitis C infection currently receiving antiviral treatment; HIV/AIDS; Huntington's Disease; hospice care; inclusion body myositis; inflammatory autoimmune?mediated arthritis; intractable nausea/vomiting; multiple sclerosis; damage to the nervous tissue of the spinal cord; painful peripheral neuropathy; Parkinson's disease; PTSD; severe chronic pain; severe anorexia/cachexia; spasmodic torticollis; ulcerative colitis

Possession/Cultivation: Patients have the right to possess up to six ounces of usable cannabis, four mature plants and 12 seedlings. Usable cannabis is defined as dried leaves and flowers; it does not include seeds, stalks or roots. A primary caregiver may provide services to a maximum of four qualified patients under the Medical Cannabis Program.

New Mexico Department of Health
Medical Cannabis Program
1190 Saint Francis Drive Suite S-3400
Santa Fe, NM 87505
Phone: 505-827-2321

medical.cannabis@state.nm.us

Website:
NM Medical Cannabis Program

Information provided by the state on sources for medical marijuana:
"Currently, there are 23 independent Licensed Nonprofit Producers (LNPP). These are the agencies where those actively enrolled in the program purchase product. The NM Department of Health does not provide medical cannabis or set the prices. Patients must contact each LNPP directly to initiate the registration process. Questions regarding the LNPP should be directed to each LNPP separately, and not to the NMDOH Medical Cannabis Program."
"Medical Cannabis List of Licensed Non-Profit Producers," nmhealth.org, Feb. 29, 2016

Patient Registry Fee:
No fee

Accepts other states' registry ID cards?
No

Registration:
Mandatory

19. New York

Assembly Bill 6357
Approved: June 19, 2014 by Assembly, 117-13; June 20, 2014 by Senate, 49-10
Signed into law by Governor Andrew Cuomo on July 5, 2014
Effective: Upon Governor's signature

The Department of Health had 18 months to establish regulations and register dispensing organizations. Marijuana will be taxed at 7%, to be paid by the dispensary. The law automatically expires after seven years.

Approved Conditions: "You are potentially eligible for medical marijuana if you have been diagnosed with a specific severe, debilitating or life threatening condition that is accompanied by an associated or complicating condition. By law, those conditions are: cancer, HIV infection or AIDS, amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, and Huntington's disease. The associated or complicating conditions are cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures, or severe or persistent muscle spasms."

Physicians must complete a four-hour New York State Department of Health (Department)-approved course and register with the Department to certify patients.

Possession/Cultivation: 30-day supply

Smoking is not a method approved by the bill.

Update:

On Nov. 11, 2015 Gov. Cuomo signed a bill to allow emergency access to medical marijuana, requiring state health officials to establish an expedited certification process for seriously ill patients and to register marijuana producers "as expeditiously as practicable."

On Jan. 7, 2016, the medical marijuana program officially launched with eight dispensaries statewide.

New York Department of Health
866-811-7957

Email Contact Form

Website:
New York State Medical Marijuana Program

Information provided by the state on sources for medical marijuana:
The medical marijuana program website lists five registered organizations, each with four dispensing sites.

"A certified patient may receive medical marijuana products from any dispensing facility of any Registered Organization in New York State."
"Frequently Asked Questions," health.ny.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$50

Accepts other states' registry ID cards?
No

Registration:
Mandatory

20. Ohio

House Bill 523

Ohio Medical Marijuana Control Program

Website:
medicalmarijuana.ohio.gov

Approved: May 10, 2016 by House, 71-26; May 25, 2016 by Senate, 18-15
Signed into law by Governor John Kasich on June 8, 2016
Effective: Sep. 8, 2016

Authorizes the use of marijuana for medical purposes and establishes the Medical Marijuana Control Program.

"Only the following forms of medical marijuana may be dispensed under this chapter: oils, tinctures, plant material, edibles, patches." The smoking or combustion of medical marijuana is prohibited while vaporization is permitted.

Approved Conditions: AIDS/HIV, Alzheimer's disease, ALS, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy, fibromyalgia, glaucoma, hepatitis C, inflammatory bowel disease, multiple sclerosis, chronic, severe, or intractable pain, Parkinson's disease, PTSD, sickle cell anemia, spinal cord disease or injury, Tourette's syndrome, traumatic brain injury, ulcerative colitis

Possession/Cultivation: The law allows for a maximum of a 90-day supply, to be determined during the rulemaking process.

Smoking is not a method approved by the bill.

"The Ohio Department of Commerce and the State of Ohio Board of Pharmacy are required by law to take all actions necessary to ensure that Ohio's Medical Marijuana Control Program is fully operational no later than September 2018. At that time, there will be an established structure for Ohioans with a qualifying medical condition to obtain a recommendation for medical marijuana, purchase medical marijuana from a licensed dispensary, and consume medical marijuana."
"Frequently Asked Questions, medicalmarijuana.ohio.gov (accessed Aug. 9, 2016)

Contact Form

Information provided by the state on sources for medical marijuana:
"Medical marijuana will be available from retail dispensaries licensed by the Board of Pharmacy. The Board of Pharmacy is currently developing rules on the licensing of medical marijuana dispensaries. The law prohibits the cultivation of medical marijuana for personal, family, or household use."
"Frequently Asked Questions, medicalmarijuana.ohio.gov (accessed Aug. 9, 2016)

Patient Registry Fee:
To be determined

Accepts other states' registry ID cards?
"The state board of pharmacy shall attempt in good faith to negotiate and enter into a reciprocity agreement with any other state under which a medical marijuana registry identification card or equivalent authorization that is issued by the other state is recognized in this state."

Registration:
Mandatory

21. Oregon

Ballot Measure 67 -- Approved by 55% of voters on Nov. 3, 1998
Effective: Dec. 3, 1998

Removes state-level criminal penalties on the use, possession and cultivation of marijuana by patients who possess a signed recommendation from their physician stating that marijuana "may mitigate" his or her debilitating symptoms.

Approved Conditions: Cancer, glaucoma, degenerative or pervasive neurological condition; positive status for HIV/AIDS, or treatment for these conditions; A medical condition or treatment for a medical condition that produces cachexia, severe pain, severe nausea, seizures, including seizures caused by epilepsy, or persistent muscle spasms, including spasms caused by multiple sclerosis. Other conditions are subject to approval by the Health Division of the Oregon Department of Human Resources.

Possession/Cultivation: A registry identification cardholder or the designated primary caregiver of the cardholder may possess up to six mature marijuana plants and 24 ounces of usable marijuana. A registry identification cardholder and the designated primary caregiver of the cardholder may possess a combined total of up to 18 marijuana seedlings. (per Oregon Revised Statutes ORS 475.300 -- ORS 475.346)

Amended: Senate Bill 1085
Effective: Jan. 1, 2006

State-qualified patients who possess cannabis in amounts exceeding the new state guidelines will no longer retain the ability to argue an "affirmative defense" of medical necessity at trial. Patients who fail to register with the state, but who possess medical cannabis in amounts compliant with state law, still retain the ability to raise an "affirmative defense" at trial.

The law also redefines "mature plants" to include only those cannabis plants that are more than 12 inches in height and diameter, and establish a state-registry for those authorized to produce medical cannabis to qualified patients.

Amended: House Bill 3052
Effective: July 21, 1999

Mandates that patients (or their caregivers) may only cultivate

Oregon Department of Human Services
Medical Marijuana Program
PO Box 14116
Portland, OR 97293
Phone: 855-244-9580 (toll-free)

medmj.dispensaries@state.or.us

Website:
healthoregon.org/ommp

Information provided by the state on sources for medical marijuana:
The Oregon Medical Marijuana Dispensary Program publishes a directory of approved dispensaries on its website.

"As of October 1, 2015, registered medical marijuana dispensaries may sell limited amounts of recreational marijuana to adults age 21 and older."

Patient Registry Fee:
$200 for new applications and renewals; Reduced fees: $60 for persons receiving SNAP (food stamp); $50 for Oregon Health Plan cardholders; $20 for persons receiving SSI benefits; $20 for individuals who have served in the Armed Forces of the United States

Accepts other states' registry ID cards?
No

Registration:
Mandatory

marijuana in one location, and requires that patients must be diagnosed by their physicians at least 12 months prior to an arrest in order to present an "affirmative defense." This bill also states that law enforcement officials who seize marijuana from a patient pending trial do not have to keep those plants alive. Last year the Oregon Board of Health approved agitation due to Alzheimer's disease to the list of debilitating conditions qualifying for legal protection.

In August 2001, program administrators filed established temporary procedures further defining the relationship between physicians and patients. The new rule defines attending physician as "a physician who has established a physician/patient relationship with the patient;... is primarily responsible for the care and treatment of the patients... has reviewed a patient's medical records at the patient's request, has conducted a thorough physical examination of the patient, has provided a treatment plan and/or follow-up care, and has documented these activities in a patient file."

Amended: SB 281
Signed by Gov. John Kitzhaber on June 6, 2013

Adds post-traumatic stress disorder (PTSD) to the list of approved conditions for medical marijuana use.

Amended: HB 3460
Signed by Gov. John Kitzhaber on Aug. 14, 2013

Creates a dispensary program by allowing the state licensing and regulation of medical marijuana facilities to transfer marijuana to registry identification cardholders or their designated primary caregivers.

Updates: On Mar. 3, 2014, the program began accepting applications from people seeking a license to operate a medical marijuana dispensary.

On Mar. 19, 2014, Senate Bill 1531 was signed into law. The bill allows local governments to restrict the operation of medical marijuana dispensaries, including the moratoriums up through May 1, 2015.

On Apr.18, 2014, the Medical Marijuana Dispensary Program approved 15 dispensary applications, bringing the total number of approved applications to 58.

HB 3400, signed into law on July 1, 2015 by Gov. Kate Brown, added a provision requiring patients to be state residents, but there is no minimum length of residency required before getting a card.

22. Pennsylvania

Senate Bill 3 -- Apr. 12, 2016 by Senate, 42-7, and Apr. 13 by House, 149-46
Signed into law by Gov. Tom Wolf (D) on Apr. 17, 2016

Effective: 30 days after passage

Approved Conditions: Cancer, HIV/AIDS, ALS, Parkinson's, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, inflammatory bowel disease, neuropathies, Huntington's disease, Crohn's disease, PTSD, intractable seizures, glaucoma, sickle cell anemia, severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention and opiate therapy is contraindicated or ineffective, autism.

Possession/Cultivation: 30-day supply; According to SB 3, "Medical marijuana may only be dispensed to a patient or caregiver in the following forms: (i) pill; (ii) oil; (iii) topical forms, including gel, creams or ointments; (iv) a form medically appropriate for administration by vaporization or nebulization, excluding dry leaf or plant form... (v) tincture; or (vi) liquid. Unless otherwise provided in regulations adopted by the department under section 1202, medical marijuana may not be dispensed to a patient or a caregiver in dry leaf or plant form."

Smoking is not a method approved by the bill.

Update:

Pennsylvania Department of Health
1-877-PA-HEALTH

Information provided by the state on sources for medical marijuana:
"The department may not initially issue permits to more than 50 dispensaries. Each dispensary may provide medical marijuana at no more than three separate locations."
"Senate Bill 3," Apr. 12, 2016

More details pending establishment of state program

Patient Registry Fee:
$50

Accepts other states' registry ID cards?
Unknown

Registration:
Mandatory

On June 24, 2016 , Pennsylvania Secretary of Health Karen Murphy announced new guidelines for a Safe Harbor provision: "In July [2016], parents, legal guardians, caregivers, and spouses will be able to apply to the department for a Safe Harbor Letter that will allow them to administer medical marijuana obtained from outside of Pennsylvania to minors in their care. Once approved, the letter should be carried whenever medical marijuana is being transported outside of an individual's home."

23. Rhode Island

Senate Bill 0710 -- Approved by state House and Senate, vetoed by the Governor. Veto was over-ridden by House and Senate.

Timeline:

1. June 24, 2005: passed the House 52 to 10
2. June 28, 2005: passed the State Senate 33 to 1
3. June 29, 2005: Gov. Carcieri vetoed the bill
4. June 30, 2005: Senate overrode the veto 28-6
5. Jan. 3, 2006: House overrode the veto 59-13 to pass the Edward O. Hawkins and Thomas C. Slater Medical Marijuana Act (Public Laws 05-442 and 05-443)
6. June 21, 2007: Amended by Senate Bill 791

Effective: Jan. 3, 2006

Approved Conditions: Cancer, glaucoma, positive status for HIV/AIDS, Hepatitis C, or the treatment of these conditions; A chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome; severe, debilitating, chronic pain; severe nausea; seizures, including but not limited to, those characteristic of epilepsy; or severe and persistent muscle spasms, including but not limited to, those characteristic of multiple sclerosis or Crohn's disease; or agitation of Alzheimer's Disease; or any other medical condition or its treatment approved by the state Department of Health.

Possession/Cultivation: Limits the amount of marijuana that can be possessed and grown to up to 12 marijuana plants or 2.5 ounces of cultivated marijuana. Primary caregivers may not possess an amount of marijuana in excess of 24 marijuana plants and five ounces of usable marijuana for qualifying patients to whom he or she is connected through the Department's registration process.

Amended: H5359 - The Edward O. Hawkins and Thomas C. Slater Medical Marijuana Act (substituted for the original bill)

Timeline:

1. **May 20, 2009:** passed the House 63-5
2. **June 6, 2009:** passed the State Senate 31-2
3. **June 12, 2009:** Gov. Carcieri vetoed the bill
4. **June 16, 2009:** Senate overrode the veto 35-3
5. **June 16, 2009:** House overrode the veto 67-0

   Effective June 16, 2009: Allows the creation of compassion centers, which may acquire, possess, cultivate, manufacture, deliver, transfer, transport, supply, or dispense marijuana, or related supplies and educational materials, to registered qualifying patients and their registered primary caregivers. Rules & Regulations last updated Dec. 2012.

The first dispensary, the Thomas C. Slater Compassion Center, opened on Apr. 19, 2013. Compassion centers must be operated on a not-for-profit basis.

Rhode Island Department of Health
Office of Health Professions Regulation, Room 104
3 Capitol Hill
Providence, RI 02908-5097
Phone: 401-222-2828

doh.mmp@health.ri.gov

Website:
RI Medical Marijuana Program (MMP)

Information provided by the state on sources for medical marijuana:
"Compassion centers are places for patients who have qualifying conditions to obtain medical marijuana as allowed by Rhode Island law. Three compassion centers are licensed in Rhode Island: the Thomas C. Slater Compassion Center in Providence; Summit Medical Compassion Center in Warwick; and Greenleaf Compassionate Care Center in Portsmouth."
"Medical Marijuana Compassion Centers," health.ri.gov (accessed Mar. 1, 2016)

Patient Registry Fee:
$100 / $10 for applicants on Medicaid or Supplemental Security Income (SSI)

Accepts other states' registry ID cards?
Yes, but only for the conditions approved in Rhode Island

Registration:
Mandatory

24. Vermont

Senate Bill 76 -- Approved 22-7; House Bill 645 -- Approved 82-59
"Act Relating to Marijuana Use by Persons with Severe Illness" (Sec. 1. 18 V.S.A. chapter 86 passed by the General Assembly) *Gov. James Douglas (R), allowed the act to pass into law unsigned on May 26, 2004*
Effective: July 1, 2004

Amended: Senate Bill 00007
Effective: May 30, 2007

Marijuana Registry
Department of Public Safety
45 State Drive
Waterbury, VT 05671-1300
Phone: 802-241-5115
Fax: 802-241-5230

DPS.MJRegistry@vermont.gov

Website:
VT Marijuana Registry Program

Approved Conditions: Cancer, AIDS, positive status for HIV, multiple sclerosis, or the treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms; or a disease, medical condition, or its treatment that is chronic, debilitating and produces severe, persistent, and one or more of the following intractable symptoms: cachexia or wasting syndrome, severe pain or nausea or seizures.

Possession/Cultivation: No more than two mature marijuana plants, seven immature plants, and two ounces of usable marijuana may be collectively possessed between the registered patient and the patient's registered caregiver. A marijuana plant shall be considered mature when male or female flower buds are readily observed on the plant by unaided visual examination. Until this sexual differentiation has taken place, a marijuana plant will be considered immature.

Amended: Senate Bill 17 "An Act Relating To Registering Four Nonprofit Organizations To Dispense Marijuana For Symptom Relief"
Signed by Gov. Peter Shumlin on June 2, 2011

The bill "establishes a framework for registering up to four nonprofit marijuana dispensaries in the state... A dispensary will be permitted to cultivate and possess at any one time up to 28 mature marijuana plants, 98 immature marijuana plants, and 28 ounces of usable marijuana."

On Sep. 12, 2012, the State of Vermont Department of Public Safety announced conditional approval of two medical marijuana dispensaries. In June 2013, two dispensaries opened in Vermont.

Information provided by the state on sources for medical marijuana:
"The Marijuana Registry is neither a source for marijuana nor can the Registry provide information to patients on how to obtain marijuana." (accessed Mar. 1, 2016)

Patient Registry Fee:
$50

Accepts other states' registry ID cards?
No

Registration:
Mandatory

25. Washington

Chapter 69.51A RCW **Ballot Initiative I-692** -- Approved by 59% of voters on Nov. 3, 1998
Effective: Nov. 3, 1998

"Qualifying patients with terminal or debilitating illnesses who, in the judgment of their physicians, may benefit from the medical use of marijuana, shall not be found guilty of a crime under state law for their possession and limited use of marijuana."

Approved Conditions: cachexia; cancer; HIV or AIDS; epilepsy; glaucoma; intractable pain (defined as pain unrelieved by standard treatment or medications); and multiple sclerosis. Other conditions are subject to approval by the Washington Board of Health. **Additional conditions as of Nov. 2, 2008:** Crohn's disease, Hepatitis C with debilitating nausea or intractable pain, diseases, including anorexia, which result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity, when those conditions are unrelieved by standard treatments or medications. **Added as of Aug. 31, 2010:** chronic renal failure

Amended: Senate Bill 6032
Effective: 2007 (rules being defined by Legislature with a July 1, 2008 due date)

Amended: Final Rule based on Significant Analysis
Effective: Nov. 2, 2008

Possession/Cultivation: "On July 1, 2016, the possession amounts will change and will depend on whether the patient or designated provider is entered into the marijuana database. Patients and designated providers who are entered into the database will be able to:

- Possess six plants and eight ounces of useable marijuana.
- Be authorized by their healthcare practitioner for up to fifteen plants and sixteen ounces of usable marijuana."

Amended: SB 5073
Effective: July 22, 2011
Gov. Christine Gregoire signed sections of the bill and partially vetoed others, as explained in the Apr. 29, 2011 veto notice. Gov. Gregoire struck down sections related to creating state-licensed medical marijuana dispensaries and a voluntary patient registry.

Department of Health
PO Box 47866
Olympia, WA 98504-7866
Phone: 360-236-4700
Fax: 360-236-4768

MedicalMarijuana@doh.wa.gov

Website:
Medical Marijuana (Cannabis)

Information provided by the state on sources for medical marijuana:
"Current Washington law provides an affirmative defense to criminal prosecution if a qualified patient or designated provider possesses up to 24 ounces of useable marijuana or 15 marijuana plants, or participates in a collective garden. Patients and designated providers age 21 or older may purchase and possess marijuana through the recreational market but are subject to the limitations in chapter 69.50 RCW. Currently, any adult age 21 or older may buy any combination of the following from a licensed retail store:

- One ounce of useable marijuana;
- Sixteen ounces of marijuana-infused product in solid form;
- Seventy-two ounces of marijuana-infused product in liquid form; or seven grams of marijuana concentrate

The laws relating to possession amounts for patients and designated providers will change on July 1, 2016.

Beginning July 1, 2016, all non-licensed medical marijuana dispensaries must close down. However, medical marijuana patients can grow up to 15 plants if authorized by healthcare practitioner."
"Medical Marijuana Other Frequently Asked Questions," doh.wa.gov (accessed Mar. 1, 2016)

Note: Washington now allows state-licensed retail stores to sell marijuana. The state website says that qualified patients "can still grow their own marijuana or participate in a collective garden if they don't want to buy from a state-licensed retail store."

Patient Registry Fee:
None

Accepts other states' registry ID cards?
No

Updates: On Jan. 21, 2010, the Supreme Court of the State of Washington ruled that Ballot Initiative "I-692 did not legalize marijuana, but rather provided an authorized user with an affirmative defense if the user shows compliance with the requirements for medical marijuana possession." *State v. Fry*

ProCon.org contacted the Washington Department of Health to ask whether it had received any instructions in light of this ruling. Kristi Weeks, Director of Policy and Legislation, stated the following in a Jan. 25, 2010 email response to ProCon.org:

> "The Department of Health has a limited role related to medical marijuana in the state of Washington. Specifically, we were directed by the Legislature to determine the amount of a 60 day supply and conduct a study of issues related to access to medical marijuana. Both of these tasks have been completed. We have maintained the medical marijuana webpage for the convenience of the public.
>
> The department has not received 'any instructions' in light of State v. Fry. That case does not change the law or affect the 60 day supply. Chapter 69.51A RCW, as confirmed in Fry, provides an affirmative defense to prosecution for possession of marijuana for qualifying patients and caregivers."

On Nov. 6, 2012, Washington voters passed Initiative 502, which allows the state to "license and regulate marijuana production, distribution, and possession for persons over 21 and tax marijuana sales." The website for Washington's medical marijuana program states that the initiative "does not amend or repeal the medical marijuana laws (chapter 69.51A RCW) in any way. The laws relating to authorization of medical marijuana by healthcare providers are still valid and enforceable."

SB 5052 passed the House by a vote of 60-36 on Apr. 10, 2015 and the Senate by a vote of 41-8 on Apr. 14, 2015. Gov. Jay Inslee signed the bill into law with partial vetoes on Apr. 24, 2015.

Qualifying patients in Washington need a valid Medical Marijuana authorization form from their healthcare practitioners.

"Beginning July 1, 2016, patients and designated providers who are entered into the Medical Marijuana Authorization Database will receive a recognition card which will entitle the patient to additional rights and protections under SB 5052:

-Arrest protection
-Purchase products sales tax free
-Purchase three times the legal limit for recreational

Patients and designated providers who hold valid authorizations but aren't entered into the database will have an affirmative defense to criminal prosecution if they possess no more than four plants and six ounces of usable marijuana. They may purchase only in accordance with the laws and rules for non-patients."

Registration:
None

For a detailed list of sources used to compile this information, please see our sources page.

HEALTH

Can Cannabis Treat Fibromyalgia Better Than Prescription Drugs?

JEREMY KOSSEN

Anyone suffering from fibromyalgia will tell you it can be devastating. On some days, simple chores like doing laundry or making breakfast can be exhausting, if not downright impossible. Just ask Teri Robnett, a Denver-based medical marijuana patient's rights advocate who runs the Rx MaryJane blog:

> "There used to be days that I didn't feel like I could get through the day. I just wanted to cry and go back to bed."

Only a decade ago, many doctors didn't believe fibromyalgia was real — "hysterical" women were just imagining it. To this day, it is still misunderstood, and often misdiagnosed. Commonly characterized as a chronic pain condition, a growing body of evidence suggests that fibromyalgia is a complex neurological disorder. Beyond chronic pain affecting muscles and connective tissue, sufferers often complain of joint stiffness, chronic fatigue, insomnia, general weakness, headaches, digestive issues, anxiety, and cognitive issues (e.g., "fibro fog").

According to the National Institutes of Health, more than 5 million Americans — mostly women — have fibromyalgia.

What Causes Fibromyalgia?

While the cause of fibromyalgia is widely debated, Dr. Ethan Russo, a prominent neurologist and pharmacologist who has dedicated much of his professional career studying cannabis and the endocannabinoid system, theorized that fibromyalgia could be related to Clinical Endocannabinoid Deficiency (CECD).

The endocannabinoid system is like the Internet of your body — a communications network facilitating communications between your brain, organs, connective tissues, glands, and immune cells. The primary goal of the ECS is homeostasis — helping your body maintain a stable internal environment.

When the endocannabinoid system is out of whack, health suffers. An imbalance can cause a whole host of issues affecting mood, sleep, gastrointestinal health, muscle spasticity, to name a few — symptoms that are also prominent among sufferers of fibromyalgia, thusly supporting Russo's theory.

Can Medical Marijuana be Used as Treatment for Fibromyalgia?

Hard to treat and impossible to cure, many sufferers are curious about whether cannabis can help treat their discomfort.

Robnett, who is also the founder and executive director of Colorado-based Cannabis Patients Alliance, was one such patient. Recalling how in 1987 a car accident triggered her fibromyalgia, she later learned that an endocannabinoid deficiency could be to blame. She fell to the floor and cried, but her sadness was swiftly replaced with anger. Recognizing cannabis might be able to help, she asked, "How could the one thing that could supplement what my body wasn't making [is something] the government could tell me I can't have?"

For years Robnett took doctor-prescribed pharmaceuticals, but she detested the side effects and was concerned about drug interactions. "In 2009, I started medical marijuana. By 2011, I had quit all of my pharmaceutical medications and now use cannabis exclusively," she explained.

Robnett said that at first it took her a bit of trial-and-error, but it didn't take long for her to become convinced cannabis was preferable to pharmaceuticals. "From season to season, even day to day, the severity of symptoms can change because of the weather, stress, or hormones," Robnett said. "Cannabis allows me to self-titrate. By being able to vary how I consume and types of strains, I can more effectively treat the symptoms."

At night, Robnett medicates with an edible. Because edibles can take a bit to kick in, she begins her routine by vaporizing with an indica strain which quickly enters the bloodstream and immediately provides relief. While vaporizing works quickly, it doesn't last through the night. "The edible takes much longer to affect me than vaporizing, but lasts much longer, and I can sleep through the night," she said. "Getting a good night's sleep helps keep my symptoms under control the next day."

During the day, she'll use something higher in CBD and lower in THC to minimize psychoactive effects while alleviating her symptoms. Chronic fatigue is also a common symptom, and Robnett said the high CBD counters the fatigue, giving her energy to get through the day.

Cannabis for Treating Fibromyalgia vs. Prescription Drugs

Robnett is not alone in her experience. The National Pain Foundation conducted a survey in 2014 of over 1,300 patients. Remarkably, nearly a third — 30 percent of respondents — reported having used medical cannabis.

Of the more than 390 survey participants who had used cannabis, compared to FDA-approved pharmaceuticals, far more people reported cannabis as being effective:

- 62% reported cannabis as “very effective” in treating their symptoms
- 33% reported that cannabis “helped a little”
- Only 5% said it did not help at all

Contrast these results to FDA-approved medications:

- A mere 8 – 10% reported Cymbalta, Lyrica, or Savella as “very effective”
- 60 – 68% responded those drugs “[did] not help at all”

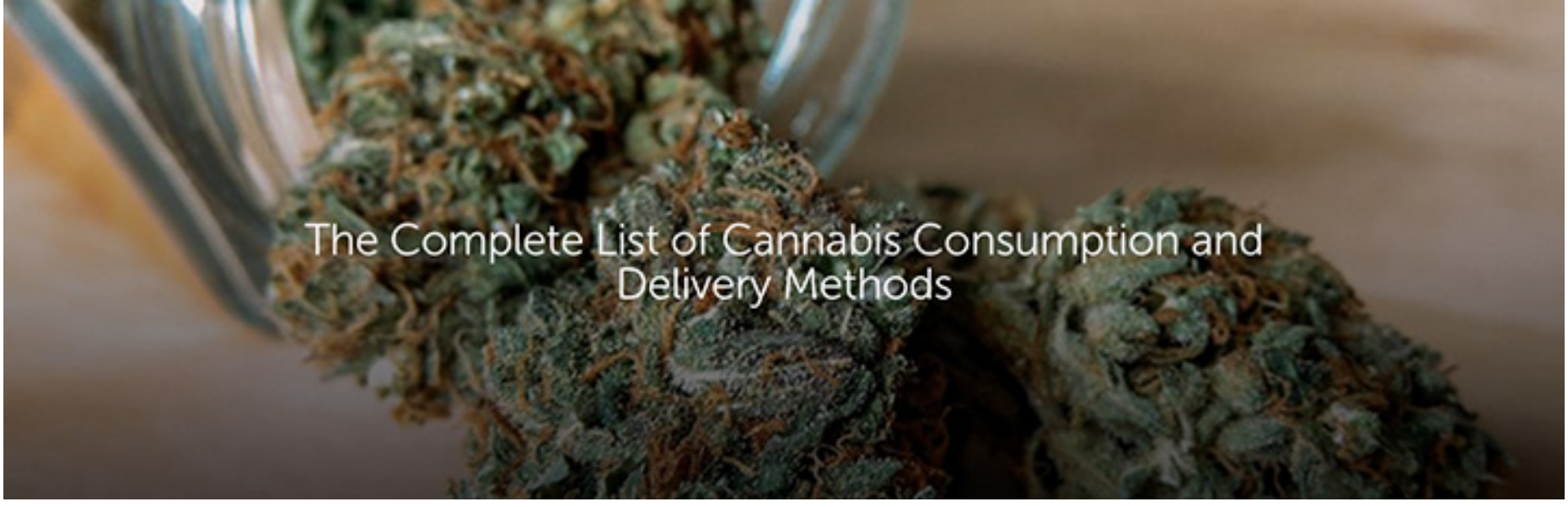
No wonder “big pharma” is scared of cannabis! In the hierarchy of evidence, a survey is not weighted the same as a random-controlled trial (RCT). However, given the relative safety profile of cannabis and absence of adverse side effects compared to the FDA-approved medications, the data clearly suggests more research is warranted.

Synthetic Cannabinoids for Fibromyalgia

There has been just one double-blind, placebo-controlled randomized, controlled trial (RCT) of synthetic cannabinoids. Researchers concluded nabilone was a "beneficial, well-tolerated treatment option" that could be a viable adjunct to other therapies.

But, anecdotally, patients report they prefer botanical cannabis. Only 10% to 20% of the THC makes its way into the bloodstream after metabolizing. Furthermore, nabilone doesn't come cheap! 30 capsules cost more than $1,000.

Robnett is happy with cannabis. "With cannabis I can vary by strain and consumption method according to how I feel or what time of day it is. More importantly, over the 28 years I've suffered from this condition, I found cannabis is by far the most effective and efficient treatment."



Given the widespread frustration patients have with available treatments, and the devastating nature of fibromyalgia on those who live under its grip, it's hard to find a morally defensible reason to deprive patients like Robnett the right to not only alleviate their suffering, but find a new lease on life.

Have you used cannabis to treat fibromyalgia? If so, share your experience with us in the comments section.

FIBROMYALGIA MEDICAL MARIJUANA PAIN

RELATED ARTICLES

A Guide to Cannabis Allergies and Symptoms

Synthetic Cannabinoids: Growing Side Effects Make Now a Great Time to Stay Away

Cannabis and Its Impact on High Blood Pressure

CONNECT WITH LEAFLY

Facebook
Twitter
Google+
Pinterest
Instagram
YouTube

RESOURCES

Brand Assets
Dispensary Log In / Sign Up
Doctor Log In / Sign Up
Advertise on Leafly
Ad Standards

DOWNLOAD THE APP

Download on the App Store

Google play

Leafly

A Brief Description

Thought to be a mental disorder in the early 1800s, fibromyalgia is a chronic condition categorized by widespread musculoskeletal pain and extreme sensitivity to pressure. Although the root cause of fibromyalgia remains unknown, it is known that interruptions in sensory pathways of the brain, spinal cord and nerves cause patients to suffer from abnormal, intensified pain sensations.

The first scientific research studying fibromyalgia was conducted in 1981, but the first medication designed to manage the debilitating symptoms was not approved by the FDA until 2007. While usually less than 40 percent of those suffering from fibromyalgia experience symptom relief from pharmaceutical medications, medical cannabis is often a successful therapy option to an otherwise resistant condition.

How Can Cannabis Help?

Fibromyalgia symptoms, including pain, fatigue, sleep deprivation, and mood instability or depression, can be effectively treated with the use of medical cannabis because the organic chemical compounds that make up the plant, called cannabinoids, mimic the body's own naturally produced endocannabinoids. The cannabinoids in cannabis bind to the same endocannabinoid receptors that are responsible for regulating many body systems including pain, appetite, mood and memory.

Although the increase in the number of states legalizing the use of medical cannabis may seem new to some, it is actually history repeating itself. Medical cannabis tinctures were available for over the counter purchase in drugstores throughout the United States until the 1930s. Phillip Leveque, the Oregon-based doctor known for being a pioneer of medical marijuana activism, was alive when cannabis tinctures could be found on store shelves, and he was also one of the first doctors to recommend medical cannabis once it was legalized in 1998. Leveque reported that he was in care of approximately 100 patients suffering from fibromyalgia, at any given time, and they all found medical cannabis to be a very effective treatment.

Many patient testimonies align with what experts and researchers have revealed about the symptom relief that results from the use of medical cannabis. Multiple cannabinoids are known for alleviating symptoms of fibromyalgia. For example, THC can significantly reduce or even eliminate pain and nausea while helping to improve mood, and CBN is a powerful sleep aid. While single cannabinoid therapy, like the use of just THC or just CBN, will be effective, the efficacy of medical cannabis increases dramatically when multiple cannabinoids are able to work together in a process known as the entourage effect. An example of this is revealed in the results of a recent online survey of fibromyalgia patients, conducted by The National Pain Foundation. Sixty-two percent of participants found medical cannabis to be "very effective" in the treatment

of multiple symptoms.

What Does The Research Say?

A study conducted in Spain and published in 2011 revealed that medical cannabis can provide fibromyalgia sufferers with both symptom relief and better quality of life. After using medical cannabis, participants reported a significant reduction in pain and stiffness as well as enhancement of relaxation, and an increase in sleeping abilities. Patients also noted feeling an improved sense of well-being after the introducing the use of medical cannabis therapies.

While clinical studies focusing exclusively on fibromyalgia may be limited, clinical trials focusing on pain in general are rapidly growing in number around the world. In a double-blind study conducted at the University of California at Davis Analgesic Research Center and published in the Journal of Pain, Dr. Barth Wilsey is quoted stating, “[w]e conducted a double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment.” Thirty-nine patients with central and peripheral neuropathic pain participated in the study and “[m]ixed effects regression models demonstrated an analgesic response to vaporized cannabis.”

Links To Research

Fibromyalgia Patients Rate Marijuana Significantly More Effective Than FDA-Approved Drugs.

READ STUDY

Cannabis Use in Patients with Fibromyalgia: Effect on Symptoms Relief and Health-Related Quality of Life.

READ STUDY

Association of herbal cannabis use with negative psychosocial parameters in patients with fibromyalgia.

READ STUDY

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

READ STUDY

While research has shown cannabis to be effective in providing palliative and therapeutic effects for some patients, always seek the advice of your physician or other qualified health provider with any questions you may have regarding a medical condition and before starting any new treatment utilizing medical cannabis or discontinuing an existing treatment. The content on this site is not intended to be a substitute for professional medical advice, diagnosis or treatment.

Interesting Fact

Cannabinoids, the organic chemical compounds that contribute

to the medical efficacy of cannabis, often fit the body's endocannabinoid receptors as perfectly as a key fits a lock, providing symptom relief for conditions like fibromyalgia because the endocannabinoid receptors are responsible for regulating body systems like pain, mood, appetite and memory.

Kill Your Fibromyalgia Pain with Cannabis

By **Prakash Janakiraman** - Apr 30, 2016

Getty

What is fibromyalgia?

Fibromyalgia is a chronic, generalized pain disorder that is characterized by abnormal sensitivity and pain at particular point(s) of the body, tiredness, sleep and affective disturbances, and morning stiffness. The exact cause of fibromyalgia is not well understood. Studies have suggested several possible mechanisms as causes of fibromyalgia, such as abnormalities in neurotransmitter metabolism, central sensitization, abnormal activation of microglia, altered hypothalamic-pituitary-adrenal-axis (HPA-axis) activity, and autonomic nervous system response which can contribute to

a dysfunctional stress response system and induction of pain pathway.

As of now, there is no effective treatment or cure for fibromyalgia. The available treatments may provide modest symptomatic relief; however, the patient's overall quality of life remains consistently poor.

For those suffering from fibromyalgia, their only option for relief is to take pain killers daily to mask the symptoms. These medications can cause serious side effects in the long run.

The Role of Endocannabinoid Deficiency in Pain Disorders

The discovery of the endocannabinoid system (ECS) in the human body and its potential role in pain modulation drives the scientific community's interest to explore the analgesic properties of cannabinoids, particularly phytocannabinoids.

Understanding the endocannabinoid system and its influential role on pain modulation, stress response, and cognitive functions can help us to understand the analgesic and anti-hyperalgesic benefits of cannabinoids. Studies have pointed out the possible role of endocannabinoid deficiency in the pathophysiology of fibromyalgia. Most of the randomized, controlled studies that have been done have shown that cannabinoids can alleviate pain in patients who cannot adequately control their symptoms by other pain management techniques. In fibromyalgia patients, chronic pain may be positively influenced by dysfunctional stress systems via the HPA-axis, in addition to a deregulated autonomous nervous system.

Endocannabinoids and their receptors are the prime responders of acute, chronic, and variable stress events by modulating the neurotransmitter release.

Recent research studies have confirmed that endocannabinoid deficiencies play a key role in the pathogenesis of fibromyalgia and other chronic pain disorders. Therapeutic benefits of cannabis against pain disorders are being studied and available data shows phytocannabinoids can provide a promising treatment approach for chronic pain disorders.

Fibromyalgia patients that do not respond to traditional treatments frequently use medical cannabis to manage their symptoms including pain, fatigue, depression, anxiety, insomnia, etc. Unlike opioid analgesics, marijuana can modulate pain signals from the spinal cord as well as from peripheral nerves.

Evidence-based clinical studies are needed to further demonstrate the health benefits of medical

cannabis in a scientifically accepted way. This is quite possible in the near future if the politico-legal barriers get broken and medical bias fades.

What Clinical Trial Studies Reveal

Upon searching the medical literature database, we are able to see a growing body of evidence that supports medical cannabis treatment as a substitute or adjunct for prescription opioids to treat chronic pain disorders, including fibromyalgia.

A Spanish clinical trial of fibromyalgia patients reported significant pain relief and relief of muscle stiffness from medical marijuana. Although no large scale clinical trials have been conducted, the available evidence demonstrates the fact that cannabinoids are an effective treatment for fibromyalgia. Not only clinical trials, but even observational studies have reported symptomatic pain relief benefits from cannabis in chronic pain disorder patients.

Recent research evidence has pointed out the synergistic effects of cannabinoids and opioid analgesics, with remarkable reduction of pain symptoms. These benefits can also reduce the associated side effects from the opioid analgesics, including drug tolerance, dependence, addiction, overdose, and related mortality. Similar results were observed in a small scale clinical trial that enrolled central neuropathy and fibromyalgia patients that were treated with 9-Tetrahydrocannabinol (delta 9-THC).

This evidence empirically indicates the possible therapeutic role of cannabinoids in fibromyalgia treatment, and more large scale studies are needed to demonstrate these findings in a larger population.

An online survey (conducted by the National Pain Foundation) that included over 1,300 chronic pain disorder patients concluded that medical cannabis can outsmart top analgesic drugs that are currently used for fibromyalgia treatment. The survey asked the participants to rate the effectiveness of treatments based on their usage experience. The participants were asked to compare the symptomatic relief benefits provided by cannabinoids, Lyrica, Savella, and Cymbalta.

Nearly 60% of the participants who have tried all three drugs reported ‘poor treatment benefits’. To our surprise, 62% of participants who tried cannabinoids have found it ‘very effective’, while 33% and 5% of patients have reported ‘little benefits’ and ‘no benefits’, respectively. Similarly, a 2012 Canadian survey found that one in every eight fibromyalgia patients relies on medical cannabis to cope with their symptoms.

One study investigated the patterns of cannabis use and associated benefits, including improvement in the quality of life among fibromyalgia patients. When compared to non-users, cannabis users experienced reduction in pain symptoms, stiffness, and somnolence enhancement of relaxation and sense of well-being. These results suggest the remarkable therapeutic benefits of cannabinoids in fibromyalgia treatment.

Based on the available knowledge on anti-nociceptive and anti-hyperalgesic effects of cannabinoids, one pilot study was conducted to demonstrate the reported benefits of THC. The study subjects were assigned to receive a daily dose of 2.5-15 mg of THC with an average increase of 2.5 mg every week until development of adverse events or tolerance. Although no effect on axon reflex flare were observed, significant reduction of pain symptoms was evident after administration of a 10-15 mg dose of THC. Reduction in daily recorded pain was also recorded. These findings suggest that THC can decrease pain perceptions by a central mode of action.

One retrospective study to investigate the medicinal benefits of cannabis on chronic pain found that both genders' use of medical cannabis were of the same rates. However, the majority of users reported significant pain alleviation, despite barriers in treatment access and delivery modes.

Due to legal restrictions, limited numbers of clinical trials on cannabis have been conducted to date. Nonetheless, we are able to see a number of ongoing and completed clinical trials, and reported analgesic benefits after synthetic cannabinoid use.

Still, most of the patients prefer to choose/use natural cannabis over synthetic cannabinoids, which may cause serious side effects, including death.

Marijuana Strain Does Matter

Research studies have shown that cannabis is generally useful for pain management. However, the efficacy of cannabis greatly depends on the cannabis strains. Among the available cannabis strains, "ACDC" has been shown to be effective for treatment of generalized pain, including fibromyalgia-related pain. This variant contains higher amounts of both THC and CBD, which can potentially relieve the pain symptoms while the CBD can counter the adverse effects of THC. Some experts believe heavy indica strains, such as Mazar I Sharif, Afghan Kush, White Widow, and Blackberry Kush are more effective in relieving pain symptoms. Cannabis activists believe strains that contain high amounts of THC can provide more pain relief. Some of the more THC-rich cannabis strains are Cannatonic and Harlequin. In addition to pain benefits, these strains typically possess anxiolytic, anti-depressive and sedative properties that are useful for alleviation of fibromyalgia symptoms. Marijuana can reduce pain and muscle stiffness while normalizing sleep

patterns, which is believed to be one of the causatives of fibromyalgia.

The emerging knowledge on the endocannabinoid system and the possible role of the stress system in the pathogenesis of fibromyalgia suggests that endocannabinoid modulators, including phytocannabinoids, can potentially treat fibromyalgia. Based on the presented evidence, it is clear that medical marijuana has significant pain-modifying potential without causing serious side effects, which can be extremely beneficial for fibromyalgia patients.

Prakash Janakiraman

Prakash is a biomedical researcher and medical writer by profession with extensive experience in pharmacology, molecular oncology, stem cells science and clinical trials. He authored medical textbooks and several research publications in peer-reviewed medical journals. Prakash is an ardent advocate of medical marijuana, wants to educate the science of medical marijuana to general public.

Hindawi Publishing Corporation
Anesthesiology Research and Practice
Volume 2009, Article ID 827290, 9 pages
doi:10.1155/2009/827290

Clinical Study

Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey

Janet Weber,[1] Marcus Schley,[2] Matthias Casutt,[1] Helmut Gerber,[1] Guido Schuepfer,[1] Roman Rukwied,[1,2] Wolfgang Schleinzer,[3] Michael Ueberall,[4] and Christoph Konrad[1]

[1] *Department of Anesthesiology, Intensive Care, Emergency Medicine and Pain Therapy, Kantonsspital Lucerne, 6000 Lucerne, Switzerland*
[2] *Department of Anesthesiology, Medical Faculty Mannheim, University of Heidelberg, 68167 Mannheim, Germany*
[3] *Department of Anesthesiology and Pain Medicine, Swiss Paraplegic Center, 6207 Nottwil, Switzerland*
[4] *Department of Neuroscience, Algesiology and Pediatrics, 90419 Nuremberg, Germany*

Correspondence should be addressed to Christoph Konrad, christoph.konrad@ksl.ch

Received 20 April 2009; Revised 30 July 2009; Accepted 7 September 2009

Recommended by Thomas J. J. Blanck

Central neuropathic pain is difficult to treat, but delta 9-Tetrahydrocannabinol (delta 9-THC) may be a promising therapeutic agent. We administered in 172 patients on average 7.5 mg delta 9-THC over 7 months. Of these, 48 patients prematurely withdrew due to side effects, insufficient analgesia, or expense of therapy. Thus, 124 patients were assessed retrospectively in a multicenter telephone survey. Reported changes in pain intensity, recorded on a numeric rating scale (NRS), Pain Disability Index (PDI), Medical Outcomes Short-Form (SF-12), Quality of Life Impairment by Pain (QLIP), Hospital Anxiety Depression Scale (HADS), and amount of concomitant pain medication were recorded. Psychometric parameters (PDI, SF-12, QLIP, HADS) and pain intensity improved significantly during delta 9-THC treatment. Opioid doses were reduced and patients perceived THC therapy as effective with tolerable side effects. About 25% of the patients, however, did not tolerate the treatment. Therapy success and tolerance can be assessed by a transient delta 9-THC titration and its maintained administration for several weeks. The present survey demonstrates its ameliorating potential for the treatment of chronic pain in central neuropathy and fibromyalgia. A supplemental delta 9-THC treatment as part of a broader pain management plan therefore may represent a promising coanalgesic therapeutic option.

1. Introduction

Various drugs belonging to different pharmacologic classes are currently prescribed and administered for the treatment of central neuropathic pain and fibromyalgia syndrome, including antidepressants, first- and second-generation anticonvulsants, antiarrhythmics, topical agents, N-methyl-D-aspartate receptor antagonists, and opioid analgesics [1, 2]. The long-term use of these drugs is often limited by adverse effects or patient's compliance. About 25% of the patients consulting pain clinics suffer from neuropathic pain states [3]; however, central neuropathic pain is often refractory to many treatments.

Over the last decades, the cannabinoids and their chemistry, the enzymes and receptors involved in their metabolism, as well as their assumed physiological and pathological roles in human pain pathways, have been characterized in detail [4–8].

Among hundreds of constituents of *cannabis sativa*, delta 9-Tetrahydrocannabinol (delta 9-THC) is the main active constituent. It is one of the natural compounds of marijuana (cannabis, hash) and was first synthesized by Mechoulam in 1967 [9]. The therapeutic use of cannabis has been widely reviewed [10–14] but the clinical use so far has been conflicting and is limited partly due to the narrow therapeutic index of delta 9-THC [15]. Several practical problems as well as ethical issues due to their potential abuse have been raised; however, delta 9-THC meanwhile is legally available for medical treatment throughout the world (US, Europe, Africa). It was reported that THC revealed beneficial

effects on pain and spasticity caused by multiple sclerosis [16, 17]. Also, THC might be effective in the treatment of chemotherapy-induced emesis, depression, low appetite, paresthesia, muscle pain, and painful neuropathy [18, 19], and cannabidiol represents a promising therapeutic agent in neurodegenerative disorders [10]. The indication for a cannabinoid-based therapy, however, demands a thorough risk/benefit evaluation. Particularly the patients' history of substance abuse has to be considered [20], as well as the specific diagnosis of the patients disease (e.g., cancer, HIV, MS, etc.). The efficacy of cannabinoids has been reported to be controversial in the literature when neuropathic pain [21, 22], experimentally induced pain [23], or hyperalgesia [24] are concerned. Therefore, delta 9-THC should be classified as a coanalgesic [25, 26] rather than pure analgesic drug.

Here, we explored the clinical applicability and efficacy of delta 9-THC administration supplemental to existing medication plan of patients suffering from refractory central neuropathic pain and fibromyalgia by means of a standardized retrospective telephone interview survey.

2. Material and Methods

After approval by the Ethics Committee II, Medical Faculty Mannheim, University of Heidelberg, 19 practitioners within different Federal States of Germany recruited 172 patients diagnosed with central neuropathic pain and fibromyalgia.

The 19 medical specialists were particularly experienced in anaesthesiology, neurology, and algesiology, as well as their extensive experience with the therapy of chronic and neuropathic pain patients. None of the 19 practitioners had received previously industry sponsored research money or were in cooperation with the authors. All practitioners had prescribed THC before and at least 10 times per year and were members of the German Association for Pain Therapy (DGS).

Delta 9-THC is available on prescription only. Inclusion criteria for prescription were primarily ineffectiveness of current pain therapy, but also sleep disturbances and decreased quality of life reported by the patients. For titration of the drug, all practitioners increased the oral delta 9-THC dose weekly by 2.5 mg and as long as no severe side effects were reported. Dosing did not exceed 15 mg per day, unless medication was ineffective. Delta 9-THC was taken in the morning and evening and therapy was maintained for at least 3 months. Each medical specialist contributed on average 5–8 patients to the survey, who signed a written informed consent prior to delta 9-THC medication. Only patients with a central neuropathic pain syndrome or fibromyalgia were included, irrespective of gender, age, or ethnic origin. The existence of central neuropathic pain was defined when patients suffered central neuropathy due to an inflammatory damage or trauma of the central nervous system. Exclusion criteria were chronic neuropathic pain states of peripheral origin. All 172 patients received, in addition to their current medication, delta 9-THC (dronabinol; Delta 9 Pharma, Neumarkt, Germany) for pain therapy. Demographic data, general health, diagnosis, and medical history were compiled from the patients' files. A researcher, who was experienced in performing telephone interviews, but had no association with the authors or the 19 medical specialists, was employed to collect the data. The interviewer was not informed about the medication plan of the patient or the objective of the survey. Following parameters were recorded: patients' self-reported pain intensity (verbal and numeric ratings), efficacy and tolerability of the pre-THC regimen, efficacy and tolerability of delta 9-THC medication, improvement in mood and quality of life, general impairment, and work performance. Efficacy and tolerability of pre-THC regimen and current analgesic therapy was recorded using a rating scale in the range from 1 to 6, with the descriptors (1) "very good," (2) "good," (3) "satisfying," (4) "critical," (5) "insufficient," and (6) "poorly." Further, a psychometric assessment was performed, including the Medical Outcomes Short-Form (SF-12), the Pain Disability Index (PDI), the Quality of Life Impairment by Pain (QLIP), and the Hospital Anxiety and Depression Scale (HADS).

The perceived pain intensity was estimated by the patients on a 6-point Verbal Rating Scale (VRS) with the particular descriptors (corresponding values given in brackets): no pain (0), slight pain (2), moderate pain (4), intense pain (6), very strong pain (8), worst pain imaginable (10). In addition, maximum pain intensity was estimated on an 11-point Numeric Rating Scale (NRS) with the endpoints 0 (no pain) and 10 (maximum pain imaginable). Also, patients were requested to evaluate possible changes of symptoms resulting from delta 9-THC treatment. In particular, characteristics of pain intensity and pain quality, tolerability of delta 9-THC therapy, and changes in coanalgesics were recorded. Patients were instructed to specify side effects by means of a list of thirty characters. Recordings made by the patients were documented independently from the practitioner's assessment regarding adverse effects and effectiveness.

Data were analyzed by means of descriptive statistical analysis using SPSS software package (SPSS Inc., Chicago, Illinois, USA). Patients' values prior to delta 9-THC therapy and values during THC treatment were evaluated for significant differences between the values identified by ANOVA. In order to analyze categorical data in which P-values were calculated for c (columns) $\times$ r (rows), StatExact 5.0 software package (Cytel Inc., Massachusetts, US) was used and Pearson's chi-square test applied ($P < .05$). Data of psychometric assessment are depicted as mean + standard deviation (SD).

3. Results

Of the 172 patients, 48 prematurely withdrew within 2 weeks from the survey due to tiredness as side effect ($n = 6$), insufficient therapy effect ($n = 5$), expenses of delta 9-THC therapy ($n = 29$), or other reasons ($n = 23$) that include mainly dizziness and an enhanced appetite. Consequently, complete data sets were recorded from 124 patients only (77 women, 47 men, average age 55 $\pm$ 13 years).

3.1. Demographic Details and Diagnosis. Most of the patients ($n = 114$) had been suffering from pain for more than three

Table 1: Etiology of the diagnosed central neuropathic pain. Neuropathies within the patient cohort were grouped by an inflammatory origin ($n = 43$) or a trauma of the central nervous system ($n = 49$). Note that fibromyalgia patients ($n = 32$) are not listed.

Inflammatory central neuropathy	Central neuropathy due to trauma
Multiple sclerosis ($n = 32$)	Paraplegia ($n = 8$)
Encephalitis (n=9)	Stroke ($n = 10$)
Others ($n = 2$)	Intracranial injury ($n = 4$)
	Neoplasm ($n = 4$)
	Others ($n = 23$)

years, other patients for 1 to 3 years ($n = 7$). Of 3 patients, however, no duration of pain history could be obtained.

The etiology of the patients diagnosed with central neuropathy ($n = 92$) was primarily of inflammatory origin ($n = 43$), such as multiple sclerosis ($n = 32$), encephalitis ($n = 9$), and others ($n = 2$), or due to a trauma of the central nervous system ($n = 49$), such as stroke ($n = 10$), paraplegia ($n = 8$), intracranial injury ($n = 4$), neoplasm ($n = 4$), or others ($n = 23$) (see Table 1). A somatic cause of pain in neoplasm patients due to the location and extent of the neoplasm was excluded by ultrasound and computer tomography examination.

In addition to central neuropathy patients, 32 fibromyalgia patients suffering also chronic pain were included in the survey. A controversy is prevailing whether fibromyalgia patients can be included as a central neuropathic pain state. It has been reported in former studies that fibromyalgia is characterized by widespread generalized pain with an abnormal nociceptive central processing [27, 28]. By contrast, most clinicians being involved in the treatment of chronic pain would argue that fibromyalgia is not a purely central neuropathic pain syndrome, as reviewed recently [29]. Therefore, we analysed in the present survey the fibromyalgia patients as independent group from patients diagnosed with central neuropathic pain (see Table 3). Fibromyalgia was diagnosed according to the criteria of the American College of Rheumatology [30], including tender point on the physical examination [31, 32]. All patients complained widespread pain and revealed soreness upon pressure in at least 11 out of 18 tender points.

3.2. Analgesic Medication and Its Efficacy prior to Therapy. Patients most commonly received nonopioids, such as NSAID's $n = 60$ (48%), COX2-inhibitors $n = 34$ (27%), paracetamol $n = 29$ (23%), metamizol $n = 44$ (36%) (see Table 2), but also opioids, tramadol $n = 35$ (28%), morphine $n = 22$ (18%), or hydromorphone $n = 17$ (14%), as well as coanalgesics, such as antidepressants $n = 68$ (55%) or anticonvulsants $n = 40$ (32%).

The efficacy of the analgesic medication prior to delta 9-THC treatment was assessed by the patients as follows: very good $n = 1$ (0.8%), good $n = 4$ (3%), satisfactory $n = 15$ (12%), sufficient $n = 24$ (19%), insufficient $n = 58$ (47%), poor $n = 20$ (16%).

3.3. Analgesic Medication during Delta 9-THC Therapy. During therapy with delta 9-THC, administration of analgesics could be reduced. Only nonopioids were maintained in 36 patients (29%), opioids continued in 39 patients (31%), and coanalgesic medication pursued in 54 patients (43%) (see Table 2).

3.4. Delta 9-THC Dose and Duration of Administration. Delta 9-THC was administered as liquid ($n = 78$, 63%), as capsule ($n = 27$, 22%), or both in combination ($n = 19$, 15%). On average, a mean daily dose below 7.5 mg delta 9-THC was administered to 47 patients (38%), dosages between 7.5 and 15 mg received 26 patients (21%), and dosages >15 mg were taken by 16 patients (13%). In 35 patients (28%) the daily taken delta 9-THC dose could not be obtained. Overall, the median administered delta 9-THC concentration was on average 7.5 mg per day (interquartile range 5–12.5 mg).

35 patients received delta 9-THC medication up to 4 months (28%), 38 patients 4–24 months (31%), and 16 patients for more than 24 months (13%). No duration recordings, however, were obtained from 35 patients (28%). Thus, on average, delta 9-THC treatment lasted 217 days (interquartile range 27–412 days).

3.5. Pain Score. Pain intensity was estimated on a verbal rating scale (VRS), as described previously.

Prior to delta 9-THC administration, light pain was recorded in $n = 2$ patients (2%), moderate pain in $n = 7$ (6%), intense pain in $n = 24$ (19%), very strong pain in $n = 71$ (57%), and worst pain imaginable in $n = 20$ (16%) (see Figure 1(a)). Following delta 9-THC administration, verbally reported pain intensity improved significantly ($P < .001$, Pearson's chi-square test), revealing a median value of 4 "moderate pain" after delta 9-THC in comparison to a median value of 8 "very strong pain" prior to THC-therapy. In particular, during delta 9-THC administration, no pain was reported on the verbal rating scale in $n = 4$ patients (3%), slight pain in $n = 26$ (21%), moderate pain in $n = 57$ (46%), intense pain in $n = 28$ (23%), very strong pain in $n = 8$ (7%), and worst pain imaginable still in 1 patient (see Figure 1(a)).

Subgroup analysis of fibromyalgia revealed no differences of pain intensity to the group of inflammatory- and trauma-evoked central neuropathic pain patients prior to and during/after delta 9-THC medication. Prior to delta 9-THC administration, mean pain intensity (VRS) of fibromyalgia was on average 7.9 ± 1.5, which was reduced to 4.4 ± 1.5 during/after THC-treatment. Similarly, inflammatory pain patients reported a mean pain intensity of on average 7.6 ± 1.7 before THC, and 4.2 ± 1.9 after delta 9-THC therapy. Trauma-induced central neuropathic pain patients estimated pain at 7.6 ± 1.4 prior to and $3.8 + 1.5$ during/after delta 9-THC medication (see Table 3).

Maximum perceived pain intensity was estimated on a numeric rating scale (NRS), as described previously. Pain reported by patients before THC-therapy was NRS < 6 in $n = 4$ (3%), NRS 6 in $n = 3$ (2%), NRS 7 in $n = 7$ (6%),

Table 2: Medication administered to the patients before and during/after delta 9-THC therapy. A substantial reduction of the medication within each group, that is, nonopioids, opioids, or nonanalgesics (primarily antidepressants and anticonvulsants), could be recorded during the treatment with delta 9-THC.

		Before delta 9-THC therapy		During/after delta 9-THC therapy	
Comedication		Number of patients	%	Number of patients	%
Nonopioids	NSAID	60	48	7	5.6
	COX2-inhibitors	34	27	7	5.6
	Paracetamol	29	23	3	2.4
	Metamizole	44	35	10	8.1
	Flupirtin	37	30	7	5.6
	others	14	11	2	1.6
Opioids	Tramadol	35	28	2	1.6
	Naloxone	36	29	5	4
	Buprenorphin/fentanyl	15	12	5	4
	Morphin	22	18	7	5.6
	Hydromorphone	17	14	10	8.1
	Oxycodone	13	10	5	4
	Others	6	5	5	4
Nonanalgesics	Antidepressants	68	55	18	14.5
	Anticonvulsants	40	32	18	14.5
	Corticosteroids	19	15	6	4.8
	NMDA-antagonists	5	4	5	4
	Others	21	17	7	5.6

Table 3: Estimated pain intensity (VRS) and maximum/minimum pain (NRS) recorded in the subgroups of "inflammatory central neuropathy"—"central neuropathic pain due to trauma"—"fibromyalgia" prior to and during/after delta 9-THC therapy. No significant differences between the groups could be analysed. In each group, delta 9-THC medication caused a noticeable amelioration of pain.

	Inflammatory central neuropathy		Central neuropathy due to trauma		Fibromyalgia	
	Prior to	After	Prior to	After	Prior to	After
	Delta 9-THC medication		Delta 9-THC medication		Delta 9-THC medication	
Pain intensity (VRS, 0–10)	7.6 ± 1.7	4.2 ± 1.9	7.6 ± 1.4	3.8 ± 1.5	7.9 ± 1.5	4.4 ± 1.5
Max. pain (NRS, 0–10)	7.6 ± 1.7	4.9 ± 2.4	9.3 ± 1	5.3 ± 1.7	9.3 ± 1.1	6.1 ± 2.1
Min. pain (NRS, 0–10)	5.4 ± 1.8	2.1 ± 1.5	6.0 ± 1	2.9 ± 1.9	6.6 ± 2	3.0 ± 1.8

NRS 8 in $n = 17$ (14%), NRS 9 in $n = 19$ (15%), and NRS 10 in $n = 74$ (60%). In contrast, maximum pain estimated by the patients after delta 9-THC therapy was perceived at NRS < 6 in $n = 55$ patients (44%), NRS 6 in $n = 27$ (22%), NRS 7 in $n = 9$ (7%), NRS 8 in $n = 23$ (19%), NRS 9 in $n = 1$ (0.8%), and NRS 10 in $n = 9$ (7%) (see Figure 1(b)).

No significant difference of maximum pain was obtained between fibromyalgia syndrome and inflammatory- or trauma-evoked central neuropathic pain patients. On average, maximum pain intensity (NRS) was in fibromyalgia recorded at 9.3 ± 1.1 prior to delta 9-THC and 6.1 ± 2.1 thereafter. Central chronic pain patients reported a maximum pain intensity of 8.7 ± 1.7 (inflammatory pain) and 9.3 + 1 (trauma pain) prior to delta 9-THC, but 4.9 + 2.4 (inflammatory pain) and 5.3 + 1.7 (trauma pain) after THC-therapy, respectively (see Table 3).

3.6. Psychometric Assessment. Prior to delta 9-THC administration, the Pain Disability Index (PDI) was on average 36.4 ± 10.7, which improved significantly to 22.8 ± 10.8 with the delta 9-THC administration ($P < .001$). Similarly, improved Medical Outcomes Short-Form scores (SF-12) were recorded, with significantly increased health-related subscale scores from 23.1 ± 6.3 before therapy to 33.4 ± 9.7 after delta 9-THC administration ($P < .001$) and a comparable increase of the mental subscale score from 35.6 ± 9.1 to 47.3 ± 7.4 ($P < .001$), respectively. Quality of life assessed by the pain summary scale (QLIP) also improved by about 150% from 9.7 + 6.6 before therapy to 24.7 + 6.9 after delta 9-THC (see Figure 2). In addition, pain-related disability of patients to perform their daily professional work reduced from a mean score impairment of 7.6 ± 2.3 prior to therapy to 5.2 ± 2.7 after delta 9-THC. Finally, mean Hospital

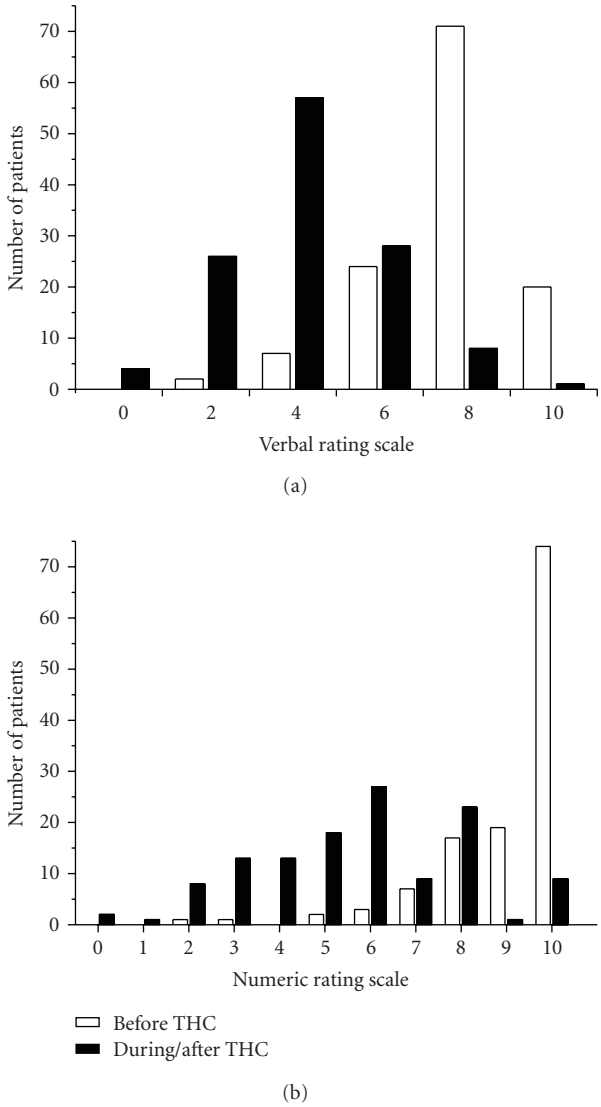


Figure 1: Number of patients and their estimation of the perceived pain intensity before (white bar) and during/after (black bar) delta 9-THC therapy by means of (a) Verbal Rating Scale (VRS) and (b) Numeric Rating Scale (NRS). Values of the VRS indicate "no pain" (0), "slight pain" (2), "moderate pain" (4), "intense pain" (6), "very strong pain" (8), "worst pain imaginable (10). The endpoints of the NRS indicate "no pain" (0) and "worst pain imaginable" (10).

Anxiety and Depression Scale (HADS) was attenuated for anxiety from 10 ± 6.1 to 5.2 ± 3.6 and for depression from 13.3 ± 5.5 to 7.3 ± 4.1, respectively ($P < .001$).

The vast majority of patients (92%) evaluated the delta 9-THC therapy as efficient and accepted its administration as coanalgesic. In contrast, no improvement was reported in 3% of the patients, and 5% complained of increased pain (data not shown).

3.7. Adverse Effects. In 12 patients (10%), adverse effects were reported but tolerated during delta 9-THC therapy, of which tiredness ($n = 3$) and sedation or dizziness ($n = 4$) were primary side effects.

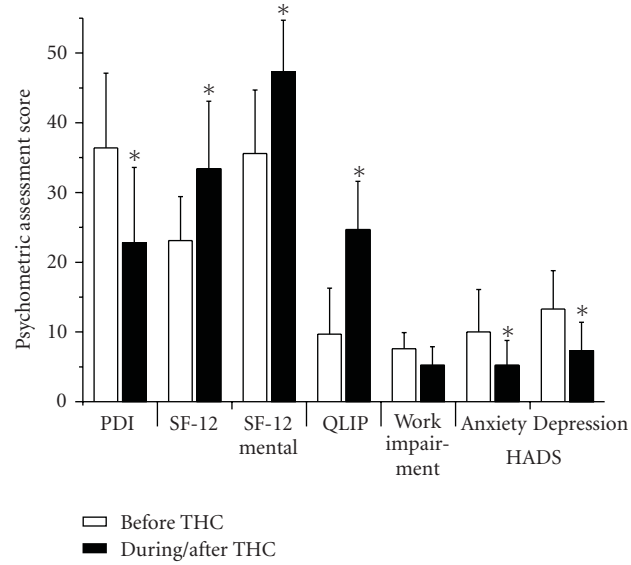


Figure 2: Psychometric assessment of the patients before (white bar) and during/after (black bar) delta 9-THC therapy. Particularly Pain Disability Index (PDI), Quality of Life (QLIP), and Hospital Anxiety Depression Scale (HADS) improved significantly in response to delta 9-THC treatment.

4. Discussion

Cannabis (delta 9-THC) has been recognized as appetite stimulant and antiemetic drug, and therefore had been administered clinically to ameliorate side effects in patients receiving, for example, cancer- or HIV-chemotherapy [33, 34]. The therapeutic index of delta 9-THC, however, is narrow. Therapeutic efficient plasma THC-levels are often accompanied by the typical cannabinoid side effects and these may be indicated in special populations, such as chemotherapy-induced nausea or cachexia. By contrast, possibly due to the narrow therapeutic index [15], conflicting reports have emerged upon the clinical use of delta 9-THC in different areas of pain therapy [14] and cannabinoids were acknowledged as coanalgesic adjunct rather than a pure analgesic [21–23, 35]. Also, delta 9-THC should be considered as a psychopharmacological analgesic medication [20]; therefore a careful risk/benefit analysis of cannabinoid treatment may be required, including the evaluation of misuse risk assessment of patients addiction behaviour [20] and withdrawal strategies in cases misuse occur.

In the present retrospective survey we assessed delta 9-THC therapy in central neuropathic pain and fibromyalgia patients. Even though it appears premature to classify fibromyalgia as a neuropathic pain syndrome [29], these patients suffer chronic pain and often from an impaired quality of life due to depression, sleep deprivation, or other functional somatic syndromes. Therefore, these patients may profit from a coanalgesic and psychopharmacologic delta 9-THC therapy. About 25% of patients, however, withdrew from delta 9-THC administration for various reasons, among others due to a self-assessed ineffective therapy. Those patients who did respond to delta 9-THC therapy, the vast

majority reported a significant reduction of pain intensity, a relevant improvement of mood and quality of life, and a lowering of concomitant opioid medication.

4.1. Pain Intensity. In our patient sample, THC treatment led to a significant reduction in pain intensity. Noteworthy, this effect could be observed when a mean daily dose of 7.5 mg THC was administered. This dosage shows high acceptance and efficacy.

According to our findings, positive reports had been reported previously in smaller patient samples in which delta 9-THC was used for therapy of refractory neuropathic pain states [16]. The authors described the combination of cannabinol and cannabidiol being effective in the treatment of central neuropathic pain in multiple sclerosis patients. A recent meta-analysis supported these findings [36]. In addition, other clinical trials in which central neuropathic pain patients were treated with cannabinoids revealed a modest but clinically relevant analgesic effect in the treatment group when compared to placebo [37, 38]. In addition, in the present survey, patients reported that efficacy and acceptance of therapy were significantly better during THC treatment. It should be noted that a cannabinoid-based analgesia is not for acute or subacute pain therapy. However, after a beneficial trial, THC may be considered as a longer term coanalgesic. As reported previously after oromucosal cannabis-based therapy of central neuropathic pain patients, the perceived pain intensity was reduced and sleep disturbances improved over a time period exceeding 1 year [39, 40].

No effects of delta 9-THC, however, were observed in postoperative pain management [41] and experimental human pain models [23]. Also, a study conducted in refractory central neuropathic pain patients did not support an overall benefit of THC on pain and quality of life upon sublingual administration of the cannabinoid nabilone [42]. In this investigation, however, treatment was terminated in 5 out of 7 patients due to intolerable side effects, probably caused by the administered doses of up to 25 mg/day. The short period of drug administration in these studies may explain a lack of analgesic effect. If a single dose exceeds 20 mg THC, side effects are likely to dominate before the appearance of pharmacological effects. THC is lipophilic and has a complex central pharmacokinetic with unexpectedly long half life in the CNS. Therefore, as reported by Rog and colleagues, an efficient cannabinoid therapy may be achieved by long-term administration of delta 9-THC at low doses [39] to enable a steady-state tissue THC-concentration, which also would meet the narrow therapeutic range of THC as a psychogenic drug.

4.2. Quality of Life. A further important and beneficial effect of delta 9-THC therapy is the change of the patient's mood that can occur in addition to pain reduction. Animal data suggested an antidepressant effect of THC [43, 44], which is supported by the present survey showing a significant reduction of depression in the patients during treatment. This effect likely is attributed to an activation of cannabinoid receptors in the brain. In human neocortex and amygdala, the CB1 receptor is frequently expressed. The amygdala, the anterior cingulate cortex, and the prefrontal cortex are key structures in the brain for memory, for the perception and emotional processing of pain, and also for the integration of mood modulation. In an animal model, Marsicano et al. demonstrated that aversive memory can be extinguished after application of THC [45]. Also, in experimental catastrophic situations, THC was able to diminish stress reaction in animals [43, 44]. Given that pain memory is a crucial mechanism of maintaining pain perception, these experimental data may be of importance to explain the beneficial effect of delta 9-THC in the treatment of chronic pain patients. The intake of antidepressants and anticonvulsants in neuropathic pain states has been linked to pain memory and mood changes. Their effectiveness apparently increased during THC-therapy, indicated by a reduced administration. Thus, therapeutic effects of delta 9-THC might be based, at least to some extent, on pain memory extinction and mood changes.

Importantly, in this context, delta 9-THC treatment additionally improved health-related quality of life, as indicated here by the PDI and SF12 scores. Previous data recorded in humans support this finding [2, 46]. Particularly, patients suffering multiple sclerosis [37] or pain from brachial plexus avulsion [46] appraise THC therapy and report better quality of life. To assess the effect of therapeutic intervention, however, pain research has mainly focused on the reduction of pain intensity, even though quality of life parameters may reflect clinical improvement for the patients much better. In this respect, ability to work or job impairment is important factors. Here, we found that work-related situations improved after THC treatment. Data on this topic with respect to central neuropathic pain and fibromyalgia are missing so far, as most studies investigating environmental aspects improving work-life refer to musculoskeletal pain [47].

4.3. Concomitant Medication. Administration of delta 9-THC supplemental to the current pain medication did not deteriorate therapy; rather patients were able to reduce the analgesics, particularly the intake of opioids. An interaction between cannabinoids and opioids has been reported in previous experimental studies before and it was suggested that delta 9-THC induced effects are mediated also through delta and kappa opioid receptors [48]. Interestingly, a reciprocal alteration of receptor density has been observed in presence of cannabinoids and opioids [49]. This observation also may include modified receptor activation, for instance, delta 9-THC enhanced opioid receptor recruitment, which would explain a reduced opioid medication. Thus, as suggested recently [50], drug combinations should be considered for therapy, and as presented here, delta 9-THC may represent one option of medication.

Intriguingly, of the concomitantly administered medication, no change in the use of NMDA antagonists was recorded. This observation might be attributed to a lacking additional effect of cannabinoids with NMDA antagonists. Also, an inhibitory action of selective NMDA antagonists on the antinociceptive efficacy of cannabinoids was reported

recently in the rat periaqueductal grey [51], which may require an increased cannabinoid administration rather than a reduced NMDA antagonist medication for therapy.

4.4. Limitations. A limitation of the study is performance of a *single* telephone survey by one interviewer. A face-to-face *serial* interviews may be suggested as a better study design alternative, which was considered during development of the study protocol. Performing a multicenter study would require a large number of interviewers conducting the face-to-face interview. The parameter assessment by different interviewers may cause variations, particularly considering psychometric parameters, and irrespective the experiences of the interviewers. A telephone survey, performed by one interviewer only, may be minimally influenced by external factors and therefore suggests consictency of the evaluated parameters in the patient.

Another limitation may be due to the heterogenous patient group with very little selection criteria. This justifiable concern actually was one objective of the survey, that is, to explore the applicability and usefulness of an additional coanalgesic cannabinoid treatment in a broad and unspecific group of pain patients. Consequently, the relatively high drop out rate of about 25% may be due to the virtually absent selection criteria of the patients, but also may have caused by the narrow therapeutic index of THC, as mentioned previously.

Amelioration of pain and quality of life improvement were major outcome parameters. In future surveys, therefore, further limiting factors like practice variation, duration of medication, assessment of addiction behaviour, and misuse risk should be considered and included in future interview protocols.

5. Conclusions

Patients taking delta 9-THC for pain therapy can be interviewed easily by phone to explore their tolerance towards the medication. Some but not all patients who respond and tolerate delta 9-THC administration may benefit considerably from this coanalgesic. Acceptance and tolerance of a short-lasting delta 9-THC trial therefore would determine a selection criterion for an additional treatment option to reduce pain, to decrease the comedication, and to improve quality of life. Transient delta 9-THC titration up to about 15 mg, its continued administration for a few weeks, the documentation of the patients tolerance to the therapy with putative side effects, and the recording of the patients' self-reported pain estimates would reveal the efficacy and tolerability of a supplemental cannabinoid-based coanalgesic medication.

Acknowledgments

This study was supported by BIONORICA, Neumarkt, Germany. The authors thank Ramona Naegeli for her outstanding assistance in collection of the data and Ilona Rossbach for her editorial assistance.

References

[1] R. Freeman, "The treatment of neuropathic pain," *CNS Spectrums*, vol. 10, no. 9, pp. 698–706, 2005.

[2] T. Saarto and P. J. Wiffen, "Antidepressants for neuropathic pain," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD005454, 2007.

[3] D. Bowsher, "Neurogenic pain syndromes and their management," *British Medical Bulletin*, vol. 47, no. 3, pp. 644–666, 1991.

[4] A. Calignano, G. La Rana, A. Giuffrida, and D. Piomelli, "Control of pain initiation by endogenous cannabinoids," *Nature*, vol. 394, no. 6690, pp. 277–281, 1998.

[5] L. Iversen, "Cannabis and the brain," *Brain*, vol. 126, no. 6, pp. 1252–1270, 2003.

[6] K. Mackie, "Cannabinoid receptors as therapeutic targets," *Annual Review of Pharmacology and Toxicology*, vol. 46, pp. 101–122, 2006.

[7] R. Rukwied, B. Gauter, M. Schley, and C. Konrad, "Cannabinoids—signal transduction and mode of action," *Schmerz*, vol. 19, no. 6, pp. 528–534, 2005.

[8] J. M. Sullivan, "Cellular and molecular mechanisms underlying learning and memory impairments produced by cannabinoids," *Learning and Memory*, vol. 7, no. 3, pp. 132–139, 2000.

[9] R. Mechoulam and Y. Gaoni, "The absolute configuration of δ1-tetrahydrocannabinol, the major active constituent of hashish," *Tetrahedron Letters*, vol. 8, no. 12, pp. 1109–1111, 1967.

[10] T. Iuvone, G. Esposito, D. De Filippis, C. Scuderi, and L. Steardo, "Cannabidiol: a promising drug for neurodegenerative disorders?" *CNS Neuroscience and Therapeutics*, vol. 15, no. 1, pp. 65–75, 2009.

[11] D. Baker and G. Pryce, "The endocannabinoid system and multiple sclerosis," *Current Pharmaceutical Design*, vol. 14, no. 23, pp. 2326–2336, 2008.

[12] J. Manzanares, M. D. Julian, and A. Carrascosa, "Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes," *Current Neuropharmacology*, vol. 4, no. 3, pp. 239–257, 2006.

[13] D. Baker, G. Pryce, G. Giovannoni, and A. J. Thompson, "The therapeutic potential of cannabis," *Lancet Neurology*, vol. 2, no. 5, pp. 291–298, 2003.

[14] E. B. Russo, "Cannabinoids in the management of difficult to treat pain," *Therapeutics and Clinical Risk Management*, vol. 4, no. 1, pp. 245–259, 2008.

[15] M. Karst and S. Wippermann, "Cannabinoids against pain. Efficacy and strategies to reduce psychoactivity: a clinical perspective," *Expert Opinion on Investigational Drugs*, vol. 18, no. 2, pp. 125–133, 2009.

[16] D. J. Rog, T. J. Nurmikko, and C. A. Young, "Oromucosal Δ^9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial," *Clinical Therapeutics*, vol. 29, no. 9, pp. 2068–2079, 2007.

[17] J. Zajicek, P. Fox, H. Sanders, et al., "Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial," *The Lancet*, vol. 362, no. 9395, pp. 1517–1526, 2003.

[18] J. L. Croxford, "Therapeutic potential of cannabinoids in CNS disease," *CNS Drugs*, vol. 17, no. 3, pp. 179–202, 2003.

[19] E. Woolridge, S. Barton, J. Samuel, J. Osorio, A. Dougherty, and A. Holdcroft, "Cannabis use in HIV for pain and other medical symptoms," *Journal of Pain and Symptom Management*, vol. 29, no. 4, pp. 358–367, 2005.

[20] D. Gourlay, "Addiction and pain medicine," *Pain Research and Management*, vol. 10, supplement A, pp. 38A–43A, 2005.

[21] D. J. Buggy, L. Toogood, S. Maric, P. Sharpe, D. G. Lambert, and D. J. Rowbotham, "Lack of analgesic efficacy of oral δ-9-tetrahydrocannabinol in postoperative pain," *Pain*, vol. 106, no. 1-2, pp. 169–172, 2003.

[22] S. Clermont-Gnamien, S. Atlani, N. Attal, F. Le Mercier, F. Guirimand, and L. Brasseur, "The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain," *Presse Medicale*, vol. 31, no. 39, part 1, pp. 1840–1845, 2002.

[23] M. Naef, M. Curatolo, S. Petersen-Felix, L. Arendt-Nielsen, A. Zbinden, and R. Brenneisen, "The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions," *Pain*, vol. 105, no. 1-2, pp. 79–88, 2003.

[24] B. Kraft, N. A. Frickey, R. M. Kaufmann, et al., "Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers," *Anesthesiology*, vol. 109, no. 1, pp. 101–110, 2008.

[25] S. Narang, D. Gibson, A. D. Wasan, et al., "Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy," *Journal of Pain*, vol. 9, no. 3, pp. 254–264, 2008.

[26] C. Toth and S. Au, "A prospective identification of neuropathic pain in specific chronic polyneuropathy syndromes and response to pharmacological therapy," *Pain*, vol. 138, no. 3, pp. 657–666, 2008.

[27] R. Staud and M. Domingo, "Evidence for abnormal pain processing in fibromyalgia syndrome," *Pain Medicine*, vol. 2, no. 3, pp. 208–215, 2001.

[28] J. A. Desmeules, C. Cedraschi, E. Rapiti, et al., "Neurophysiologic evidence for a central sensitization in patients with fibromyalgia," *Arthritis and Rheumatism*, vol. 48, no. 5, pp. 1420–1429, 2003.

[29] M. C. Rowbotham, "Is fibromyalgia a neuropathic pain syndrome?" *Journal of Rheumatology*, vol. 32, supplement 75, pp. 38–40, 2005.

[30] F. Wolfe, H. A. Smythe, M. B. Yunus, et al., "The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee," *Arthritis and Rheumatism*, vol. 33, no. 2, pp. 160–172, 1990.

[31] R. S. Katz, F. Wolfe, and K. Michaud, "Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria," *Arthritis and Rheumatism*, vol. 54, no. 1, pp. 169–176, 2006.

[32] D. J. Clauw, "Assessing and diagnosing fibromyalgia in the clinical setting," *The Journal of Clinical Psychiatry*, vol. 69, no. 11, article e33, 2008.

[33] M. R. Tramèr, D. Carroll, F. A. Campbell, D. J. M. Reynolds, R. A. Moore, and H. J. McQuay, "Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review," *British Medical Journal*, vol. 323, no. 7303, pp. 16–21, 2001.

[34] J. E. Beal, R. Olson, L. Lefkowitz, et al., "Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia," *Journal of Pain and Symptom Management*, vol. 14, no. 1, pp. 7–14, 1997.

[35] J. D. Roberts, C. Gennings, and M. Shih, "Synergistic affective analgesic interaction between delta-9- tetrahydrocannabinol and morphine," *European Journal of Pharmacology*, vol. 530, no. 1-2, pp. 54–58, 2006.

[36] M. Iskedjian, B. Bereza, A. Gordon, C. Piwko, and T. R. Einarson, "Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain," *Current Medical Research and Opinion*, vol. 23, no. 1, pp. 17–24, 2007.

[37] K. B. Svendsen, T. S. Jensen, and F. W. Bach, "Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial," *British Medical Journal*, vol. 329, no. 7460, pp. 253–257, 2004.

[38] D. T. Wade, P. Robson, H. House, P. Makela, and J. Aram, "A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms," *Clinical Rehabilitation*, vol. 17, no. 1, pp. 21–29, 2003.

[39] D. J. Rog, T. J. Nurmikko, and C. A. Young, "Oromucosal Δ^9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial," *Clinical Therapeutics*, vol. 29, no. 9, pp. 2068–2079, 2007.

[40] D. J. Rog, T. J. Nurmikko, T. Friede, and C. A. Young, "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis," *Neurology*, vol. 65, no. 6, pp. 812–819, 2005.

[41] W. Seeling, L. Kneer, B. Büchele, et al., "Δ^9-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain," *Anaesthesist*, vol. 55, no. 4, pp. 391–400, 2006.

[42] N. Attal, L. Brasseur, D. Guirimand, S. Clermond-Gnamien, S. Atlami, and D. Bouhassira, "Are oral cannabinoids safe and effective in refractory neuropathic pain?" *European Journal of Pain*, vol. 8, no. 2, pp. 173–177, 2004.

[43] M. N. Hill and B. B. Gorzalka, "Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test," *European Neuropsychopharmacology*, vol. 15, no. 6, pp. 593–599, 2005.

[44] J. M. Witkin, E. T. Tzavara, and G. G. Nomikos, "A role for cannabinoid CB1 receptors in mood and anxiety disorders," *Behavioural Pharmacology*, vol. 16, no. 5-6, pp. 315–331, 2005.

[45] G. Marsicano, C. T. Wotjak, S. C. Azad, et al., "The endogenous cannabinoid system controls extinction of aversive memories," *Nature*, vol. 418, no. 6897, pp. 530–534, 2002.

[46] J. S. Berman, C. Symonds, and R. Birch, "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial," *Pain*, vol. 112, no. 3, pp. 299–306, 2004.

[47] W. S. Marras, S. A. Ferguson, D. Burr, P. Schabo, and A. Maronitis, "Low back pain recurrence in occupational environments," *Spine*, vol. 32, no. 21, pp. 2387–2397, 2007.

[48] D. L. Cichewicz, "Synergistic interactions between cannabinoid and opioid analgesics," *Life Sciences*, vol. 74, no. 11, pp. 1317–1324, 2004.

[49] D. Viganò, T. Rubino, and D. Parolaro, "Molecular and cellular basis of cannabinoid and opioid interactions," *Pharmacology Biochemistry and Behavior*, vol. 81, no. 2, pp. 360–368, 2005.

[50] T. S. Jensen and N. B. Finnerup, "Management of neuropathic pain," *Current Opinion in Supportive and Palliative Care*, vol. 1, no. 2, pp. 126–131, 2007.

[51] E. Palazzo, I. Marabese, V. de Novellis, et al., "Metabotropic and NMDA glutamate receptors participate in the cannabinoid-induced antinociception," *Neuropharmacology*, vol. 40, no. 3, pp. 319–326, 2001.

Arthritis Care & Research
Vol. 66, No. 6, June 2014, pp 797–801
DOI 10.1002/acr.22267

REVIEW ARTICLE

The Dilemma of Medical Marijuana Use by Rheumatology Patients

MARY-ANN FITZCHARLES,[1] DANIEL J. CLAUW,[2] PETER A. STE-MARIE,[1] AND YORAM SHIR[1]

Introduction

"Severe pain" is the most common reason for medicinal herbal cannabis use, with arthritis and musculoskeletal pain cited as the most prevalent specific medical condition (1,2). Eighty percent of marijuana users in a US pain clinic report use for myofascial pain, whereas up to one-third of persons in population studies in the UK and Australia reported use for treatment of arthritis pain (1–3). Similarly, "severe arthritis" is the diagnosis for 65% of Canadians authorized to possess cannabis for medicinal purposes as of June 2013 (4). Medical marijuana has, however, never been recommended by any rheumatology group worldwide for symptom relief in rheumatic conditions. As the health care professionals best placed to advise on issues of rheumatic diseases, rheumatologists must have a voice in the current debate concerning medical marijuana, hereafter identified as herbal cannabis.

Advocacy for access to cannabinoid treatments has led to a societal groundswell, with regulatory bodies around the globe considering the legalization of herbal cannabis for medicinal use. Currently, herbal cannabis is legalized for medicinal use in 20 states in the US as well as in the District of Columbia. Physicians will therefore be caring for patients who may be self-medicating with herbal cannabis or may request medical advice about cannabis. In order to responsibly advise patients on any medical issue, and in particular herbal cannabis, it is essential that the health care professional has a competent knowledge of the subject based on sound scientific study. In this review, we examined the current evidence for dosing and administration, efficacy, and risks of herbal cannabis in rheumatic pain management, and thereby addressed practical issues confronting rheumatologists whose patients request advice. We confined our comments to herbal cannabis as it pertains to rheumatic conditions, acknowledging that evidence and information may differ for other conditions. We did not enter into the debate addressing the legalization of recreational herbal cannabis.

[1]Mary-Ann Fitzcharles, MBChB, Peter A. Ste-Marie, LLB, Yoram Shir, MD: McGill University Health Centre, Montreal, Quebec, Canada; [2]Daniel J. Clauw, MD: University of Michigan Medical Center, Ann Arbor.

Dr. Fitzcharles has received consulting fees, speaking fees, and/or honoraria (less than $10,000 each) from Abbott, Amgen, Lilly, Pfizer, Purdue, and Valeant. Dr. Clauw has received consulting fees, speaking fees, and/or honoraria (less than $10,000 each) and/or research grants from Cerephex, Forest, Johnson & Johnson, Lilly, Merck, Nuvo, Pfizer, Purdue, Theravance, and Tonix.

Address correspondence to Mary-Ann Fitzcharles, MBChB, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada, H3G 1A4. E-mail: mary-ann.fitzcharles@muhc.mcgill.ca.

Submitted for publication September 26, 2013; accepted in revised form December 3, 2013.

Herbal cannabis

Prior to present day pharmacology, healers and patients sought relief from pain and suffering by using natural products. The plant *Cannabis sativa,* commonly known as marijuana, has been used for pain relief for millennia, with additional effects on appetite, sleep, and mood, but with psychoactive properties leading to recreational use (5). The analgesic effects of herbal cannabis, derived from the dried leaves and flowers, have been most studied in neuropathic pain conditions.

C sativa contains more than 450 compounds, with at least 70 classified as phytocannabinoids, two of which have particular medical interest (6). The acid precursor of Δ^9-tetrahydrocannabinol (Δ^9-THC), transformed by heat into THC, has psychoactive and pain-relieving properties. The second molecule is cannabidiol, with lesser affinity for the cannabinoid receptors and the potential to counteract the negative effects of THC on memory, mood, and cognition. Cannabinoid molecules interact with at least two receptors of the human endocannabinoid system to induce physiologic effects (7,8).

Herbal cannabis may be ingested or inhaled, with the latter route preferred by users due to onset of action within a few minutes. Smoking of cannabis is, however, not medically recommended due to the potential respiratory tract dangers of noxious compounds such as polycyclic aromatic hydrocarbons, tar, and carbon monoxide. Furthermore, plasma concentrations of THC achieved by smoking a "joint," containing between 0.5 and 1.0 gm of dried substance, are extremely variable, with blood levels varying between 7 and 100 ng/ml. Finally, blood levels are influenced by the plant concentration of THC, variable THC delivered in the smoke, and characteristics of the

Significance & Innovations

- Legitimate use should be reserved only for patients with pain refractory to standard pharmacologic and nonpharmacologic therapies.
- Herbal cannabis should not be smoked.
- The risk/benefit profile of herbal cannabis is inferior to all other analgesic classes other than opioids.
- Persons ages <25 years should be strongly discouraged from any use of herbal cannabis.

smoking method (frequency of inhalation, hold time, and inhalation volume) (9,10). There is also discordance between the measured THC plasma peak and the maximum subjective psychoactive effects that occur an hour later, and can be augmented by opioids. Oral administration results in a more delayed effect, lower peak plasma levels, more protracted pharmacologic effects, and less abuse-related psychoactive effects (11). However, gastrointestinal absorption is more erratic and much of the ingested cannabinoid is eliminated by first-pass metabolism in the liver (11).

The mean concentration of THC in illicit marijuana has almost doubled worldwide in the past decade (12). With THC content of the plant material varying between 1% and 30%, and the bioavailability varying between 2% and 56%, there is no reasonable method to estimate dosing of the herbal compound (13). Since acquisition of herbal cannabis for medical reasons is mostly via the illegal route, even where medical use is legalized, these higher concentrations of THC might lead to increased physical and psychomotor effects. Therefore, the lack of the most elementary requirements for responsible drug administration must call into question any use of herbal cannabis for rheumatic pain treatment at this time.

Pain management of patients with rheumatic pain

As arthritis pain contributes to poor patient global well-being, pain relief is an important outcome goal, but unfortunately, pain treatments remain suboptimal in most patients (14). The overriding principle for any pain treatment is to maintain function without sacrificing cognitive or psychomotor function, a concept clearly different from pain management for medical conditions predominantly requiring palliation.

Chronic rheumatic pain remains a challenge, since pain mechanisms are complex dynamic interactions of molecules and nerve pathways subject to nervous system plasticity. Available drugs generally offer a modest effect only, and pain co-associates with sleep disturbance and mood disorders. As treatment success is considered a 30% reduction in pain, and because most pain-relieving medications are associated with considerable side effects, the compliance with prescribed treatments is often poor. It is therefore understandable that patients will continue to seek other remedies to reduce symptoms. Patients with rheumatic disease commonly use complementary and alternative medicine, and with increasing advocacy for legalization of herbal cannabis as a recreational drug, cannabis may be perceived as a safe treatment option.

Evidence for herbal cannabis in rheumatic conditions

To date, there is no formal study examining the efficacy or adverse effects of herbal cannabis in rheumatic diseases (15). Since our previous review, there has been only a single additional study reporting poorer function and psychological health in fibromyalgia patients using cannabinoids (16). While there is good evidence for efficacy of cannabinoids for treating some chronic pain conditions, such as cancer and neuropathic pain, these pain types have a different underlying mechanism from the mostly peripheral/nociceptive pain in rheumatic diseases (17). Therefore, one cannot extrapolate efficacy to patients with rheumatic conditions.

Information about the effects of cannabinoids in rheumatic diseases is currently derived from anecdotal reports, two small epidemiologic studies, a single study of the oromucosal spray of nabiximols, a combination of Δ^9-THC and cannabidiol, in patients with rheumatoid arthritis, and two studies of nabilone, a synthetic analog of THC, in fibromyalgia (1,2,18–20). The two population studies from the UK and Australia, with prevalent use for musculoskeletal symptoms, raise a number of concerns: diagnosis and outcome were by patient self-report, patients self-medicated without knowledge of dosing or concomitant treatments, and one-third of the users reported recreational use (1,2). Conclusions based on these studies are therefore questionable. In contrast, when the nabiximol was examined in a randomized clinical trial of 58 patients with rheumatoid arthritis over a 5-week period, there was improvement in pain and quality of sleep (20). The nabilone studies in fibromyalgia patients showed improved pain in one, and noninferiority to amitriptyline for the effect on sleep for the other (18,19). However, the reported effects of these agents, which indeed belong to the class of cannabinoids, cannot necessarily be applied to herbal cannabis, which is a different substance, as described above.

It therefore follows that critical evaluation of safety issues that pertain to both short-term and long-term effects of herbal cannabis also have never been formally reported in persons with classic rheumatic diseases. There is also no sound information regarding the recommended dosing of herbal cannabis, other than patient report. Therefore, the available evidence for efficacy of medical herbal cannabis represents the least convincing form of scientific evidence.

Evidence for risks

Contrary to public belief, inhaled herbal cannabis is not innocuous. Risks can be categorized as the immediate effects on cognition, psychomotor function, cardiovascular effects, and mood, and the chronic consequences on mental ability, pulmonary function, potential cancer risk, and drug dependence. Information on risks of herbal can-

nabis is also mostly derived from reports of recreational users, who are usually younger and in better health than those with a chronic disease. Additionally, the interaction of herbal cannabis with other medications that are being used therapeutically is mostly unknown.

Acute risks

The acute dose-related effects on cognition and psychomotor function are the most well-known immediate consequences of herbal cannabis use, with implications for patient safety. Following administration of inhaled cannabis in varying THC concentrations, regular cannabis users showed impairment in reaction time, selective attention, short-term memory, and motor control for up to 5 hours following consumption, with increasing effects for increasing doses (21). Similarly, the memory-impairing effects of acute cannabis use, possibly specifically attributable to THC, should be kept in mind. These acute effects have implications for medicinal use for two reasons: THC content in street cannabis is increasing and chronic pain management requires continued treatment.

Adverse acute effects on psychomotor function are particularly relevant when subjects drive motorized vehicles. Arthritis per se is seldom a contraindication to drive, and driving in the developed world is an important contribution to independence and quality of life. Acute cannabis use is increasingly appreciated as an accident risk for drivers. In a systematic review and meta-analysis of 9 studies, with inclusion of 49,000 participants, acute cannabis use was associated with at least twice the risk of serious and fatal motor vehicle collisions (22). Indeed, cannabis was also the most prevailing illicit drug identified in 0.5–7.6% of seriously injured drivers from 6 European countries (23). Although alcohol remains the most common substance identified in injured drivers, cannabis was ranked second, with the risk increased when combined with alcohol. Health Canada warns that the ability to drive or perform activities requiring alertness or coordination may be impaired for up to 24 hours following a single consumption (24). Therefore, driving with the concomitant use of herbal cannabis is both a personal and a societal safety risk, which may be further compounded in the presence of other medications. At the very least, medical practitioners must now advise patients that herbal cannabis may impair motor coordination, particularly when driving. However, advising patients not to drive is a recommendation counterintuitive to maintaining normal function.

A less appreciated effect of acute cannabis is noted for the cardiovascular system. Tachycardia and hypotension could compromise cardiovascular status in those with underlying heart disease and be a risk for cardiovascular events (25). Cannabis increases the risk of myocardial infarction 5-fold and reduces the exercise capacity of those with angina pectoris by half (26,27). Lastly, immediate psychiatric effects are increasingly associated with acute cannabis use, including anxiety, agitation, suicidal ideation, and acute psychosis (28).

Chronic risks

The long-term risks of herbal cannabis use in patients with rheumatic disease are unknown. Risks generic to all persons using herbal cannabis include effects on psychological health and association with mental illness, development of dependence and addiction, effects on memory, and cognition and respiratory health (28). Aggravation of depression- and smoking-associated risks may be particularly important for rheumatology patients. These issues seem to be particularly problematic in younger individuals, where we appreciate that many neuroactive drugs may have additional or more pronounced side effects (29). For example, just as suicidality with selective serotonin reuptake inhibitors seems more pronounced in individuals ages <25 years, there is a similar age predisposition for the increased risk of psychosis in young cannabis users.

Although the long-term effect on mood and especially depression still remains unclear, depression is more prevalent in current cannabis users (30). In a US study of more than 8,000 adults, those with cannabis use in the past year had 1.4 times higher odds of current depression than nonusers (30). Aggravation or unmasking of serious psychiatric disease also occurs with herbal cannabis use. Although previously disputed, cannabis is now generally accepted as an agent with addictive potential, especially in a context of an adverse psychosocial setting. Over a 3-year period, the cumulative incidence of cannabis dependence was 37.2% (95% confidence interval [95% CI] 30.7–43.8%) for young recreational users (31).

While cigarette smoking–associated risks for arthritis patients cannot immediately be attributed to the smoking of herbal cannabis, the potential for these adverse effects exists. Apart from the consequences of inhalation of an irritant on respiratory mucosa with development of chronic respiratory disease, there is increasing evidence that herbal cannabis may independently increase risk of lung cancer (32–34). When Swedish military conscripts ages 18–20 years were tracked over a 40-year period, those who had smoked cannabis on at least 50 occasions had a 2-fold risk (hazard ratio 2.12, 95% CI 1.08–4.14) of developing lung cancer, even after adjustments for other risks for lung cancer (34). Although it is recommended that herbal cannabis not be smoked, this remains the most common route of administration for most persons.

Finally, the true motive for use of herbal cannabis, even in persons with an identifiable medical condition, requires careful scrutiny. Often, persons using marijuana for medical reasons have previously been recreational users, raising the possibility of misusing a medical diagnosis to justify use primarily for nonmedical reasons (1,2,35).

Understanding the dilemma for the health care professional

Responsible medical practice requires a physician to provide empathetic and judicious patient care without harm. In light of the current lack of concrete medical evidence for either the efficacy or risks of herbal cannabis for the management of rheumatic symptoms, physicians are obligated to caution patients about the known risks of herbal cannabis that have been reported for recreational users. Simply

acceding to patient demands for a treatment on the basis of popular advocacy, without comprehensive knowledge of an agent, does not adhere to the ethical standards of medical practice. It is understandable that this lack of current scientific evidence must translate into physician insecurity and even distress when attempting to provide rational advice to a patient. Furthermore, any recommended therapy requires proof of concept by sound scientific study that attests to both efficacy and safety. Therefore, before physicians can provide medical recommendation or support for use of herbal cannabis, the minimal standards for pharmacotherapy must be met. At present, these elementary criteria are not fulfilled. In the absence of knowledge of effective dosing or true benefits for herbal cannabis for rheumatic symptoms, the risks extrapolated from study of persons with recreational use seem to tip the balance against use. Therefore, we believe that herbal cannabis should not at this time be allowed exceptional status as a therapy, different from other modes of therapy.

The question arises, then, whether physicians have any basis on which to provide responsible advice to patients beyond the known risk of serious adverse effects. In many jurisdictions, legislation is forcing physicians to accept medical responsibility for their patients who may be using herbal cannabis. For example, in Canada, physicians will be required to provide a document equivalent to a prescription stipulating dosing, frequency, and duration of use (24,36). An additional challenge is presented by the ambiguous terminology used by the courts whereby legal access to herbal cannabis is deemed a Charter Right when a "medical need" has been demonstrated by the patient. If physicians are to "prescribe" medical cannabis for their patients, medical ethics and deontology require physician competence with the prescribed treatment. It is also increasingly recognized that sanctioning use of herbal cannabis for therapeutic reasons is currently provided by small numbers of physicians for the majority of patients (35). In the state of Colorado, almost half of the recommendations had been made by only 15 physicians. Motives for this medical behavior should be questioned and raise ethical concerns.

It is therefore not surprising that recent surveys report that physicians lack confidence in their knowledge of cannabinoids and in their competence to effectively advise patients on the use of medicinal cannabinoids (35). In a survey of family physicians in Colorado, only 19% thought that physicians should recommend medical marijuana, with 92% reporting the need for more education (35). Similarly, two-thirds of Canadian rheumatologists recently surveyed expressed poor confidence in their knowledge of cannabinoid medical use, with 70% stating that there is currently no role for herbal cannabis in the treatment of rheumatic symptoms (37). Even in the setting of some reasonable knowledge of cannabinoid molecules and the endocannabinoid system, the absence of evidence for clinical use of herbal cannabis in rheumatic conditions must be discomforting for any health care professional or rheumatologist intending to provide an herbal cannabis treatment recommendation. Additional knowledge of these molecules is required, but knowledge alone will not fill the void due to absence of clinical study. This evident mismatch between dictates from regulatory bodies, patient advocacy, and prudent clinical care is troubling; irresponsible requirements by regulatory authorities might compromise patient and society well-being. In light of other available treatment options for the management of arthritis pain, lack of sound evidence for effect, and potential for harm, herbal cannabis cannot be recommended for arthritis pain management at this time.

Conclusion

There is an ever-increasing hiatus between public advocacy for herbal cannabis as a therapeutic agent in rheumatic conditions and the medical evidence for efficacy and side effects. This serious shortfall covers many aspects of herbal cannabis as a therapeutic agent, including uncertainty of compound content, unknown dosing, recommendations not to use by inhalation, and the indicators of harm, both in the acute as well as chronic setting. Taking all factors into consideration, health care professionals should currently dissuade rheumatology patients from using herbal cannabis as a therapy. The evident mismatch between patients' needs and good medical practice may in part be politically driven, with regulatory bodies acceding to public pressure. Rheumatologists should advocate for further study of individual cannabinoid molecules whereby dosing can be accurately controlled and efficacy and safety can be assessed using a standard scientific method.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

REFERENCES

1. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J 2005;2:18.
2. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract 2005;59:291–5.
3. Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. J Opioid Manag 2009;5:257–86.
4. Office of the Information Commissioner of Canada. Information request (ATI 2013-00282) under the Access to Information Act. 2013.
5. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag 2001;6:80–91.
6. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci 2005;78:539–48.
7. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006;147 Suppl:S163–71.
8. Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol 2001;63:569–611.
9. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182:E694–701.
10. Cooper ZD, Haney M. Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts. Drug Alcohol Depend 2009;103:107–13.
11. Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers 2007;4:1770–804.

12. Cascini F, Aiello C, Di Tanna G. Increasing Δ-9-tetrahydrocannabinol (Δ-9-THC) content in herbal cannabis over time: systematic review and meta-analysis. Curr Drug Abuse Rev 2012;5:32–40.
13. Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, Δ9-tetrahydrocannabinol, cannabidiol and cannabinol. Handb Exp Pharmacol 2005;168:657–90.
14. Goldenberg DL, Clauw DJ, Fitzcharles MA. New concepts in pain research and pain management of the rheumatic diseases. Semin Arthritis Rheum 2011;41:319–34.
15. Fitzcharles MA, McDougall J, Ste-Marie PA, Padjen I. Clinical implications for cannabinoid use in the rheumatic diseases: potential for help or harm? [review]. Arthritis Rheum 2012; 64:2417–25.
16. Ste-Marie PA, Fitzcharles MA, Gamsa A, Ware MA, Shir Y. Association of herbal cannabis use with negative psychosocial parameters in patients with fibromyalgia. Arthritis Care Res (Hoboken) 2012;64:1202–8.
17. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735–44.
18. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 2010;110:604–10.
19. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.
20. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006; 45:50–2.
21. Mensinga TT, de Vries I, Kruidenier M, Hunault CC, van den Hengel-Koot IS, Fijen JW, et al. A double-blind, randomized, placebo-controlled, cross-over study on the pharmacokinetics and effects of cannabis. 2006. URL: http://rivm.openrepository.com/rivm/bitstream/10029/7272/2/267002002.pdf.txt.
22. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 2012;344: e536.
23. Legrand SA, Isalberti C, der Linden TV, Bernhoft IM, Hels T, Simonsen KW, et al. Alcohol and drugs in seriously injured drivers in six European countries. Drug Test Anal 2013;5: 156–65.
24. Canada Department of Justice, Acts, Regulations, and Health. Marihuana medical access regulations. 2001. URL: http://laws-lois.justice.gc.ca/eng/regulations/sor-2001-227/FullText.html.
25. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: speculation or scientific certainty? Int J Cardiol 2007;118:141–4.
26. Aronow WS, Cassidy J. Effect of marihuana and placebo-marihuana smoking on angina pectoris. N Engl J Med 1974; 291:65–7.
27. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation 2001;103:2805–9.
28. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:849–63.
29. Fernandez-Espejo E, Viveros MP, Nunez L, Ellenbroek BA, Rodriguez de Fonseca F. Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology 2009;206:531–49.
30. Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. Addiction 2006; 101:1463–72.
31. Van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. Drug Alcohol Depend 2013;133:352–9.
32. Taylor DR, Hall W. Respiratory health effects of cannabis: position statement of the Thoracic Society of Australia and New Zealand. Intern Med J 2003;33:310–3.
33. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and risk of lung cancer: a case-control study. Eur Respir J 2008;31:280–6.
34. Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control 2013;24:1811–20.
35. Kondrad E, Reid A. Colorado family physicians' attitudes toward medical marijuana. J Am Board Fam Med 2013;26: 52–60.
36. Fletcher J. Marijuana is not a prescription medicine [editorial]. CMAJ 2013;185:369.
37. Fitzcharles M, Ste-Marie PA, Clauw DJ, Jamal S, Karsh J, LeClercq S, et al. Rheumatologists lack confidence in knowledge of cannabinoids in the management of rheumatic conditions: a needs assessment of Canadian rheumatologists [abstract]. Arthritis Rheum 2013;65 Suppl:S49.

The Pharmacologic and Clinical Effects of Medical Cannabis

Laura M. Borgelt, Kari L. Franson, Abraham M. Nussbaum, and George S. Wang

Cannabis, or marijuana, has been used for medicinal purposes for many years. Several types of cannabinoid medicines are available in the United States and Canada. Dronabinol (schedule III), nabilone (schedule II), and nabiximols (not U.S. Food and Drug Administration approved) are cannabis-derived pharmaceuticals. Medical cannabis or medical marijuana, a leafy plant cultivated for the production of its leaves and flowering tops, is a schedule I drug, but patients obtain it through cannabis dispensaries and statewide programs. The effect that cannabinoid compounds have on the cannabinoid receptors (CB_1 and CB_2) found in the brain can create varying pharmacologic responses based on formulation and patient characteristics. The cannabinoid Δ^9-tetrahydrocannabinol has been determined to have the primary psychoactive effects; the effects of several other key cannabinoid compounds have yet to be fully elucidated. Dronabinol and nabilone are indicated for the treatment of nausea and vomiting associated with cancer chemotherapy and of anorexia associated with weight loss in patients with acquired immune deficiency syndrome. However, pain and muscle spasms are the most common reasons that medical cannabis is being recommended. Studies of medical cannabis show significant improvement in various types of pain and muscle spasticity. Reported adverse effects are typically not serious, with the most common being dizziness. Safety concerns regarding cannabis include the increased risk of developing schizophrenia with adolescent use, impairments in memory and cognition, accidental pediatric ingestions, and lack of safety packaging for medical cannabis formulations. This article will describe the pharmacology of cannabis, effects of various dosage formulations, therapeutics benefits and risks of cannabis for pain and muscle spasm, and safety concerns of medical cannabis use.

Key Words: medical marijuana, cannabis, cannabinoids, marijuana therapeutics, medical cannabis, pain, pharmacology.

(**Pharmacotherapy 2013;33(2):195–209**)

Cannabis, or marijuana, was first used for medicinal purposes in 2737 B.C.[1, 2] The United States Pharmacopeia initially classified marijuana as a legitimate medical compound in 1851.[3] Although criminalized in the United States in 1937 against the advice of the American Medical Association, cannabis was not removed from the United States Pharmacopoeia until 1942.[2] Given the schedule I status of this drug, patients have continued to obtain cannabis for medical purposes through statewide programs and cannabis dispensaries, which are facilities or locations where medical cannabis is made available to qualified patients.

Two categories of cannabinoid medicines are currently used in North America. First, cannabis-derived pharmaceuticals include dronabinol (schedule III), nabilone (schedule II), and nabiximols (not approved by the U.S. Food and Drug Administration [FDA]). Dronabinol and nabilone were approved in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy.[4–6] In 1992, dronabinol was also approved for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome.[5, 6] Nabiximols is a cannabis-derived liquid extract formulated from two strains of *Cannabis sativa* into an oromucosal spray. It is approved in Canada, New Zealand, and eight European countries for three indications: (1) symptomatic relief of spasticity in adults with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy, (2) symptomatic relief of neuropathic pain in patients with multiple sclerosis, and (3) intractable cancer pain.[7] It is being evaluated in several trials in the United States, and it is anticipated that it may receive FDA approval by the end of 2013.[8–11]

Second, phytocannabinoid-dense botanicals (i.e., medical cannabis or marijuana) include the schedule I medicinal plants *Cannabis sativa* or *Cannabis indica*. *Cannabis ruderalis,* a third cannabis variety, has little psychogenic properties. The patients that are enrolled in U.S. medical cannabis studies are provided with a cannabis strain or blend grown and created under contract at a federal research farm at the University of Mississippi.[2] However, most patients in the United States grow their own medical cannabis or purchase it from dispensaries.

Currently, 18 U.S. states and the District of Columbia have laws that allow the use and possession of cannabis for medicinal reasons (Table 1).[12] Colorado and Washington have also passed legislation for recreational use of marijuana. With a growing number of states allowing medical cannabis and with patient use increasing, it has becomes progressively important for pharmacists and other health care providers to understand the potential benefits and risks of medical cannabis. The purpose of this article is to describe the pharmacology, therapeutic benefits and risks, and various dosage formulations that have been studied with medical cannabis. Specifically, medical cannabis for pain and muscle spasms, the most common uses of medical cannabis, will be evaluated using an in-depth evidence-based approach.

Clinical Pharmacology of Medical Cannabis

Marijuana is classified as a schedule I substance by the FDA, so it is difficult for contemporary researchers to study marijuana even though its therapeutic properties have been known for more than 5000 years.[13] Cannabis contains many compounds, of which at least 60 are known to be cannabinoids (active components of cannabis).[13] In the 1960s, when marijuana was increasingly used as a recreational drug, the cannabinoid Δ^9-tetrahydrocannabinol (THC) was isolated and determined to be the principal cause of marijuana's psychoactive effects.[14] Other cannabinoids have been isolated and found to be present in cannabis, but they are not nearly as psychoactive.

Pharmacodynamics

In the 1990s, the mechanism of action for many of the cannabinoids was determined with the discovery of the cannabinoid CB_1 and CB_2 receptors. The CB_1 receptors are found in high densities in the neuron terminals of the basal ganglia (affecting motor activity), cerebellum (motor coordination), hippocampus (short-term memory), neocortex (thinking), and hypothalamus and limbic cortex (appetite and sedation).[13] To a lesser extent, the CB_1 receptors are found in periaqueductal gray dorsal horn (pain) and immune cells. CB_2 receptors are primarily found on immune cells and tissues and, when activated, can affect inflammatory and immunosuppressive activity.[15] For example, CB_2 receptors on leukocytes may modulate cell migration, although these effects are difficult to elicit from standard dosing. CB_2 receptors are also found in the brain

From the Departments of Clinical Pharmacy (L.M. Borgelt and K.L. Franson) and Family Medicine (L.M. Borgelt), and the Department of Psychiatry, Denver Health, Behavioral Health (A.M. Nussbaum), University of Colorado, Aurora, Colorado, and the Rocky Mountain Drug and Poison Center, Denver Health Hospitals, Aurora, Colorado (G.S. Wang).

Presented, in part, at the Colorado Medical Society continuing education meeting on July 20, 2011.

For questions or comments, contact Laura M. Borgelt, Pharm.D., FCCP, BCPS, University of Colorado, Anschutz Medical Campus, Skaggs School of Pharmacy and Pharmaceutical Sciences, Mail Stop C238, 12850 E. Montview Blvd., V20-2124 Aurora, CO 80045; e-mail: laura.borgelt@ucdenver.edu.

Table 1. States with Enacted Laws to Allow Marijuana Use for Medical Purposes[12]

State	Year Passed	Possession Limit
Alaska	1998	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona	2010	2.5 oz usable; 0–12 plants[a]
California	1996	8 oz usable; 6 mature or 12 immature plants
Colorado	2000	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut	2012	1-mo supply (exact amount to be determined)
District of Columbia	2010	2 oz dried; limits on other forms to be determined
Delaware	2011	6 oz usable
Hawaii	2000	3 oz usable; 7 plants (3 mature, 4 immature)
Maine	1999	2.5 oz usable; 6 plants
Massachusetts	2012	60 day supply for personal medical use
Michigan	2008	2.5 oz usable; 12 plants
Montana	2004	1 oz usable; 4 plants (mature), 12 seedlings
Nevada	2000	1 oz usable; 7 plants (3 mature, 4 immature)
New Jersey	2010	2 oz usable
New Mexico	2007	6 oz usable; 16 plants (4 mature, 12 immature)
Oregon	1998	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island	2006	2.5 oz usable; 12 plants
Vermont	2004	2 oz usable; 9 plants (2 mature, 7 immature)
Washington	1998	24 oz usable; 15 plants

[a]If the patient lives > 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.

on microglia; thus, cannabinoids have begun to be studied for the treatment of Alzheimer's disease, but their role has not been established. Numerous cannabinoid compounds present in medical cannabis interact with these receptors to create varying responses (Figure 1). It is unknown how the major nonpsychotropic compound in cannabis, cannabidiol (CBD), exerts its activity, but it may be an inverse agonist, because several studies have shown that it decreases the psychotropic activity of THC.[15] It has no direct affinity for CB_1 and CB_2 receptors, yet it appears to enhance the activity of the endogenous cannabinoid, anandamide.[16] Because of the uncontrolled production of medical cannabis in various preparations (dried to be smoked or in oils to be applied, eaten, or drunk), there can be vastly different concentrations of the cannabinoid compounds in each product. As such, it is difficult to predict what pharmacologic response any cannabis product is likely to elicit. However, because of the relative efficacy (the ability of a drug to induce a biologic response at its molecular target when bound) of THC compared to other cannabinoids, it is routinely found to be the compound associated with the most pharmacologic effects of cannabis. Current researchers are trying to further differentiate the poorly binding cannabinoids by looking into the noncannabinoid targets linked to pain.[13] In these studies, other G-protein receptors (e.g., GPR55), G-protein–coupled receptors (coupling with μ- and δ-opioid receptors), and transient receptor potential channels (TRPVs), which are responsive to capsaicin, are being identified as targets.[13] In the TRPV example, it is interesting that non-CB_1 and non-CB_2 active phytocannabinoids (and not THC) have been shown to have the most effects.[15]

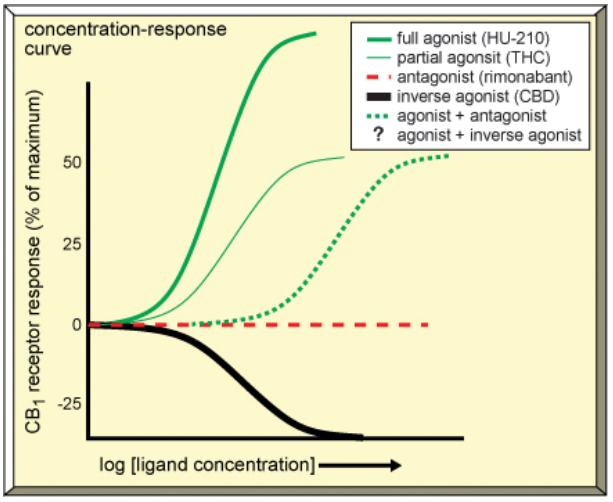


Figure 1. Concentration-response curves of cannabinoid compounds on the CB_1 receptor. The full agonist is the compound HU-210, which is a synthetic cannabinoid; the partial agonists are Δ^9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid found in humans; the antagonist is rimonabant, a synthetic cannabinoid studied for weight control; the inverse agonist is cannabidiol (CBD), which has no direct CB_1 activity but is postulated to be an example of an inverse agonist. It is unknown what the exact combination of agonists, antagonists, and inverse agonists are in cannabis and the result of this combination.

Pharmacokinetics

The pharmacokinetic characteristics of cannabinoids have been primarily evaluated in small clinical pharmacology studies. The half-life of the distribution phase is 0.5 hour, whereas the half-life for the terminal phase is highly variable with a mean of 30 hours.[17] Both are consistent with THC being highly lipophilic. Cannabidiol has a similar lipophilic profile to THC but has a terminal half-life of 9 hours.[16]

Smoking cannabis turns approximately 50% of the THC content into smoke, with the remainder lost by heat or from smoke that is not inhaled. Up to 50% of inhaled smoke is exhaled again, and some of the remaining smoke undergoes localized metabolism in the lung. The end result is that the estimated bioavailability of a smoked dose of THC is between 0.10 and 0.25.[18, 19] The absorption of smoked THC occurs within minutes, and the half-life of the distribution phase and that of terminal phase of smoked cannabis mimics those of intravenously administered THC.[18]

Although smoking remains the most common mode of ingestion for medical cannabis, vaporization of cannabis is becoming increasingly popular among medical cannabis users due to its perceived reduction of harm given the release of a significantly lower percentage of noxious chemicals.[20, 21] Given the volatility of cannabinoids, they will vaporize at a temperature much lower than the actual combustion of plant matter. When heated air is drawn through the cannabis, the active components will aerosolize and can be inhaled without the generation of smoke.[2]

Orally administered THC has a bioavailability ranging from 5–20% in the controlled environments of clinical studies but is often lower in users because of variations in gastric degradation (with the presence of acids) and extensive first-pass effects.[18, 22] The bioavailability of oral cannabidiol is also variable (reported to be 13–19%), but one primate model found that intoxication required 20–50 times an oral versus an intravenous dose.[16, 23] The peak concentrations of the THC component of orally administered medical marijuana are delayed compared to intravenous or inhaled administration and are reached in 1–3 hours.[22] Orally administered medical cannabis presents concerns because absorption may be incomplete and delayed, resulting in intrapatient variability and difficulty with self-titration for appropriate dosing.

Drug–Dose, Drug–Disease and Drug–Drug Relationships

There is wide variation in the reported dose of THC needed to produce central nervous system effects. A review of 165 clinical pharmacology studies attempted to normalize the various doses and routes of administration of THC and defined a low dose as less than 7 mg, a medium dose as 7–18 mg, and a high dose as greater than 18 mg.[24] However, there is known tolerance to THC through downregulation of CB_1 receptors and G-protein activation. There is a high probability of tolerance with as few as 4 days of daily use, and low probability with intermittent use. In this review, it was determined that an elevation in heart rate (average > 19 beats/min), an increase in subjectively feeling "high," a decrease in subjective alertness, and a decrease in motor stability were the consistent pharmacodynamic effects of THC regardless of route of administration. When the pharmacokinetics and pharmacodynamics of these physiologic effects were modeled after pulmonary administration of THC, a delay was found between the serum concentrations and peak cardiac (8 min) and central nervous system (> 30 min) effects. There was also evidence that THC accumulates in the brain, and serum concentrations do not correlate with effects because the effects in the brain lasted longer than the elevated serum concentrations and peripheral cardiac effects. In addition, it was determined that the maximal effects at some compartments (heart) plateau, whereas effects on alertness are linear presumably to the point of loss of consciousness. These results indicate that it is difficult to correlate a single serum concentration to any physiologic effect or impairment, as is often done reliably with alcohol.[24]

Different patient populations may have varying responses to medical cannabis. Levels of hormones such as luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone are known to decline with long-term exposure to medical cannabis. Hormones alter the pharmacodynamic profile of THC, as female patients with higher estrogen levels are more sensitive to the effects of medical cannabis on pain, behavior, and reward.[25] Using marijuana concomitantly with tobacco leads to greater increases in heart rate and carbon monoxide levels, despite lower THC concentrations.[26] Conversely, medical cannabis may complicate the clinical picture of a patient who has various disorders and is receiving other

medications. Cannabis may increase the risks in patients with psychiatric and cardiovascular conditions. Patients with cardiovascular conditions who use cannabis are subjected to increases in heart rate and decreases in heart rate variability (a known cardiovascular parameter associated with reduced autonomic response and increased morbidity and mortality).[24] These effects may be worsened if the patient is receiving other medications that increase heart rate (e.g., anticholinergics, α-agonists, theophylline, tricyclic antidepressants, naltrexone, and amphetamines).[27] The decrease in alertness experienced with marijuana can be potentiated by benzodiazepines, opiates, and tricyclic antidepressants.[27] Because medical cannabis is not controlled or regularly used in mainstream medicine, the actual drug–disease and drug–drug interaction profiles remain to be elucidated.

Clinical Effects of Medical Cannabis

In 1999, the Institute of Medicine released a report indicating cannabinoids may have a role in the treatment of pain, movement, and memory but observed that risks are associated with use.[28] Their report made six major recommendations to the medical community to better establish the safety and efficacy of marijuana. These recommendations included the evaluation of the physiologic and psychological effects, individual health risks, and various delivery systems of medical cannabis, as well as short-term (< 6 mo) clinical trials to determine effectiveness of medical cannabis for targeted medical conditions. Despite this call to action, there have been relatively few controlled clinical trials to evaluate the effects of various delivery systems for medical cannabis. Some states that permit the use of medical cannabis have incorporated patient registries for possession of a predetermined amount of cannabis for conditions such as cachexia, cancer, glaucoma, human immunodeficiency virus infection/acquired immune deficiency syndrome, muscle spasms, seizures, severe nausea, severe pain, and sleep disorders. At this time, Colorado and Arizona have the most robust state medical marijuana registries, which provide demographic data about who is permitted to use medical cannabis and for which indication. In both states, where a person may use medical cannabis for more than one condition, 89% (Arizona) and 94% (Colorado) of patients are registered for severe or chronic pain and 14% (Arizona) and 17% (Colorado) are registered for muscle spasms.[29, 30] Given that pain and muscle spasms are the most common reasons that medical cannabis is used, this article focuses on the therapeutic effects of medical cannabis for these two conditions.

Pain

The analgesic effects of cannabis may be due to several different mechanisms including, but not limited to, modulation of rostral ventromedial medulla neuronal activity, antinociceptive effects in descending pain pathways, and antiinflammatory properties by acting through prostaglandin synthesis inhibition.[2] Various forms of medicinal cannabis have provided mostly positive responses for patients with different types of pain: neuropathic, chronic, postoperative, and that related to fibromyalgia, rheumatoid arthritis, multiple sclerosis, and cancer.[28, 31–37]

In studies evaluating smoked cannabis compared to placebo, significant improvements in pain were observed (Table 2).[38–43] These studies included a small number of patients (15–56) and used cigarettes with varying THC contents. THC content varies based on the strain of cannabis plant that is used. In general, a higher THC content (up to 9.4%) appears to be more effective for pain relief. One group of investigators considered the neuropathic pain reduction from smoked cannabis to be modest compared to that from other drugs used for neuropathic pain, such as gabapentin and pregabalin (0.7 reduction on a 10-cm scale compared to 1.2 and 1.3, respectively).[42] Although relatively few serious adverse effects were reported in these studies, some mild-to-moderate adverse effects were commonly noted: somnolence, headache, dry mouth, sedation, dizziness, conjunctival irritation/dry eyes, hypotension, and difficulty with concentration and/or memory. The range of doses used in these trials is shown in Table 2. Although it appears that some dose-response relationship occurs (i.e., higher THC content provides better therapeutic response), many other variables factor into an effective dose, such as individual tolerance, dosage form used, frequency of dosing, and adverse effects experienced. Therefore, the most effective dose for pain will vary among individuals.

Nabiximols, the oromucosal spray with an equal mixture of THC and CBD not yet approved by the FDA, is being evaluated in several trials of patients with neuropathic and chronic pain.[44–47] Each of these studies

Table 2. Clinical Trials of Smoked Cannabis for Pain

Study Drug (% of THC)	Condition Studied	No. of Patients	Outcome	Adverse Effects
Smoked cannabis only (11%), oral cannabis only (46%), combined oral + smoked cannabis (43%) vs nonuser of cannabis[41]	Fibromyalgia	56 (28 users and 28 nonusers)	Improvement in pain and stiffness ($p<0.001$), enhancement of relaxation ($p<0.05$), and increased somnolence ($p<0.05$) and feeling of well-being ($p<0.001$) on visual analog scale	Most frequent adverse effects were somnolence (18/28), dry mouth (17/28), sedation (12/28), dizziness (10/28), high (9/28), tachycardia (8/28), conjunctival irritation (7/28), and hypotension (6/28); no serious events occurred
Smoked cannabis (0%, 2.5%, 6%, 9.4%) 3 times/day × 5 days (crossover every 14 days)[42]	Posttraumatic or postsurgical neuropathic pain	21	Daily pain intensity was lower with cannabis with 9.4% THC content than with 0% ($p=0.023$) on numeric rating scale	Total of 248 mild and 6 moderate adverse events reported; no serious or unexpected adverse events; most frequent events in group receiving cannabis with 9.4% THC content were headache, dry eyes, burning sensation, dizziness, numbness, and cough
Smoked cannabis (1–8%) or placebo 5 days/wk × 2 wks[43]	Neuropathic pain in patients infected with human immunodeficiency virus	28	Improvement in pain on descriptor differential scale with cannabis ($p<0.016$)	Most events were mild and self-limiting; 3 were treatment-limiting toxicities (cannabis-induced psychosis, cough, intractable diarrhea); other effects that were more frequent with cannabis use were concentration difficulties, fatigue, sleepiness, and sedation
Smoked cannabis (3.5% or 7%) or placebo[40]	Central and peripheral neuropathic pain	38	Cannabis improved pain on visual analog scale ($p=0.016$); cannabis improved the following types of pain: sharp ($p<0.001$), burning ($p<0.001$), aching ($p<0.001$), sensitive ($p=0.03$), superficial ($p<0.01$), and deep ($p<0.001$); cannabis provided greater relief as shown on the global impression scale ($p<0.01$)	Psychoactive effects were minimal and well-tolerated; some acute cognitive effects were noted at high doses, especially with memory
Smoked cannabis (3.56%) or placebo TID × 5 days[39]	Human immunodeficiency virus–associated sensory neuropathy	50 (25 users and 25 nonusers)	> 30% pain reduction reported by 52% of the cannabis group and by 24% of the placebo group ($p<0.04$)	No serious events reported
Smoked cannabis single doses (2%, 4%, and 8%) given in random order or placebo[38]	Capsaicin-induced pain and hyperalgesia	15	Pain reduction with medium dose only on pain scores and McGill Pain Questionnaire at 45 min after cannabis administration	Generally well tolerated; dyspnea, dry mouth, feeling cold, and somnolence were reported

demonstrated a statistically significant reduction of pain intensity compared to placebo. In most of these trials, the patients continued their existing analgesic medication in addition to starting the study medication; therefore, symptom relief obtained from the study drug was beyond the effects achieved with the patients' existing analgesia. Adverse events reported included dizziness, sedation, feeling intoxicated, and nausea. As a limitation, most of these studies had varying definitions for types of pain and included patients already using standard analgesic agents; therefore, nabiximols may be best reserved for patients with refractory pain.

Oral THC (dronabinol 5–20 mg) has not demonstrated significant improvements in visual analog pain assessments for healthy volunteers (under experimental pain conditions) or patients with chronic gastrointestinal pain or posthysterectomy pain.[48–50] Among patients with cancer pain given a single dose of placebo or THC 5, 10, 15, or 20 mg, analgesia was achieved only with THC at the higher 15- and 20-mg doses.[51, 52] The authors stated that 10 and 20 mg of oral THC were equivalent to 60 and 120 mg of codeine, respectively, for pain relief, but that the adverse effects of oral THC (somnolence, dizziness, ataxia, and blurred vision) may not make it an ideal medication for chronic cancer pain. The analgesic effect of dronabinol 10 mg/day for 3 weeks in 24 patients with multiple sclerosis revealed a relative reduction in pain scores (−20.5%, 95% confidence interval [CI] −37.5% to −4.5%) compared to placebo.[53] No serious adverse events were reported, but patients receiving dronabinol reported more dizziness and light-headedness.

Nabilone has also been evaluated for the treatment of pain. In a randomized double-blind study of 40 patients with fibromyalgia, pain and quality-of-life measurements were assessed using a visual analog scale and the Fibromyalgia Impact Questionnaire. The visual analog scale was a continuous scale from 0–10 on a 10-cm (or 100-mm) line that was anchored by descriptors (e.g., 0 is "no pain" and 10 is "worst imaginable pain"). The Fibromyalgia Impact Questionnaire is an instrument designed to quantify the overall impact of fibromyalgia over many dimensions (e.g., function, pain level, fatigue, sleep disturbance, and psychological distress) and is scored from 0–100, with the latter number being the worst case. Significant decreases in scores from the visual analog scale (−2.04, $p<0.02$), Fibromyalgia Impact Questionnaire (−12.07, $p<0.02$), and 10-point anxiety scale (−1.67, $p<0.02$) were observed after 4 weeks of nabilone treatment when the drug was titrated from 0.5 mg/day to 1 mg twice/day; these results indicate that pain, disease impact, and anxiety were significantly reduced.[54] Although no serious events were reported, the patients receiving nabilone experienced more adverse effects (1.54, $p<0.05$), with the most common being drowsiness, dry mouth, vertigo, and ataxia. The authors stated that the pain relief seen in the treatment group was similar to that for other treatments used for fibromyalgia, including fluoxetine, tramadol, and pramipexole. In a different study, high-dose nabilone (2 mg given at 8-hour intervals for 24 hours) showed an increase or worsening in pain scores for patients also receiving morphine after surgery compared to ketoprofen and placebo.[55] The authors concluded that this unexpected finding may have been due to paradoxical or sedative effects of cannabinoids at high doses.

Two meta-analyses have evaluated various forms of cannabis treatment for pain. The first was a systematic review and meta-analysis of 18 double-blind randomized controlled trials that compared any cannabis preparation to placebo among patients with chronic pain.[36] The cannabis preparation contained THC and could be administered by any route of administration. Most trials included nabiximols, dronabinol, or nabilone. Cannabis treatment demonstrated a statistically significant standardized mean difference of −0.61 (95% CI −0.84, –0.37) in pain intensity from baseline scores. This review and meta-analysis also evaluated harms and found significant changes with cannabis use for mood disturbances such as euphoria (odds ratio [OR] 4.11, 95% CI 1.33–12.72, number needed to harm [NNH] 8). Other harms found to be significantly associated with cannabis use included alterations in perception (OR 4.51, 95% CI 3.05 –6.66, NNH 7), events affecting motor function (OR 3.93, 95% CI 2.83–5.47, NNH 5), and events that altered cognitive function (OR 4.46, 95% CI 2.37–8.37, NNH 8) for patients taking cannabis compared to those taking placebo or another analgesic drug. The authors concluded that cannabis may offer moderate efficacy for treatment of chronic pain, but benefits may be partially or completely offset by potential harms.

Painful human immunodeficiency virus–associated sensory neuropathy has been evaluated through a systematic review and meta-analysis involving 14 randomized controlled trials.[37]

Interventions that showed greater efficacy for pain on a visual analog scale included smoked cannabis (relative risk 2.38, 95% CI 1.38–4.10, NNT 3.38), topical capsaicin 8% patch (p=0.0026, NNT 6.46), and recombinant human nerve growth factor, which is not available clinically. No superiority over placebo was reported for amitriptyline, gabapentin, pregabalin, prosaptide, peptide-T, acetyl-L-carnitine, mexilitine, lamotrigine, and topical capsaicin 0.075%. The authors concluded that although smoked cannabis may have superior effectiveness, other routes of cannabis should be investigated to avoid the potential negative impact of smoking.

Overall, these studies show statistically significant improvement in various types of pain when medical cannabis is used. Trials indicate that smoked cannabis or cannabis extract (THC:CBD) are effective for several different types of pain, primarily neuropathic pain. Oral THC (dronabinol) does not appear to be as effective for pain but has not been widely studied in various pain conditions. Nabilone may be effective for pain related to fibromyalgia but also has not been widely studied. There is a paucity of well-designed studies evaluating medical cannabis for pain. Limitations of these studies include widely varying doses and dosage forms of medical cannabis, lack of validated criteria or assessment for some types of pain (e.g., neuropathic), lack of comparative trials for various formulations and routes of administration, self-selection bias (i.e., some patients have already had a previous positive response to the drug), difficulty blinding participants to potentially psychoactive substances, and small study populations. Given its legal status, the need for more efficacy data, and its unknown safety and tolerability profile, medical cannabis should be considered only when treatment failure with standard therapy has occurred or when adjunctive therapy is appropriate.

Muscle Spasms

Nabiximols (THC:CBD extract) has been the primary cannabis agent studied for the treatment of spasticity in patients with multiple sclerosis. Spasticity is commonly associated with painful spasms and sleep disturbance and contributes to increased morbidity.[56] Endogenous and exogenous cannabinoids have been shown to be effective for multiple sclerosis spasticity in animal models, primarily through effects at the CB_1 receptor.[57] Nabiximols has been shown to be effective as monotherapy and as add-on therapy for patients not fully relieved with other antispasticity therapy.[31]

One large multicenter parallel-group, double-blind, randomized placebo-controlled study included 160 patients with multiple sclerosis who were experiencing primary symptoms of spasticity, spasms, bladder problems, tremor, or pain.[58] Treatment evaluated was oromucosal sprays of matched placebo or whole plant cannabis–based medicinal extract (CBME) containing equal amounts of THC and CBD at a dosage of 2.5–120 mg/day, in divided doses. A visual analog scale score for each patient's most troublesome symptom was used. This primary symptom score improved in both groups with no statistically significant difference; the scores of patients using CBME reduced from a mean ± standard error of 74.36 ± 11.1 to 48.89 ± 22.0, and those using placebo from 74.31 ± 12.5 to 54.79 ± 26.3. Spasticity scores were significantly reduced with CBME in comparison to placebo (p=0.001). No significant adverse effects on cognition or mood were reported, and intoxication was generally mild.

In another double-blind study evaluating nabiximols, 189 patients with diagnosed multiple sclerosis and spasticity were randomized to receive daily doses of active preparation (124 patients) or placebo (65 patients) over 6 weeks.[59] The primary efficacy analysis on the intent-to-treat population (184 patients) showed the active preparation to be significantly superior (p=0.048) as measured with a numeric rating scale of spasticity. For the responders, 40% of patients receiving active preparation achieved greater than 30% benefit (p=0.014). Eight withdrawals were attributed to adverse events: six received active preparation and two received placebo.

A meta-analysis of three studies (two of which were described here earlier) evaluated 666 patients with multiple sclerosis and spasticity.[32] These were randomized, placebo-controlled, double-blind parallel-group studies of nabiximols. On a 0–11 numeric rating scale, the adjusted mean decrease from baseline was 1.30 with nabiximols compared to 0.97 with placebo. Using a linear model, the treatment difference was −0.32 (95% CI −0.61 to −0.04, p=0.026). A greater proportion of the treated patients were responders (OR 1.62; 95% CI 1.15–2.28, p=0.0073) and they also reported greater improvement (OR 1.67; 95% CI 1.05–2.65, p=0.030). Many patients experienced at least one adverse event (288 of 363 patients for nabiximols, 169 of 303 patients for placebo),

although most events were mild to moderate in severity and all serious adverse events resolved. Forty (11%) and 11 (3.6%) patients withdrew from the study due to adverse events in the nabiximols and placebo groups, respectively.

A consecutive series of randomized, double-blind placebo-controlled single-patient crossover trials evaluated muscle spasms as one outcome for 24 patients (18 with multiple sclerosis) with plant extracts of THC and CBD and a 1:1 mixture of THC:CBD in a sublingual spray.[60] The THC and THC:CBD groups both reported significant improvement in the spasticity severity rating versus placebo ($p<0.05$). Three patients experienced transient hypotension and intoxication with rapid initial dosing of CBME. The authors acknowledged that this was a preliminary study and that larger well-controlled studies were needed.

Oral cannabis has been evaluated in several trials for spasticity due to multiple sclerosis. In a double-blind crossover placebo-controlled randomized trial of 50 patients, the intent-to-treat analysis showed no significant difference in Ashworth spasticity scores compared to placebo.[61] However, in the 37 patients who received more than 90% of the treatment (per protocol analysis), there was a significant improvement in the number of spasms and spasticity scores ($p=0.013$) and mobility ($p=0.01$). In a large multicenter double-blind randomized controlled trial of 630 patients with multiple sclerosis, 576 responded to questions about their spasticity. There was a significant improvement in patient-reported pain and spasticity ($p=0.003$) with a reduction in spasticity of 61% for the 197 patients receiving cannabis extract (95% CI 54.6–68.2) and of 60% for the 181 patients receiving oral THC (95% CI 52.5–66.8).[62, 63] Of note, of the 198 patients receiving placebo, 46% reported improvement in spasticity (95% CI 39.0–52.9). A double-blind placebo-controlled crossover study in 13 patients showed significant improvement in patient-reported subjective spasticity scores after receiving THC at doses ranging from 7.5 to 15 mg/day for 5 days.[64] No objective outcomes were measured.

In one double-blind crossover placebo-controlled randomized trial of 12 patients, nabilone twice/day was given for 4 weeks to determine if it improved spasticity caused by spinal cord injury.[65] There was a significant reduction in the Ashworth scale and total Ashworth score ($p=0.003$ and $p=0.001$, respectively).

Overall, cannabis-derived pharmaceuticals appear effective for muscle spasticity related to multiple sclerosis. Nabiximols is approved for this purpose in 10 different countries. Limited data exist on the use of other forms and doses of medical cannabis for muscle spasms. Furthermore, most states list "muscle spasm" as an indication for medical cannabis use but do not require that the diagnosis of multiple sclerosis be present. The evidence of effectiveness of medical cannabis in muscle spasm not related to multiple sclerosis is scarce. Limitations of published studies include differences in spasticity assessment between patients (subjective) and providers (objective with Ashworth scale scoring), presence of other multiple sclerosis symptoms, lack of comparative trials for various formulations and routes of administration, self-selection bias, blinding participants to potentially psychoactive substances, and having many studies (especially those evaluating nabiximols) sponsored by the manufacturer or the medical marijuana industry. Most of these studies evaluated patients with inadequate spasticity relief using existing treatments, suggesting that the included patient populations would likely respond well to medical cannabis. Nabiximols or medical cannabis may be best reserved for the patient population who have not shown efficacy or are intolerant to other standard therapies for muscle spasm.

Safety Concerns

Adverse Effects, Drug Interactions, and Contraindications

Although most trials indicate that medical cannabis produces mild to moderate adverse effects, one of the ongoing concerns about using medical cannabis is the unfavorable and somewhat variable adverse effect profile when used in different formulations as a medicinal product. In a systematic review of 31 studies (23 randomized controlled trials and 8 observational studies), 4779 adverse events were reported in patients receiving a medicinal cannabinoid for 8–12 months.[66] Most (4615 [96.6%] events) were not serious, with the most common nonserious event being dizziness (714 [15.5%] events). Of the 164 serious events, the most common were relapse of multiple sclerosis (21 [12.8%] events), vomiting (16 [9.8%] events), and urinary tract infection (15 [9.1%] events). More nonserious adverse events were

reported in the treatment groups compared to the control groups (rate ratio 1.86, 95% CI 1.57–2.21); however, there was no significant difference in the rate of serious events (rate ratio 1.04, 95% CI 0.78–1.39). Limitations of this review include lack of inclusion of smoked cannabis and short-term evaluation of cannabis use (up to 12 mo).

There is minimal information available about drug interactions and contraindications with cannabis-derived pharmaceuticals and medical cannabis. A contraindication to dronabinol use is hypersensitivity to the drug; one noted drug interaction is with ritonavir, when increased dronabinol serum concentrations may occur leading to potential toxicity.[67] The Canadian product insert for nabiximols states the following contraindications: known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil (ingredients/excipients in the product); serious cardiovascular disease (such as ischemic heart disease), arrhythmias, poorly controlled hypertension or severe heart failure; history of schizophrenia or any other psychotic disorder; children under 18 years of age; women of child-bearing potential not on a reliable contraceptive or men intending to start a family; and pregnant or nursing women.[7] A serious drug interaction warning is provided for patients receiving sedatives, drugs with sedating or psychotropic effects, and hypnotics, as there may be an additive effect with nabiximols. In addition, alcohol may interact with nabiximols, particularly in affecting coordination, concentration, and ability to respond quickly. No clinically apparent drug interactions were noted in clinical trials where nabiximols was taken with other cytochrome P450 (CYP) agents; however, there may be a potential risk of drug–drug interactions due to CYP inhibition by nabiximols.[7] The product monograph recommends caution be exercised in patients taking drugs known to be substrates for CYP3A4 or CYP2C19.[7] Given the lack of information about medical cannabis, it would be reasonable to apply these contraindications and drug interaction concerns especially with the variability in formulation, dose, and frequency of administration with these products.

Psychiatric Implications

Marijuana's chief psychoactive ingredient, THC, is a partial agonist at the CB_1 receptors, the predominant endocannabinoid receptors in the brain that help modulate appetite, mood, and motivation.[68, 69] While the response to marijuana depends on dose, strain, and frequency of use, most cannabis users experience mild euphoria, sedation, relaxation, hunger, and enhanced sensory input but also impaired attention, balance, cognition, judgment, memory, and sense of time. Some users experience anxiety, disorientation, paranoia, and psychosis; there is some reason to believe that strains with greater relative cannabidiol concentrations are associated with fewer psychotic symptoms.[70, 71]

Frequent use of cannabis, especially in adolescence, is associated with the development of schizophrenia, a chronic neurodevelopmental disorder. During adolescence, when schizophrenia typically presents, profound changes occur in the brain, often through synaptic pruning, a process that endocannabinoids help regulate.[72] Using cannabis interferes with adolescent neurodevelopment, and imaging studies associate marijuana use with adverse development of the hippocampus and the cerebellum.[73–75] Epidemiologic data associate heavy adolescent use of marijuana with both an earlier onset of schizophrenia and a 2-fold increased risk of developing schizophrenia.[76] To be clear, the use of cannabis in adolescence does not cause schizophrenia but increases the risk of its onset, suggesting interplay between marijuana use and genetic predisposition for schizophrenia.[77] For people who develop schizophrenia, ongoing use of marijuana is associated with more severe psychosis and impaired performance on tests of attention and impulsivity.[78, 79] Marijuana is a psychoactive substance whose psychiatric complications are known to increase with early onset and regular use.

Cannabis use is associated with impairments in memory and cognition. Heavy cannabis users have deficits in the encoding, storage, and retrieval of memory.[80] A recent animal model found that cannabis impairs working memory by activating astroglial cannaboid receptors in the hippocampus.[81] These findings correlate well with the association between heavy marijuana use and bilateral volume reduction of structures involved in memory like the amygdala and hippocampus.[82] Marijuana users often perform poorly on tests of executive function, information processing, and visuospatial perception.[83]

The use of cannabis is more modestly associated with depression and suicide in epidemiologic data. Frequent cannabis use is significantly associated with depressive disorders in both

animal models and epidemiologic studies.[84] Hyperactivity of the endocannabinoid system is associated with impulsivity and suicidality, which is borne out in epidemiologic studies where a significant association is observed between marijuana use and suicidal ideation and attempt.[85]

Finally, cannabis is the most commonly used and abused illicit substance in the world. In the United States each year, approximately 6500 individuals begin to use marijuana daily, of whom 10–20% will develop cannabis dependence.[86, 87] Among people admitted to substance treatment facilities in the United States, marijuana is the most frequently identified illicit substance.[88]

Pediatric Implications

The National Poison Data Center reported 5371 calls pertaining to marijuana exposures in 2011; 358 (7%) were for children aged 12 years or younger.[89] Compared to previous years, total calls and calls pertaining to children aged 12 years or younger increased (Figures 2 and 3). Acute cannabinoid toxicity usually presents with various neurologic symptoms: decreased coordination, decreased muscle strength, lethargy, sedation, difficulties concentrating, altered psychomotor activity, slurred speech, and slow reaction time. Other common symptoms include tachycardia and dry mouth. These effects can be more pronounced in children, especially at lower doses. Common symptoms include ataxia, somnolence, lethargy, altered mental status, and obtundation. Rarely, pediatric patients present with more severe symptoms such as apnea, cyanosis, bradycardia, hypotonia, and opisthotonus (severe hyperextension and spasticity).[90]

With the increased availability of cannabinoids in states with legalized medical cannabis, there is also an increased risk for accidental exposure. Several reports of adverse events relating to cannabis exposure in children and adolescents have been made.[91–93] In Colorado, we reported a case series of five patients over 4 months who presented to the emergency department with altered mental status and lethargy.[94] After most patients received an extensive work up, including lab work, lumbar puncture, and imaging, urine drug screens showed they had been exposed to cannabis. Only on further questioning did care providers admit to the cannabis exposure. Four of the five sources of cannabis were confirmed to be marijuana card

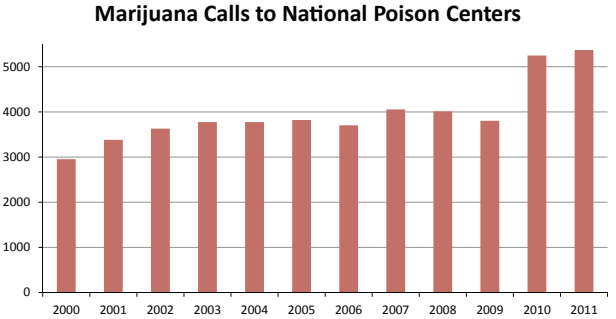


Figure 2. Telephone calls to national poison control centers pertaining to marijuana exposures.[89]

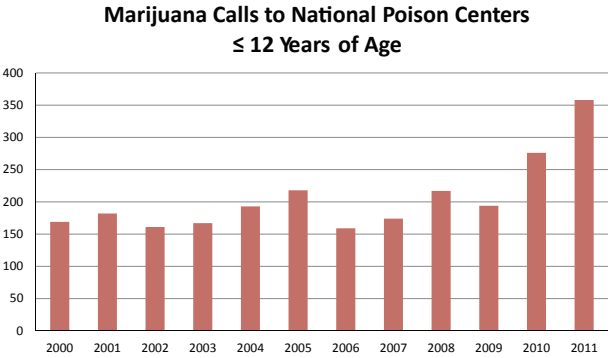


Figure 3. Telephone calls to national poison control centers pertaining to marijuana exposures in children aged 12 years or younger.[89]

holders (registered patients using medical marijuana), and the products ingested included food products in many of the cases (e.g., cookies, candies). Since the time of the report, there have been several additional cases of pediatric exposure at our institution, mostly from medical marijuana in the form of food. Although no deaths related to marijuana have been reported to national poison centers, there can be significant morbidity. When patients present with an unclear history, they often receive invasive procedures (e.g., urine catheterization, intravenous lines, and lumbar punctures) and imaging (e.g., head computed tomography scans).

The availability of medical cannabis in consumer-friendly forms (soda drinks, desserts, candies, and tinctures) continues to increase and most, if not all, products lack regulatory or safety packaging. These products are concerning because they have labels and packaging that can be easily mistaken for conventional food products by young children. Consumption of these products may be tempting to young children, and it seems likely that exposures will increase. Like any other medication, patients should be instructed of the risks of the products and to

store them safely and securely. Manufacturers may also consider warnings and child-proof packaging. Finally, health care providers should consider marijuana exposure in pediatric patients who present with altered mental status, somnolence, or lethargy.

Future Directions

Medical cannabis appears to have some benefit in patients with certain conditions. However, the use of medical cannabis within the current legal system faces a number of challenges.[34] First, the method of delivery (e.g., smoked, vaporized, oral) and patient individuality (e.g., severity of condition, inhalation and exhalation habits, functional lung capacity, gastrointestinal absorption) cause great variability in the effect of medical cannabis. The lack of quality control (e.g., contaminated products, nonstandardized doses) makes it difficult for clinicians to recommend particular formulations. Other concerns about medical cannabis include the need for adequate monitoring and prevention of addiction. Close surveillance of patients will ensure appropriate use of these medications, and training and education should be made available to providers whose patients use cannabis. Unfortunately, surveillance, training, and education are not available in most health systems, which often delimit the patient–physician relationship to a recommendation to use cananbis.[95] Similar to any other medication, improved safety measures and regulations for packaging should be examined. Additional research is needed to understand the role of the endocannabinoid system in various pathways such as antinociception (pain) and antispasticity. Improved study methodologies, including the use of standard formulations and/or dosages and larger study populations, are needed for future investigative efforts to determine appropriate uses of medical cannabis. Further research evaluating the addition of CBD to THC needs to occur to determine if the nonpsychotropic effects of this compound can improve the tolerance and safety of THC. Therefore, education and research are needed to address these concerns and to review the original intent of the Institute of Medicine's report to determine the safe and effective use of marijuana.

Conclusion

Cannabinoids produce a variety of actions by activating CB_1 and CB_2 receptors and through other possible effects in the central nervous system. The pharmacologic and pharmacodynamics effects of cannabis can vary widely based on patient and drug characteristics, which can make it difficult to use effectively and safely. Various cannabis-derived pharmaceuticals are available. Dronabinol and nabilone are oral agents available in the United States as schedule III and II medications, respectively. Nabiximols is an oromucosal spray containing a 1:1 mixture of THC: CBD, which is available in 10 countries and will be evaluated this year by the FDA for approval in the United States. Medical cannabis containing hundreds of various cannabinoids is available in 18 U.S. states and the District of Columbia and will most likely be made more widely available in the next legislative year.

Medical cannabis has been evaluated for many different purposes, and medical cannabis registrants are using it particularly for pain and muscle spasms. Data indicate medical cannabis may be effective for these conditions, especially when standard therapy has failed. However, common adverse effects involving the central nervous system and gastrointestinal system may not make this an appropriate option in many patients. Extreme caution should be used in patients with a history of cardiovascular disease or mental disorders and in adolescents. Just as is recommended with other medications, patients using medical cannabis should minimize the risk of accidental pediatric ingestion by securing the drug in a safe place with child-proof locks. Although dronabinol and nabilone are regulated in the United States and have demonstrated sufficient efficacy and safety, evidence for medical cannabis is still lacking; thus, the drug should be used with caution in patients.

References

1. **Hi HL**. An archaeological and historical account of cannabis in China. Econ Bot 1974;28:437–48.
2. **Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD**. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. J Opioid Manag 2009;5:153–68.
3. Extractum cannabis. In: The pharmacopoeia of the United States of America, 3rd ed. Philadelphia: Lippincott, Grambo & Co., 1851.
4. Cesamet (nabilone) package insert. Meda Pharmaceuticals, 2009. Available from http://www.cesamet.com/pdf/Cesamet_PI_50_count.pdf. Accessed June 20, 2012.
5. **Food and Drug Administration.** Label and approval history: marinol. Available from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseactionSearch.Label_ApprovalHistory#apphist. Accessed June 20, 2012.
6. Marinol (dronabinol): package insert. Unimed Pharmaceuticals, Inc., September 2004. Available from http://www.fda.

gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf. Accessed December 30, 2011.
7. Sativex (nabiximols) package insert (Canada). Bayer Pharmaceuticals, Inc, 2010. Available from http://www.bayer.ca/files/SATIVEX-PM-ENG-11AUG2010-132251.pdf. Accessed June 20, 2012.
8. **NY Daily News.** Marijuana-based drug Sativex may get FDA approval?, 2012. Available from at http://articles.nydailynews.com/2012-01-22/news/30653996_1_fda-approval-sativex-drug-companies. Accessed June 20, 2012.
9. A study of Sativex® for relieving persistent pain in patients with advanced cancer. ClinicalTrials.gov, 2011. Available from http://clinicaltrials.gov/ct2/show/study/NCT01262651?term=sativex+malignancy&rank=8&show_locs=Y#locn. Accessed June 20, 2012.
10. Sativex® for relieving persistent pain in patients with advanced cancer (SPRAY III). ClinicalTrials.gov, 2011. Available from http://clinicaltrials.gov/ct2/show/NCT01361607?term=sativex+malignancy&rank=2. Accessed June 20, 2012.
11. Effects of sativex and oral THC on attention, affect, working memory, reversal learning, physiology and brain activation. ClinicalTrials.gov, 2011. Available from http://clinicaltrials.gov/ct2/show/NCT01037608. Accessed December 30, 2011.
12. 18 legal medical marijuana states and DC: laws, fees, and possession limits. 2012. Available from http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Accessed January 6, 2013.
13. **Pertwee RG.** Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006;147(suppl 1):S163–71.
14. **Gaoni Y, Mechoulam R.** Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964;86:1646–7.
15. **Pertwee RG, Howlett AC, Abood ME, et al.** International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB and CB. Pharmacol Rev 2010;62:588–631.
16. **Mechoulam R, Parker LA, Gallily R.** Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol 2002;42:11S–9S.
17. **Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M.** Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 1983;34:352–63.
18. **Agurell S, Halldin M, Lindgren JE, et al.** Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev 1986;38:21–43.
19. **Strougo A, Zuurman L, Roy C, et al.** Modelling of the concentration–effect relationship of THC on central nervous system parameters and heart rate – insight into its mechanisms of action and a tool for clinical research and development of cannabinoids. J Psychopharmacol 2008;22:717–26.
20. **Reinarman C, Nunberg H, Lanthier F, Heddleston T.** Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs 2011;43:128–35.
21. **Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL.** Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther 2007;82:572–8.
22. **Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK.** Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 1980;28:409–16.
23. **Rosenkrantz H, Fleischman RW, Grant RJ.** Toxicity of short-term administration of cannabinoids to rhesus monkeys. Toxicol Appl Pharmacol 1981;58:118–31.
24. **Zuurman L, Ippel AE, Moin E, van Gerven JM.** Biomarkers for the effects of cannabis and THC in healthy volunteers. Br J Clin Pharmacol 2009;67:5–21.
25. **Lopez HH.** Cannabinoid-hormone interactions in the regulation of motivational processes. Horm Behav 2010;58:100–10.
26. **Cooper ZD, Haney M.** Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts. Drug Alcohol Depend 2009;103:107–13.
27. **Seamon MJ, Fass JA, Maniscalco-Feichtl M, Abu-Shraie NA.** Medical marijuana and the developing role of the pharmacist. Am J Health Syst Pharm 2007;64:1037–44.
28. **Joy J, Watson S, Benson J (eds).** Marijuana and medicine: assessing the science base. Washington, D.C.: National Academy Press, 1999:267.
29. **Colorado Department of Public Health and Environment.** The Colorado Medical Marijuana Registry. 2011. Available from http://www.cdphe.state.co.us/hs/medicalmarijuana/statistics.html. Accessed June 20, 2012.
30. **Arizona Department of Health Services.** Arizona medical marijuana program. 2012. Available from http://www.azdhs.gov/medicalmarijuana/documents/reports/120531_Patient-Application-Report.pdf. Accessed June 20, 2012.
31. **Novotna A, Mares J, Ratcliffe S, et al.** A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex [R], as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011;18:1122–31.
32. **Wade DT, Collin C, Stott C, Duncombe P.** Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. Mult Scler 2010;16:707–14.
33. **Turcotte D, Le Dorze JA, Esfahani F, Frost E, Gomori A, Namaka M.** Examining the roles of cannabinoids in pain and other therapeutic indications: a review. Expert Opin Pharmacother 2010;11:17–31.
34. **Leung L.** Cannabis and its derivatives: review of medical use. J Am Board Fam Med 2011;24:452–62.
35. **Bowles DW, O'Bryant CL, Camidge DR, Jimeno A.** The intersection between cannabis and cancer in the United States. Crit Rev Oncol Hematol 2012;83:1–10.
36. **Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL.** Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009;10:1353–68.
37. **Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS.** Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2010;5:e14433.
38. **Wallace M, Schulteis G, Atkinson JH, et al.** Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007;107:785–96.
39. **Abrams DI, Jay CA, Shade SB, et al.** Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68:515–21.
40. **Wilsey B, Marcotte T, Tsodikov A, et al.** A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9:506–21.
41. **Fiz J, Duran M, Capella D, Carbonell J, Farre M.** Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS ONE 2011;6:e18440.
42. **Ware MA, Wang T, Shapiro S, et al.** Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182:E694–701.
43. **Ellis RJ, Toperoff W, Vaida F, et al.** Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672–80.
44. **Blake DR, Robson P, Ho M, Jubb RW, McCabe CS.** Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006;45:50–2.
45. **Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D.** Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133:210–20.
46. **Rog DJ, Nurmikko TJ, Friede T, Young CA.** Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812–9.
47. **Rog DJ, Nurmikko TJ, Young CA.** Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther 2007;29:2068–79.

48. **Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ.** Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. Pain 2003;106:169–72.
49. **Holdcroft A, Smith M, Jacklin A, et al.** Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia 1997;52:483–6.
50. **Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R.** The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain 2003;105:79–88.
51. **Noyes R Jr, Brunk SF, Avery DA, Canter AC.** The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975;18:84–9.
52. **Noyes R Jr, Brunk SF, Baram DA, Canter A.** Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol 1975;15: 139–43.
53. **Svendsen KB, Jensen TS, Bach FW.** Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004;329:253.
54. **Skrabek RQ, Galimova L, Ethans K, Perry D.** Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.
55. **Beaulieu P.** Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can J Anaesth 2006;53:769–75.
56. **Beard S, Hunn A, Wight J.** Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003;7:iii, ix–x, 1–111.
57. **Baker D, Pryce G, Croxford JL, et al.** Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000;404:84–7.
58. **Wade DT, Makela P, Robson P, House H, Bateman C.** Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler 2004;10:434–41.
59. **Collin C, Davies P, Mutiboko IK, Ratcliffe S.** Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007;14:290–6.
60. **Wade DT, Robson P, House H, Makela P, Aram J.** A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003;17:21–9.
61. **Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al.** Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004;10:417–24.
62. **Zajicek JP, Sanders HP, Wright DE, et al.** Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005;76:1664–9.
63. **Zajicek J, Fox P, Sanders H, et al.** Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003;362:1517–26.
64. **Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW.** Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv Alcohol Subst Abuse 1987;7:39–50.
65. **Pooyania S, Ethans K, Szturm T, Casey A, Perry D.** A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Archi Phys Med Rehabil 2010;91:703–7.
66. **Wang T, Collet JP, Shapiro S, Ware MA.** Adverse effects of medical cannabinoids: a systematic review. CMAJ 2008;178:1669–78.
67. **Dronabinol.** DRUGDEX® system. Thomson Reuters (Healthcare) Inc.; 2012. Available from http://www.thomsonhc.com. Accessed March 1, 2012.
68. **Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M.** The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol 2005;40:2–14.
69. **Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O.** Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology 2002;159:379–87.
70. **Green B, Kavanagh D, Young R.** Being stoned: a review of self-reported cannabis effects. Drug Alcohol Rev 2003;22:453–60.
71. **Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP.** Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res 2011;130:216–21.
72. **Freund TF, Katona I, Piomelli D.** Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017–66.
73. **Malone DT, Hill MN, Rubino T.** Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. Br J Pharmacol 2010;160:511–22.
74. **Ashtari M, Avants B, Cyckowski L, et al.** Medial temporal structures and memory functions in adolescents with heavy cannabis use. J Psychiatr Res 2011;45:1055–66.
75. **Cohen M, Rasser PE, Peck G, et al.** Cerebellar grey-matter deficits, cannabis use and first-episode schizophrenia in adolescents and young adults. Int J Neuropsychopharmacol 2012;15:297–307.
76. **Fergusson DM.** Is there a causal linkage between cannabis use and increased risks of psychotic symptoms? Addiction 2010;105:1336–7.
77. **Minozzi S, Davoli M, Bargagli AM, Amato L, Vecchi S, Perucci CA.** An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. Drug Alcohol Rev 2010;29:304–17.
78. **Foti DJ, Kotov R, Guey LT, Bromet EJ.** Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. Am J Psychiatry 2010;167:987–93.
79. **Lev-Ran S, Segev A, Braw Y, Levkovitz Y.** Neurocognitive functions of heavy cannabis using schizophrenia patients. Eur Psychiatry 2012;27:365–8.
80. **Solowij N, Battisti R.** The chronic effects of cannabis on memory in humans: a review. Curr Drug Abuse Rev 2008;1:81–98.
81. **Han J, Kesner P, Metna-Laurent M, et al.** Acute cannabinoids impair working memory through astroglial CB(1) receptor modulation of hippocampal LTD. Cell 2012;148:1039–50.
82. **Yucel M, Solowij N, Respondek C, et al.** Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry 2008;65:694–701.
83. **Honarmand K, Tierney MC, O'Connor P, Feinstein A.** Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology 2011;76:1153–60.
84. **Serra G, Fratta W.** A possible role for the endocannabinoid system in the neurobiology of depression. Clin Pract Epidemiol Ment Health 2007;3:25.
85. **Nussbaum A, Thurstone C, Binswanger I.** Medical marijuana use and suicide attempt in a patient with major depressive disorder. Am J Psychiatry 2011;168:778–81.
86. **Substance Abuse and Mental Health Services Administration.** Results from the 2009 national survey on drug use and health: volume I. Summary of national findings. Office of applied studies, NSDUH Serics H-38A, HHS Publication No. SMA 10-4586 Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2010.
87. **Hall W, Degenhardt L.** Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383–91.
88. **United States Department of Health and Human Services.** Substance Abuse and Mental Health Services Administration. Office of Applied Studies. Treatment Episode Data Set – Admissions (TEDS-A), 2008 [Computer file]. ICPSR27241-v2. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2010-03-31. doi:10.3886/ICPSR27241.
89. **National Poison Data System.** Marijuana human exposure data 2000–2010. Available from www.aapcc.org. Accessed August 23, 2011.
90. **McGuigan M.** Cannabinoids. Goldfrank's toxicologic emergencies. New York: McGraw Hill; 2011.

91. **Carstairs SD, Fujinaka MK, Keeney GE, Ly BT.** Prolonged coma in a child due to hashish ingestion with quantitation of THC metabolites in urine. J Emerg Med 2011;41:e69–71.
92. **Macnab A, Anderson E, Susak L.** Ingestion of cannabis: a cause of coma in children. Pediatr Emerg Care 1989;5:238–9.
93. **Weinberg D, Lande A, Hilton N, Kerns DL.** Intoxication from accidental marijuana ingestion. Pediatrics 1983;71:848–50.
94. **Wang GS, Narang SK, Wells K, Chuang R.** A case series of marijuana exposures in pediatric patients less than 5 years of age. Child Abuse Negl 2011;35:563–5.
95. **Nussbaum AM, Boyer JA, Kondrad EC.** "But my doctor recommended pot": medical marijuana and the patient-physician relationship. J Gen Int Med 2011;26:1364–7.

Neuro Endocrinol Lett. 2014;35(3):198-201.

Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Smith SC, Wagner MS.

Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.

PMID: 24977967

[PubMed - indexed for MEDLINE]

0 comments

How to join PubMed Commons

Neuro Endocrinol Lett. 2008 Apr;29(2):192-200.

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Russo EB[1].

Author information

Abstract

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-HT1A and inhibits 5-HT2A 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.

Republished from

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? [Neuro Endocrinol Lett. 2004]

PMID: 18404144

[PubMed]

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

How to join PubMed Commons

OPEN ACCESS Freely available online

PLoS one

Cannabis Use in Patients with Fibromyalgia: Effect on Symptoms Relief and Health-Related Quality of Life

Jimena Fiz[1,2], Marta Durán[3], Dolors Capellà[2,3], Jordi Carbonell[4], Magí Farré[1,2]*

1 Human Pharmacology and Neurosciences Unit, Institut de Recerca Hospital del Mar – IMIM, Parc de Salut Mar, Barcelona, Spain, **2** Universitat Autònoma de Barcelona, Barcelona, Spain, **3** Fundació Institut Català de Farmacologia, Barcelona, Spain, **4** Rheumatology Unit, Parc Salut Mar, Barcelona, Spain

Abstract

Background: The aim of this study was to describe the patterns of cannabis use and the associated benefits reported by patients with fibromyalgia (FM) who were consumers of this drug. In addition, the quality of life of FM patients who consumed cannabis was compared with FM subjects who were not cannabis users.

Methods: Information on medicinal cannabis use was recorded on a specific questionnaire as well as perceived benefits of cannabis on a range of symptoms using standard 100-mm visual analogue scales (VAS). Cannabis users and non-users completed the Fibromyalgia Impact Questionnaire (FIQ), the Pittsburgh Sleep Quality Index (PSQI) and the Short Form 36 Health Survey (SF-36).

Results: Twenty-eight FM patients who were cannabis users and 28 non-users were included in the study. Demographics and clinical variables were similar in both groups. Cannabis users referred different duration of drug consumption; the route of administration was smoking (54%), oral (46%) and combined (43%). The amount and frequency of cannabis use were also different among patients. After 2 hours of cannabis use, VAS scores showed a statistically significant ($p<0.001$) reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well being. The mental health component summary score of the SF-36 was significantly higher ($p<0.05$) in cannabis users than in non-users. No significant differences were found in the other SF-36 domains, in the FIQ and the PSQI.

Conclusions: The use of cannabis was associated with beneficial effects on some FM symptoms. Further studies on the usefulness of cannabinoids in FM patients as well as cannabinoid system involvement in the pathophysiology of this condition are warranted.

Citation: Fiz J, Durán M, Capellà D, Carbonell J, Farré M (2011) Cannabis Use in Patients with Fibromyalgia: Effect on Symptoms Relief and Health-Related Quality of Life. PLoS ONE 6(4): e18440. doi:10.1371/journal.pone.0018440

Editor: Antonio Verdejo García, University of Granada, Spain

Received November 16, 2010; **Accepted** March 7, 2011; **Published** April 21, 2011

Funding: The work was partially supported by grants from Ministerio de Sanidad - Plan Nacional sobre Drogas (SOC/3386/2004), Instituto de Salud Carlos III (FIS-Red de Transtornos Adictivos -RTA RD06/0001/1009) and Generalitat de Catalunya (AGAUR 2009 SGR 718). No additional external funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: mfarre@imim.es

Introduction

The main complaint of patients with fibromyalgia (FM) is chronic generalized pain, although many patients suffer from concomitant symptoms, such as tiredness, morning stiffness, sleep and affective disturbances [1]. The pathophysiology of the disorder is poorly understood. Several mechanisms have been suggested including central sensitization, suppression of descending inhibitory pathways, excessive activity of glial cells, and abnormalities of neurotransmitter release [2]. In addition, blunting of the hypothalamic-pituitary-adrenal-axis (HPA-axis) and increased autonomic nervous system responsiveness have been consistently reported in FM patients. Emerging clues suggest that such dysfunction of the stress response system may be crucial in the onset of the symptoms of FM [3]. Treatment is based on the symptomatic relief of symptoms but usually modest results are obtained. The overall patient's satisfaction and the health-related quality of life are consistently poor.

Potential therapeutic uses of cannabis in different types of pain are currently extensively investigated. Data from clinical trials with synthetic and plant-based cannabinoids provide a promising approach for the management of chronic neuropathic pain of different origins [4]. Additionally, a large body of evidence currently supports the presence of cannabinoid receptors and ligands, thus an endocannabinoid neuromodulatory system appears to be involved in multiple physiological functions [5].

There is little clinical information on the effectiveness of cannabinoids in the amelioration of FM symptoms. Three clinical trials have suggested the possible benefit of cannabinoid in the management of FM [6–8]. Furthermore, a clinical endocannabinoid deficiency (CECD) has been hypothesized to underlie the pathophysiology of fibromyalgia, but a clear evidence to support this assumption is lacking [9].

The aim of this study was to describe the patterns of cannabis use and the associated benefits reported by patients with fibromyalgia (FM) who were consumers of this drug. In addition, the quality of life of FM patients who consumed cannabis was compared with FM subjects who were not cannabis users.

Methods

Patients

A cross-sectional survey was performed. Participants were identified through an advertisement from one Rheumatology Outpatients Unit, 15 associations of FM patients and 1 association of cannabis consumers, all of them located in the city of Barcelona, Spain. Recruitment began in August 2005, and the study was completed in April 2007. Patients were eligible if they were ≥18 years of age, had been diagnosed with FM according to the American College of Rheumatology criteria [1], had moderate to severe symptomatology, and were resistant to pharmacological treatment. Exclusion criteria were severe illness and history of abuse or dependence for cannabis or others psychoactive substances.

Ethics statement

The study was approved by the local Institutional Review Board (CEIC-IMAS) and all volunteers gave their written informed consent before inclusion.

Study procedures and evaluation

Patients were divided according their status of therapeutic cannabis use. Eligibility and exclusion criteria were checked through an accurate telephone interview. Demographic (age, gender and employment status) and clinical variables (duration of FM, number of medical consultations in the last year, associated symptoms, current pharmacological treatment, comorbid conditions, and alternative and complementary medicines) were also collected through a structured telephone interview. Patients were informed that a specific questionnaire to collect information on medicinal cannabis use will be posted to them as well as visual analogue scales (VAS) to record perceived benefits with comprehensive instructions how to fill them out.

The following variables were recorded: duration of cannabis use, previous use, cannabis derivative used (hashish or marijuana), route of administration, amount and frequency of use, supply source, physician's acknowledgement about cannabis use and changes of pharmacological treatment. Symptoms from which cannabis was used and perceived relief was recorded using 5-point Likert scale (strong relief, mild relief, not change, slight worsening, great worsening). Patients were further asked to record the perceived benefits of cannabis on a range of symptoms (pain, stiffness, relaxation, drowsiness, well-being) using 100-mm VAS scales (VAS) before and at 2 hours of cannabis consumptions. The occurrence and frequency of side effects were indicated based on a list of symptoms.

In order to compare the quality of life between users and non users of cannabis, three questionnaires were used:

The 36-item Short Form Health Survey (SF-36) is a self-administered questionnaire, validated in Spanish, in which eight dimensions of health-related quality of life are assessed: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Each scale is scored using norm-based methods, with higher scores indicating better health. Scores are aggregated further to produce physical and mental component summary measures of health status, using norm-based methods. The subscale scores are standardized and range from 0 to 100 with higher scores reflecting better health-related quality of life in the domain being measured [10].

The Fibromyalgia Impact Questionnaire (FIQ) is a self-administered questionnaire, validated in Spanish to assess health-related quality of life specifically in patients with fibromyalgia over the previous week. It consists of VAS and questions regarding limitations of daily living activities. The total score ranges from 0 to 80; a higher score indicates a more negative impact [11].

The Pittsburg Sleep Quality Index (PSQI) is a self-administered questionnaire, validated in Spanish, to measure the quality and patterns of sleep over the last month. It consists of 7 components that sum each other and give a total score range from 0 (no difficulties) to 21 (severe difficulties) [12].

Statistical analysis

Data obtained from the questionnaires were analysed using the SPSS software (version 12.0.1). Comparisons were carried out using Fisher Exact tests for categorical variables and Student t test for continuous variables. The Mann-Whitney U test was used when the size of a comparison group was too small to assume normality. Statistical significance was at the 5% level and all tests were two sided.

Results

In response to the advertisement, 70 patients contacted the researchers to inquire about the study and were screened by telephone. A total of 14 subjects, –6 cannabis users and 8 non-users–, did not meet the eligibility criteria. Therefore, 56 FM patients completed the study protocol, 28 of them were cannabis users (mainly recruited through FM association and cannabis association) and 28 were non-cannabis users (mainly recruited through FM associations and the Rheumatology Outpatients Unit of the hospital).

As shown in Table 1, there were no statistically significant differences between the cannabis users and non-users groups in any demographic or clinical variables. The most frequent comorbid diseases were also balanced between the study groups. No significant differences were observed for the percentage of patients with irritable bowel syndrome, chronic fatigue syndrome, restless legs syndrome, osteoarthritis, Sjögren's syndrome, and hypothyroidism (data not shown in Table 1). With regard to treatment based on complementary and alternative medicines, there were no significant differences between groups, neither in number (cannabis group 64%; non-users group, 75%) or modalities chosen (data not shown in Table 1).

Patterns of cannabis use

Of the 28 FM patients using cannabis, 11 (40%) reported a duration of cannabis use of less than one year, 9 (32%) between 1 and 3 years, and 8 (29%) more than 3 years. Only 8 patients in the cannabis group have used cannabis recreationally before the medicinal use. Cannabis derivate used in every case was marijuana. The usual methods of administration were smoking and eating, and some patients use to combine both methods. Only smokers were 11%, only eaters were 46% and those using both methods were 43%. The amount and frequency of cannabis use were diverse among patients. The most frequent doses were between 1 and 2 cigarettes each time when patients smoked and 1 spoonful each time when eating. Most of the patients (n = 12) used cannabis daily, while 5 used it 2–4 days per week, 3 used it less than twice a week and 8 patients used it only occasionally. Related amount of cannabis used in one day, 12 reported once a day, 11 reported 2–3 times a day and 3 reported more than 3 times a day. Source of supply of cannabis were from family and friends (n = 14), illicit market (n = 7), growing (n = 5) and associations (n = 2). A total of 19 patients have informed their doctor about cannabis use, and reduction of pharmacological treatment was accomplished in 19 (68%) patients as well when they started using cannabis.

Table 1. Patient characteristics*.

	Cannabis (n = 28)	Control (n = 28)	*P*-values
Age, mean ± SD	50±11.9	50±7.7	0.94[a]
Female	26 (93)	27 (96)	1.00[b]
Employment status			0.89[b]
Work disability	10 (36)	10 (36)	
Unemployment	6 (21)	5 (18)	
Currently working	5 (18)	6 (21)	
Illness dismissed	3 (11)	5 (18)	
Retired	4 (14)	2 (7)	
Disease duration (years), median (range)	5.0 (1–20)	4.0 (1–14)	0.07[c]
N° of physician visits in last year, median (range)	6.0 (0–26)	6.0 (0–46)	0.76[c]
Associated symptoms			
Widespread pain	27 (96)	28 (100)	1.00[b]
Tiredness	25 (89)	28 (100)	0.23[b]
Morning tiredness	27 (96)	27 (96)	1.00[b]
Stiffness	25 (89)	27 (96)	0.61[b]
Anxiety	24 (86)	25 (89)	1.00[b]
Sleep disturbances	24 (86)	24 (86)	1.00[b]
Headaches	22 (79)	20 (71)	0.75[b]
Mood disorders	19 (68)	22 (79)	0.54[b]
Pharmacological treatment	26 (93)	26 (93)	1.00[b]
Analgesic/Anti-inflammatory drugs	21 (75)	18 (64)	0.56[b]
Antidepressants	14 (50)	17 (61)	0.59[b]
Anxiolytics	10 (36)	10 (36)	1.00[b]
Opioids	6 (21)	11 (39)	0.24[b]
Myorelaxants	1 (4)	6 (21)	0.10[b]
Hypnotics	5 (18)	8 (29)	0.52[b]

*Except where indicated otherwise, values are n° (%);
[a]: t-test;
[b]: Fisher test;
[c]: U Mann-Whitney.
doi:10.1371/journal.pone.0018440.t001

Perceived effects of cannabis use

Main symptoms leading to cannabis use and perceived benefits is shown in Figure 1. Patients used cannabis not only to alleviate pain but for almost all the symptoms associated to FM, and no one reported worsening of symptoms following cannabis use. The proportion of patients who reported strong relief ranged from 81% for sleep disorders to 14% for headache.

All symptoms assessed by VAS showed statistically significant improvement following 2 hours of cannabis self-administration (Figure 2). The mean reduction of pain was 37.1 mm ($p<0.001$, t-Test) and of stiffness 40.7 mm ($p<0.001$). The change from baseline in VAS relaxation and somnolence scores also significantly increased (27.6 mm, $p<0.05$ and 20.0 mm, $p<0.05$ respectively). In addition, perception of well-being was significantly higher as compared with baseline (40.0 mm, $p<0.001$).

Perceived side effects of cannabis use

At least one side effect was reported by 96% (n = 27) of patients. The most frequent were somnolence (n = 18), dry mouth (n = 17), sedation (n = 12), dizziness (n = 10), high (n = 9), tachycardia (n = 8), conjunctival irritation (n = 7) and hypotension (n = 6). The frequency most commonly reported were 'sometimes' for somnolence, sedation, dizziness, high, tachycardia and conjunctival irritation, and 'always' for dry mouth, sedation and hypotension. No serious adverse events occurred.

Quality of life

The mental health component summary score of the SF-36 questionnaire was slightly but significantly higher in the cannabis group (mean (M) = 29.6±standard deviation (SD) = 8.2) than in the non-users group (M = 24.9±SD = 8.9), p<0,05, t-Test. In the physical component summary score the differences were non significant between groups (cannabis group: M = 26.29±SD = 6.7; non-users group: M = 27.34±SD = 5.8; p = 0,53, t-Test).

No differences were found either in the Fibromyalgia Impact Questionnaire (M = 65.5±SD = 11.9; M = 65.5±SD = 12.8; p = 0.36, t-Test) or in the Pittsburg Sleep Quality Index (M = 14.1±SD = 3.2; M = 14.4±SD = 3.3; p = 0.73, t-Test).

Discussion

This observational study provides information on the patterns of cannabis use for therapeutic purposes among a group of patients with FM. Most of them were middle-aged women that did not respond to current treatment and self-administered marijuana, devoid of medical advice. Patients referred cannabis use in order to alleviate pain as well as other manifestations of FM. Significant relief of pain, stiffness, relaxation, somnolence and perception of well-being, evaluated by VAS before and 2 hours after cannabis self-administration was observed.

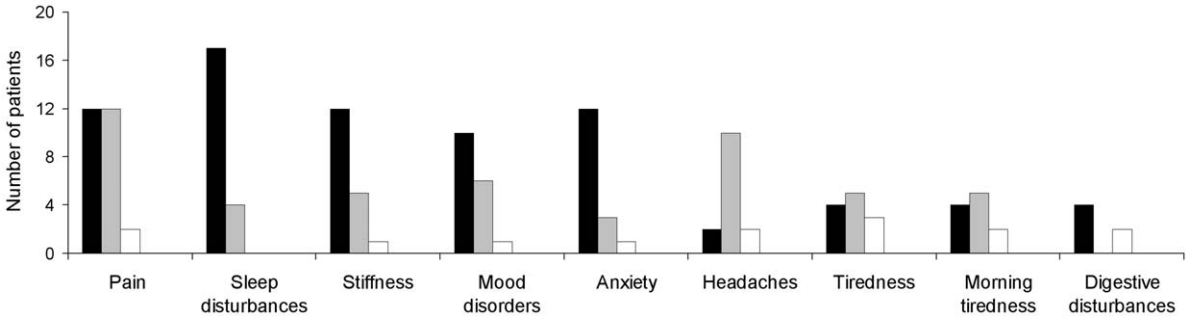


Figure 1. Symptoms and perceived relief reported by FM patients using cannabis. Note: Perceived relief was recorded using 5-point Likert scale (strong relief, mild relief, not change, slight worsening, great worsening). Black bars: strong relief; grey bars: mild relief; white bars: not change.
doi:10.1371/journal.pone.0018440.g001

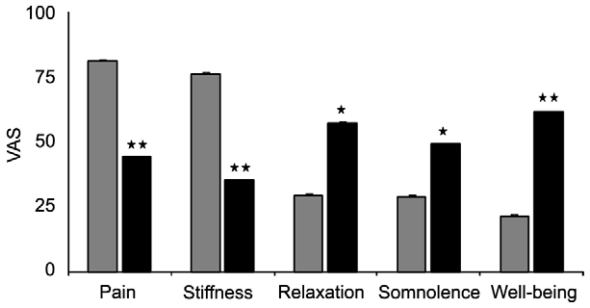


Figure 2. Perceived effects of cannabis self-administration. Note: Perceived benefits of cannabis recorded by patients on a range of symptoms using 100-mm VAS scales before and at 2 hours of cannabis consumptions. Grey bars: pre-cannabis; black bars: post-cannabis. * * = $p<0.001$; * = $p<0.05$.
doi:10.1371/journal.pone.0018440.g002

Although the mental health component summary score of the SF-36 questionnaire was slightly but significantly higher in the cannabis group than in the non-users group, whether these findings are clinically significant remains unclear.

The external validity of this study can be limited for some factors. The main limitation is the self-selection bias, mainly related to the fact that the majority of patients in the cannabis group were recruited from a cannabis association. It is not known how these patients are different from the ones recruited from FM associations or from the rheumatology unit. In addition the patients included in the study were all responders to cannabis self-administration. Consequently, characteristics of the patients that have used cannabis and have not obtained symptoms relief are unidentified. Others limitations were the small size of the sample and, the variability of patterns of cannabis use among FM patients.

A previous observational study of patients with chronic pain of different origins using cannabis has revealed similar results regarding symptoms relief [13]. Furthermore, significant reductions in VAS score for pain, FIQ global score and FIQ anxiety score were also seen in the first randomized controlled trial of 40 FM patients with continued pain despite the use of other medications treated with nabilone (synthetic cannabinoid agonist) during 4 weeks [7]. In a recent randomized, equivalency and crossover trial, nabilone was found to have a greater effect on sleep than amitriptyline on the ISI (Insomnia Severity Index), and was marginally better on the restfulness based on the LSEQ (Leeds Sleep Evaluation Questionnaire) [8]. These results seem to indicate a possible role of cannabinoids on the treatment of FM, although it should be confirmed in further clinical trials.

Moreover, according to hypothetical and experimental evidence, a Clinical Endocannabinoid Deficiency has been proposed to be involved on the pathophysiology of FM and other functional conditions alleviated by cannabis [9]. The participation of the endocannabinoid system in multiple physiological functions such as pain modulation, stress response system, neuroendocrine regulation and cognitive functions among others, is well known [5]. Additionally, the innovative psychoneuro-endocrinology-inmunology (PNEI) studies have shown that chronic pain may be strongly influenced by dysfunctions of the stress system and, particularly, the HPA-axis [14]. Studies have shown that the HPA-axis and the autonomic nervous system is disturbed in patients with fibromyalgia [3] and, polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems may also play a role in the pathogenesis of FM [15]. Notably, these polymorphisms all affect the metabolism or transport of monoamines, compounds that have a critical role in both sensory processing and the human stress response [16]. Endocannabinoids and cannabinoid receptors are involved in the responses of animals to acute, repeated and variable stress [17] and there is good evidence that the cannabinoid receptors play a major role in modulating neurotransmitter release such as serotonin and dopamine among others [18]. However, the endocannabinoid system and its implication in stress response in humans have not been so far investigated. Because of many methodological pitfalls in life stress research, high quality studies of the role of stress in the etiopathogenesis of unexplained chronic pain syndromes, such as fibromyalgia, are scarce.

We observe significant improvement of symptoms of FM in patients using cannabis in this study although there was a variability of patterns. This information, together with evidence of clinical trials and emerging knowledge of the endocannabinoid system and the role of the stress system in the pathopysiology of FM suggest a new approach to the suffering of these patients.

The present results together with previous evidence seem to confirm the beneficial effects of cannabinoids on FM symptoms. Further studies regarding efficacy of cannabinoids in FM as well as cannabinoid and stress response system involvement in their pathophysiology are warranted.

Acknowledgments

We thank Klaus Langohr for the supervision of the statistical analyses, and Marta Pulido for medical editing on behalf of IMIM. Grateful thanks are given to all participants.

Author Contributions

Conceived and designed the experiments: JF DC MF. Performed the experiments: JF. Analyzed the data: JF MF. Wrote the paper: JF MD DC JC MF.

References

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, et al. (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 33: 160–172.
2. Abeles AM, Pillinger MH, Solitar BM, Abeles M (2007) Narrative review: the pathophysiology of fibromyalgia. Ann Intern Med 146: 726–734.
3. Martinez-Lavin M (2007) Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 9: 216.
4. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR (2007) Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin 23: 17–24.
5. Pacher P, Bátkai S, Kunos G (2006) The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 58: 389–462.
6. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, et al. (2006) Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Curr Med Res Opin 22: 1269–1276.
7. Skrabek RQ, Galimova L, Ethansand Daryl K (2008) Nabilone for the Treatment of Pain in Fibromyalgia. J Pain 9: 164–73.
8. Ware MA, Fitzcharles MA, Joseph L, Shir Y (2010) The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 110: 604–610.
9. Russo EB (2008) Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett 29: 192–200.
10. Alonso J, Prieto L, Antó JM (1995) La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): Un instrumento para la medida de los resultados clínicos. Med Clin (Barc) 104: 771–776.
11. Rivera J, Gonzalez T (2004) The Fibromyalgia Impact Questionnaire: A Validated Spanish version to asses the health status in women with fibromyalgia. Clin Exp Rheumatol 22: 554–560.

12. Royuela Rico A, Macías Fernández JA (1997) Propiedades clinimétricas de la versión castellana del cuestionario de Pittsburg. Vigilia-Sueño 9: 81–94.
13. Lynch ME, Young J, Clark AJ (2006) A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage 32: 497–501.
14. Blackburn-Munro G (2004) Hypothalamo-pituitary-adrenal axis dysfunction as a contributory factor to chronic pain and depression. Curr Pain Headache Rep 2004; 8: 116–24.
15. Buskila D (2009) Developments in the scientific and clinical understanding of fibromyalgia. Arthritis Res Ther 11: 242.
16. Dadabhoy D, Clauw DJ (2006) Therapy insight: fibromyalgia a different type of pain needing a different type of treatment. Nat Clin Pract Rheumatol 2: 364–372.
17. Carrier EJ, Patel S, Hillard CJ (2005) Endocannabinoids in neuroimmunology and stress. Curr Drug Targets CNS Neurol Disord 4: 657–665.
18. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, et al. (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 54: 161–202.

Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy

Explore this journal >

View issue TOC
Volume 33, Issue 2
February 2013
Pages 195–209

Review of Therapeutics

The Pharmacologic and Clinical Effects of Medical Cannabis

Laura M. Borgelt, Kari L. Franson, Abraham M. Nussbaum, George S. Wang

First published:
5 February 2013 Full publication history

DOI:
10.1002/phar.1187 View/save citation

Presented, in part, at the Colorado Medical Society continuing education meeting on July 20, 2011.

For questions or comments, contact Laura M. Borgelt, Pharm.D., FCCP, BCPS, University of Colorado, Anschutz Medical Campus, Skaggs School of Pharmacy and Pharmaceutical Sciences, Mail Stop C238, 12850 E. Montview Blvd., V20-2124 Aurora, CO 80045; e-mail: laura.borgelt@ucdenver.edu.

Abstract

Cannabis, or marijuana, has been used for medicinal purposes for many years. Several types of cannabinoid medicines are available in the United States and Canada. Dronabinol (schedule III), nabilone (schedule II), and nabiximols (not U.S. Food and Drug Administration approved) are cannabis-derived pharmaceuticals. Medical cannabis or medical marijuana, a leafy plant cultivated for the production of its leaves and flowering tops, is a schedule I drug, but patients obtain it through cannabis dispensaries and statewide programs. The effect that cannabinoid compounds have on the cannabinoid receptors (CB_1 and CB_2) found in the brain can create varying pharmacologic responses based on formulation and patient characteristics. The cannabinoid Δ^9-tetrahydrocannabinol has been determined to have the primary psychoactive effects; the effects of several other key cannabinoid compounds have yet to be fully elucidated. Dronabinol and nabilone are indicated for the treatment of nausea and vomiting associated

with cancer chemotherapy and of anorexia associated with weight loss in patients with acquired immune deficiency syndrome. However, pain and muscle spasms are the most common reasons that medical cannabis is being recommended. Studies of medical cannabis show significant improvement in various types of pain and muscle spasticity. Reported adverse effects are typically not serious, with the most common being dizziness. Safety concerns regarding cannabis include the increased risk of developing schizophrenia with adolescent use, impairments in memory and cognition, accidental pediatric ingestions, and lack of safety packaging for medical cannabis formulations. This article will describe the pharmacology of cannabis, effects of various dosage formulations, therapeutics benefits and risks of cannabis for pain and muscle spasm, and safety concerns of medical cannabis use.

Cannabis, or marijuana, was first used for medicinal purposes in 2737 B.C.[1, 2] The United States Pharmacopeia initially classified marijuana as a legitimate medical compound in 1851.[3] Although criminalized in the United States in 1937 against the advice of the American Medical Association, cannabis was not removed from the United States Pharmacopoeia until 1942.[2] Given the schedule I status of this drug, patients have continued to obtain cannabis for medical purposes through statewide programs and cannabis dispensaries, which are facilities or locations where medical cannabis is made available to qualified patients.

Two categories of cannabinoid medicines are currently used in North America. First, cannabis-derived pharmaceuticals include dronabinol (schedule III), nabilone (schedule II), and nabiximols (not approved by the U.S. Food and Drug Administration [FDA]). Dronabinol and nabilone were approved in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy.[4-6] In 1992, dronabinol was also approved for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome.[5, 6] Nabiximols is a cannabis-derived liquid extract formulated from two strains of *Cannabis sativa* into an oromucosal spray. It is approved in Canada, New Zealand, and eight European countries for three indications: (1) symptomatic relief of spasticity in adults with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy, (2) symptomatic relief of neuropathic pain in patients with multiple sclerosis, and (3) intractable cancer pain.[7] It is being evaluated in several trials in the United States, and it is anticipated that it may receive FDA approval by the end of 2013.[8-11]

Second, phytocannabinoid-dense botanicals (i.e., medical cannabis or marijuana) include the schedule I medicinal plants *Cannabis sativa* or *Cannabis indica* . C *annabis ruderalis,* a third cannabis variety, has little psychogenic properties. The patients that are enrolled in U.S. medical cannabis studies are provided with a cannabis strain or blend grown and created under contract at a federal research farm at the University of Mississippi.[2] However, most patients in the United States grow their own medical cannabis or purchase it from dispensaries.

Currently, 18 U.S. states and the District of Columbia have laws that allow the use and possession of cannabis for medicinal reasons (Table 1).[12] Colorado and Washington have also passed legislation for recreational use of marijuana. With a growing number of states allowing medical cannabis and with patient use increasing, it has becomes progressively important for pharmacists and other health care providers to understand the potential benefits and risks of medical cannabis. The purpose of this article is to describe the pharmacology, therapeutic benefits and risks, and various dosage formulations that have been studied with medical cannabis. Specifically, medical cannabis for pain and muscle spasms, the most common uses of

medical cannabis, will be evaluated using an in-depth evidence-based approach.

Table 1. States with Enacted Laws to Allow Marijuana Use for Medical Purposes[12]

State	Year Passed	Possession Limit
Alaska	1998	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona	2010	2.5 oz usable; 0–12 plants [a]
California	1996	8 oz usable; 6 mature or 12 immature plants
Colorado	2000	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut	2012	1-mo supply (exact amount to be determined)
District of Columbia	2010	2 oz dried; limits on other forms to be determined
Delaware	2011	6 oz usable
Hawaii	2000	3 oz usable; 7 plants (3 mature, 4 immature)
Maine	1999	2.5 oz usable; 6 plants
Massachusetts	2012	60 day supply for personal medical use
Michigan	2008	2.5 oz usable; 12 plants
Montana	2004	1 oz usable; 4 plants (mature), 12 seedlings
Nevada	2000	1 oz usable; 7 plants (3 mature, 4 immature)
New Jersey	2010	2 oz usable
New Mexico	2007	6 oz usable; 16 plants (4 mature, 12 immature)
Oregon	1998	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island	2006	2.5 oz usable; 12 plants
Vermont	2004	2 oz usable; 9 plants (2 mature, 7 immature)
Washington	1998	24 oz usable; 15 plants

a If the patient lives > 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.

Clinical Pharmacology of Medical Cannabis

Marijuana is classified as a schedule I substance by the FDA, so it is difficult for contemporary researchers to study marijuana even though its therapeutic properties have been known for more than 5000 years.[13] Cannabis contains many compounds, of which at least 60 are known to be cannabinoids (active components of cannabis).[13] In the 1960s, when marijuana was increasingly used as a recreational drug, the cannabinoid Δ^9-tetrahydrocannabinol (THC) was isolated and determined to be the principal cause of marijuana's psychoactive effects.[14] Other cannabinoids have been isolated and found to be present in cannabis, but they are not nearly as psychoactive.

Pharmacodynamics

In the 1990s, the mechanism of action for many of the cannabinoids was determined with the discovery of the cannabinoid CB_1 and CB_2 receptors. The CB_1 receptors are found in high densities in the neuron terminals of the basal ganglia (affecting motor activity), cerebellum (motor coordination), hippocampus (short-term memory), neocortex (thinking), and hypothalamus and limbic cortex (appetite and sedation).[13] To a lesser extent, the CB_1 receptors are found in periaqueductal gray dorsal horn (pain) and immune cells. CB_2 receptors are primarily found on immune cells and tissues and, when activated, can affect inflammatory and immunosuppressive activity.[15] For example, CB_2 receptors on leukocytes may modulate cell migration, although these effects are difficult to elicit from standard dosing. CB_2 receptors are also found in the brain on microglia; thus, cannabinoids have begun to be studied for the treatment of Alzheimer's disease, but their role has not been established. Numerous cannabinoid compounds present in medical cannabis interact with these receptors to create varying responses (Figure 1). It is unknown how the major nonpsychotropic compound in cannabis, cannabidiol (CBD), exerts its activity, but it may be an inverse agonist, because several studies have shown that it decreases the psychotropic activity of THC.[15] It has no direct affinity for CB_1 and CB_2 receptors, yet it appears to enhance the activity of the endogenous cannabinoid, anandamide.[16] Because of the uncontrolled production of medical cannabis in various preparations (dried to be smoked or in oils to be applied, eaten, or drunk), there can be vastly different concentrations of the cannabinoid compounds in each product. As such, it is difficult to predict what pharmacologic response any cannabis product is likely to elicit. However, because of the relative efficacy (the ability of a drug to induce a biologic response at its molecular target when bound) of THC compared to other cannabinoids, it is routinely found to be the compound associated with the most pharmacologic effects of cannabis. Current researchers are trying to further differentiate the poorly binding cannabinoids by looking into the noncannabinoid targets linked to pain.[13] In these studies, other G-protein receptors (e.g., GPR55), G-protein–coupled receptors (coupling with μ- and δ-opioid receptors), and transient receptor potential channels (TRPVs), which are responsive to capsaicin, are being identified as targets.[13] In the TRPV example, it is interesting that non-CB_1 and non-CB_2 active phytocannabinoids (and not THC) have been shown to have the most effects.[15]

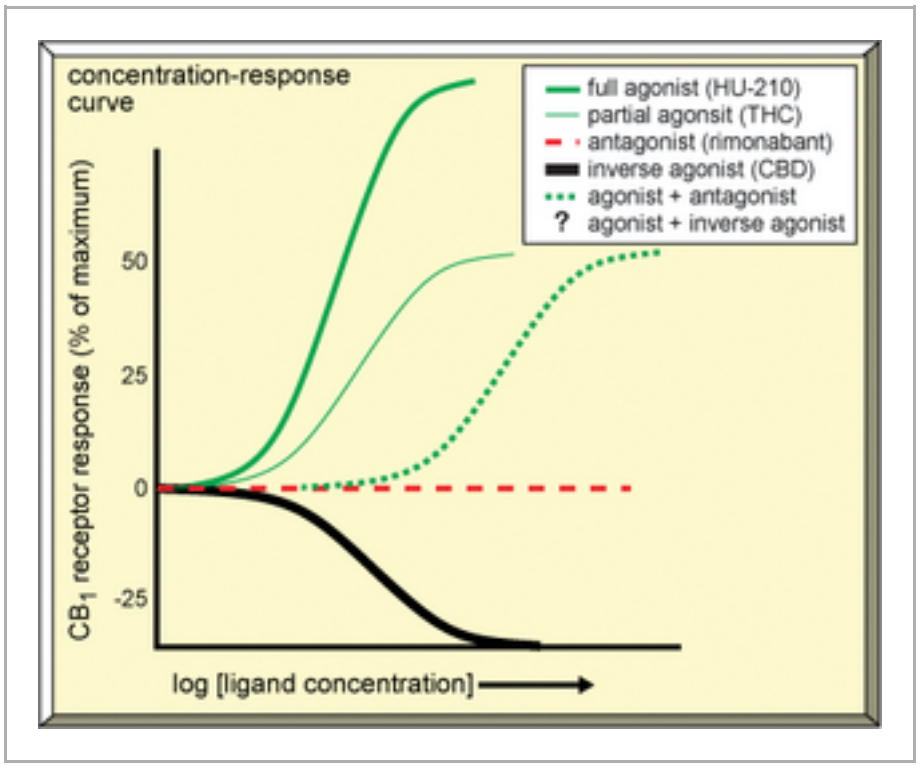


Figure 1.

Open in figure viewer

Concentration-response curves of cannabinoid compounds on the CB_1 receptor. The full agonist is the compound HU-210, which is a synthetic cannabinoid; the partial agonists are Δ^9-tetrahydrocannabinol (THC), which is a cannabinoid found in cannabis, and anandamide, which is an endocannabinoid found in humans; the antagonist is rimonabant, a synthetic cannabinoid studied for weight control; the inverse agonist is cannabidiol (CBD), which has no direct CB_1 activity but is postulated to be an example of an inverse agonist. It is unknown what the exact combination of agonists, antagonists, and inverse agonists are in cannabis and the result of this combination.

Pharmacokinetics

The pharmacokinetic characteristics of cannabinoids have been primarily evaluated in small clinical pharmacology studies. The half-life of the distribution phase is 0.5 hour, whereas the half-life for the terminal phase is highly variable with a mean of 30 hours.[17] Both are consistent with THC being highly lipophilic. Cannabidiol has a similar lipophilic profile to THC but has a terminal half-life of 9 hours.[16]

Smoking cannabis turns approximately 50% of the THC content into smoke, with the remainder lost by heat or from smoke that is not inhaled. Up to 50% of inhaled smoke is exhaled again, and some of the remaining smoke undergoes localized metabolism in the lung. The end result is that the estimated bioavailability of a smoked dose of THC is between 0.10 and 0.25.[18, 19] The absorption of smoked THC occurs within minutes, and the half-life of the distribution phase and that of terminal phase of smoked cannabis mimics those of intravenously administered THC.[18]

Although smoking remains the most common mode of ingestion for medical cannabis, vaporization of cannabis is becoming increasingly popular among medical cannabis users due to its perceived reduction of harm given the release of a significantly lower percentage of noxious chemicals.[20, 21] Given the volatility of cannabinoids, they will vaporize at a temperature much lower than the actual combustion of plant matter.

When heated air is drawn through the cannabis, the active components will aerosolize and can be inhaled without the generation of smoke.[2]

Orally administered THC has a bioavailability ranging from 5–20% in the controlled environments of clinical studies but is often lower in users because of variations in gastric degradation (with the presence of acids) and extensive first-pass effects.[18, 22] The bioavailability of oral cannabidiol is also variable (reported to be 13–19%), but one primate model found that intoxication required 20–50 times an oral versus an intravenous dose.[16, 23] The peak concentrations of the THC component of orally administered medical marijuana are delayed compared to intravenous or inhaled administration and are reached in 1–3 hours.[22] Orally administered medical cannabis presents concerns because absorption may be incomplete and delayed, resulting in intrapatient variability and difficulty with self-titration for appropriate dosing.

Drug–Dose, Drug–Disease and Drug–Drug Relationships

There is wide variation in the reported dose of THC needed to produce central nervous system effects. A review of 165 clinical pharmacology studies attempted to normalize the various doses and routes of administration of THC and defined a low dose as less than 7 mg, a medium dose as 7–18 mg, and a high dose as greater than 18 mg.[24] However, there is known tolerance to THC through downregulation of CB_1 receptors and G-protein activation. There is a high probability of tolerance with as few as 4 days of daily use, and low probability with intermittent use. In this review, it was determined that an elevation in heart rate (average > 19 beats/min), an increase in subjectively feeling “high,” a decrease in subjective alertness, and a decrease in motor stability were the consistent pharmacodynamic effects of THC regardless of route of administration. When the pharmacokinetics and pharmacodynamics of these physiologic effects were modeled after pulmonary administration of THC, a delay was found between the serum concentrations and peak cardiac (8 min) and central nervous system (> 30 min) effects. There was also evidence that THC accumulates in the brain, and serum concentrations do not correlate with effects because the effects in the brain lasted longer than the elevated serum concentrations and peripheral cardiac effects. In addition, it was determined that the maximal effects at some compartments (heart) plateau, whereas effects on alertness are linear presumably to the point of loss of consciousness. These results indicate that it is difficult to correlate a single serum concentration to any physiologic effect or impairment, as is often done reliably with alcohol.[24]

Different patient populations may have varying responses to medical cannabis. Levels of hormones such as luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone are known to decline with long-term exposure to medical cannabis. Hormones alter the pharmacodynamic profile of THC, as female patients with higher estrogen levels are more sensitive to the effects of medical cannabis on pain, behavior, and reward.[25] Using marijuana concomitantly with tobacco leads to greater increases in heart rate and carbon monoxide levels, despite lower THC concentrations.[26] Conversely, medical cannabis may complicate the clinical picture of a patient who has various disorders and is receiving other medications. Cannabis may increase the risks in patients with psychiatric and cardiovascular conditions. Patients with cardiovascular conditions who use cannabis are subjected to increases in heart rate and decreases in heart rate variability (a known cardiovascular parameter associated with reduced autonomic response and increased morbidity and mortality).[24] These effects may be worsened if the patient is receiving other medications that increase heart rate (e.g., anticholinergics, α-agonists, theophylline, tricyclic antidepressants, naltrexone, and amphetamines).[27] The decrease in alertness experienced with marijuana can be potentiated by benzodiazepines, opiates, and tricyclic antidepressants.[27] Because medical cannabis is not

controlled or regularly used in mainstream medicine, the actual drug–disease and drug–drug interaction profiles remain to be elucidated.

Clinical Effects of Medical Cannabis

In 1999, the Institute of Medicine released a report indicating cannabinoids may have a role in the treatment of pain, movement, and memory but observed that risks are associated with use.[28] Their report made six major recommendations to the medical community to better establish the safety and efficacy of marijuana. These recommendations included the evaluation of the physiologic and psychological effects, individual health risks, and various delivery systems of medical cannabis, as well as short-term (< 6 mo) clinical trials to determine effectiveness of medical cannabis for targeted medical conditions. Despite this call to action, there have been relatively few controlled clinical trials to evaluate the effects of various delivery systems for medical cannabis. Some states that permit the use of medical cannabis have incorporated patient registries for possession of a predetermined amount of cannabis for conditions such as cachexia, cancer, glaucoma, human immunodeficiency virus infection/acquired immune deficiency syndrome, muscle spasms, seizures, severe nausea, severe pain, and sleep disorders. At this time, Colorado and Arizona have the most robust state medical marijuana registries, which provide demographic data about who is permitted to use medical cannabis and for which indication. In both states, where a person may use medical cannabis for more than one condition, 89% (Arizona) and 94% (Colorado) of patients are registered for severe or chronic pain and 14% (Arizona) and 17% (Colorado) are registered for muscle spasms.[29, 30] Given that pain and muscle spasms are the most common reasons that medical cannabis is used, this article focuses on the therapeutic effects of medical cannabis for these two conditions.

Pain

The analgesic effects of cannabis may be due to several different mechanisms including, but not limited to, modulation of rostral ventromedial medulla neuronal activity, antinociceptive effects in descending pain pathways, and antiinflammatory properties by acting through prostaglandin synthesis inhibition.[2] Various forms of medicinal cannabis have provided mostly positive responses for patients with different types of pain: neuropathic, chronic, postoperative, and that related to fibromyalgia, rheumatoid arthritis, multiple sclerosis, and cancer.[28, 31-37]

In studies evaluating smoked cannabis compared to placebo, significant improvements in pain were observed (Table 2).[38-43] These studies included a small number of patients (15–56) and used cigarettes with varying THC contents. THC content varies based on the strain of cannabis plant that is used. In general, a higher THC content (up to 9.4%) appears to be more effective for pain relief. One group of investigators considered the neuropathic pain reduction from smoked cannabis to be modest compared to that from other drugs used for neuropathic pain, such as gabapentin and pregabalin (0.7 reduction on a 10-cm scale compared to 1.2 and 1.3, respectively).[42] Although relatively few serious adverse effects were reported in these studies, some mild-to-moderate adverse effects were commonly noted: somnolence, headache, dry mouth, sedation, dizziness, conjunctival irritation/dry eyes, hypotension, and difficulty with concentration and/or memory. The range of doses used in these trials is shown in Table 2. Although it appears that some dose-response relationship occurs (i.e., higher THC content provides better therapeutic response), many other variables factor into an effective dose, such as individual tolerance, dosage form used, frequency of dosing, and

adverse effects experienced. Therefore, the most effective dose for pain will vary among individuals.

Table 2. Clinical Trials of Smoked Cannabis for Pain

Study Drug (% of THC)	Condition Studied	No. of Patients	Outcome	Adverse Effects
Smoked cannabis only (11%), oral cannabis only (46%), combined oral + smoked cannabis (43%) vs nonuser of cannabis[41]	Fibromyalgia	56 (28 users and 28 nonusers)	Improvement in pain and stiffness ($p<0.001$), enhancement of relaxation ($p<0.05$), and increased somnolence ($p<0.05$) and feeling of well-being ($p<0.001$) on visual analog scale	Most frequent adverse effects were somnolence (18/28), dry mouth (17/28), sedation (12/28), dizziness (10/28), high (9/28), tachycardia (8/28), conjunctival irritation (7/28), and hypotension (6/28); no serious events occurred
Smoked cannabis (0%, 2.5%, 6%, 9.4%) 3 times/day × 5 days (crossover every 14 days)[42]	Posttraumatic or postsurgical neuropathic pain	21	Daily pain intensity was lower with cannabis with 9.4% THC content than with 0% ($p=0.023$) on numeric rating scale	Total of 248 mild and 6 moderate adverse events reported; no serious or unexpected adverse events; most frequent events in group receiving cannabis with 9.4% THC content were headache, dry eyes, burning sensation, dizziness, numbness, and cough
Smoked cannabis (1–8%) or placebo 5 days/wk × 2 wks[43]	Neuropathic pain in patients infected with human immunodeficiency virus	28	Improvement in pain on descriptor differential scale with cannabis ($p<0.016$)	Most events were mild and self-limiting; 3 were treatment-limiting toxicities (cannabis-induced psychosis, cough, intractable diarrhea); other effects that were more frequent with cannabis use were concentration difficulties, fatigue, sleepiness, and sedation
Smoked cannabis (3.5% or 7%) or placebo[40]	Central and peripheral neuropathic pain	38	Cannabis improved pain on visual analog scale ($p=0.016$); cannabis improved the following types of pain: sharp ($p<0.001$), burning ($p<0.001$), aching ($p<0.001$), sensitive ($p=0.03$), superficial ($p<0.01$), and deep ($p<0.001$); cannabis provided greater relief as shown on the global impression scale ($p<0.01$)	Psychoactive effects were minimal and well-tolerated; some acute cognitive effects were noted at high doses, especially with memory
Smoked cannabis (3.56%) or placebo TID × 5 days[39]	Human immunodeficiency virus–associated sensory neuropathy	50 (25 users and 25 nonusers)	> 30% pain reduction reported by 52% of the cannabis group and by 24% of the placebo group ($p<0.04$)	No serious events reported

Smoked cannabis single doses (2%, 4%, and 8%) given in random order or placebo[38]	Capsaicin-induced pain and hyperalgesia	15	Pain reduction with medium dose only on pain scores and McGill Pain Questionnaire at 45 min after cannabis administration	Generally well tolerated; dyspnea, dry mouth, feeling cold, and somnolence were reported

Nabiximols, the oromucosal spray with an equal mixture of THC and CBD not yet approved by the FDA, is being evaluated in several trials of patients with neuropathic and chronic pain.[44-47] Each of these studies demonstrated a statistically significant reduction of pain intensity compared to placebo. In most of these trials, the patients continued their existing analgesic medication in addition to starting the study medication; therefore, symptom relief obtained from the study drug was beyond the effects achieved with the patients' existing analgesia. Adverse events reported included dizziness, sedation, feeling intoxicated, and nausea. As a limitation, most of these studies had varying definitions for types of pain and included patients already using standard analgesic agents; therefore, nabiximols may be best reserved for patients with refractory pain.

Oral THC (dronabinol 5–20 mg) has not demonstrated significant improvements in visual analog pain assessments for healthy volunteers (under experimental pain conditions) or patients with chronic gastrointestinal pain or posthysterectomy pain.[48-50] Among patients with cancer pain given a single dose of placebo or THC 5, 10, 15, or 20 mg, analgesia was achieved only with THC at the higher 15- and 20-mg doses.[51, 52] The authors stated that 10 and 20 mg of oral THC were equivalent to 60 and 120 mg of codeine, respectively, for pain relief, but that the adverse effects of oral THC (somnolence, dizziness, ataxia, and blurred vision) may not make it an ideal medication for chronic cancer pain. The analgesic effect of dronabinol 10 mg/day for 3 weeks in 24 patients with multiple sclerosis revealed a relative reduction in pain scores (−20.5%, 95% confidence interval [CI] −37.5% to −4.5%) compared to placebo.[53] No serious adverse events were reported, but patients receiving dronabinol reported more dizziness and light-headedness.

Nabilone has also been evaluated for the treatment of pain. In a randomized double-blind study of 40 patients with fibromyalgia, pain and quality-of-life measurements were assessed using a visual analog scale and the Fibromyalgia Impact Questionnaire. The visual analog scale was a continuous scale from 0–10 on a 10-cm (or 100-mm) line that was anchored by descriptors (e.g., 0 is "no pain" and 10 is "worst imaginable pain"). The Fibromyalgia Impact Questionnaire is an instrument designed to quantify the overall impact of fibromyalgia over many dimensions (e.g., function, pain level, fatigue, sleep disturbance, and psychological distress) and is scored from 0–100, with the latter number being the worst case. Significant decreases in scores from the visual analog scale (−2.04, $p<0.02$), Fibromyalgia Impact Questionnaire (−12.07, $p<0.02$), and 10-point anxiety scale (−1.67, $p<0.02$) were observed after 4 weeks of nabilone treatment when the drug was titrated from 0.5 mg/day to 1 mg twice/day; these results indicate that pain, disease impact, and anxiety were significantly reduced.[54] Although no serious events were reported, the patients receiving nabilone experienced more adverse effects (1.54, $p<0.05$), with the most common being drowsiness, dry mouth, vertigo, and ataxia. The authors stated that the pain relief seen in the treatment group was similar to that for other treatments used for fibromyalgia, including fluoxetine, tramadol, and pramipexole. In a different study, high-dose nabilone (2 mg given at 8-hour intervals for 24 hours) showed an increase or worsening in pain scores for patients also receiving morphine after surgery compared to ketoprofen and placebo.[55] The authors concluded that this unexpected finding may have been due to paradoxical or sedative effects of cannabinoids at high doses.

Two meta-analyses have evaluated various forms of cannabis treatment for pain. The first was a systematic review and meta-analysis of 18 double-blind randomized controlled trials that compared any cannabis preparation to placebo among patients with chronic pain.[36] The cannabis preparation contained THC and could be administered by any route of administration. Most trials included nabiximols, dronabinol, or nabilone. Cannabis treatment demonstrated a statistically significant standardized mean difference of −0.61 (95% CI −0.84, –0.37) in pain intensity from baseline scores. This review and meta-analysis also evaluated harms and found significant changes with cannabis use for mood disturbances such as euphoria (odds ratio [OR] 4.11, 95% CI 1.33–12.72, number needed to harm [NNH] 8). Other harms found to be significantly associated with cannabis use included alterations in perception (OR 4.51, 95% CI 3.05–6.66, NNH 7), events affecting motor function (OR 3.93, 95% CI 2.83–5.47, NNH 5), and events that altered cognitive function (OR 4.46, 95% CI 2.37–8.37, NNH 8) for patients taking cannabis compared to those taking placebo or another analgesic drug. The authors concluded that cannabis may offer moderate efficacy for treatment of chronic pain, but benefits may be partially or completely offset by potential harms.

Painful human immunodeficiency virus–associated sensory neuropathy has been evaluated through a systematic review and meta-analysis involving 14 randomized controlled trials.[37] Interventions that showed greater efficacy for pain on a visual analog scale included smoked cannabis (relative risk 2.38, 95% CI 1.38–4.10, NNT 3.38), topical capsaicin 8% patch (p=0.0026, NNT 6.46), and recombinant human nerve growth factor, which is not available clinically. No superiority over placebo was reported for amitriptyline, gabapentin, pregabalin, prosaptide, peptide-T, acetyl-L-carnitine, mexilitine, lamotrigine, and topical capsaicin 0.075%. The authors concluded that although smoked cannabis may have superior effectiveness, other routes of cannabis should be investigated to avoid the potential negative impact of smoking.

Overall, these studies show statistically significant improvement in various types of pain when medical cannabis is used. Trials indicate that smoked cannabis or cannabis extract (THC:CBD) are effective for several different types of pain, primarily neuropathic pain. Oral THC (dronabinol) does not appear to be as effective for pain but has not been widely studied in various pain conditions. Nabilone may be effective for pain related to fibromyalgia but also has not been widely studied. There is a paucity of well-designed studies evaluating medical cannabis for pain. Limitations of these studies include widely varying doses and dosage forms of medical cannabis, lack of validated criteria or assessment for some types of pain (e.g., neuropathic), lack of comparative trials for various formulations and routes of administration, self-selection bias (i.e., some patients have already had a previous positive response to the drug), difficulty blinding participants to potentially psychoactive substances, and small study populations. Given its legal status, the need for more efficacy data, and its unknown safety and tolerability profile, medical cannabis should be considered only when treatment failure with standard therapy has occurred or when adjunctive therapy is appropriate.

Muscle Spasms

Nabiximols (THC:CBD extract) has been the primary cannabis agent studied for the treatment of spasticity in patients with multiple sclerosis. Spasticity is commonly associated with painful spasms and sleep disturbance and contributes to increased morbidity.[56] Endogenous and exogenous cannabinoids have been shown to be effective for multiple sclerosis spasticity in animal models, primarily through effects at the CB_1 receptor.[57] Nabiximols has been shown to be effective as monotherapy and as add-on therapy for patients not fully relieved with other antispasticity therapy.[31]

One large multicenter parallel-group, double-blind, randomized placebo-controlled study included 160

patients with multiple sclerosis who were experiencing primary symptoms of spasticity, spasms, bladder problems, tremor, or pain.[58] Treatment evaluated was oromucosal sprays of matched placebo or whole plant cannabis–based medicinal extract (CBME) containing equal amounts of THC and CBD at a dosage of 2.5–120 mg/day, in divided doses. A visual analog scale score for each patient's most troublesome symptom was used. This primary symptom score improved in both groups with no statistically significant difference; the scores of patients using CBME reduced from a mean ± standard error of 74.36 ± 11.1 to 48.89 ± 22.0, and those using placebo from 74.31 ± 12.5 to 54.79 ± 26.3. Spasticity scores were significantly reduced with CBME in comparison to placebo (p=0.001). No significant adverse effects on cognition or mood were reported, and intoxication was generally mild.

In another double-blind study evaluating nabiximols, 189 patients with diagnosed multiple sclerosis and spasticity were randomized to receive daily doses of active preparation (124 patients) or placebo (65 patients) over 6 weeks.[59] The primary efficacy analysis on the intent-to-treat population (184 patients) showed the active preparation to be significantly superior (p=0.048) as measured with a numeric rating scale of spasticity. For the responders, 40% of patients receiving active preparation achieved greater than 30% benefit (p=0.014). Eight withdrawals were attributed to adverse events: six received active preparation and two received placebo.

A meta-analysis of three studies (two of which were described here earlier) evaluated 666 patients with multiple sclerosis and spasticity.[32] These were randomized, placebo-controlled, double-blind parallel-group studies of nabiximols. On a 0–11 numeric rating scale, the adjusted mean decrease from baseline was 1.30 with nabiximols compared to 0.97 with placebo. Using a linear model, the treatment difference was −0.32 (95% CI −0.61 to −0.04, p=0.026). A greater proportion of the treated patients were responders (OR 1.62; 95% CI 1.15–2.28, p=0.0073) and they also reported greater improvement (OR 1.67; 95% CI 1.05–2.65, p=0.030). Many patients experienced at least one adverse event (288 of 363 patients for nabiximols, 169 of 303 patients for placebo), although most events were mild to moderate in severity and all serious adverse events resolved. Forty (11%) and 11 (3.6%) patients withdrew from the study due to adverse events in the nabiximols and placebo groups, respectively.

A consecutive series of randomized, double-blind placebo-controlled single-patient crossover trials evaluated muscle spasms as one outcome for 24 patients (18 with multiple sclerosis) with plant extracts of THC and CBD and a 1:1 mixture of THC:CBD in a sublingual spray.[60] The THC and THC:CBD groups both reported significant improvement in the spasticity severity rating versus placebo (p<0.05). Three patients experienced transient hypotension and intoxication with rapid initial dosing of CBME. The authors acknowledged that this was a preliminary study and that larger well-controlled studies were needed.

Oral cannabis has been evaluated in several trials for spasticity due to multiple sclerosis. In a double-blind crossover placebo-controlled randomized trial of 50 patients, the intent-to-treat analysis showed no significant difference in Ashworth spasticity scores compared to placebo.[61] However, in the 37 patients who received more than 90% of the treatment (per protocol analysis), there was a significant improvement in the number of spasms and spasticity scores (p=0.013) and mobility (p=0.01). In a large multicenter double-blind randomized controlled trial of 630 patients with multiple sclerosis, 576 responded to questions about their spasticity. There was a significant improvement in patient-reported pain and spasticity (p=0.003) with a reduction in spasticity of 61% for the 197 patients receiving cannabis extract (95% CI 54.6–68.2) and of 60% for the 181 patients receiving oral THC (95% CI 52.5–66.8).[62, 63] Of note, of the 198 patients receiving placebo, 46% reported improvement in spasticity (95% CI 39.0–52.9). A double-blind placebo-controlled crossover study in 13

patients showed significant improvement in patient-reported subjective spasticity scores after receiving THC at doses ranging from 7.5 to 15 mg/day for 5 days.[64] No objective outcomes were measured.

In one double-blind crossover placebo-controlled randomized trial of 12 patients, nabilone twice/day was given for 4 weeks to determine if it improved spasticity caused by spinal cord injury.[65] There was a significant reduction in the Ashworth scale and total Ashworth score (p=0.003 and p=0.001, respectively).

Overall, cannabis-derived pharmaceuticals appear effective for muscle spasticity related to multiple sclerosis. Nabiximols is approved for this purpose in 10 different countries. Limited data exist on the use of other forms and doses of medical cannabis for muscle spasms. Furthermore, most states list “muscle spasm” as an indication for medical cannabis use but do not require that the diagnosis of multiple sclerosis be present. The evidence of effectiveness of medical cannabis in muscle spasm not related to multiple sclerosis is scarce. Limitations of published studies include differences in spasticity assessment between patients (subjective) and providers (objective with Ashworth scale scoring), presence of other multiple sclerosis symptoms, lack of comparative trials for various formulations and routes of administration, self-selection bias, blinding participants to potentially psychoactive substances, and having many studies (especially those evaluating nabiximols) sponsored by the manufacturer or the medical marijuana industry. Most of these studies evaluated patients with inadequate spasticity relief using existing treatments, suggesting that the included patient populations would likely respond well to medical cannabis. Nabiximols or medical cannabis may be best reserved for the patient population who have not shown efficacy or are intolerant to other standard therapies for muscle spasm.

Safety Concerns

Adverse Effects, Drug Interactions, and Contraindications

Although most trials indicate that medical cannabis produces mild to moderate adverse effects, one of the ongoing concerns about using medical cannabis is the unfavorable and somewhat variable adverse effect profile when used in different formulations as a medicinal product. In a systematic review of 31 studies (23 randomized controlled trials and 8 observational studies), 4779 adverse events were reported in patients receiving a medicinal cannabinoid for 8–12 months.[66] Most (4615 [96.6%] events) were not serious, with the most common nonserious event being dizziness (714 [15.5%] events). Of the 164 serious events, the most common were relapse of multiple sclerosis (21 [12.8%] events), vomiting (16 [9.8%] events), and urinary tract infection (15 [9.1%] events). More nonserious adverse events were reported in the treatment groups compared to the control groups (rate ratio 1.86, 95% CI 1.57–2.21); however, there was no significant difference in the rate of serious events (rate ratio 1.04, 95% CI 0.78–1.39). Limitations of this review include lack of inclusion of smoked cannabis and short-term evaluation of cannabis use (up to 12 mo).

There is minimal information available about drug interactions and contraindications with cannabis-derived pharmaceuticals and medical cannabis. A contraindication to dronabinol use is hypersensitivity to the drug; one noted drug interaction is with ritonavir, when increased dronabinol serum concentrations may occur leading to potential toxicity.[67] The Canadian product insert for nabiximols states the following contraindications: known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil (ingredients/excipients in the product); serious cardiovascular disease (such as ischemic heart disease), arrhythmias, poorly controlled hypertension or severe heart failure; history of schizophrenia or any other

psychotic disorder; children under 18 years of age; women of child-bearing potential not on a reliable contraceptive or men intending to start a family; and pregnant or nursing women.[7] A serious drug interaction warning is provided for patients receiving sedatives, drugs with sedating or psychotropic effects, and hypnotics, as there may be an additive effect with nabiximols. In addition, alcohol may interact with nabiximols, particularly in affecting coordination, concentration, and ability to respond quickly. No clinically apparent drug interactions were noted in clinical trials where nabiximols was taken with other cytochrome P450 (CYP) agents; however, there may be a potential risk of drug–drug interactions due to CYP inhibition by nabiximols.[7] The product monograph recommends caution be exercised in patients taking drugs known to be substrates for CYP3A4 or CYP2C19.[7] Given the lack of information about medical cannabis, it would be reasonable to apply these contraindications and drug interaction concerns especially with the variability in formulation, dose, and frequency of administration with these products.

Psychiatric Implications

Marijuana's chief psychoactive ingredient, THC, is a partial agonist at the CB_1 receptors, the predominant endocannabinoid receptors in the brain that help modulate appetite, mood, and motivation.[68, 69] While the response to marijuana depends on dose, strain, and frequency of use, most cannabis users experience mild euphoria, sedation, relaxation, hunger, and enhanced sensory input but also impaired attention, balance, cognition, judgment, memory, and sense of time. Some users experience anxiety, disorientation, paranoia, and psychosis; there is some reason to believe that strains with greater relative cannabidiol concentrations are associated with fewer psychotic symptoms.[70, 71]

Frequent use of cannabis, especially in adolescence, is associated with the development of schizophrenia, a chronic neurodevelopmental disorder. During adolescence, when schizophrenia typically presents, profound changes occur in the brain, often through synaptic pruning, a process that endocannabinoids help regulate.[72] Using cannabis interferes with adolescent neurodevelopment, and imaging studies associate marijuana use with adverse development of the hippocampus and the cerebellum.[73-75] Epidemiologic data associate heavy adolescent use of marijuana with both an earlier onset of schizophrenia and a 2-fold increased risk of developing schizophrenia.[76] To be clear, the use of cannabis in adolescence does not cause schizophrenia but increases the risk of its onset, suggesting interplay between marijuana use and genetic predisposition for schizophrenia.[77] For people who develop schizophrenia, ongoing use of marijuana is associated with more severe psychosis and impaired performance on tests of attention and impulsivity.[78, 79] Marijuana is a psychoactive substance whose psychiatric complications are known to increase with early onset and regular use.

Cannabis use is associated with impairments in memory and cognition. Heavy cannabis users have deficits in the encoding, storage, and retrieval of memory.[80] A recent animal model found that cannabis impairs working memory by activating astroglial cannaboid receptors in the hippocampus.[81] These findings correlate well with the association between heavy marijuana use and bilateral volume reduction of structures involved in memory like the amygdala and hippocampus.[82] Marijuana users often perform poorly on tests of executive function, information processing, and visuospatial perception.[83]

The use of cannabis is more modestly associated with depression and suicide in epidemiologic data. Frequent cannabis use is significantly associated with depressive disorders in both animal models and epidemiologic studies.[84] Hyperactivity of the endocannabinoid system is associated with impulsivity and suicidality, which is borne out in epidemiologic studies where a significant association is observed between

marijuana use and suicidal ideation and attempt.[85]

Finally, cannabis is the most commonly used and abused illicit substance in the world. In the United States each year, approximately 6500 individuals begin to use marijuana daily, of whom 10–20% will develop cannabis dependence.[86, 87] Among people admitted to substance treatment facilities in the United States, marijuana is the most frequently identified illicit substance.[88]

Pediatric Implications

The National Poison Data Center reported 5371 calls pertaining to marijuana exposures in 2011; 358 (7%) were for children aged 12 years or younger.[89] Compared to previous years, total calls and calls pertaining to children aged 12 years or younger increased (Figures 2 and 3). Acute cannabinoid toxicity usually presents with various neurologic symptoms: decreased coordination, decreased muscle strength, lethargy, sedation, difficulties concentrating, altered psychomotor activity, slurred speech, and slow reaction time. Other common symptoms include tachycardia and dry mouth. These effects can be more pronounced in children, especially at lower doses. Common symptoms include ataxia, somnolence, lethargy, altered mental status, and obtundation. Rarely, pediatric patients present with more severe symptoms such as apnea, cyanosis, bradycardia, hypotonia, and opisthotonus (severe hyperextension and spasticity).[90]

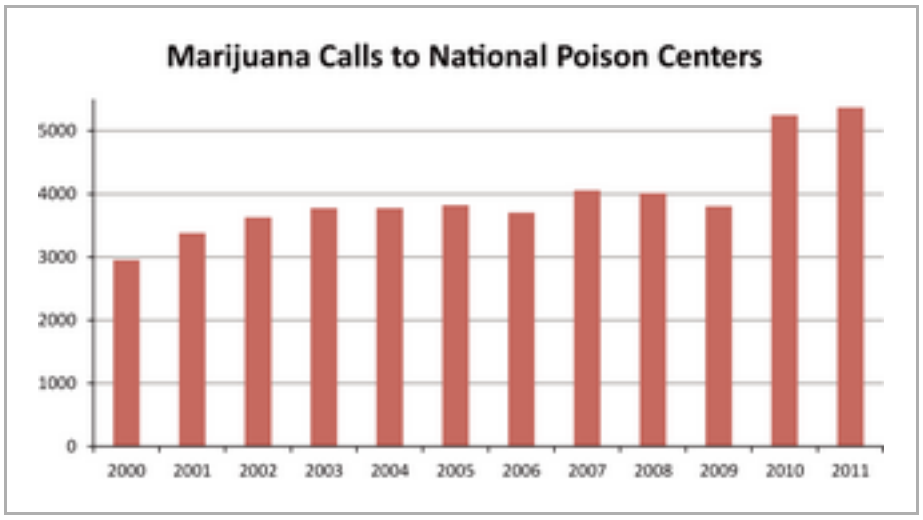


Figure 2.

Open in figure viewer

Telephone calls to national poison control centers pertaining to marijuana exposures.[89]

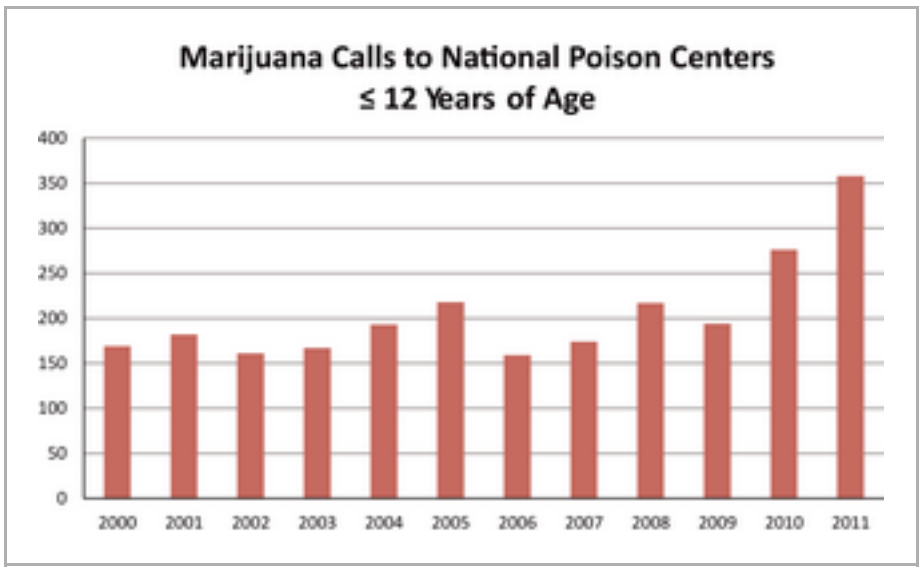


Figure 3.

Open in figure viewer

Telephone calls to national poison control centers pertaining to marijuana exposures in children aged 12 years or younger.[89]

With the increased availability of cannabinoids in states with legalized medical cannabis, there is also an increased risk for accidental exposure. Several reports of adverse events relating to cannabis exposure in children and adolescents have been made.[91-93] In Colorado, we reported a case series of five patients over 4 months who presented to the emergency department with altered mental status and lethargy.[94] After most patients received an extensive work up, including lab work, lumbar puncture, and imaging, urine drug screens showed they had been exposed to cannabis. Only on further questioning did care providers admit to the cannabis exposure. Four of the five sources of cannabis were confirmed to be marijuana card holders (registered patients using medical marijuana), and the products ingested included food products in many of the cases (e.g., cookies, candies). Since the time of the report, there have been several additional cases of pediatric exposure at our institution, mostly from medical marijuana in the form of food. Although no deaths related to marijuana have been reported to national poison centers, there can be significant morbidity. When patients present with an unclear history, they often receive invasive procedures (e.g., urine catheterization, intravenous lines, and lumbar punctures) and imaging (e.g., head computed tomography scans).

The availability of medical cannabis in consumer-friendly forms (soda drinks, desserts, candies, and tinctures) continues to increase and most, if not all, products lack regulatory or safety packaging. These products are concerning because they have labels and packaging that can be easily mistaken for conventional food products by young children. Consumption of these products may be tempting to young children, and it seems likely that exposures will increase. Like any other medication, patients should be instructed of the risks of the products and to store them safely and securely. Manufacturers may also consider warnings and child-proof packaging. Finally, health care providers should consider marijuana exposure in pediatric patients who present with altered mental status, somnolence, or lethargy.

Future Directions

Medical cannabis appears to have some benefit in patients with certain conditions. However, the use of medical cannabis within the current legal system faces a number of challenges.[34] First, the method of delivery (e.g., smoked, vaporized, oral) and patient individuality (e.g., severity of condition, inhalation and exhalation habits, functional lung capacity, gastrointestinal absorption) cause great variability in the effect of medical cannabis. The lack of quality control (e.g., contaminated products, nonstandardized doses) makes it difficult for clinicians to recommend particular formulations. Other concerns about medical cannabis include the need for adequate monitoring and prevention of addiction. Close surveillance of patients will ensure appropriate use of these medications, and training and education should be made available to providers whose patients use cannabis. Unfortunately, surveillance, training, and education are not available in most health systems, which often delimit the patient–physician relationship to a recommendation to use cananbis.[95] Similar to any other medication, improved safety measures and regulations for packaging should be examined. Additional research is needed to understand the role of the endocannabinoid system in various

pathways such as antinociception (pain) and antispasticity. Improved study methodologies, including the use of standard formulations and/or dosages and larger study populations, are needed for future investigative efforts to determine appropriate uses of medical cannabis. Further research evaluating the addition of CBD to THC needs to occur to determine if the nonpsychotropic effects of this compound can improve the tolerance and safety of THC. Therefore, education and research are needed to address these concerns and to review the original intent of the Institute of Medicine's report to determine the safe and effective use of marijuana.

Conclusion

Cannabinoids produce a variety of actions by activating CB_1 and CB_2 receptors and through other possible effects in the central nervous system. The pharmacologic and pharmacodynamics effects of cannabis can vary widely based on patient and drug characteristics, which can make it difficult to use effectively and safely. Various cannabis-derived pharmaceuticals are available. Dronabinol and nabilone are oral agents available in the United States as schedule III and II medications, respectively. Nabiximols is an oromucosal spray containing a 1:1 mixture of THC:CBD, which is available in 10 countries and will be evaluated this year by the FDA for approval in the United States. Medical cannabis containing hundreds of various cannabinoids is available in 18 U.S. states and the District of Columbia and will most likely be made more widely available in the next legislative year.

Medical cannabis has been evaluated for many different purposes, and medical cannabis registrants are using it particularly for pain and muscle spasms. Data indicate medical cannabis may be effective for these conditions, especially when standard therapy has failed. However, common adverse effects involving the central nervous system and gastrointestinal system may not make this an appropriate option in many patients. Extreme caution should be used in patients with a history of cardiovascular disease or mental disorders and in adolescents. Just as is recommended with other medications, patients using medical cannabis should minimize the risk of accidental pediatric ingestion by securing the drug in a safe place with child-proof locks. Although dronabinol and nabilone are regulated in the United States and have demonstrated sufficient efficacy and safety, evidence for medical cannabis is still lacking; thus, the drug should be used with caution in patients.

» References

» Related content

The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial

Mark A. Ware, MBBS, MSc, MRCP*†

Mary-Ann Fitzcharles, MBBS, FRCPC‡

Lawrence Joseph, PhD§

Yoram Shir, MD*†

BACKGROUND: Sleep disorders affect many patients with chronic pain conditions. Cannabis has been reported by several patient populations to help sleep. We evaluated the safety and efficacy of nabilone, a synthetic cannabinoid, on sleep disturbance in fibromyalgia (FM), a disease characterized by widespread chronic pain and insomnia.

METHODS: We conducted a randomized, double-blind, active-control, equivalency crossover trial to compare nabilone (0.5–1.0 mg before bedtime) to amitriptyline (10–20 mg before bedtime) in patients with FM with chronic insomnia. Subjects received each drug for 2 wk with a 2-wk washout period. The primary outcome was sleep quality, measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire. Secondary outcomes included pain, mood, quality of life, and adverse events (AEs).

RESULTS: Thirty-one subjects were enrolled and 29 completed the trial (26 women, mean age 49.5 yr). Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2–5.3). Nabilone was marginally better on the restfulness (Leeds Sleep Evaluation Questionnaire difference = 0.5 [0.0–1.0]) but not on wakefulness (difference = 0.3 [−0.2 to 0.8]). No effects on pain, mood, or quality of life were observed. AEs were mostly mild to moderate and were more frequent with nabilone. The most common AEs for nabilone were dizziness, nausea, and dry mouth.

CONCLUSIONS: Nabilone is effective in improving sleep in patients with FM and is well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline. Longer trials are needed to determine the duration of effect and to characterize long-term safety.

(Anesth Analg 2010;110:604–10)

Fibromyalgia (FM) is a chronic pain syndrome characterized by diffuse body pain with associated pressure allodynia. The diagnosis is clinical with no confirmatory test and is based on a history of widespread pain and the presence of tenderness at 11 of 18 specific tender point sites.[1] This condition, predominantly affecting adult women, is worldwide and common with a prevalence of 2% in North America.[2–4]

Although the pathophysiology of FM is not clearly understood, evidence is emerging of widespread central nervous system sensitization,[5] which may be mediated by dopaminergic,[6] serotonergic,[7] and glutamatergic[8] mechanisms. Autonomic dysregulation has also been postulated in FM.[9–11]

In addition to the report of pain, patients with FM experience numerous other somatic symptoms such as fatigue, mood disorder, and sleep disturbance that have an important effect on well-being. Insomnia has been reported in >75% of patients with FM.[12] Unique sleep patterns have been identified in patients with FM, for example, increased α non-rapid eye movement (REM) spindles on electroencephalogram recordings.[13] The use of antidepressant therapy has been shown to improve sleep quality in patients with FM.[14]

Pregabalin has been shown to be effective for pain in FM[15] and was recently approved by the United States Food and Drug Administration for the management of pain associated with FM. Before this, standard treatment for FM has included low-dose tricyclic antidepressants such as amitriptyline, cardiovascular

From the *Pain Clinic, McGill University Health Centre; †Alan Edwards McGill Centre for Research on Pain; ‡Division of Rheumatology, and §Department of Biostatistics and Epidemiology, McGill University, Montreal, Quebec, Canada.

Accepted for publication September 18, 2009.

Supported by an unrestricted grant from Valeant (Canada) Inc.

MAW and MAF have received honoraria from Valeant Canada for CME activities. YS and LJ have no conflicts to declare.

MW conceived of, designed, and supervised the trial and wrote the first draft of the manuscript. MAF and YS contributed to study design and conduct. LJ prepared the statistical plan and conducted the analyses. All authors contributed to writing the study report. MW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Address correspondence and reprint requests to Dr. Mark A. Ware, E19.145 Montreal General Hospital, 1650 Cedar Ave., Montreal, Quebec, Canada H3G 1A4. Address e-mail to mark.ware@muhc.mcgill.ca.

DOI: 10.1213/ANE.0b013e3181c76f70

exercise, cognitive behavioral therapy, and patient education.[16,17] Nabilone, a synthetic cannabinoid, has been observed in a small case series to improve sleep in patients with chronic pain.[18] A recent small randomized controlled trial of nabilone in FM was shown to reduce pain, but sleep changes were not reported.[19] To our knowledge, no study has specifically evaluated sleep quality as a primary outcome in FM. This study was therefore designed to investigate the effects of nabilone on sleep in patients with FM.

METHODS

We conducted a randomized, active-control, equivalency clinical trial using a 2-period crossover design. Each period was of 2 wk duration separated by a 2-wk washout phase. The total study period was for 10 wk, including the initial and final 2-wk washout periods.

Participants

Subjects were recruited from the Pain Clinic of the McGill University Health Centre. Eligible subjects were adult men and nonpregnant women aged 18 yr or older with a diagnosis of FM[1] who had self-reported chronic insomnia. Insomnia was defined as disturbed sleep either every night or every other night for the past 6 mo.[20] Subjects remained on stable analgesic therapy and had to have a negative urine screen for cannabinoids at the baseline visit. Subjects who were using a cannabinoid or amitriptyline at screening underwent a 2-wk washout period before entering the study. Subjects were excluded if they had cancer pain, unstable cardiac disease, a history of psychotic disorder, schizophrenia, or recent manic episode (within the past year), seizure disorder, glaucoma, urinary retention, hypersensitivity to cannabinoids, amitriptyline, or related tricyclic antidepressants, or were taking monoamine oxidase inhibitors.

Eligible and consenting subjects underwent a medical history, physical examination, and chart review. Vital signs and concomitant medications were recorded, and urinary drug screening, full blood counts, and renal and liver function tests were performed and required to be negative or normal. At the baseline visit, eligible subjects completed questionnaires on pain, mood, and quality of life (see below), and underwent a urine drug test before randomization.

Study Drug

Doses of nabilone 0.5 mg or amitriptyline 10 mg were prepared by an independent pharmacy in sealed opaque capsules. Subjects received either nabilone 0.5 mg or amitriptyline 10 mg at the start of the treatment cycle of the study according to the randomization schedule. On Day 7 of each treatment cycle, the study physician evaluated whether the subject might benefit from an increase in dose. If an increase was indicated, the dose of the assigned medication was doubled (to either nabilone 1 mg or amitriptyline 20 mg) for the second week. At the end of the second week, subjects stopped the study medication for a 2-wk washout period and began the second treatment cycle on the other study drug following the same procedures as above.

Objectives

The primary objective of this study was to determine whether nabilone is equivalent to amitriptyline in improving quality of sleep in patients with FM. The secondary objective was to describe the effects of nabilone on the other clinical variables of pain, mood, quality of life, and global satisfaction. Adverse events (AEs) were recorded.

Study Outcomes

Primary Outcome

The primary outcome was the quality of sleep. Two measures were used to assess sleep, the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ). The ISI is a reliable and valid instrument used to quantify perceived insomnia severity and is used as an outcome measure in insomnia treatment research.[21] A score of <8 on the ISI implies no clinical insomnia, 8–14 implies moderate insomnia, and >15 implies severe insomnia. The LSEQ is a well-validated instrument that has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigations with a variety of psychoactive drugs including sedative hypnotics, anxiolytics, central nervous system stimulants, and antihistamines.[22] The LSEQ comprises ten 100-mm visual analog scales measuring 4 characteristics of sleep: getting to sleep, quality of sleep, awakening from sleep, and behavior after wakefulness. We used the full LSEQ at clinic visits and in a study diary. During telephone interviews, patients responded to the questions on a 0–10 numerical scale. Sleep diaries were completed daily and returned at the end of each 2-wk cycle. Sleep data were also collected on 3 occasions by telephone during each week of the study including the washout period.

Secondary Outcomes

The secondary outcomes were pain, mood, quality of life, global satisfaction with treatment, and AEs. Pain was measured with the McGill Pain Questionnaire, a widely used and validated instrument frequently used in clinical trials of analgesic medications.[23] Mood was assessed using the short-form Profile of Mood States.[24] Quality of life was assessed using the Fibromyalgia Impact Questionnaire, a validated and disease-specific questionnaire for FM.[25] Patient global satisfaction was assessed using the question "Would you wish to continue with this medication?" (Y/N). Data on pain, mood, quality of life, and satisfaction were collected on Days 1 and 14 of each treatment cycle. At the end of the third and last washout phase, patients were asked to give their preference (if any) for 1 of the study

medications. Vital signs were recorded at each clinic visit. AEs were recorded throughout the study.

Urine samples were obtained at the screening visit and on Days 1 and 14 of each treatment cycle and tested by semiquantitative assay for the principal urinary metabolite (9-COOH-THC) of tetrahydrocannabinol (THC) to ensure that no other cannabinoid was used during the study.

Sample Size Estimation

The LSEQ has demonstrated differences in sleep quality from baseline of >1.5 on a 10-cm scale with samples of 30 subjects or fewer.[22] An equivalence study comparing the analgesic efficacy of amitriptyline with gabapentin concluded equivalence with 24 subjects. There are no specific data on sleep scores after amitriptyline therapy. We therefore estimated that a sample of 30 subjects would be sufficient to conclude equivalence based on within-subject SD of 1.0 around the primary outcome, because this would provide a confidence interval (CI) width for the between-treatment difference of approximately ±0.7 on the LSEQ scale. To account for a dropout rate of up to 25%, we aimed to recruit 40 subjects for this trial for a final sample size of at least 30 subjects. No interim analyses were planned.

Randomization

The randomization schedule was prepared (ralloc procedure, Stata version 8.0, Houston, TX) using randomly assigned block sizes ranging from 2 to 8. The schedule was kept by the study pharmacist away from the investigators. Study subjects were consecutively assigned to treatment order by the study nurse based on the randomization schedule. A coded script was given to the subject with instructions on the use of the allocated treatment. The subject then collected the medication from the study pharmacy and began taking the medication the same night.

Blinding

The study physician, study nurse, and subjects were blinded to the allocated treatment order. At the end of the study, the subjects were asked to estimate the order of allocated drugs as a means of estimating the success of blinding.

Statistical Analyses

The principal hypothesis for this study was that nabilone at a dose of 0.5–1 mg is equivalent to amitriptyline at a dose of 10–20 mg in improving sleep quality in patients with FM. The primary outcome of sleep quality was derived from the average scores obtained during the second week of each cycle of the ISI and of the sleep quality items (questions 4 and 5 on restfulness and wakefulness, respectively) from the LSEQ. The sleep scores during nabilone therapy were compared with those during amitriptyline using CIs of the within-subject difference in scores. Regression models were created with treatment, period, and order as terms in the model. Examination of treatment by period interactions was included to assess potential carryover effects. For inferences, 95% CIs were generated for all parameters. Secondary outcomes were assessed using similar procedures for each variable. AEs were tabulated by severity and study drug.

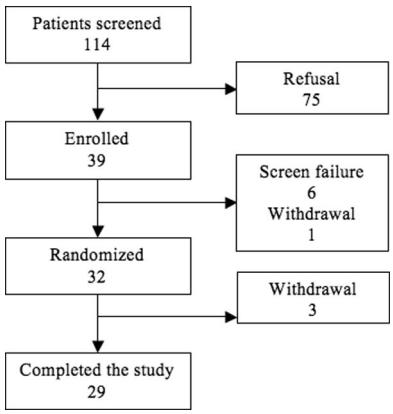


Figure 1. Trial flow diagram.

Table 1. Baseline Demographic Characteristics of Trial Participants ($n = 32$)

Characteristic	
Mean age (SD), range (yr)	49.5 (11.2), 26–76
Gender	
Female	26
Male	5
Education level attained	
University/college	25
Secondary/high school	6
Primary/elementary	1
Employment status	
Full time employed	12
Retired	6
Long term disability	4
Short term disability	4
Part time employed	2
Home maker	2
Other	2

Ethics and Trial Registration

Ethics approval was obtained from the McGill University Health Centre Research Ethics Board; all subjects provided written informed consent. Approval to use the study drugs was obtained through a Clinical Trial Application to the Therapeutic Products Directorate of Health Canada (Clinical Trial Application number 099547). The trial was conducted following Good Clinical Practice guidelines and was registered at www.clinicaltrials.gov (registration number NCT00381199).

RESULTS

One hundred fourteen subjects were screened, 39 were enrolled, and 32 were recruited and randomized to study drug (Fig. 1). Enrollment began in August 2005 and the last enrolled subject completed follow-up

Table 2. Baseline Self-Reported Symptom Data for Study Participants ($n = 32$)

Variable	Mean	SD
Insomnia severity index	18.3	5.2
McGill pain questionnaire		
Present pain intensity (PPI)	2.3	0.8
Sensory	15.8	9.0
Affective	4.7	3.1
Evaluative	2.3	1.3
Miscellaneous	6.0	3.0
Fibromyalgia impact questionnaire total score	62.6	15.2
Rested	81.6	15.3
Fatigue	80.5	20.2
Stiffness	74.5	19.5
Pain	69.3	20.5
Do work	66.4	25.1
Anxiety	51.6	30.1
Depression	37.5	32.5
Feel good	5.3	1.6
Physical impairment	1.4	0.8
Work missed	0.4	0.5
Profile of mood states total score	29.5	16.6
Fatigue	10.6	4.3
Tension/anxiety	7.3	3.7
Depression	5.8	4.4
Confusion	5.6	2.9
Anger	5.2	4.0
Vigor	4.6	3.3

Note the Leeds Sleep Evaluation Questionnaire is not measured at baseline because it requires a comparison with normal sleep.

in January 2007. Three subjects withdrew after randomization, 1 for noncompliance with study protocol, 1 for lack of effect, and 1 because of side effects after a single dose (edema of arms and legs, decreased concentration, dizziness, nausea, hyper-alert state, and insomnia). Twenty-nine subjects completed the study per protocol; there were no dropouts. All randomized subjects' data were included in the safety analysis.

Of the 32 randomized subjects, 26 were women and 5 were men (1 missing data). The mean age was 49.5 yr (SD 11.2) with a range of 26–76 yr. Baseline demographic and clinical data of recruited subjects are shown in Tables 1 and 2. Five subjects were taking tricyclic antidepressants at screening (4 amitriptyline and 1 nortriptyline), and all successfully withdrew from these medications before randomization. No subject was taking cannabinoid medications at screening, and all baseline urine tests were negative for THC.

Primary Outcome

Although both drugs improved sleep, after controlling for period effects, nabilone was found to have a greater effect on sleep than amitriptyline on the ISI (adjusted difference = −3.25; CI, −5.26 to −1.24) (Fig. 2). Based on the LSEQ sleep quality outcomes, there was no evidence of superiority of either drug, although subjects had a more restful sleep taking nabilone compared with amitriptyline (difference = 0.48; CI, 0.01–0.95) (Fig. 3). There were no marked differences in other scales of the LSEQ between the 2 drugs, although there was a suggestion of nabilone performing better than amitriptyline for ease (difference = −0.7; CI, −1.4 to 0.02) and speed (difference = −0.7; CI, −1.36 to 0.03) of falling asleep.

Other Outcomes

No differences were noted between treatments for pain (McGill PPI difference = −0.1; 95% CI = −0.3 to 0.2; other scales of McGill Pain Questionnaire also not significant), mood (Profile of Mood States difference = 1.4; 95% CI = −4.3 to 7.2), or quality of life (Fibromyalgia Impact Questionnaire difference = −0.7; 95% CI = −7.3 to 5.8).

Satisfaction and Preference

At the completion of the trial, preference for nabilone was reported by 41% (12 of 29) and for amitriptyline by 32% (9 of 28) of subjects (difference = 9%; 95% CI = −16% to 32%).

Dose Adjustment

The dose of amitriptyline was more frequently increased at 1 wk (26 of 28; 92%) compared with nabilone (21 of 29; 72%) (difference = 20%; 95% CI = −2%–43%).

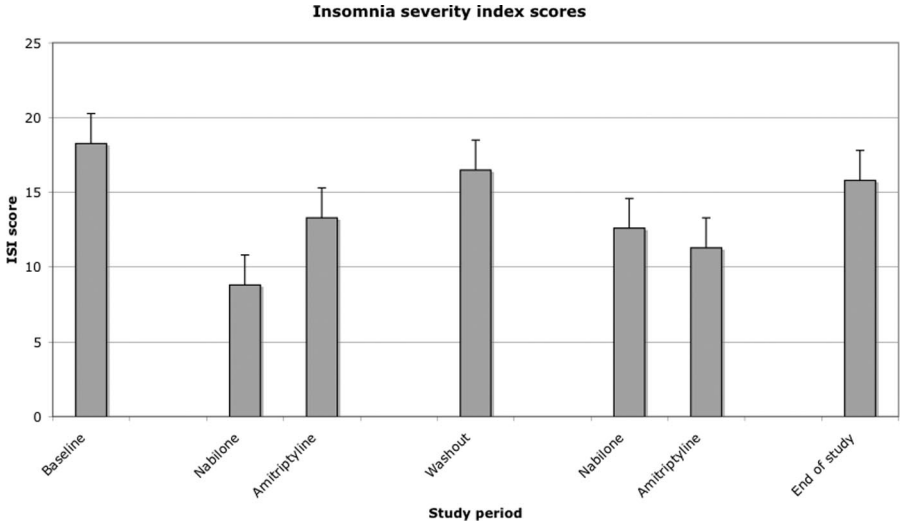


Figure 2. Effects of nabilone and amitriptyline on the Insomnia Severity Index (ISI).

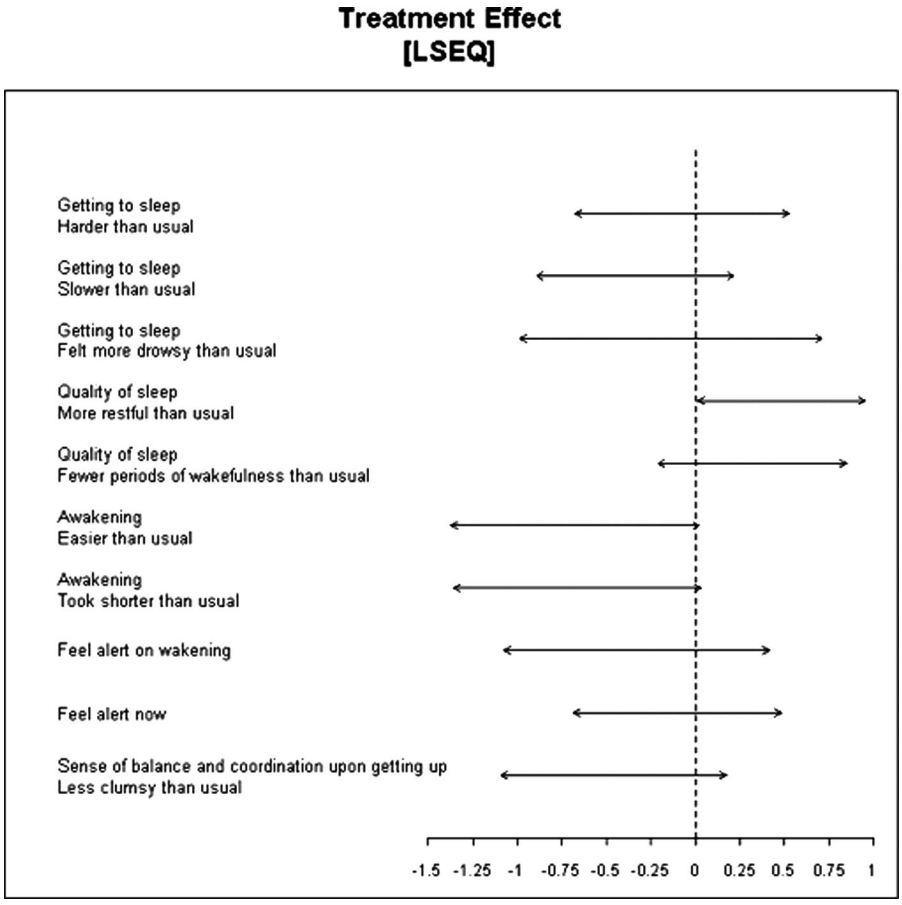


Figure 3. Treatment effects of nabilone compared with amitriptyline on sleep items in the Leeds Sleep Evaluation Questionnaire (LSEQ). Note that treatment effects shifted to the right favor nabilone, whereas effects shifted to the left favor amitriptyline. The *x* axis is the magnitude of the effect on a scale from 0 to 10. Shifts to the right represent improvements on the sleep subscales (shown on the *y* axis).

Table 3. Absolute Number of Adverse Events Occurring on >1 Occasion During the Trial

Description	Nabilone	Amitriptyline	Total
Dizziness	10	4	16
Headache	4	6	14
Nausea	9	1	14
Dry mouth	7	3	10
Drowsiness	6	1	7
Constipation	4	1	5
Diarrhea	2	2	4
Insomnia	3		3
Vomiting	3		3
Blurred vision	2	3	5
Fatigue	2	1	3
Cognitive impairment	2		2
Disorientation	2		2
Migraine	2		2

Discernment

When asked at the end of the study to guess which treatment had been administered, 8 subjects (29%) correctly identified the period in which they received amitriptyline, and 12 (41%) correctly identified the period in which they received nabilone.

Adverse Events

A total of 187 AEs were reported during the trial of which 120 were mild, 64 were moderate, and 3 severe. Of the 3 severe AEs, 2 occurred during amitriptyline therapy (headache and insomnia) and 1 occurred during nabilone (drowsiness). No serious AEs occurred during the trial. Fifty-three AEs were deemed possibly or probably related to amitriptyline therapy, and 91 AEs were deemed possibly or probably related to nabilone therapy. The most common AEs reported for nabilone and amitriptyline are shown in Table 3. AEs occurring in >2 subjects, which were more common for nabilone, were dizziness (10 subjects), nausea (9), dry mouth (7), drowsiness (6), constipation (4), insomnia (3), and vomiting (3).

DISCUSSION

We have observed that both the synthetic cannabinoid nabilone and the tricyclic antidepressant amitriptyline had a favorable effect on sleep in patients with FM, with nabilone showing overall superiority to amitriptyline for sleep quality. The effects of nabilone on pain, mood, and quality of life were similar to those seen with amitriptyline. Adverse effects were more common with nabilone, particularly drowsiness and dizziness, although global satisfaction with both drugs was similar.

The effects of cannabinoids on sleep have been recognized for many years. The hypnotic effects of THC were evaluated in the 1970s, and it was shown that THC increased Stage 3 sleep and reduced REM sleep[26]; amitriptyline has not been found to have any effect on non-REM sleep in patients with FM.[27]

Researchers conducting clinical trials of cannabinoids for other chronic pain disorders have reported improved sleep as secondary outcomes.[28] Endogenous cannabinoids have also been postulated to have an effect on normal sleep induction.[29] To our knowledge, this is the first study to evaluate sleep as a primary outcome for a chronic noncancer pain condition.

Our study has several important strengths. First, because both drugs cause similar side effects (e.g., drowsiness and dry mouth), we postulated that amitriptyline would be a suitable active control for nabilone, and therefore would preserve the blinded nature of the trial. Our data on blinding suggest that blinding was preserved, suggesting that amitriptyline is a good active control for further trials of nabilone. Second, because amitriptyline is frequently used for promoting sleep in FM, and because we have observed improvement of sleep among subjects taking amitriptyline, we believe that the study has demonstrated internal and external validity and was sufficiently powered to show clinically meaningful sleep improvements. For these reasons, we believe that the effects of nabilone on sleep quality are valid.

There are a number of limitations to this study that require comment. First, because the exposure to each drug was for a single 2-wk period, we are unable to extrapolate any conclusions regarding the long-term safety and efficacy of nabilone for sleep disturbance in FM. Because FM is a chronic condition, favorable treatments will likely require prolonged administration. Second, because both study drugs were used in relatively low dosage, this may have influenced the final outcome either favorably for nabilone (if nabilone was more effective at lower doses) or unfavorably for amitriptyline (if amitriptyline was more effective at higher doses). Because no other equivalency studies have previously been conducted with these drugs, the selected doses of the study drugs were based on clinical experience. Further dose-finding studies, specifically for nabilone, may be needed to explore safety and efficacy if higher doses are to be considered.

The mainstay of management for FM remains a multidisciplinary treatment approach, which includes exercise, education, pharmacological interventions, and behavioral therapies.[17,30] Sleep disturbances in FM are associated with poor quality of life and function, and increased pain and fatigue.[31] Although nabilone has been shown to have analgesic effects on pain in FM,[19] the effects of nabilone on sleep have not hitherto been addressed in this population.

In conclusion, we report that the synthetic cannabinoid nabilone is an effective drug in promoting sleep in patients with FM who have chronic insomnia and may be superior to amitriptyline, which is currently widely used for this purpose. Further studies on the effects of nabilone on sleep architecture and long-term safety and efficacy in FM and other pain conditions are warranted.

ACKNOWLEDGMENTS

The authors thank Lynda Oliveros, Laura Pallett, Linda Ferguson, and Nicole Poitras for administrative and nursing support during this trial. They also thank the subjects for their generous participation.

REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72
2. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol 1999;26:1570–6
3. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. Chronic Dis Can 2006;27:9–16
4. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28
5. Staud R. New evidence for central sensitization in patients with fibromyalgia. Curr Rheumatol Rep 2004;6:259
6. Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 2007;25:3576–82
7. Seidel MF, Weinreich GF, Stratz T, Muller W. 5-HT3 receptor antagonists regulate autonomic cardiac dysfunction in primary fibromyalgia syndrome. Rheumatol Int 2007;27:1025–30
8. Sarchielli P, Di Filippo M, Nardi K, Calabresi P. Sensitization, glutamate, and the link between migraine and fibromyalgia. Curr Pain Headache Rep 2007;11:343–51
9. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. Ann N Y Acad Sci 2006;1069:109–17
10. Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang Leistad R, Helde G, Rø M. Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. Eur J Pain 2007;11:743–55
11. Martinez-Lavin M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. Semin Arthritis Rheum 2000;29:197–9
12. Drewes AM. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. Rheumatology (Oxford) 1999;38:1035–8
13. Drewes AM, Nielsen KD, Taagholt SJ, Bjerregard K, Svendsen L, Gade J. Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. Br J Rheumatol 1995;34:629–35
14. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000;15:659–66
15. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, LaMoreaux LK, Martin SA, Sharma U; Pregabalin 1008–105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–73
16. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388–95
17. Rooks DS. Fibromyalgia treatment update. Curr Opin Rheumatol 2007;19:111–7
18. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med 2006;7:25–9
19. Skrabek RQ, Galimova L, Ethansand Daryl K. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;2:164–73
20. About insomnia. Available at: www.americaninsomniaassociation.org/aboutaia.htm. Accessed November 16, 2007

21. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307
22. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations—a review. Psychopharmacology (Berl) 1980;71:173–9
23. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–7
24. Curran SL, Andrykowski MA, Studts JL. Short form of the Profile of Mood States (POMS-SF): psychometric information. Psychol Assess 1995;7:80–3
25. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728–33
26. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. Clin Pharmacol Ther 1975;17:458–66
27. Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. Arthritis Rheum 1995;38:1211–7
28. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chem Biodivers 2007;4:1729–43
29. Mechoulam R, Fride E, Hanus L, Sheskin T, Bisogno T, Di Marzo V, Bayewitch M, Vogel Z. Anandamide may mediate sleep induction. Nature 1997;389:25–6
30. Staud R. Treatment of fibromyalgia and its symptoms. Expert Opin Pharmacother 2007;8:1629–42
31. Theadom A, Cropley M, Humphrey KL. Exploring the role of sleep and coping in quality of life in fibromyalgia. J Psychosom Res 2007;62:145–51

Medical Marijuana: Clearing Away the Smoke

Igor Grant*[1], J. Hampton Atkinson[1,2], Ben Gouaux[1] and Barth Wilsey[3]

[1]*Center for Medicinal Cannabis Research; University of California, San Diego; San Diego, CA, USA*

[2]*Psychiatry Service; VA San Diego Healthcare System; San Diego, CA, USA*

[3]*Department of Physical Medicine and Rehabilitation; University of California, Davis; Sacramento, CA, USA*

Abstract: Recent advances in understanding of the mode of action of tetrahydrocannabinol and related cannabinoid ingredients of marijuana, plus the accumulating anecdotal reports on potential medical benefits have spurred increasing research into possible medicinal uses of cannabis. Recent clinical trials with smoked and vaporized marijuana, as well as other botanical extracts indicate the likelihood that the cannabinoids can be useful in the management of neuropathic pain, spasticity due to multiple sclerosis, and possibly other indications. As with all medications, benefits and risks need to be weighed in recommending cannabis to patients. We present an algorithm that may be useful to physicians in determining whether cannabis might be recommended as a treatment in jurisdictions where such use is permitted.

Keywords: Cannabis, chronic pain, pain.

INTRODUCTION

In this article we review evidence that cannabis may be useful as medicine. We discuss potential indications for its use and provide an algorithm to guide medicinal cannabis recommendations.

The reasons for a revival of interest in medicinal cannabis are multiple, and beyond the scope of this review, but include increasing anecdotal and clinical study reports of potential benefit, advances in understanding of the endocannabinoid signaling system upon which cannabis acts, as well as growing public acceptance that cannabis should be available as a medicine if a physician recommends it.

BRIEF REVIEW OF PAST CLINICAL STUDIES ON MEDICINAL CANNABINOIDS

As recently as a decade ago a review of the world literature on the status of the efficacy and safety of cannabinoids for pain and spasticity revealed that only nine randomized studies of acceptable quality had been conducted [1]. All of these were single dose studies comparing oral synthetic THC (or cannabinoid analogs or congeners) to codeine or placebo. Two were "N of 1" randomized trials and two were of very small samples of acute post-operative pain. The remaining trials primarily addressed chronic cancer-related pain. Taken as a group it appeared that oral cannabinoids (e.g., THC 10mg) outperformed placebo and were analgesically equivalent to codeine 60mg; higher doses (THC 20mg) were comparable to codeine 120mg, but had a much higher incidence of adverse effects, particularly sedation [2]. Authoritative reviews judged cannabinoids as being unlikely to have a role in acute pain management, but suggested there was enough evidence for efficacy in chronic neuropathic pain and muscle spasticity to warrant further research [1].

*Address correspondence to this author at the Department of Psychiatry, School of Medicine; University of California San Diego, 9500 Gilman Drive; La Jolla, CA, 92093-0680; Tel: (858) 534-3652;
Fax: (858) 534-7723; E-mail: igrant@ucsd.edu

RECENT STUDIES ON MEDICINAL CANNABIS

In the past decade, the scope and rigor of research has increased dramatically. This research has employed cannabis, cannabis-based extracts, and synthetic cannabinoids delivered by smoking, vaporization, oral, and sublingual or mucosal routes.

Studies on Smoked Cannabis

Smoking cannabis provides rapid and efficient delivery of THC to brain. THC can be detected immediately in plasma after the first puff of a cigarette; peak concentrations occur within 10 minutes, then decrease to approximately 60% of peak by 15 minutes and 20% of peak by 30 minutes, but there can be wide inter-individual variation in concentrations achieved [3]. Rapid onset and predictable decay means that self-titration of dosing is attainable.

Chronic Pain

A series of randomized clinical trials at the University of California Center for Medicinal Cannabis Research (CMCR) investigated the short-term efficacy of smoked cannabis for neuropathic pain. Sponsored by the State of California Medical Marijuana Research Act of 1999, and conducted under the auspices of the Department of Health and Human Services, the National Institute on Drug Abuse, and the Food and Drug Administration, this research allocated participants to smoke cannabis cigarettes containing from 1% to 8% THC by weight (4 to 32 mg THC) or to placebo cannabis cigarettes from which THC had been extracted. The total daily dose of THC ranged from 4 mg to 128 mg. Two trials enrolled patients with painful HIV peripheral neuropathy [4, 5]; one consisted of mixed neuropathic pain due to peripheral or central dysfunction of the nervous system (i.e., com-

1874-205X/12

plex regional pain syndrome, peripheral neuropathy, and traumatic focal nerve or spinal cord injury) [6]. Patients were allowed to continue their usual regimen of analgesics. Results consistently indicated that cannabis significantly reduced pain intensity, with patients reporting 34%-40% decrease on cannabis compared to 17-20% on placebo. Moreover a significantly greater proportion of individuals reported at least 30% reduction in pain on cannabis (46%-52%) compared to placebo (18%-24%) [4-6], which is relevant since 30% decrease in pain intensity is generally associated with reports of improved life quality [7]. The number needed-to-treat to achieve a 30% reduction in pain intensity was 3.5-4.5, a range achieved by standard non-opioid analgesics (i.e., noradrenergic antidepressants and anticonvulsants). Interestingly "medium" dose cannabis cigarettes (3.5% THC) were as effective as higher dose (7% THC) [6]. In this same vein, a fourth trial employing an experimental model of neuropathic pain (intradermal injection of capsaicin) in healthy volunteers suggested that there may be a "therapeutic window" or optimal dose for smoked cannabis: low dose cigarettes (2% THC) had no analgesic effect, high dose (8%) was associated with reports of significant pain increase, and medium dose cannabis cigarettes (4% THC) provided significant analgesia [8]. Separately, another recent placebo-controlled, cross-over study of neuropathic pain due to surgery or injury examined the effect of 25 mg doses of smoked cannabis at various potencies (2.5%, 6%, and 9.4% THC by weight), administered three times daily for 14 days [9]. Results suggested that although lower potency dosing was ineffective, 9.4% THC produced modest but significant analgesic effects compared to placebo, in a sample selected for failure to respond to conventional therapy.

Studies of Oral Preparations.

Oral preparations are available as synthetic THC (dronabinol, Marinol^{R}) and a synthetic analog of THC (nabilone, Cesamet^{R}). Absorption from the gut is slower and exhibits a delayed peak plasma concentration compared to smoking with bioavailability ranging from about 5-20% of dose; peak concentrations occur 1-6 hours after ingestion, with a magnitude approximately 10% of that achieved with smoking [3].

Chronic Pain

Most research using oral preparations has targeted neuropathic pain and spasticity associated with multiple sclerosis (MS). These randomized trials suggest that dronabinol (up to 25 mg daily) significantly reduces pain compared to placebo (50% "improved" on dronabinol compared to 30% on placebo, $p < .05$) [10], with a number-needed-to-treat for 50% pain reduction of 3.5, which is in the range of efficacy observed for standard non-opioids [11]. Effects on spasticity are mixed: there may be no observable change in examiner-rated muscle tone, but patients report significant relief [10].

There is less research with nabilone, although one three-week randomized crossover trial reported that nabilone 2mg provided modest analgesia, comparable to dihydrocodeine 240mg daily in neuropathic pain [12].

Nausea-Emesis and Appetite Stimulation

Although serotonin receptor (5 HT3) antagonists (e.g., ondansetron, Zofran^{R}) and Substance P/neurokinin-1 (NK-1) receptor antagonists (e.g., aprepitant, Emend^{R}) are the mainstays for treatment, dronabinol and nabilone are also FDA-approved for control of acute and delayed nausea and emesis due to cancer chemotherapy. Meta-analyses indicate these cannabinoids are equivalent to or more effective than metoclopraminde and neuroleptics, but their side effect profile is less favorable in terms of sedation, dizziness, dysphoria, hypotension, and anxiety [13, 14]. There are no head-to-head comparisons of cannabinoids with serotonin 5 HT3 receptor or Substance P/NK-1 receptor antagonists.

Anorexia, early satiety, weight loss and cachexia are prevalent in late stage cancer and advanced HIV disease, but there are few effective treatments. Trials in AIDS patients with clinically significant weight loss indicated that dronabinol 5mg daily significantly outperformed placebo in terms of short term appetite enhancement (38% vs. 8% at 6 weeks), and that these effects persisted for up to 12 months [15, 16], but were not accompanied by significant differences in weight gain, perhaps because of disease-associated energy wasting. The major practical limitations are the accompanying psychoactive side effects, and the problems of oral administration (eg, delayed onset of action, variable absorption, extended duration of effects).

Studies on Cannabis-based Extracts

Outside the US, extracts of whole plant are licensed and available in capsules (Cannador^{R}), with the main constituents being THC and the non-psychoactive plant cannabinoid, cannabidiol, in a ratio of 2:1. Rectal suppositories are also used to deliver THC hemisuccinate. Several small to medium-sized, randomized, controlled trials in MS suggest improvements in pain and perceived spasticity at daily doses of THC ranging from 7.5mg to 27.5mg [10, 17, 18]. In some trials [19] but not others [10, 20] observer-assessed spasticity also improved.

Studies with Alternative Delivery Systems

The hazards of smoking and the pharmacokinetic limitations of ingestion of cannabinoids has led to a search for alternative systems of administration. One alternative is devices which vaporize cannabis leaves by heating the plant product to below the temperature of combustion (175-225 degrees C), permitting inhalation of volatilized gases minus hazardous pyrroles produced by burning. Preliminary work using plant material with a range of THC content (e.g., 1-7% THC) suggests that there is rapid onset, with peak concentrations and six-hour area under the plasma concentration curves comparable to those achieved by smoking [21]. Vaporization is not a perfect solution since carbon monoxide is formed, but levels are significantly lower than with smoking [21]. Clinical trials are currently in progress at the CMCR assessing the efficacy of vaporized cannabis as an analgesic in chronic neuropathic pain.

Sublingual delivery systems of whole cannabis plant extract, which employ metered spray devices to deliver measured doses of THC (2.7mg) and cannabidiol (2.5mg), are undergoing Phase IIb/III trials in the US, and are licensed elsewhere for cancer pain and multiple sclerosis-associated neuropathic pain and spasticity (nabiximols, Sativex^{R}). The apparent advantages of such systems are known cannabinoid

concentrations, predetermined dosing aliquots, and time-out systems which may help prevent overuse. Some placebo-controlled trials suggest significant analgesia in neuropathic pain due to multiple sclerosis [22] and mixed neuropathy (e.g., post-herpetic, traumatic, vascular neuropathies, [23] but others do not [20]. Other controlled trials suggest efficacy for cancer-related pain inadequately responsive to opioid analgesia [24]. Responders participating in the open label extension phases of controlled trials appear to maintain analgesia on one-year follow-up [23].

In regard to spasticity in multiple sclerosis, a recent meta-analysis combining three trials with nabiximols in over 600 patients noted that mean intensity of patient rated spasticity was significantly reduced compared to placebo [20, 25, 26], and that the proportion of "responders" (30% reduction) was also significantly greater, with about 37% on the cannabinoid compared to 26% on placebo experiencing relief. Those reporting relief of spasticity seemed to maintain their gains over one year follow-up [27]. As with other studies noted above, observer-rated spasticity is often not reduced [20, 25, 28]; however, a recent CMCR study did find a significant reduction in observed spasticity among those administered active smoked marijuana vs. placebo marijuana [58].

PRESERVATION OF MASKING IN CLINICAL TRIALS

Because of the acute psychoactive effects of the experimental agent there is understandable concern that blinding cannot be preserved in placebo-controlled clinical trials of cannabinoids, particularly with cross-over designs. Few studies assess masking, but two cross-over trials tested maintenance of the blind by asking participants to "guess" assignment at different points of the study. Results suggest that participants, whether they are naïve or experienced cannabis users, are in the first week of a trial no more likely than by chance to guess assignment [5, 9]. With continued exposures rates of correct guesses exceed 75%, but exceed chance only in a high potency arm (9%) [9]. In another study correct guessing was related to two factors: whether the subject received placebo or cannabis first; and when during the study the participant guessed assignment [5]. Among individuals randomized to receive placebo first, guessing was no better than chance through the end of the first treatment week, whereas the majority of those randomized to receive cannabis first correctly guessed their treatment assignment at all time points. Furthermore, by the conclusion of the study, when all subjects had been given the opportunity to compare the cannabis placebo and treatments, even those randomized to receive placebo first correctly guessed their treatment assignment [5]. This raised the possibility that some of the pain reduction was placebo driven. Secondary analyses to assess whether correct treatment guessing influenced treatment responses showed that in the placebo group during the first treatment week, when guessing was no better than chance, cannabis still provided pain relief superior to that of placebo. This finding suggests that although placebo effects were present, treatment effects were independent [5].

RISKS AND MANAGEMENT OF MEDICINAL USE OF CANNABINOIDS

Acutely and over the longer term cannabis may have unwanted systemic and psychoactive adverse effects that must be taken into consideration in chronic pain populations, who have high rates of co-occurring medical illness (eg, cardiovascular disease) and co-morbid psychiatric and substance use disorders. In general these effects are dose-related, are of mild to moderate severity, appear to decline over time, and are reported less frequently in experienced than in naïve users. Reviews suggest the most frequent side effects are dizziness or lightheadedness (30%-60%), dry mouth (10%-25%), fatigue (5%-40%), muscle weakness (10%-25%), myalgia (25%), and palpitations (20%) [17]. Cough and throat irritation are reported in trials of smoked cannabis [9]. Tachycardia and postural hypotension are infrequent but caution is warranted in patients with cardiovascular disease, and possibly younger adults who intend to embark on very vigorous physical activity. At higher doses, sedation and ataxia with loss of balance are frequent. Participants in some but not all studies report euphoria: the relative absence of psychoactive effect has been attributed to the observation that plasma concentrations obtained in clinical trials are often <25% of those achieved by "recreational" users (eg, 25ng/ml vs >100ng/ml) [9]. After repeated smoked or oral marijuana doses, tolerance is rapidly acquired (in two to 12 days) to many of its adverse effects, e.g., cardiovascular, autonomic, and many subjective and cognitive effects [29]. After exposure is stopped, tolerance is lost with similar rapidity.

There is little systematic data on timeline to tolerance of either adverse or therapeutic effects, like analgesia. Concerns have long been voiced that rapid tolerance to adverse effects might portend tolerance to beneficial effects [29]. Data from studies using oral sprays of cannabinoids or dronabinol in multiple sclerosis report that individuals can reduce the incidence and severity of adverse effects by downward self-titration without loss of analgesia [17]. Other studies in this population note that overall the incidence and severity of adverse effects diminishes over time without evidence of tolerance to analgesic effects [20, 22]. Yet it is rare that clinical trials of cannabinoids extend follow-up beyond 12 weeks, leaving questions on maintenance of gains or need for dose escalation unanswered [10, 26]. One study with 12-month follow-up concluded there may be sustained analgesia for pain associated with multiple sclerosis, where about 30% of cannabinoid-treated participants report continued "improvement" at 12 months compared to about 15% on placebo [30] on doses conservatively limited to a maximum of 25mg THC daily. This suggests that pain relief may be sustained without dose increases. But the study design was not intended to determine the proportion of patients who experienced diminution of effect, or whether dose escalation, even within the set boundary, was needed for maintenance of efficacy.

There are risks to be considered in assessing the potential of cannabinoid therapeutics. Cannabis, like other analgesics, can be associated with dependence and a withdrawal syndrome, occurring in a dose-dependent fashion [29]. Under controlled conditions in healthy, experienced users of marijuana, withdrawal from a "low" daily dose (ie, oral THC 10 mg every 3-4 hours for 5-21 days) commences within 12 hours, is diminished by 24 hours, and is complete in 48 to 72 hours [29]. Other short term experiments with oral THC (20 to 30mg four times daily) and smoked cannabis (1% and 3% THC cigarettes four times daily) reveal an abstinence syn-

drome characterized by anxiety, irritability-restlessness, insomnia, stomach pain and decreased appetite [31, 32], with mood effects more prominent at the higher dosages. In research specifically designed to establish the time line of abstinence among regular heavy users (4 cigarettes daily), symptoms peak at 2 to 3 days, and persist for up to 2 weeks, although sleep disturbance may continue for up to 6 weeks [33]. In light of abstinence effects, standard practice in clinical trials administering a maximum of 25 mg THC daily is to use a tapering scheme to conclude therapy, with a 20% per day dose reduction [30]. Patients discontinuing higher dose cannabinoids for analgesia might warrant a longer tapering regimen, but this has not been studied.

Fatal overdose with cannabis alone has not been reported. In terms of acute drug interactions, additive effects of cannabis, anticholinergics, and CNS depressants should expected (e.g., increased sedation, dizziness, dry mouth, confusion). Cannabinoids are metabolized by several enzyme systems, including Cytochrome P450 (CYP 2C9, CYP 3A4) and can induce or inhibit CYP 3A4, but there is little evidence of important drug-drug interactions based on CYP 450 systems. Smoking itself (e.g., cannabis or tobacco) induces CYP 1A2, and may increase clearance of some antipsychotics (e.g., olanzapine, clozapine) and antidepressants (e.g., some tricyclics, mirtazepine) [34, 35]. Overall then, the acute medical risks of THC as used in clinical trials are rather low.

There can be adverse psychiatric side effects. THC intoxication and euphoria can be disturbing, particularly to elderly patients. Anxiety and panic attacks occur, as do frank psychotic reactions (principally paranoia), as well as so-called "paradoxical" effects of dysphoria, dejection, and depressed mood [36, 37]. Although unlikely to be a factor in the application of cannabinoids for pain, there is concern that early adolescent use of cannabis may heighten later risk of psychosis [36, 38], and evidence that genetic variation (single nucleotide polymorphisms) heightens vulnerability [39].

Acute cannabinoid intoxication adversely impacts processing speed, attention, learning and recall, perception of time and velocity, reaction time and psychomotor abilities in a dose-dependent fashion [40]. Formal neuropsychological testing in clinical trials reveals mild impairment at usual analgesic doses [6, 23]. While cannabis can acutely impair skills required to drive motor vehicles in a dose-related fashion, epidemiological data are inconclusive with regard to the association of traffic accidents and use of cannabis [41]. There is speculation that cannabis use is associated with increased awareness of impairment (e.g., altered perception of time and speed), which results in compensatory behavioral strategies. What is clearer from experimental and epidemiologic data is that driving under the influence of both alcohol and cannabis in combination confers greater risk of accidents than the risk of either drug alone [41].

The longer-term health risks of cannabis are unclear, and the evidence is based on non-medical use [42]. Long-term use of inhaled cannabis may be associated with dependence and increased respiratory symptoms; but some epidemiological studies have not found more lung disease in long-term users, once the effects of tobacco are accounted [43]. Long-term use of inhaled cannabis has not been associated with increased risk of lung or gastrointestinal cancers [44], although a meta-analysis found evidence of premalignant changes in the respiratory tract [45]. There is some evidence that among individuals with pre-existing cardiac disease, cannabis users have an increased risk of myocardial infarction in the hour after smoking cannabis compared to non-users [46]. A recent meta-analysis showed no major residual effects on neurocognitive functioning in long term daily-users of cannabis [47]. THC rapidly crosses the placenta and accumulates in breast milk of nursing mothers [3], but there is no systematic evidence of direct or behavioral teratogenicity.

In reviewing the possible acute and long term adverse effects of cannabinoids as therapeutic agents one needs also to be mindful that other agents that are used for treatment of pain or spasticity also have adverse effects. Opioids produce sedation, nausea, constipation and dependence, withdrawal from which results in serious abstinence syndrome with much more severe effects – e.g. severe autonomic, gastrointestinal, and psychiatric – than the rather mild cannabis withdrawal phenomena. Tricyclic antidepressants and antiepileptic drugs commonly prescribed for chronic pain have psychotropic (e.g. sedation), anticholinergic (e.g. constipation, dizziness, palpitations, visual disturbance, urinary retention), and neuromuscular effects. Drugs for spasticity produce sedation (e.g. baclofen), hypotension (e.g. tizanidine) and serious interactions with antibiotics (e.g. tizanidine and ciprofloxacin). Benzodiazepines that are sometimes prescribed for spasticity can produce sedation, psychomotor incoordination, memory lapses, and paradoxical reactions, as well as dependence and withdrawal syndromes. Opioids and sedative-hypnotics are also drugs of abuse, and their ability to induce physiological dependence and serious withdrawal states exceed those of cannabis. Therefore, judgements on relative benefits and risks of cannabinoids as medicines need to be viewed within the broader context of risk-benefit of other agents as well [48].

PATIENT SELECTION FOR CANNABINOID THERAPY

Oral THC (eg, dronabinol) is FDA-approved as a second line agent for chemotherapy-associated nausea and emesis, and appetite stimulation. Dronabinol (and nabilone) have some evidence of efficacy for chronic neuropathic pain; whole plant cannabis extracts delivered by capsule or oral-mucosal spray has been approved in Europe for analgesia in neuropathic pain and control of painful muscle spasticity. Patient selection for these agents would seem to be rather straightforward, and focus on therapeutic response to conventional treatments, consideration of possible psychotropic (eg, sedation effects if combined with alcohol) and cardiovascular effects, risk of dependence and an abstinence syndrome, and acknowledgement that there is narrow empirical basis for efficacy compared to standard treatments. Patients should be educated about expected adverse effects. The pharmacokinetics of orally administered cannabinoids would seem to decrease likelihood of diversion or abuse.

On the other hand, prescription of inhaled cannabis for medical purposes is legal in some US jurisdictions, and neurologic consultants, who are likely to be asked about the advisability of prescribing or recommending "medical mari-

juana," may be justifiably uncertain of how to proceed. There are no published consensus statements or systematic approaches to identify candidates for "medical marijuana" or guide treatment; although some regulatory agencies, such as the Medical Board and the Office of the Attorney General of California have proposed guidelines (Table **1**).

It should be noted that the evidence for efficacy is based primarily on relatively few short-term studies with small sample sizes of selected, mostly neuropathic pain conditions (ie, Phase II/III trials). "Medical cannabis", now available from dispensaries in some jurisdictions, is not subject to governmental standardization, and its constituents and potency are consequently unknown. Moreover, the mean potency of marijuana seized by federal and state authorities has more than doubled over the past 15 years to about 6% THC, well over 20% of confiscated plants have a potency exceeding 9%, and some specimens exceed 25% THC [49]. Thus, cannabis obtained from dispensaries or other sources may have potency far exceeding that used in clinical trials described in this review. Furthermore, cannabis elicits concerns among regulators, clinicians, and patients regarding issues of misuse, abuse, and other liabilities. With these facts in mind, a potentially useful framework for evaluating advisability of medical marijuana are guidelines released by professional pain societies concerning prescription of long-term opioid therapy for chronic, non-cancer pain [50, 51]. The guidelines are framed by several questions. One question regards not only the legality of cannabis, but the standard of practice in the clinician's community, since either prescription or recommendation for use of cannabis is outside of "conventional practice." As with prescription of opioids there are potential issues of legal liability [52]. A second question asks whether other treatments offer a more favorable risk-benefit ratio. The answer depends upon a careful differential diagnosis, identification of a potentially responsive pain syndrome (e.g., the strongest evidence is for neuropathic pain), consideration of other approaches (e.g., disease-modifying treatment, ablative interventions, other analgesics like anticonvulsants, noradrenergic antidepressants, opioids, or nonsteroidals, and cognitive-behavioral or rehabilitative therapy, or complementary treatments). A third question is whether there are medical and psychiatric risks. The shorter-term medical risks of cannabis are relatively low overall. Risks of hypotension and tachycardia should be evaluated in patients with cardiovascular diseases, as these may be associated with elevated risk of cannabis-associated myocardial infarction. Elderly patients with neurocognitive impairment may be predisposed to adverse effects of cannabis on memory and concentration, while even intact older individuals may be susceptible to over-sedation, and falls due to ataxia. The intoxicating effects of cannabis may be disturbing. A history of severe anxiety or paranoia on prior exposure to cannabis should be sought and would be a contraindication; since patients with serious mental illness (bipolar disorder or schizophrenia) may be particularly vulnerable to these adverse effects, they are unlikely to be candidates.

Moreover, there must be assessment of the potential for misuse, abuse, or addiction. This requires a careful examination for history of substance use disorders, and psychiatric illness, perhaps supplemented by formal psychiatric consultation. Screening questionnaires, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP-R) [53], have been validated in chronic pain clinic populations to stratify patients into "lower" or "higher" risk of future opioid-related aberrant behaviors, and suitably modified might be applicable to assessment of risks for cannabis misuse. Most pain experts consider sobriety a foundation of successful pain treatment. Cannabis use is prevalent in chronic pain patients prescribed opioids and may be associated with current or future opioid misuse [54]. Patients screened "at risk" for aberrant opioid use, or a history of cannabis or other substance use disorders usually would not be considered eligible for medicinal cannabis. There might be exceptions. For example, there is some evidence that patients with sustained remission from alcohol dependence (ie, sober for $\geq$ 5 years) are at no greater risk for developing a new onset substance abuse problem than non-alcohol controls, so this population would not necessarily be excluded automatically [55]. Also, a recent randomized trial suggests highly-structured approaches may result in successful analgesia and restoration of function without aberrant opioid use in "high risk" patients prescribed opioids for chronic pain [56]. Such methods, which involve a regimen of systematic urine toxicology testing, use of compliance checklists to evaluate for "red flags" of non-adherence to the program (eg, unsanctioned dose escalations, illicit drug use), and enrollment in a substance misuse counseling [56], might be adapted for use in high-risk candidates for medical marijuana. Before embarking on a trial of medical marijuana in patients with prior history of substance use disorders, it would be prudent to

Table 1. Medical Board/Office of the Attorney General of California Guidelines for Medical Marijuana

Physicians Recommending Medical Marijuana Need to:
1 Take a history and conduct a good faith examination of the patient;
2 Develop a treatment plan with objectives;
3 Provide informed consent, including discussion of side effects;
4 Periodically review the treatment's efficacy;
5 Obtain consultations, as necessary; and
6 Keep proper records supporting the decision to recommend the use of medical marijuana.
http://www.mbc.ca.gov/board/media/releases_2004_05-13_marijuana.html
http://ag.ca.gov/cms_attachments/press/pdfs/n1601_medicalmarijuanaguidelines.pdf

establish a similar routine of urine toxicology testing, compliance checklists, and co-enrollment in a formal substance abuse treatment facility, just as is recommended for a trial of opioid analgesics [52]. Finally, chronic pain may be associated with major depression, which complicates treatment, and which must be diagnosed and independently treated for successful pain management. All of these factors being considered, if the decision is made to proceed, the clinician must formulate and document a treatment plan and the patient's agreement to abide by whatever guidelines are established. The clinical "trial" would entail establishing a therapeutic "dose," appropriately monitoring for adverse effects and misuse, and assessing outcome in terms of pain, mood, and function. Based on the literature of efficacy in neuropathic pain, there could be evidence of an effect within a minimum of two weeks. Response rates have been noted to increase, however, between two and four weeks in previous neuropathic pain registration trials for gabapentin and duloxetine [57]; one might select a longer duration in difficult-to-treat cases. Considering all these factors, one would then decide with the patient whether continued treatment is warranted. A possible algorithm to guide physician decision-making is presented in Fig. (**1**).

CONCLUSION

Evidence is accumulating that cannabinoids may be useful medicine for certain indications. Control of nausea and vomiting and the promotion of weight gain in chronic inanition are already licensed uses of oral THC (dronabinol cap-

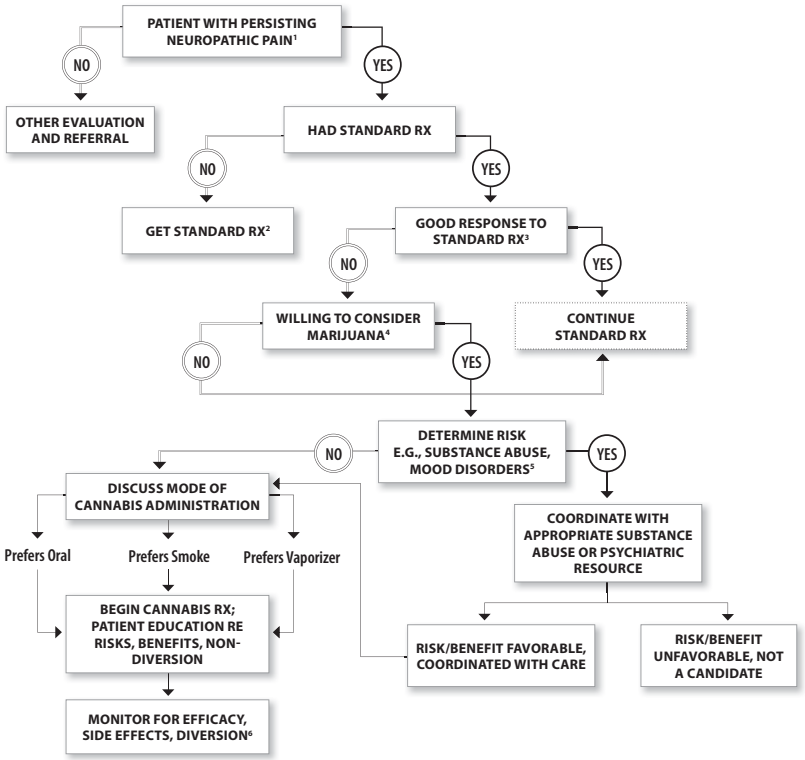


Fig. (1). A decision tree approach for physicians who may be considering recommending medicinal cannabis to a patient. This decision tree suggests some key points that a physician may need to consider in making his/her determination. In this case, a patient is assumed to present with persistent neuropathic pain. Initially, a determination needs to be made that the patient's signs and symptoms are indeed consistent with this diagnosis. Assuming a patient does not respond favorably to more standard treatments (e.g., antidepressants, anticonvulsants, etc), or cannot tolerate those, and the patient is willing to consider medicinal cannabis, the physician needs to determine risk versus benefit. Among these considerations is whether there is a history of substance abuse or serious psychiatric disorder that might be exacerbated by medicinal cannabis. Even if such risks exists, this does not necessarily preclude the use of medicinal cannabis; rather coordination with appropriate substance abuse and psychiatric resources is necessary, and based on such consultation a risk benefit ratio can be determined. In patients in whom the ratio appears favorable, the physician needs to discuss alternative modes of cannabis administration which may include oral, smoked, or vaporized systems. Once risks and benefits are evaluated and discussed with the patient, cannabis treatment may commence as with other psychotropic medications, with attention being paid to side effects as well as efficacy. In addition, there needs to be attentiveness to potential for misuse and diversion, which can then trigger a decision to discontinue.

Key

1. Daily or almost daily pain with typical neuropathic characteristics for at least 3 months; affects life quality.
2. Standard Rx = e.g., antidepressants, anticonvulsants; opioids; nonsteroidal anti-inflammatory drugs.
3. For example, at least 30% reduction in pain intensity.
4. Consider past experience, possible past history of side effects; willingness to smoke.
5. Determine history of substance abuse. If yes, or at "high risk" aberrant for drug behavior; proceed with close observation; possibly coordinate with substance abuse treatment program.
6. Efficacy = at least 30% reduction in pain intensity.

sules). Recent research indicates that cannabis may also be effective in the treatment of painful peripheral neuropathy and muscle spasticity from conditions such as multiple sclerosis [58]. Other indications have been proposed, but adequate clinical trials have not been conducted. As these therapeutic potentials are confirmed, it will be useful if marijuana and its constituents can be prescribed, dispensed, and regulated in a manner similar to other medications that have psychotropic effects and some abuse potential. Given that we do not know precisely which cannabinoids or in which combinations achieve the best results, larger and more representative clinical trials of the plant product are warranted. Because cannabinoids are variably and sometimes incompletely absorbed from the gut, and bioavailability is reduced by extensive first pass metabolism, such trials should include delivery systems that include smoking, vaporization, and oral mucosal spray in order to achieve predictable blood levels and appropriate titration. Advances in understanding the medical indications and limitations of cannabis in its various forms should facilitate the regulatory and legislative processes.

The classification of marijuana as a Schedule I drug as well as the continuing controversy as to whether or not cannabis is of medical value [59] are obstacles to medical progress in this area. Based on evidence currently available the Schedule I classification is not tenable; it is not accurate that cannabis has no medical value, or that information on safety is lacking. It is true cannabis has some abuse potential, but its profile more closely resembles drugs in Schedule III (where codeine and dronabinol are listed). The continuing conflict between scientific evidence and political ideology will hopefully be reconciled in a judicious manner [60, 61]. In the meantime, the decision to recommend this treatment in jurisdictions where use of medical marijuana is already permitted needs to be based on a careful assessment that includes proper diagnosis of a condition for which there is evidence that cannabis may be effective, along with consideration as to response to more standard treatments. Prior substance abuse history, psychiatric comorbidity, and other factors need to be weighed in a risk benefit analysis. Part of this analysis should consider that the potential longer-term harms of the cannabinoids are not fully understood: these include abuse and a dependence syndrome, adverse psychiatric and medical effects in vulnerable populations, and documented risk to traffic safety when combined with alcohol, and perhaps singly [62]. In the long term, as further studies demonstrate whether cannabis is effective for various indications, this should lead to development of novel modulators of the endocannabinoid system which may be prescribed and used as more traditional medicines.

CONFLICTS OF INTEREST

This work was supported by the University of California Center for Medicinal Cannabis Research. I. Grant served as consultant to Abbott Pharmaceuticals. J. H. Atkinson has served as a consultant to Eli Lilly and Company. B.L. Wilsey has served as a consultant to Ortho-McNeil Janssen Pharmaceuticals, Inc.

ACKNOWLEDGEMENT

Supported by the Center for Medicinal Cannabis Research at the University of California, San Diego.

REFERENCES

[1] Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001; 323(7303):13-6.

[2] Noyes R, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975;18(1): 84-9.

[3] Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabinol. Handb Exp Pharmacol 2005; (168): 657-90.

[4] Abrams DI, Jay CA, Shade SB, *et al*. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68(7): 515-21.

[5] Ellis RJ, Toperoff W, Vaida F, *et al.* Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacol 2009; 34(3): 672-80.

[6] Wilsey B, Marcotte T, Tsodikov A, *et al*. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9(6): 506-21.

[7] Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94(2):149-58.

[8] Wallace M, Schulteis G, Atkinson JH, *et al* . Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007;107(5):785-96.

[9] Ware MA, Wang T, Shapiro S, *et al*. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182(14): E694-701.

[10] Zajicek J, Fox P, Sanders H, *et al*. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362(9395): 1517-26.

[11] Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004; 329(7460):253.

[12] Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008; 336(7637):199-201.

[13] Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001; 323(7303):16-21.

[14] Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol 2006; 105(1-2):1-25.

[15] Beal JE, Olson R, Laubenstein L, *et al*. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manag 1995;10(2): 89-97.

[16] Beal JE, Olson R, Lefkowitz L, *et al* . Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manag 1997; 14(1):7-14.

[17] Pertwee RG. Cannabinoids and multiple sclerosis. Mol Neurobiol 2007; 36(1): 45-59.

[18] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003;17(1): 21-9.

[19] Vaney C, Heinzel-Gutenbrunner M, Jobin P, *et al*. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004; 10(4): 417-24.

[20] Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized,

placebo-controlled study on 160 patients. Mult Scler 2004; 10(4): 434-41.

[21] Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther 2007; 82(5): 572-8.

[22] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65(6):812-9.

[23] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007 ;133(1-3): 210-20.

[24] Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manag 2010; 39(2): 167-79.

[25] Collin C, Davies P, Mutiboko IK, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007; 14(3): 290-6.

[26] Wade DT, Collin C, Stott C, Duncombe P. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. Mult Scler 2010; 16(6): 707-14.

[27] Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler 2006; 12(5): 639-45.

[28] Farrar JT, Troxel AB, Stott C, Duncombe P, Jensen MP. Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. Clin Ther 2008; 30(5): 974-85.

[29] Jones RT, Benowitz NL, Herning RI. Clinical relevance of cannabis tolerance and dependence. J Clin Pharmacol 1981; 21(8-9 Suppl):143S-52S.

[30] Zajicek JP, Sanders HP, Wright DE, *et al*. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005; 76(12):1664-9.

[31] Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology (Berl) 1999;141(4): 385-94.

[32] Haney M, Ward AS, Comer SD. Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology (Berl) 1999;141(4): 395-404.

[33] Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 2004; 161(11): 1967-77.

[34] Williamson EM. Drug interactions between herbal and prescription medicines. Drug Safety 2003; 26: 1075-92.

[35] Wills S. Drugs of Abuse. 2nd ed. London: Pharmaceutical Press 2005.

[36] Moore TH, Zammit S, Lingford-Hughes A, *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370(9584): 319-28.

[37] D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. Eur Arch Psychiatry Clin Neurosci 2009; 259(7): 413-31.

[38] McGrath J, Welham J, Scott J, *et al*. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry 2010; 67(5): 440-7.

[39] van Winkel R. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. Arch Gen Psychiatry 2011; 68(2): 148-57.

[40] Miller LL, McFarland D, Cornett TL, Brightwell D. Marijuana and memory impairment: effect on free recall and recognition memory. Pharmacol Biochem Behav 1977; 7(2): 99-103.

[41] Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am J Addict 2009; 18(3):185-93.

[42] Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374(9698):1383-91.

[43] Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 2007; 167(3): 221-8.

[44] Hashibe M, Morgenstern H, Cui Y, *et al*. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomark Prev 2006;15(10):1829-34.

[45] Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med 2006 ;166(13):1359-67.

[46] Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation 2001; 103(23): 2805-9.

[47] Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 2003; 9(5):679-89.

[48] Brunton L, Chabner B, Knollman B, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill 2010.

[49] Mehmedic Z, Chandra S, Slade D, *et al*. Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci 2010; 55(5): 1209-17.

[50] Chou R, Fanciullo GJ, Fine PG, *et al*. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009; 10(2): 113-30.

[51] Fine PG, Portenoy RK. A Clinical Guide to Opioid Analgesia. 2nd ed. New York: Vendome Group 2007.

[52] Jamison RN, Clark JD. Opioid medication management: clinician beware! Anesthesiology 2010; 112(4):777-8.

[53] Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised screener and opioid assessment for Patients with Pain (SOAPP-R). J Pain 2008; 9(4): 360-72.

[54] Reisfield GM, Wasan AD, Jamison RN. The prevalence and significance of cannabis use in patients prescribed chronic opioid therapy: a review of the extant literature. Pain Med 2009; 10(8): 1434-41.

[55] Schuckit MA. Drug and alcohol abuse: a clinical guide to diagnosis and treatment. 6th ed. New York: Springer 2006.

[56] Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. Pain 2010;150(3):390-400.

[57] Ho TW, Backonja M, Ma J, Leibensperger H, Froman S, Polydefkis M. Efficient assessment of neuropathic pain drugs in patients with small fiber sensory neuropathies. Pain 2009;141(1-2):19-24.

[58] Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. A randomized, placebo-controlled trial of smoked cannabis for spasticity in multiple sclerosis. CMAJ (In press).

[59] Drug Enforcement Agency. The DEA Position on Marijuana. January 2011; Available from: http://www.justice.gov/dea/marijuana_position.pdf. [cited 2012 March 26]

[60] Cohen PJ. Medical marijuana: the conflict between scientific evidence and political ideology. Part two of two. J Pain Palliat Care Pharmacother 2009; 23(2): 120-40.

[61] Cohen PJ. Medical marijuana: the conflict between scientific evidence and political ideology. Part one of two. J Pain Palliat Care Pharmacother 2009; 23(1): 4-25.

[62] Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 2012; 344:e536

Received: January 09, 2012 Revised: February 21, 2012 Accepted: March 02, 2012

October 07, 2016
Medical Marijuana Petition
Open Letter

To whom it may concern,

As you read my petition I do hope you think of all the people who suffer from fibromyalgia. Before I felt it for myself I did think it could possibly be as bad as people described. I was wrong. For me fibromyalgia feels like every cell in my body screaming, like my skin and skeleton are trying to switch places, like my fingers are in electrical outlets and like complete and utter exhaustion. Take your worst all nighter in college and multiply it by 10 then add your worst hang over, nausea, sensitity to light and sound and migraines that's what it feels like when I take my medication, so you see not doing anything is not an option for me. However with only three FDA approved medications that have failed to help me, my options are limited. This is my story and my plea for a chance at a better life.

I am 25 years old, after having gastric sleeve surgery in December 2014 to try and take my life back I quickly lost almost 100lbs and with that expected to start a new better life. However shortly after I started experiencing extreme fatigue, pain, tingling, numbness and nausea among other symptoms. My depression and anxiety started to spiral out of control so I sought out help from my doctor. I was referred to a rheumatologist who basically told me I was hypermobile it was genetic, I was "built wrong" and there wasn't really much he could do for me. I refused to accept that, I am just 25, I am too young to live everyday in pain and so utterly exhausted that there was no joy in doing anything. So I did what any strong willed 20 year old would do, I got a new rheumatologist, I needed a second opinion before I gave up. I was then diagnosed with fibromyalgia and have proceeded to try and fight everyday to get my life back. An endless parade of medications have failed me my chronic pain is a mix of tendonitis, hypermobility, fibromyalgia, osteoarthritis and migraines, each one has a different medication and each medication comes with a new risk to my already damaged struggling body.

Now on medications I can function, for lack of a better word. I am always in pain and because of the pain medications and antidepressants that it takes to make me functional I am constantly severely nauseous which interferes with my work as well as my focus and ability to eat healthy and work out which are important factors for improving my fibromyalgia and controlling my Polycystic Ovary Syndrome. The only options I have for medication makes me sick, I take them so that even though every step I take hurts I can get up and push through it. Everyday I think there has to be another option, a better way, I shouldn't have to take medications that make me sick just so I can get out of bed.

I have never smoked marijuana. Apparently that makes me an oddity in my age group and todays society. I do not know for sure that marijuana will help me, but I didn't know for sure if gabapentin would, or duloxetine, or Lyrica, Trintellix, or any other medication I have been put on. What I do know is that like with those medications other individuals with symptoms similar to mine have been able to

improve their quality of life by being allowed to use marijuana in a medical context. What I am asking for, not only for me but others in my position as well is a chance to try something that may improve my life when other medications have failed me. I want the opportunity to use a natural substance that has been used for thousands of years to improve my life, to take away some of the pain, to improve my sleep, nausea, depression and anxiety, all of which of symptoms medical cannabis has been used to treat. I do not claim to be a medical professional I am an anthropologist by trade, so I have no desire to try to tell you how to treat a medical condition. However I am asking you to consider it, to think about the fact that fibromyalgia only has three FDA approved medications for treatment, that individuals like me, having had gastric sleeve, may not be able to tolerate this medications and that I have no desire to be high, if I did I honestly would have smoked marijuana a long time ago. I just want to feel better. I am sick and tired of being sick and tired and having to choose between medications that dull the pain somewhat but make me feel terrible or pain that feels like my skeleton and skin are trying to switch places. The last time I couldn't take the nausea and I tried to stop taking my pain medication I made it two days, 24 hours before I had to take the medication to be able to stand. Fibromyalgia took my life away from me; I went from being at a 3.89 in graduate school to barely making a 3.0 in pre-medical requirements and falling asleep in class from exhaustion. I lost friends who wanted me to go out and I couldn't get up. I lost a year of my twenties that I could have spent doing so many things and I refuse to lose anymore because of this. I am willing to look into every option and try anything I can all I ask of you is the opportunity to do it and to do it right and legally and safely so that I know what I am getting and what strain it is exactly.

I thank you for your consideration and I do hope this has been helpful,

[redacted] B.S. M.A.